

First independent assessment of pharmaceutical company action on AMR

# Antimicrobial Resistance Benchmark 2018



access to  
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FOUNDATION

# Antimicrobial Resistance Benchmark 2018

**ACCESS TO MEDICINE FOUNDATION**

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## ACCESS TO MEDICINE FOUNDATION

The Access to Medicine Foundation is an independent non-profit organisation based in the Netherlands. It aims to advance access to medicine in low- and middle-income countries by stimulating and guiding the pharmaceutical industry to play a greater role in improving access to medicine.

For 10 years, the Foundation has been building consensus on the role for the pharmaceutical industry in improving access to medicine and vaccines. It publishes the Access to Medicine Index every two years, with the next Index due in late 2018. In 2017, the Foundation published the first Access to Vaccines Index. This is the first Antimicrobial Resistance Benchmark.

## ACKNOWLEDGEMENTS

The 2018 Antimicrobial Resistance Benchmark has been made possible through collaboration with experts and specialists working across the spectrum of organisations working to curb antimicrobial resistance.<sup>1</sup> The Foundation is grateful for their time and expertise, and would like to thank them for providing valuable insights throughout the development of this research and its methodology.

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Dulce Calçada  
Karrar Karrar  
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Marijn Verhoef

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Emma Ross

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Ministry of Health, Welfare and Sport

### Address

Naritaweg 227 A  
NL-1043 CB Amsterdam  
The Netherlands

### Contact

For questions about this report, please contact  
Jayasree K. Iyer, Executive Director  
[jiyer@accesstomedicinefoundation.org](mailto:jiyer@accesstomedicinefoundation.org)  
+31 (0) 20 215 35 35  
[www.amrbenchmark.org](http://www.amrbenchmark.org)

<sup>1</sup> This acknowledgement is not intended to imply that the individuals and institutions referred to above endorse the Antimicrobial Resistance Benchmark methodology, analyses or results. Decisions regarding the final analysis were ultimately made by the Access to Medicine Foundation.

# The superbugs can be stopped – if we put good ideas into action

At the Access to Medicine Foundation, we have been analysing how pharmaceutical companies tackle access to medicine for more than a decade. This first Antimicrobial Resistance Benchmark is the first independent, detailed evaluation of how pharmaceutical companies are halting the rise of drug resistance.

Drug resistance – also called antimicrobial resistance or AMR – is on the increase and it can spread fast. But if action is taken now, it can be contained. Global AMR strategies focus on improving how we all use antimicrobials, so that bacteria and other pathogens have less chance to develop resistance. These strategies must also ensure people can still get hold of these lifesaving medicines when they need them: many millions of people around the world lack reliable access to antimicrobials or to good information on how to use them.

The ‘superbug’ threat cannot be removed by one single person, organisation or sector working alone. Coordination, commitment and collaboration are key, from political leaders and policymakers to doctors, farmers and pharmaceutical executives. In recent years, the international community and the private sector have swung their collective weight behind efforts to contain AMR – these commitments now need to lead to real action, with progress toward set targets being publicly monitored. New ideas and new opportunities are also needed to limit AMR, including new ways of incentivising further action. Importantly, good practices must be shared, so that companies and other stakeholders can seize more opportunities to make change.

As a global community, we look to pharmaceutical companies to bring us safe and effective antimicrobials. It is widely acknowledged to be a challenging and commercially unattractive market, with little incentive to develop



new antimicrobials. Nevertheless, a core group of companies remain committed to providing these critical medicines, with some continuing to develop innovative new products to replace the ones that don't work anymore. Without antibiotics, common infections will become harder to treat. Many other areas of modern medicine will become riskier, such as cancer therapy, surgery and even childbirth.

In this first AMR Benchmark, we found that almost all companies we looked at are taking some action to limit AMR. There are good practices in most areas we examined, although there is also much more to be done.

I invite you to use this first Benchmark as you review AMR strategies – use it as a book showing the good ideas now being implemented, and as a map of the opportunities to amplify current efforts to contain AMR. The power of business, the public sector and individuals to radically transform society is immense.

Jayasree K. Iyer  
Executive Director  
Access to Medicine Foundation

# Table of contents

## 6 EXECUTIVE SUMMARY

## 10 INTRODUCTION

## 16 BENCHMARK PERFORMANCE

- 16 AMR: what are the priorities and where are pharmaceutical companies focussing?
- 18 The Antimicrobial Resistance Benchmark – which companies lead?

## 24 KEY FINDINGS

- 24 Out of 28 antibiotics in late stages of clinical development, only two have both access and stewardship provisions in place
- 25 Nearly half of companies with products on the market are involved in AMR surveillance
- 26 Eight companies are setting limits on antibiotic wastewater discharge
- 27 Four companies move to decouple antibiotic sales volumes from sales agents' bonuses

## 28 PORTFOLIO ANALYSIS

- 28 Antimicrobial portfolios: what medicines are on the market?
- 30 Case studies: how three companies are addressing access and stewardship in tandem
- 34 Vaccines in the push to limit antimicrobial resistance

## 39 RESEARCH AREAS

- 40 Research & Development: What is in companies' antimicrobial pipelines?
- 58 Manufacturing & Production: How pharmaceutical companies ensure the production of antibiotics does not contribute to resistance
- 66 Access & Stewardship: How pharmaceutical companies approach access and stewardship for antibiotics

## 83 COMPANY REPORT CARDS

- 84 Achaogen, Inc.
- 86 Aspen Pharmacare Holdings Limited
- 88 Aurobindo Pharma Limited
- 90 Cempra, Inc.
- 92 Cipla Limited
- 96 Dr. Reddy's Laboratories Ltd.
- 98 Entasis Therapeutics Inc.
- 100 Fresenius Kabi AG
- 102 GlaxoSmithKline plc
- 106 Johnson & Johnson
- 110 Lupin Limited
- 112 Macleods Pharmaceuticals Ltd.
- 115 Melinta Therapeutics, Inc.
- 117 Merck & Co., Inc.
- 120 MGB Biopharma
- 122 Motif Bio plc
- 124 Mylan NV
- 127 Nabriva Therapeutics plc
- 129 Novartis AG
- 132 Pfizer Inc.
- 135 Polyphor Ltd.
- 137 Roche Holding AG
- 140 Sanofi
- 143 Shionogi & Co., Ltd.
- 146 Summit Therapeutics plc
- 148 Sun Pharmaceutical Industries Ltd.
- 150 Tetrphase Pharmaceuticals, Inc.
- 152 Teva Pharmaceutical Industries Ltd.
- 154 The Medicines Company\*
- 156 Wockhardt Limited

## 159 APPENDICES

- 160 I - Methodology scopes
- 163 II - Priority pathogens for R&D
- 164 III - Products for access
- 169 IV - Countries for access
- 170 V - Analysis, scoring and review
- 173 VI - Limitations
- 174 VII - Scoring guidelines
- 179 VIII - Guide to report cards
- 180 IX - List of figures
- 181 X - Definitions
- 183 XI - Acronyms

# About this report

The Antimicrobial Resistance Benchmark provides the first independent assessment of how pharmaceutical companies are responding to AMR. The 30 companies in scope include those with the largest R&D divisions, the largest market presence, and specific expertise in developing critically needed medicines and vaccines. The goal of the Antimicrobial Resistance Benchmark is to guide and incentivise such companies to adopt and implement effective actions for tackling AMR. It highlights where good ideas for limiting AMR are being implemented and where action is still required. The AMR Benchmark is independently funded by UK AID and the Dutch Ministry of Health, Welfare and Sport.

## Framework of analysis

The analytical framework is structured across three Research Areas: Research & Development; Manufacturing & Production; and Appropriate Access & Stewardship. The Benchmark assesses company behaviour regarding infectious diseases and product types and in a specific geographic scope, depending on the Research Area in question. Its metrics correspond to areas where experts and stakeholders agree that pharmaceutical companies can and should be taking action to limit AMR.

## What the Benchmark analyses

The Benchmark evaluated data gathered via a detailed survey of company behaviour regarding AMR and from public sources. It included ongoing/active projects up until 8 September 2017. Data submitted by the companies or

gathered from public sources was verified, cross-checked and supplemented by the Foundation's research team using public databases, sources and supporting documentation.

## The first baseline for companies

AMR is increasingly recognised as a growing public health problem. Governments, policy-makers, farmers, doctors and pharmaceutical executives have a role to play. The Antimicrobial Resistance Benchmark provides an initial baseline measure of how pharmaceutical companies are limiting AMR. Companies and stakeholders can use this analysis to inform priorities and strategies, and learn where new incentives or stronger strategies would spur companies towards greater engagement in tackling AMR.

## SECTIONS IN THIS REPORT

### Benchmark performance and Key Findings

A comparative analysis of how pharmaceutical companies performed, with Key Findings in R&D for priority pathogens, AMR surveillance, environmental risk management, and promotion practices.

### Portfolio analysis and case studies

A breakdown of the antimicrobials marketed by the companies evaluated and an analysis of how they correspond to medicines on the WHO Model List of Essential Medicines, with case studies of companies balancing access and stewardship.

### Three Research Areas

In-depth analyses of company performances in three Research Areas: Research & Development; Manufacturing & Production; Appropriate Access & Stewardship.

### 30 Company Report Cards

Each company report card provides a detailed overview of how the company is addressing AMR, as evaluated by the metrics used by the Benchmark. Each report card includes overviews of the company's portfolio and pipeline.



# Executive Summary

Antimicrobial resistance (AMR) is increasingly recognised as a growing global health problem. Without effective antibiotics, infections become more difficult to treat, and medical and surgical procedures can become high-risk interventions. Antimicrobials are losing their effectiveness at an increasing rate, accelerated by their misuse in humans and in the agricultural sector. To slow the rise of resistance, antimicrobials must be used only when needed. Global stewardship strategies are being developed that address how antimicrobials are used in humans and animals, as well as the antimicrobial load in the environment. AMR strategies also focus on developing new antimicrobial medicines to replace those that are becoming less effective. Pharmaceutical companies, including 24 of the companies in scope, have signed up to industry-wide commitments to tackling AMR.

Strategies to improve the rational use of antimicrobials must also address access issues. Millions of people currently live without reliable access to antimicrobials or to good information on how to use them. This lack is particularly acute in low- and middle-income countries, where weaknesses in healthcare delivery systems can limit access to antimicrobials while also promoting their inappropriate use. For many pathogens, resistance rates are generally higher in low- and middle-income countries than in wealthier countries.

Bringing AMR under control requires consolidated, concerted action by multiple stakeholders. Governments have a central role to play, as do policy-makers, public health authorities, academic institutions and agricultural and pharmaceutical companies. Pharmaceutical companies can determine to a large extent where their products are available and how they are priced and promoted. They have significant influence on manufacturing chains and have extensive expertise in researching, developing and commercialising new medicines.

## First independent report

The Antimicrobial Resistance Benchmark is the first independent report to systematically evaluate how a cross-section of the pharmaceutical industry is responding to the AMR threat. It compares 30 companies selected on their market presence, expertise in developing critically needed antimicrobials and their public commitments to tackling AMR. They include eight large research-based pharmaceutical companies, ten generic medicine manufacturers and 12

biopharmaceutical companies. The antimicrobial market is increasingly consolidated, with companies facing commercial, scientific and regulatory challenges. Nevertheless, the recent prioritisation of AMR appears to have encouraged a few companies to return to this space. The Benchmark methodology was developed through consultation with a wide range of stakeholders and experts working in AMR.

This report sets out the results of this first Benchmark, assessing and comparing companies' activities to address internationally agreed AMR priorities. It outlines the key findings and presents detailed analysis of companies' performances in three areas of corporate activity: R&D for new antimicrobials, policies for ensuring responsible antibiotic manufacturing, and approaches to ensuring antimicrobials are accessible and being used wisely. The business models, sizes and portfolios of the different groups give them different roles and responsibilities regarding AMR. Thus, companies are evaluated only in metrics relevant to their businesses. The report concludes with detailed company report cards, including portfolio and pipeline analyses. These cards explain each company's performance in the Benchmark and any industry-leading practices, and present company-specific opportunities to further support efforts to control AMR.

## The 2018 AMR Benchmark – which companies lead?

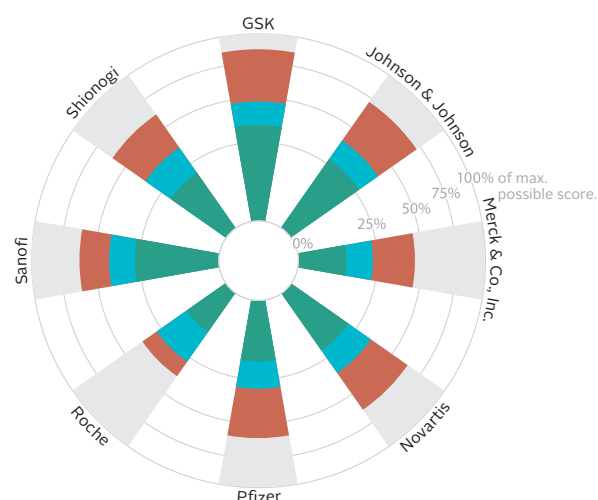
The AMR Benchmark identified 10 areas where alignment exists on AMR priorities for pharmaceutical companies between the final report of the UK Review on AMR, the Interagency Coordination Group (IACG) on Antimicrobial Resistance and the Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance. There is evidence of action by multiple companies in each area, with most companies active in antimicrobial R&D. Some companies, such as GSK, are active in all areas. Other companies are active in only a few areas, while low disclosure prevents a full analysis of a few companies.

The eight large research-based pharmaceutical companies are led by two companies: GSK, which has the largest antimicrobial pipeline for priority pathogens, and Johnson & Johnson, which has a focus on tuberculosis. They are followed by Novartis, Pfizer and Sanofi together. Compared to the other two groups of companies analysed, the large

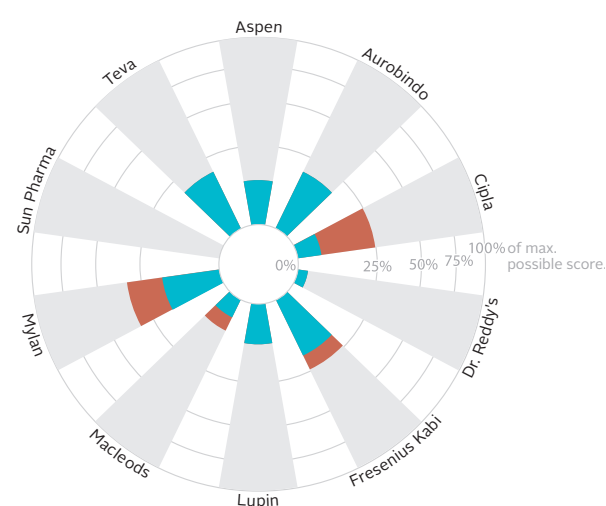
## Figure 1. Antimicrobial Resistance Benchmark – Company Performances

The radials compare how close companies are to achieving 100% of their maximum potential score. 13 companies achieve over 50%.

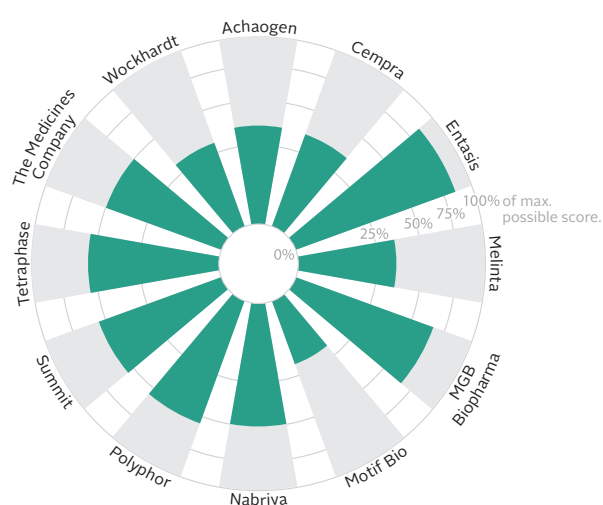
### Eight large research-based pharmaceutical companies



### Ten generic medicine manufacturers



### Twelve biopharmaceutical companies



● Research & Development ● Manufacturing & Production  
● Appropriate Access & Stewardship ● Remaining potential score

research-based pharmaceutical companies are the most active against AMR: six out of eight achieved more than 50% of the points available.

Mylan, Cipla and Fresenius Kabi lead the 10 generic medicine manufacturers in scope. All three are active in stewardship. Mylan and Cipla are the only two companies in this group to report equitable pricing approaches. Disclosure among generic medicine manufacturers is generally lower than among the other two groups of companies.

Of the 12 biopharmaceutical companies included, the strongest performance comes from Entasis, particularly when it comes to planning ahead for access and stewardship of clinical-stage candidates. Entasis is followed by Polyphor, Summit and Tetraphase in joint second place, when comparing companies by points earned. However, when comparing companies by how close they are to achieving 100% of their maximum potential score, MGB Biopharma comes second in this group.

### Key Findings

- There are 28 antibiotics for high-priority pathogens in late stages of development. However, only two of these are supported by plans to ensure the successful candidate can be made accessible and used wisely once it reaches the market.
- Nearly half of companies evaluated are involved in efforts to track patterns in antibiotic drug resistance, with AMR surveillance programmes running in 147 countries. Pneumonia is the most widely-tracked infection.
- Eight companies are setting limits on the levels of antibiotics that can be released into the environment in wastewaters at their antibiotic manufacturing facilities. Yet no company publishes what is released in practice.
- Four companies are taking steps to separate sales agents' bonuses from the volume of antibiotics they sell. GSK and Shionogi have fully separated the two globally, Pfizer is piloting that approach in certain territories, and Novartis is taking steps toward adjusting its sales teams' incentives.

### Portfolio analysis and case studies

The companies in scope have at least 741 antimicrobial medicines on the market – more than half target bacterial infections and a further quarter are antivirals. The antibacterials include 189 beta-lactam antibiotics, which remain important antibiotics for their broad-spectrum effectiveness. Ensuring access to these is a public health priority.

Out of 741 marketed products, 268 correspond to antibiotics on Section 6 of the WHO Model List of Essential Medicines (EML). In 2017, the WHO EML grouped antibiotics into 'Access', 'Watch' and 'Reserve' groups. The Benchmark found that companies have far more antibiotics in the Access group than in the Reserve group. Access antibiotics should be widely available, affordable and quality-assured. Reserve group antibiotics should only be used for the most severe cases when all alternative treatments have failed.

The Benchmark describes three examples of how pharmaceutical companies are balancing access to treatment and stewardship for specific products. Johnson & Johnson's breakthrough medicine for multidrug-resistant tuberculosis (bedaquiline, Sirturo®) is being tightly controlled through national TB programmes and donations. GSK combines broad registration and pricing strategies with measures to promote the appropriate use of an off-patent first-line antibiotic (amoxicillin/clavulanic acid, Augmentin™). Cipla is the only generic medicine manufacturer of those evaluated in the Benchmark that runs educational activities for healthcare professionals on antibiotic stewardship.

## FINDINGS PER RESEARCH AREA

### Research & Development

#### *20 companies analysed*

- 1 GSK is the leader among large research-based pharmaceutical companies, followed by Johnson & Johnson and Sanofi. Among biopharmaceutical companies, Entasis leads. Four generic medicine manufacturers are active in antimicrobial R&D: Aurobindo, Cipla, Macleods and Mylan.
- 2 The majority of R&D projects target pathogens deemed priority AMR threats by the WHO and/or the US Centers for Disease Control and Prevention (referred to in this report as priority pathogens).
- 3 Around half of R&D projects targeting priority pathogens are being conducted through partnerships.
- 4 Companies have varied plans for ensuring successful candidates are accessible and appropriately used. Licensing plans, equitable pricing and AMR surveillance are the most common components of such plans.
- 5 Only two antibiotics in late-stage development for priority bacteria are supported by plans addressing both access and appropriate use of a successful candidate.

### Manufacturing & Production

#### *18 companies analysed*

- 1 Six companies pull ahead in this area: GSK, followed by Johnson & Johnson, Novartis, Pfizer, Roche and Sanofi.
- 2 Most companies have environmental risk-management strategies in place; the depth and breadth of strategies vary.
- 3 Eight companies set discharge limits for antibiotics, but none disclose actual discharge levels.
- 4 Only one company discloses names of third-party manufacturers, seen as important for bringing accountability into environmental risk management for antibiotic production.

## Appropriate Access & Stewardship

*18 companies analysed*

- 1 Four companies stand out in this area: GSK, Johnson & Johnson, Pfizer and Novartis. All four demonstrate a range of activities across the indicators measured.
- 2 Looking at companies' most recently introduced antibiotics, only four have been filed in more than half of the countries where access to medicine is likely limited.
- 3 Companies report using a range of mechanisms to mitigate conflict of interest in AMR educational programmes targeting healthcare professionals.
- 4 Two of 10 generic medicine manufacturers evaluated report having an equitable pricing strategy that covers countries with poorer populations.
- 5 Nine companies are active in AMR surveillance programmes. Between them, the programmes are running in 147 countries.
- 6 The line between marketing and educational activities about AMR for healthcare professionals appears blurred.
- 7 Four companies are taking steps to adjust incentives for sales teams to decouple them from antibiotic sales volume: GSK, Shionogi, Pfizer and Novartis. One other company (Johnson & Johnson) is carrying out no direct promotion of a specific product (bedaquiline, Sirturo®).

## CONCLUSION

The actions by pharmaceutical companies to address AMR priorities evaluated here represent only a start. Overall there is more that all companies in scope can do. It is likely that this is true for other pharmaceutical companies active in antimicrobials but not analysed by the Benchmark.

There are important products being developed. Yet, there are too few to replace the antimicrobials now losing effectiveness. The pipeline needs to be further strengthened. Once candidates reach late stages of clinical development, they must be supported by concrete plans to ensure they will be accessible yet used responsibly when they reach the market.

For products already on the market, the Benchmark finds some examples of companies addressing both access and stewardship. All companies should look at how they can expand these practices, particularly for antibiotics that fall into the WHO's 'Access', 'Watch' and 'Reserve' groups. Such products must take priority as companies review their strategies for improving access and for stewardship.

Governments and other funders must act to ensure the antimicrobial market can offer sufficient commercial incentive to keep pharmaceutical companies active in this space: for example by acting on commitments to develop additional and robust market-shaping mechanisms that support access objectives, stewardship, global supply and quality. Governments and NGOs can forge partnerships with pharmaceutical companies to ensure antimicrobial supplies are sufficient to meet demand, with reliable supply chains, and support pharmaceutical companies in managing the access and stewardship of antimicrobials.

## INTRODUCTION

# The rise of AMR and the role of the pharmaceutical industry

Antimicrobial resistance (AMR) is a widely recognised and growing global public health problem. Though there are no exact figures that capture the true global burden of AMR, let alone in low- and middle-income countries (LMICs), latest estimates show that AMR causes over 700,000 deaths annually worldwide.<sup>1,2</sup> At the same time, millions of people lack access to much needed antimicrobial medicines for curable infections, which is evident by the 445,000 community-acquired pneumonia deaths that occur in children under five.<sup>3</sup> The issue of AMR and lack of access must be addressed in tandem. Steps to increase access must include measures to prevent resistance, and steps to curb resistance must include measures to enable appropriate access. Addressing both requires a coordinated effort from various stakeholders, not least in government, but also across the healthcare and farming industries, and the development and global health communities.

## AMR threatens all countries

AMR affects human health when appropriate antimicrobial medicines cease to work, exist, are unavailable, are of poor quality, or come at a prohibitively high cost to individuals and society. AMR is widespread, irrespective of countries' level of income. In Europe, it has been estimated that 25,000 people die every year from antibiotic-resistant bacteria (see figure 2).<sup>4</sup> A recent report by the US Centers for Disease Control and Prevention (CDC) estimated that at least 2 million illnesses and 23,000 deaths a year in the USA could be attributed to antibiotic resistance.<sup>5</sup>

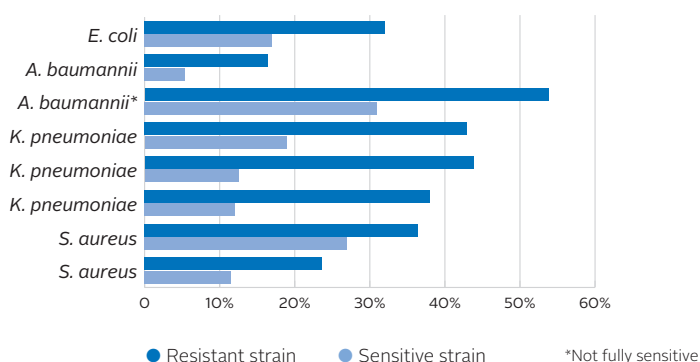
The true extent of the burden of AMR is even less well characterised for low and middle-income countries. Using population attributable fraction (PAF), which is an estimate of the proportion of cases of a disease that could be averted by modifying or removing an exposure to a risk factor (resistance), the number of resistance attributable neonatal sepsis deaths is estimated to be 214,500 globally.<sup>3</sup>

Exacerbating the situation is a widespread absence of local disease surveillance systems, which are critical for monitoring and preventing the rise and spread of diseases. The ability of different stakeholders to understand and respond to the challenges raised by AMR is affected by significant data limitations. For instance, information about antibiotic use, resistance levels and transmission patterns is still scarce in many countries, particularly

in low- and middle-income countries. Yet change is occurring as multiple initiatives have arisen in previous years that address this challenge. The Global Antimicrobial Resistance Surveillance System (GLASS), supported by WHO, supports a standardised approach to the collection, analysis and sharing of data at a global level. In October 2017, the Bill & Melinda Gates Foundation, the UK government and the Wellcome Trust launched a global project, Global Burden of Disease AMR, to help track and document diseases associated with AMR in 195 countries. Low- and middle-income countries (such as Zimbabwe)<sup>6</sup> are creating national plans to curb AMR through the help of WHO, with surveillance being an integral part of these plans. These data collection initiatives are critical in the fight to understand and curb the true burden of AMR globally.

**Figure 2. Antibiotic resistance and increased risk of death**

The figure compares death rates (mortality) in patients with resistant and sensitive strains of selected bacteria. Some pathogens are shown more than once, representing available data sets.



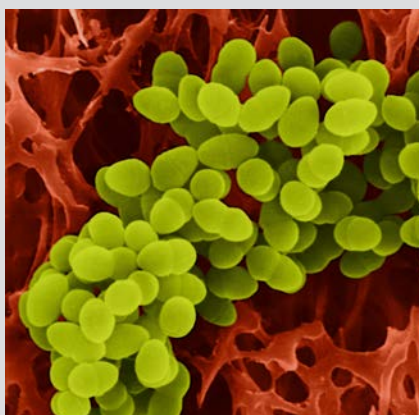
Source: Adapted from ReAct: Action on Antibiotic Resistance, [www.reactgroup.org](http://www.reactgroup.org), May 2012

## **PATHOGENS AND RESISTANCE**

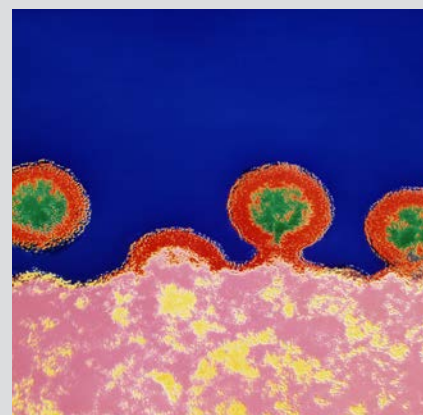
Four main groups of pathogenic microorganisms are relevant to current efforts to curb AMR: bacteria (such as those causing pneumonia and meningitis), viruses (such as HIV), fungi (such as *Candida* spp.) and parasites (such as *Plasmodium falciparum*, which causes malaria). There is large variation among these groups in how resistance emerges and is transferred.

Certain pathogens are already resistant to most antimicrobials on the market. Resistance emerges due to a variety of reasons such as the inappropriate use of medicines, low-quality medicines, incorrect prescriptions and issues with infection prevention and control.

New and adapted medicines targeting different pathogens must take into account their modes of resistance. Resistance mechanisms can comprise, for example, structural changes in or around a medicine's target molecule; reduced permeability of the cell membrane to the medicine; and the production of enzymes that inactivate the medicine.



Most infections with methicillin-resistant *Staphylococcus aureus* (MRSA, above) occur in a hospital setting.



The HIV virus (above) has been identified by WHO as a priority for strategies to address AMR.



Some strains of the *Candida auris* fungus (above) are resistant to all three major classes of antifungal drugs.



There is a limited number of drugs available to treat or prevent malaria caused by certain strains of the protozoan parasite *Plasmodium falciparum* (above).

### **Balancing access and stewardship**

The exact impact of AMR on individuals and communities depends on an interplay of factors, including the distribution of pathogens, the prevalence of resistance to each, and the availability of economic and healthcare delivery resources. Weaknesses in healthcare delivery systems can limit appropriate access to existing antimicrobial medicines while also promoting their overuse. There is also a risk that lack of access could not only lead prescribers to resort to multiple therapeutic courses using first-line drugs, but also drive use of falsified and substandard drugs, both of which could result in the increase of AMR - at an even greater scale.<sup>7</sup> These issues are

closely interlinked, attempts to increase access can lead to overuse, which leads in turn to greater resistance. This then increases the need for second- and third-line products that are more expensive, and thus harder to access. The need for new strategies and programmes to appropriately increase access to antimicrobial medicines remains particularly acute in low- and middle-income countries.<sup>3</sup>

In the hospital setting, particularly in high-income countries, the main public health focus is shifting to the increasing burden of chronic diseases, including cancers, relative to infectious diseases. Where this shift has taken place, the infections that persist now tend to occur in sicker patients and in

challenging settings such as hospital intensive care units. The resistant pathogens that have emerged here are not as common as the underlying conditions and invasive procedures that set the stage for their presence. Yet, the consequences of such infections for those with otherwise treatable conditions are life-threatening. Unless addressed early, the chance exists for a dramatic increase in high-risk infections.

### **Growing demand**

Infectious disease products may broadly be broken down into three categories: vaccines, diagnostics and antimicrobial medicines. The global market for such products reached USD 108.4 billion in 2015, and is forecast to reach

USD 183.2 billion in 2021.<sup>8</sup> The antibiotic market is expected to grow from USD 27.1 billion in 2015 to USD 35.6 billion in 2022, in step with growing demand for generic antibiotics from emerging markets.<sup>9</sup> Between 2002 and 2010, global consumption of antibiotics increased by 36%, and three quarters of this increase was accounted for by Brazil, Russia, India, China and South Africa (BRICS).<sup>3</sup> Growing demand coupled with poor surveillance and stewardship is likely to drive the emergence of resistant strains, particularly in high-burden areas.

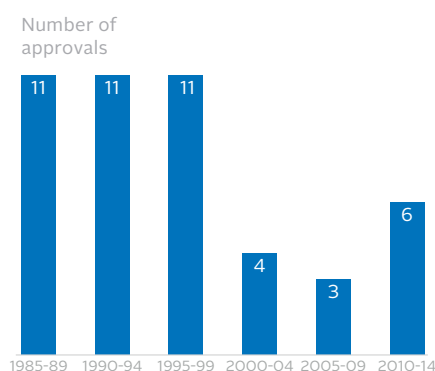
The majority of antibiotics are generic; only a small number remains on patent.<sup>10</sup> In general, new antibiotics, antimicrobial medicines and vaccines are developed by either large research-based pharmaceutical companies or smaller biopharmaceutical companies. However, some large research-based pharmaceutical companies have generic medicine divisions (such as Novartis, Pfizer and Sanofi), while some generic medicine manufacturers also invest in R&D (such as Aurobindo, Cipla, Macleods and Mylan).

### A FUNDAMENTAL ROLE BUT A FRAGILE MARKET

Finding the right balance between access and stewardship requires a concerted effort by multiple sectors (including farming and agriculture)

**Figure 3: Change in the Number of New Antibacterial Drug Approvals in USA 1980–2014.**

Source: Ventola, C (2015)<sup>16</sup>



and stakeholders (including governments and healthcare professionals). Pharmaceutical companies also play a fundamental role, given their unique expertise in translating scientific advancements into promising candidates and deploying marketed products to millions of patients. As a result, it is key to maintain pharmaceutical companies engaged in the efforts to limit AMR.

Unfortunately, market incentives to develop and deploy antimicrobials (and, in particular, antibiotics) are weak.<sup>11</sup> The main reason why the market is failing is simple: new antibiotics are urgently needed, yet will be tightly controlled once they reach the market to limit the risk of resistance emerging. Moreover, in comparison with medicines for other conditions, antibiotics are cheaper and taken for a shorter time period.<sup>12</sup> These factors, together with significant scientific and regulatory hurdles, make high-volume and/or high-margin pharmaceutical markets less likely to develop.<sup>13</sup>

The consequence is that there is little money to be made today from deploying old antibiotics and there is little money to be made tomorrow from developing new antibiotics. Regarding the deployment of old antibiotics, a 2015 study showed that 25 out of 36 old but potentially useful antibiotics were marketed in a little over half of the countries in Europe, USA, Canada, and Australia (in 20 out of 39 countries). Economic factors were the major reasons for not marketing these antibiotics, including high registration costs, limited volume sales and low prices.<sup>14</sup> Regarding the development of new antibiotics, pharmaceutical companies assess the business case for R&D projects by looking at the risk-adjusted net present value (rNPV): the expected return adjusted for investments, opportunity costs and risks. In comparison with other therapeutic categories, the rNPV of antibiotics is low: –\$50 million against +\$720 million for a neurological drug and +\$1.15 billion for a musculoskeletal drug.<sup>15</sup> This is one of the reasons why, since 2000, the number of new antibiotic market approvals has fallen significantly (see figure 3).<sup>16</sup>

These fragile market incentives increase the risk that pharmaceutical companies, including those controlling key antimicrobials, will leave the antimicrobial market and thereby weaken multi-stakeholder efforts to limit AMR. There are signs that the level of consolidation is already increasing. In August 2016, AstraZeneca announced the divestment of its late-stage small molecule antibiotics business, explaining its decision by stating an objective to reinforce its strategic focus in three other main therapy areas: Oncology, Cardiovascular & Metabolic Diseases and Respiratory.<sup>17</sup> In January 2018, The Medicines Company sold its infectious disease business unit to Melinta Therapeutics, explaining its decision by stating an objective to focus on cardiovascular care.<sup>18</sup>

The level of consolidation in the market also poses challenges to small-to medium-sized biopharmaceutical companies (SMEs) that are active today in AMR.<sup>11</sup> They generally have few revenue-generating streams to support their investments in antimicrobial R&D, and there is a shrinking group of large pharmaceutical companies stepping in early to support development. As a result, SMEs can struggle to finance clinical trials and commercialisation of promising candidates. This all being said, the recent prioritisation of AMR has encouraged a few companies, such as Roche, to reconsider this space.

### The imperative of maintaining companies engaged

In January 2016, more than 100 pharmaceutical companies and associations signed the Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance (referred to as the 'Davos Declaration'). This document outlines a set of principles for global action on AMR.<sup>19</sup> In September 2016, 13 pharmaceutical companies, all signatories to the Davos Declaration, published the Industry Roadmap for Progress on Combating Antimicrobial Resistance (referred to as the 'Industry Roadmap'), which laid out a more detailed set of commitments for pharmaceutical

companies.<sup>20</sup> These documents are clear signs that a group within the pharmaceutical industry is willing to address AMR. Recognising the efforts that these and other pharmaceutical companies make, and maintaining their engagement in addressing AMR is essential. Indeed, several organisations have developed financial and non-financial incentives that offset the weakness of current market incentives for antimicrobials.

### Financial incentives

In a bid to reinforce antimicrobial R&D pipelines and encourage pharmaceutical companies to invest in antimicrobial R&D, several 'push' incentives have been established to reduce the costs of necessary inputs for developers. For instance, the US government's Biomedical Advanced Research and Development Authority (BARDA) and the Wellcome Trust provide funding to the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), which finances companies working on promising early-stage antibiotics and rapid diagnostics to treat drug-resistant bacterial infections. The World Health Organization (WHO) and the Drugs for Neglected Diseases initiative (DNDi) have created the Global Antibiotic Research and Development Partnership (GARDP), a product development partnership that aims to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists. GARDP is supported by several European governments, the government of South Africa and the NGO Médecins Sans Frontières (MSF).

'Pull' incentives are also being developed, but at a slower pace. Pull incentives involve the promise of a reward for the development of new antimicrobials that target pathogens that represent a high AMR risk. For instance, the United States' Generating Antibiotic Incentives Now (GAIN) Act grants an additional five years of market exclusivity for companies developing antibiotics that target a selected group of qualifying pathogens. Several initiatives, such as the DRIVE-AB,<sup>21</sup> the Duke-Margolis

Center for Health Policy,<sup>22</sup> the German Global Union for Antibiotics Research and Development (GUARD) Initiative<sup>23</sup> and the UK Review on AMR,<sup>24</sup> have produced policy recommendations on how to best structure new pull incentives.

Efforts should be made to make better use of old antibiotics as well. Governments have been called to facilitate their registration, encourage the transference of technology to new manufacturers and to develop appropriate economic incentives to improve the commercial availability of these medicines.<sup>25</sup>

### Non-financial incentives, such as the AMR Benchmark

As supported by the example of the Access to Medicine Index, public recognition of pharmaceutical companies' contribution to global health targets is a powerful supplement to strengthened market dynamics.<sup>26</sup> If society gives credit to those companies that have remained committed to developing and deploying life-saving antimicrobials, it increases the likelihood that companies will continue and reinforce relevant activities. Such public reporting also gives other pharmaceutical companies the opportunity to learn from the leaders, and gives investors the ability to factor AMR risks and opportunities into decision-making processes.

The Access to Medicine Foundation, with funding from the UK government's Department for International Development and the Dutch Ministry of Health, has responded to this need, drawing on its expertise in developing industry metrics related to public health. The Foundation has produced the Antimicrobial Resistance Benchmark, the first independent and public tool that compares how pharmaceutical companies are responding to AMR.

## A BENCHMARK TO GUIDE DEEPER PHARMACEUTICAL INDUSTRY ENGAGEMENT IN AMR

The Antimicrobial Resistance Benchmark has been developed to give pharmaceutical companies, governments, investors, NGOs and others an independent and public tool for deepening industry engagement in efforts to curb AMR. It maps the responses of a cross-section of the pharmaceutical industry to AMR against the consensus view on where they can and should be taking action.

To develop the Benchmark's methodology, the Foundation has applied its proven process for building consensus on the role of pharmaceutical companies in tackling global health priorities. The Foundation's research team sought input and gathered feedback from a wide range of stakeholders, such as governments, non-governmental organisations, pharmaceutical companies and industry associations, investors, academia, public-private partnerships and relevant international organisations. The aim of this process was two-fold: to build consensus on the pharmaceutical industry's role in limiting AMR; and to ensure the Antimicrobial Resistance Benchmark is a useful tool for pharmaceutical companies and others seeking to curb AMR. The methodology was developed in consultation with experts on AMR and reviewed by an independent Expert Committee that included representation from top-level academic centres, donor governments, local governments in low- and middle-income countries, investors and pharmaceutical industry bodies.

The Benchmark analysis highlights where there is good practice and where progress can be expanded. It examines company actions in R&D, access and stewardship, and in manufacturing and production. This first Benchmark focusses on those areas where companies have a core responsibility to act. Future iterations of the Benchmark will both deepen and expand this analysis.

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# Antimicrobial Resistance Benchmark 2018

This first section of the report includes the top-level comparative analyses of how the 30 companies in scope are addressing antimicrobial resistance, comparing their performances in the three Research Areas analysed by the Benchmark. It looks ahead to where companies and other stakeholders can do more.

In this section:

## **Benchmark Performance**

Analysis and discussion of how the 30 companies in scope are addressing antimicrobial resistance. Companies are compared with their peers in three groups: large research-based pharmaceutical companies, generic medicine manufacturers and biopharmaceutical companies.

## **Key Findings**

Covering R&D for priority pathogens, AMR surveillance, environmental risk management, and promotion practices.

## **Portfolio analysis and case studies**

Breakdown of the antimicrobials on the market from companies in scope and analysis of how they correspond to medicines on Section 6 of the WHO Model List of Essential Medicines.

## **Vaccines and AMR**

Looking at the importance of vaccines for AMR and companies' activities regarding vaccines R&D, manufacturing and access.

## BENCHMARK PERFORMANCE

# AMR: what are the priorities and where are pharmaceutical companies focussing?

The AMR Benchmark has evaluated how a cross-section of the pharmaceutical industry is responding to the threat of antimicrobial resistance (AMR). The 30 companies in scope include those with the largest R&D divisions, the largest market presence, and specific expertise in developing critically needed medicines and vaccines. These companies have chosen to remain in a market that is increasingly challenging. The scientific and regulatory hurdles involved in developing new antimicrobial products are large, and the market is not commercially attractive. To tackle AMR, companies must also limit their misuse (stewardship) while ensuring they are available to people when needed.

Nevertheless, as developers and producers of antimicrobials, pharmaceutical companies must join efforts to control AMR. Companies have different roles to play depending on their business models, sizes and portfolios. Most companies evaluated in the Benchmark

have acknowledged their role in limiting AMR, by signing the Davos Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating AMR (Davos Declaration),<sup>3</sup> or its counterpart the Industry Roadmap for Progress on Combating Antimicrobial Resistance (Industry Roadmap).<sup>5</sup> By signing up to these initiatives and engaging with the Benchmark, companies recognise the need to develop new and more effective antimicrobials, the need to ensure affordable access to antimicrobials and the need to actively conserve the effectiveness of antimicrobials.

## AMR priorities for pharma companies

Several initiatives have set priorities for limiting AMR for different stakeholders. Some, such as the UK government's Review on AMR<sup>1</sup> and the AMR Framework for Action developed by the Interagency Coordination Group on Antimicrobial Resistance (IACG),<sup>2</sup> have focussed on broad multi-sector objectives. Others have focussed specifically on the role of the pharmaceutical industry, including the Davos Declaration and Industry Roadmap. The AMR Benchmark also focusses exclusively on the role for pharmaceutical companies.<sup>4</sup>

There is general agreement between the sets of AMR priorities defined by these initiatives. For example, the Review on AMR identifies ten 'fronts' where action is needed to curb AMR, which cover almost all areas measured by the Benchmark. These include antimicrobial R&D, the release of antibiotics into the environment, AMR surveillance and education for healthcare professionals.

The AMR Benchmark has identified ten areas where alignment exists regarding AMR priorities for pharmaceutical companies. It looked at priorities defined by the Benchmark, the UK Review on AMR, the AMR Framework for Action by the IACG and industry-led initiatives. The ten aligned priorities include six of the ten 'fronts' identified by the UK Review on AMR and ten of the 14 areas identified by the IACG's framework. They also align with the commitments in the Davos Declaration and Industry Roadmap. There are other priorities that may require participation by pharmaceutical companies but are not central to their role, and were thus not evaluated in the first iteration of the Benchmark. These include areas such as sanitation and hygiene, food safety and animal infection prevention and control.

## Which priorities get most attention?

Figure 4 shows how many of the 30 companies evaluated in the Benchmark disclose activities that address each of the ten priority areas where alignment exists. It also includes two further priority areas not in the scope of the Benchmark: diagnostics and agriculture/animal health. Companies' activities are reported by the Benchmark but not evaluated further (scored).

More companies are addressing R&D priorities, particularly the development of new antimicrobial medicines, than are active in priorities related to either manufacturing and production or access and stewardship. GSK is taking steps to address all of the priorities mapped in figure 4: for example, it has the largest antimicrobial pipeline evaluated, a strategy to limit the impact of

### BACKGROUND

- The Benchmark aligns with AMR priorities defined by the UK Review on AMR, IACG and industry-led initiatives, among others.
- It compares 30 companies against 16 metrics that cover R&D, Manufacturing & Production and Appropriate Access & Stewardship.
- The Benchmark methodology was independently developed through consultation with a wide range of AMR experts.

antibiotic manufacturing on the environment and the most widely registered antibiotic assessed. Several other companies, such as Johnson & Johnson, Merck & Co., Inc., Novartis, Pfizer and Sanofi, are taking comparable steps for many priorities. Others, such as Cipla, Macleods, Mylan and Wockhardt, are active on a few key fronts.

### R&D gains most attention

There are 24 companies in the scope of the Benchmark developing antimicrobial medicines, including five that are also working on vaccines. Pipelines are still small, particularly considering the attrition rates of projects in R&D, and the high number of new treatments needed to combat resistance. Out of 67 antimicrobial medicines in clinical development, only 17 (including nine antibiotics) are novel candidates with new modes of action. New modes of action offer the best chance that a new antibiotic will remain effective longer. Only 16 of the companies active in antimicrobial R&D are putting plans in place to make successful candidates either accessible or to limit their misuse (stewardship). Yet, many of the plans that are being put in place are not yet fully developed. New push and pull incentives are needed to stimulate further R&D; many organisations are already working on this issue. These incentives should require recipient companies to take specific and measurable actions to address access and stewardship.

### Access and stewardship

In total, 21 companies have antimicrobial medicines on the market, which means they have the power to improve

access and limit misuse. This includes 18 companies with significant volumes of antimicrobials on the market, 11 of which are taking action to address priorities linked to access.

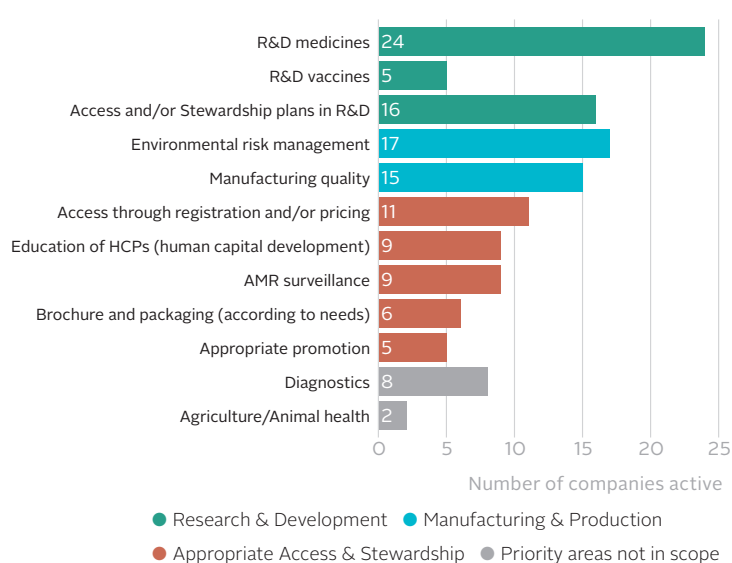
For six companies, there is no evidence they are addressing access, whether by registering products where needed, addressing affordability or strengthening supply chains. Together, these six companies have at least 127 medicines on the WHO Model List of Essential Medicines (Section 6),<sup>6</sup> meaning they are thought essential to the functioning of a basic healthcare system. Considering how many people die because they cannot access antimicrobial medicines in low- and middle-income countries, access cannot be ignored by the pharmaceutical industry.

In stewardship, nine companies are involved in efforts to track resistance as it emerges. They are running or supporting 19 AMR surveillance programmes across 147 countries. Surveillance data must be shared openly, and programmes must be expanded and integrated, particularly for pathogens that can be markers for resistance to multiple antibiotics, such as *S. aureus* and *E. coli*.

Some pharmaceutical companies have shown that they can develop structured access approaches for products in therapeutic areas such as diabetes and HIV/AIDS.<sup>7</sup> Companies with antimicrobials on the market can transfer this knowledge and experience to programmes for limiting AMR.

**Figure 4. Pharmaceutical companies are active in ten AMR priority areas.**

The AMR Benchmark identified ten areas where alignment exists between the UK Review on AMR, UN IACG and the Industry Roadmap on AMR priorities for pharmaceutical companies. There is evidence of action by multiple companies in each area, with most companies active in antimicrobial R&D.



## BENCHMARK PERFORMANCE

## The Antimicrobial Resistance Benchmark – which companies lead?

The Benchmark compares companies in three groups. The business models, sizes and portfolios of the different groups give them different roles and responsibilities regarding AMR.

There are eight large research-based pharmaceutical companies in scope. They have a prominent role to play in the R&D of new antimicrobials. With many products on the market, they also have the power to help ensure the appropriate use of antimicrobials, while leveraging their geographic reach in supply and manufacturing chains. Generic medicine manufacturers have a similar role, due to their business model based on delivering off-patent medicines at volume. There are 10 generic medicine manufacturers in scope, the largest players by volume in the antibiotics market. The 12 biopharmaceutical companies in scope are all developing at least one promising clinical-stage R&D candidate.

They generally market few or no products and their main potential lies in filling the pipelines further with novel antimicrobials, supported by plans to facilitate access and stewardship should they reach the market.

The companies are evaluated only in metrics that are relevant to their main business focus. For example, companies with products on the market are evaluated in metrics related to improving access, preventing misuse and ensuring responsible manufacturing practices.

There are two ways of looking at how companies are performing. The radial graphs compare how close the companies are to achieving 100% of their maximum potential score. The bar charts compare actual scores and the number of points on offer to each company.

## THE LEADERS

The large research-based pharmaceutical companies are led by two companies: GSK, which has the largest antimicrobial pipeline for priority pathogens, and Johnson & Johnson, which has a focus on tuberculosis. The large research-based companies are the most active against AMR: six out of eight achieved more than 50% of the points available. Mylan, Cipla and Fresenius Kabi lead the generic medicine manufacturers in scope. Both Mylan and Cipla are active in stewardship and they are the only two companies in this group to report having equitable pricing approaches. Disclosure among generic medicine manufacturers is generally lower than among the other two groups of companies. Of the 12 clinical-stage biopharmaceutical companies included, the strongest performance comes from Entasis, particularly when it comes to planning ahead for access and stewardship of clinical-stage candidates.

Figure 5. 30 companies in scope

Large research-based pharmaceutical companies			Generic medicine manufacturers			Biopharmaceutical companies		
	Country	Revenue (bn USD)		Country	Revenue (bn USD)		Country	Revenue (mn USD)
GSK	GBR	34.4	Aspen	ZAF	2.4	Achaogen	USA	41.8
Johnson & Johnson	USA	71.9	Aurobindo	IND	2.3	Cempra	USA	18.0
Merck & Co., Inc.	USA	39.8	Cipla	IND	2.3	Entasis	USA	–
Novartis	CHE	47.6	Dr. Reddy's	IND	2.2	Melinta	USA	–
Pfizer	USA	52.8	Fresenius Kabi	DEU	6.3	MGB Biopharma	GBR	–
Roche	CHE	49.6	Lupin	IND	2.6	Motif Bio	GBR	0.0
Sanofi	FRA	35.6	Macleods	IND	–	Nabriva	IRL	6.5
Shionogi	JPN	3.0	Mylan	USA	11.0	Polyphor	CHE	–
			Sun Pharma	IND	4.7	Summit	GBR	3.0
			Teva	ISR	21.9	Tetraphase	USA	5.1
						The Medicines Company	USA	167.8
						Wockhardt	IND	619.0

Due to the variation between companies in scope, not all indicators are applicable to every company.

See Appendix for full overview.

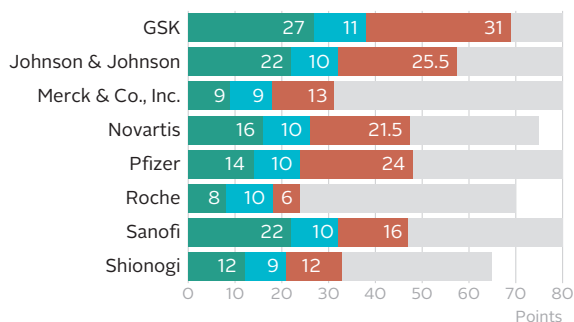
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## BENCHMARK PERFORMANCE

## Which companies lead the Benchmark?

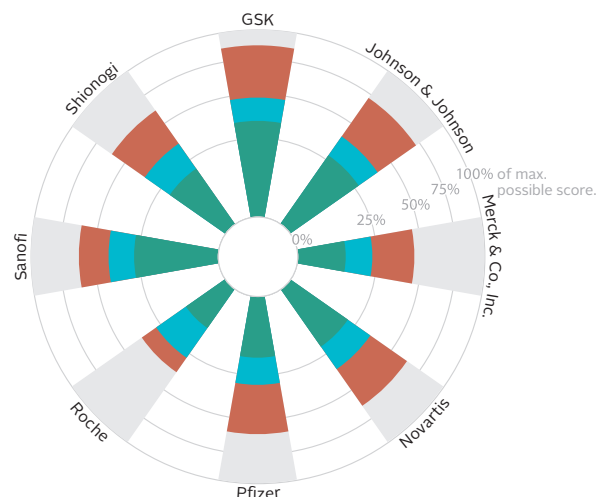
The Benchmark evaluates companies only in the metrics that are relevant to their businesses. The radial graphs compare how close the companies are to achieving 100% of their maximum potential score. The bar charts compare actual scores – and the number of points on offer to each company.

## LARGE RESEARCH-BASED PHARMACEUTICAL COMPANIES

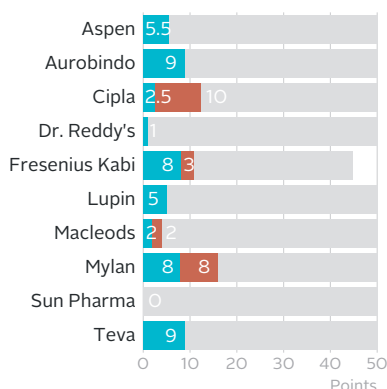


This is the most active group of companies against AMR: six out of eight achieved more than 50% of the points available. GSK and Johnson & Johnson lead.

● Research & Development ● Manufacturing & Production  
● Appropriate Access & Stewardship ● Remaining potential score

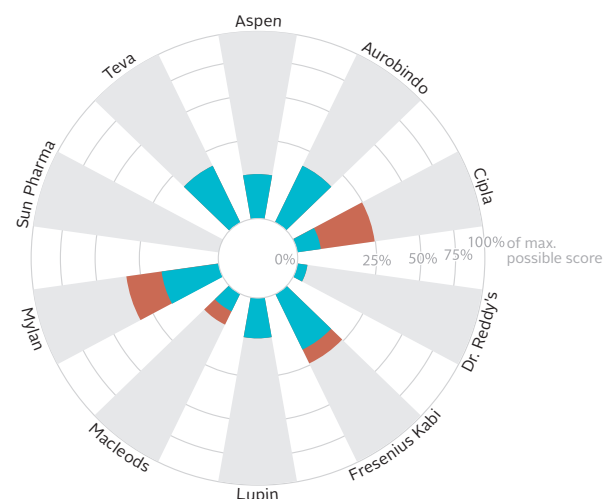


## GENERIC MEDICINE MANUFACTURERS

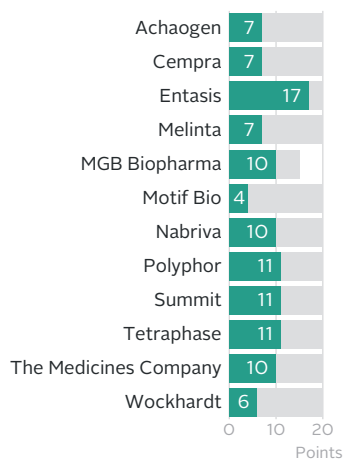


Mylan, Cipla and Fresenius Kabi lead this group. All three are active in stewardship. Mylan and Cipla are the only two in this group to report having equitable pricing approaches. Disclosure among generic medicine manufacturers is generally lower than among the other two groups of companies.

● Research & Development ● Manufacturing & Production  
● Appropriate Access & Stewardship ● Remaining potential score

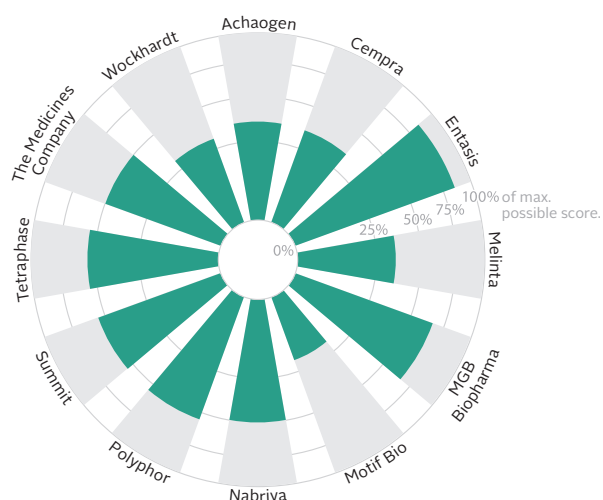


## BIOPHARMACEUTICAL COMPANIES



The biopharmaceutical companies in scope are all developing important antimicrobial candidates. Entasis leads. It has a novel antibiotic candidate with a new mode of action in its pipeline, for which it has a licensing agreement in place with GARDP. It is followed by Polyphor, Summit and Tetraphase in joint second place.

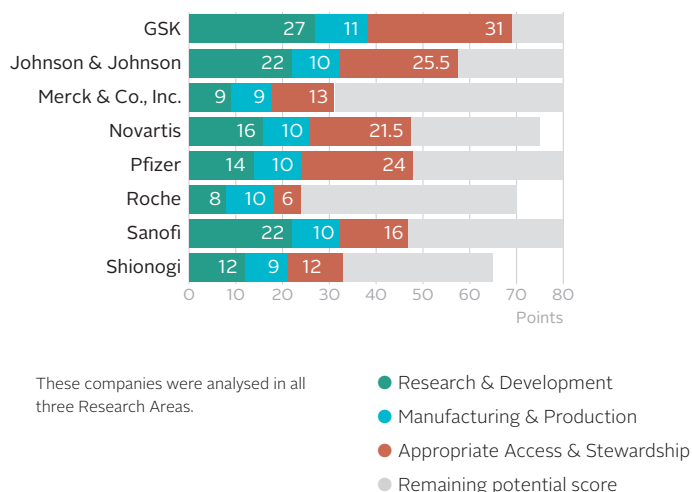
● Research & Development ● Remaining potential score



## BENCHMARK PERFORMANCE

## Large research-based pharmaceutical companies

Figure 6. Comparing scores: large research-based pharmaceutical companies.



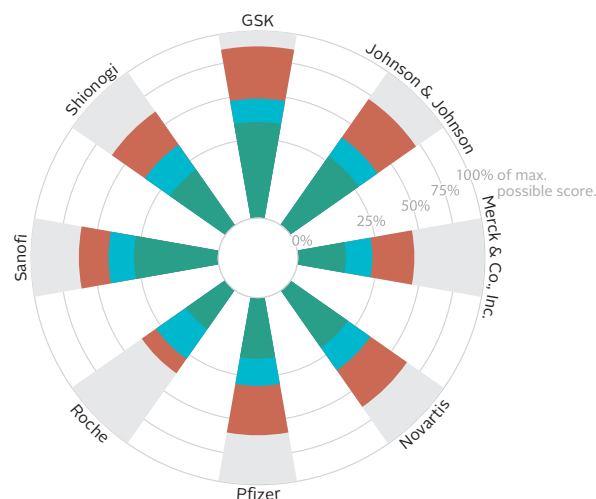
GSK and Johnson & Johnson lead, followed closely by Novartis, Pfizer and Sanofi. GSK leads all research areas, with the largest antimicrobial pipeline (55 projects). It has 55 R&D projects, including 13 vaccines, and access or stewardship provisions for more projects than other companies. It also discloses the most comprehensive environmental risk-management strategy. For marketed products, it undertakes a range of access and stewardship activities, including a comparatively broad equitable pricing approach. It has uncoupled the remuneration of sales staff from sales volume.

Johnson & Johnson also delivers a strong performance, with a focus on tuberculosis. For example, in stewardship, Johnson & Johnson engages in several tuberculosis-related educational programmes for healthcare professionals, taking action to mitigate conflict of interest. It also supports surveillance programmes for tuberculosis, sharing data with public health authorities. Pfizer, Novartis and Sanofi are close behind the leaders. Pfizer has a pipeline of seven projects, six of which

target priority pathogens and four are vaccine projects. It is involved in a number of educational and surveillance programmes, sharing data. Sanofi performs strongly in R&D, developing 32 projects, with 18 targeting pathogens prioritised by WHO and/or the US CDC for AMR, including six vaccine candidates. It is engaged in a number of educational and long-term surveillance programmes. Novartis also performs well, especially in Manufacturing & Production and Appropriate Access & Stewardship. It has a pipeline of 32 projects (16 target a priority pathogen, including two novel antimalarials).

Shionogi and Merck & Co., Inc. follow. Shionogi currently only has operations in Japan, Taiwan and the USA and does not yet have a worldwide response to AMR. However, it is transparent on its activities in combating AMR, and has uncoupled the remuneration of its sales staff from the volume of antibiotic sales. According to publicly available information, Merck & Co., Inc. has 16 antimicrobial R&D projects in its pipeline, including nine that target priority pathogens. It is involved in multiple

Figure 7. Comparing potential: large research-based pharmaceutical companies.



AMR-related educational activities for healthcare professionals. Roche has a low performance in this group. It has been historically active in antimicrobials, concentrating in only a few markets. It is now taking steps to re-enter the field of AMR.

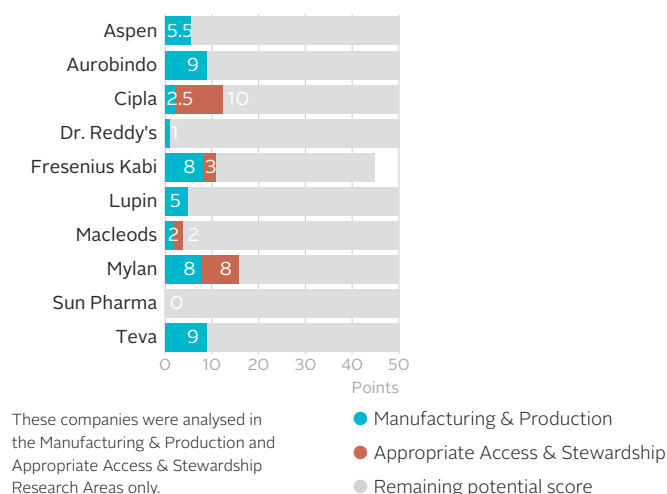
## Looking ahead

All three Research Areas are being addressed by all eight companies. GSK came closest to achieving 100% of its maximum potential score in this first Benchmark, with most other companies surpassing the 50% mark. Companies in this group have the potential to improve across all areas measured, including explicitly linking access and stewardship strategies to more products. Antimicrobials marketed by some companies do not yet appear to be widely available in many markets (based on how widely newer products are being filed for registration). All companies are encouraged to look at whether their products are in the WHO's 'Access', 'Watch' and 'Reserve' groups, as they review strategies for registering products and for stewardship.

## BENCHMARK PERFORMANCE

## Generic medicine manufacturers

Figure 8. Comparing scores: generic medicine manufacturers.



In evaluating these companies, the Benchmark faced a low level of disclosure; their low scores must be interpreted with this in mind. Mylan, Cipla and Fresenius Kabi take the lead. They perform well for two reasons: their response to AMR is more defined and broader than other generic medicine manufacturers, and they report publicly about their plans, giving greater credibility to their actions. They delivered varying performances across the two research areas.

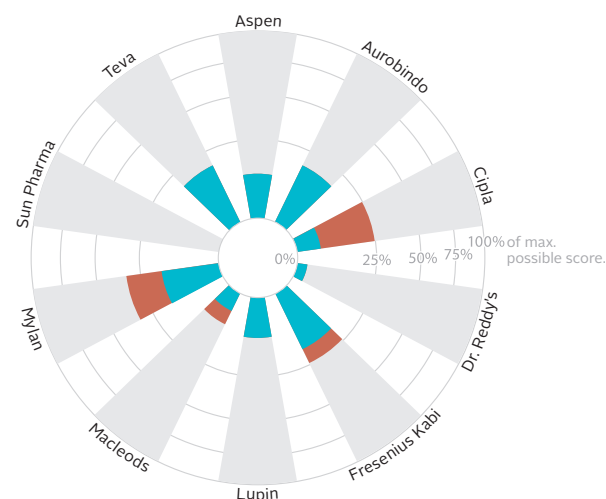
Overall, Mylan performed best. It discloses its environmental risk-management strategy, which it also applies to API and drug-product suppliers. It also commits to GMP at its suppliers' sites. Mylan reports an intra-country equitable pricing approach for antimicrobials, and takes several steps to improve supply chain efficiency. Cipla delivered a strong performance in Appropriate Access & Stewardship, yet its performance in Manufacturing & Production is lower. It reported having an environmental risk-management strategy in development. Fresenius Kabi performed on par with Mylan for environmental

risk management, but did not perform as well in access and affordability. Aurobindo and Teva performed equally well in Manufacturing & Production. Macleods has filed two of its newest antibiotics for registration in several low- and middle-income countries, yet does not report an equitable pricing strategy. Lupin and Aspen performed moderately in Manufacturing & Production. Neither Aspen, Aurobindo, Lupin, Macleods nor Teva reports any information regarding stewardship, despite producing antimicrobials for the market. Dr. Reddy's and Sun Pharma disclose limited information about their AMR responses, despite having at least 22 and 69 antimicrobials on the market, respectively.

#### Looking ahead

For decades, generic medicine manufacturers have brought off-patent medicines to billions worldwide. The distinction between these and large research-based companies is blurring, as some generic medicine manufacturers invest in incremental R&D units, and as research-based companies establish

Figure 9. Comparing potential: generic medicine manufacturers.



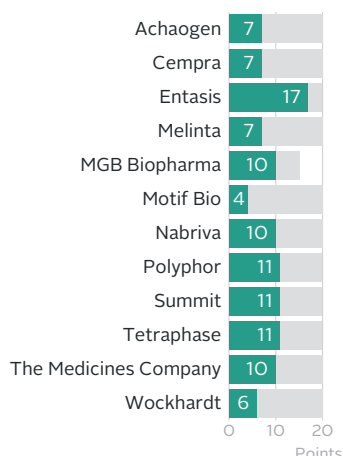
generic medicine divisions. Generic medicine manufacturers are also more involved in global health challenges and the international collectives addressing them. For example, Cipla, Fresenius Kabi, Lupin, Mylan and Teva have signed the Davos Declaration, and Cipla has signed the Industry Roadmap on AMR (as has Wockhardt, evaluated in this Benchmark as a biopharmaceutical company).

Regarding disclosure, many of these companies do not report consistently about non-financial activities. Nevertheless, there is little evidence of leadership in stewardship, despite this being critical for combating AMR, and only a few companies are taking some action identified by the Benchmark to support access. This is concerning, considering that the core business of such companies is to make off-patent medicines available and affordable at volume. There is tremendous potential to limit AMR, through strengthening environmental risk management, ensuring efficient supply and ensuring stewardship, should these and other companies continue to develop and expand their actions on this front.

## BENCHMARK PERFORMANCE

## Biopharmaceutical companies

Figure 10. Comparing scores: biopharmaceutical companies.



These companies were analysed in the Research & Development Research Area only.

● Research & Development  
● Remaining potential score

These 12 biopharmaceutical companies were selected, as they had at least one investigational antibiotic in their clinical pipeline that targeted a priority pathogen, as identified by the WHO and the CDC. The strongest and most comprehensive response to AMR comes from Entasis, followed by Polyphor, Summit and Tetraphase and then MGB Biopharma, Nabriva, and The Medicines Company.

All 12 of these companies are developing important antimicrobials, including several that have novel mechanisms of action. Entasis, Nabriva and Wockhardt have the largest pipelines targeting bacteria prioritised by WHO and/or CDC. Entasis engages actively in public-private partnerships for antimicrobial R&D, such as GARDP. Together with Tetraphase, Entasis also stands out for ensuring access or stewardship initiatives are in place for antibiotic candidates in late-stage clinical development. However, only Tetraphase has developed a concrete access and stewardship provision for one of its late-stage products. Only five out of the 12 companies assessed explicitly include an

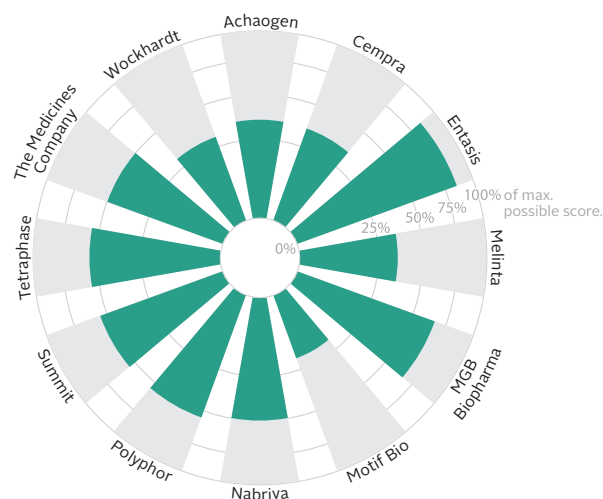
access and/or stewardship commitment or plan for products in their clinical pipeline.

### Looking ahead

With few or no products on the market, these companies must continually compete for sufficient resources to further develop their R&D pipelines. This is why the role of push funding provided by organisations such as GARDP and CARB-X is key. Venture capital funding into antibiotics development has decreased by 33% between 2008 and 2013.<sup>8</sup> These companies are generally also small- to medium sized, without the resources, operations or expertise that a larger company can call on to introduce a product while prioritising access and stewardship. Success in combating AMR is only possible for companies that attract more funding, and can forge collaborations that help plan access and stewardship programmes.

Despite these challenges, the Benchmark recognises the commendable efforts these companies are making to replace redundant antimicrobials.

Figure 11. Comparing potential: biopharmaceutical companies.



A few notable companies are also addressing access and stewardship for their products on the market. For examples, Wockhardt runs a surveillance programme in India.

To fulfil their potential in addressing AMR, these companies are encouraged to think systematically about access and stewardship already during clinical development. Funders can work with the biopharmaceutical companies they support to ensure such provisions are put into practice. Such steps will go a long way in ensuring that the promising candidates from these companies have the maximum useful lifespan.

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## KEY FINDING 1

# Out of 28 antibiotics in late stages of clinical development, only two have both access and stewardship plans in place

As more microbes develop drug resistance, a robust pipeline of new antimicrobial medicines is critical for replacing less effective medicines.

The pipelines captured in the Benchmark have 175 antimicrobial medicines targeting pathogens seen by WHO and CDC as the biggest AMR threats. Of those, 40 – one quarter – are drug candidates in late stages of clinical development, including 28 antibiotics. Several are novel, with new modes of action, including new classes of antibiotics to treat multidrug-resistant *S. aureus*. In much of the world, more than half of *S. aureus* infections are reported to be resistant to standard treatment with methicillin (known as methicillin-resistant *S. aureus*, or MRSA).<sup>1</sup>

Once a new antibiotic has market approval, AMR response strategies call for it to be used prudently, to slow the emergence of resistance and maximise the antibiotic's useful lifespan. Such stewardship measures must be pursued

alongside efforts to ensure appropriate access to antimicrobials. More people die from lack of access to antimicrobials than from drug-resistant microbes. Companies must put access and stewardship plans in place at the same time to ensure they are most effective, and before a new product enters the market.

Of the 28 antibiotics in late-stages of clinical development, only two (eravacycline, Phase III; bedaquiline for paediatrics, Phase II) have both access and stewardship provisions in place. Eravacycline is being developed by Tetrphase to treat complicated intra-abdominal and urinary tract infections caused by a range of pathogens, including *A. baumannii*, *S. aureus*, and *C. difficile*. To plan for access, Tetrphase is seeking licensing partners to increase access in several regions of the world. For stewardship, it provides hospitals with testing strips that check whether a patient's infection is susceptible to the

drug, which is important to ensure its appropriate use.

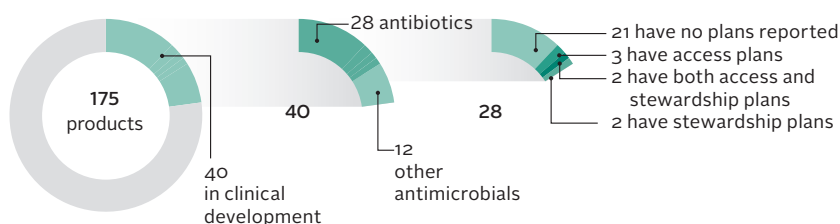
Bedaquiline (Sirturo®), conditionally approved for the treatment of multidrug-resistant tuberculosis (MDR-TB) in adults, is now being developed by Johnson & Johnson for the treatment of MDR-TB in children. The company will use the same access and stewardship provisions that are in place for the adult formulation. These include a managed access programme through the Global Drug Facility (GDF) and with its own subsidiaries. To limit resistance to bedaquiline, the company's stewardship provisions include educational activities for paediatric healthcare professionals that aim to improve knowledge and awareness on the appropriate use of the antibiotic.

Two other antibiotics in the late-stage clinical pipeline have stewardship provisions, but no access plan: GSK's gepotidacin (Phase II) for gonorrhoea; and Pfizer's avibactam/aztreonam (Phase II) for multidrug-resistant gram-negative bacterial infections. Three have an access plan in place, but no stewardship provisions: a second gonorrhoea medicine, an antibiotic for acute skin infections, and a gel for treating umbilical stump infections (being developed by Entasis, Melinta and GSK respectively).

Besides antibiotics, there are 12 other medicines in late-stage clinical development targeting priority pathogens, including five with both access and stewardship provisions. All are antivirals for HIV/AIDS being developed by GSK, either alone (three) or in partnership with Johnson & Johnson (two).

**Figure 12. Few late-stage antibiotics with access and stewardship plans.**

The Benchmark identified 28 antibiotics in clinical development that target pathogens posing significant threats due to AMR (according to WHO and CDC). Only two have plans in place to ensure they will be accessible, yet used prudently: eravacycline from Tetrphase and paediatric bedaquiline from Johnson & Johnson.



## KEY FINDING 2

# Nearly half of companies with products on the market are involved in AMR surveillance

Curbing AMR depends on knowing which pathogens are developing resistance and where. Yet there are major gaps in global AMR surveillance, with countries having differing levels of surveillance capacity and a lack of data harmonisation, making it more difficult to use the data that are shared.

The pharmaceutical industry can make an important contribution in this area. Companies that signed the 2016 Industry Roadmap for Progress in Combating Antimicrobial Resistance (including 10 the Benchmark measures) agreed to support efforts to increase

AMR surveillance.

The Benchmark found that nine of the 19 companies reporting such efforts are running or supporting 19 AMR surveillance programmes across 147 countries. These are seven of the eight large research-based companies in scope, one of the 10 generic medicine manufacturers, and one of the 12 biopharmaceutical companies.

The activities are diverse in terms of scale, focus and duration. For instance, GSK periodically monitors international resistance trends in community-acquired respiratory infections;

Wockhardt collects data from a representative sample of the entire health-care infrastructure in India; and Pfizer's ATLAS project tracks susceptibility and resistance patterns for a variety of pathogens and medicines across more than 60 countries.

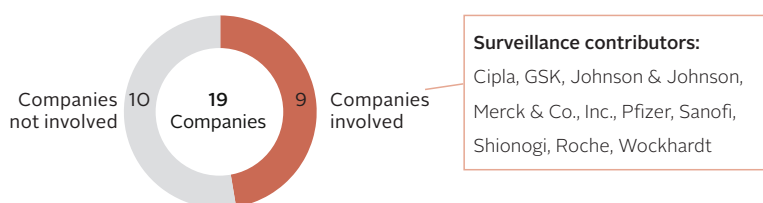
Pneumonia gets the most attention, followed by other respiratory infections, including tuberculosis. Resistance is also being tracked in a variety of pathogens considered a priority for monitoring, including *S. aureus*, *E. coli* and *H. influenzae*. Some programmes track a single pathogen (e.g., Johnson & Johnson's DREAM programme, focussed on *M. tuberculosis*), while others monitor several pathogens and medicines in the same project (e.g., GSK's SOAR and Merck & Co., Inc.'s SMART programmes).

Sharing the surveillance data with third-party initiatives that track AMR trends is a fundamental next step. At least eight companies reported their data are presented at public conferences or published in journals, while two – Merck & Co., Inc. and Pfizer – publish their surveillance data on the Internet. GSK reported plans to publish all its surveillance data on the Internet and to collaborate with other organisations aiming to publish an online database conglomerating pharmaceutical industry AMR surveillance data.

Key challenges for ensuring that industry AMR surveillance efforts have maximum impact include increasing involvement, harmonising data, converting prevalence studies into long-term monitoring programmes and increasing collaboration with public health bodies coordinating surveillance.

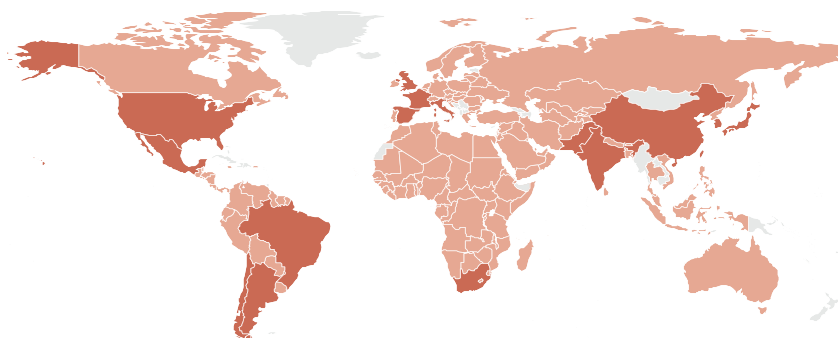
**Figure 13a. Nine out of 19 companies support AMR surveillance.**

The Benchmark found that nine of the 19 companies evaluated in this area are running or supporting 19 AMR surveillance programmes, spanning 147 countries.



**Figure 13b. AMR surveillance programmes are being conducted in 147 countries worldwide.**

Nine companies assessed by the Benchmark in this area are engaged in surveillance programmes, active in 75% of countries in the world.



● No surveillance programmes ● 1-2 surveillance programmes ● ≥3 surveillance programmes

## KEY FINDING 3

# Eight companies are setting limits on antibiotic wastewater discharge

Antibiotics released into the environment in factory wastewaters are increasingly thought to be contributing to AMR. The exposure of bacteria in soil and water to discharged antibiotic ingredients can trigger the emergence of resistance genes.<sup>2</sup> Large volumes of antibiotics are manufactured in some countries where local populations often

rely on untreated groundwater for their household water supplies.<sup>3</sup> Significantly curtailing the release of antibiotics into the environment is seen as an important measure for slowing AMR. Consensus around safe limits for antibiotic discharge has yet to emerge.

On this issue, the Benchmark questioned the 18 companies in scope with significant manufacturing presence.\* Of these, 15 reported having some form of an environmental risk-management strategy in place, with eight also reporting that they have set factory discharge limits for antibiotics. In a further step, four said they also require their suppliers of antibiotic active ingredients and drug products to adhere to the same limits. All eight also disclosed that they audit the implementation of their environmental risk-management strategies. However, no company publishes its environmental audit results, or its discharge levels.

For the remaining ten companies, four reported they do not set limits and four did not respond to the question. The Benchmark was unable to find independent information on the performance in this area for the four companies who declined to answer the question. The two remaining companies, Aurobindo and Dr. Reddy's, report that they do not set limits as they do not release wastewater. Instead they vaporise the waste and dispose of the residual solids by other means.

Ten of the companies included in this Benchmark have signed the 2016 Industry Roadmap for Combatting Antimicrobial Resistance, thereby committing to establishing a common framework for managing antibiotic

factory discharges, to developing a mechanism to demonstrate their supply chains meet the standards set, and to agreeing, by 2020, on targets for antibiotic levels released in waste discharge. They also committed to reviewing their actions to identify good practice. Seven of the eight companies that reported setting limits were signatories of this Roadmap.

## Figure 14. Eight companies set discharge limits. No company publishes discharge levels.

Eight of 18 companies evaluated in this research area reported that they have set discharge limits for antibiotics. Four of these companies also require upstream suppliers of antibiotic APIs and drug products to adhere to the same limits. Yet no company publishes its discharge levels. All eight companies reported that they audit the implementation of their environmental risk-management strategies at their own manufacturing sites.

	Signed Industry Roadmap	Sets discharge limits	Publishes discharge levels	Applies limits to suppliers' sites	Audits strategy implementation
GSK	●	●		●	●
Johnson & Johnson	●	●		●	●
Novartis	●	●			●
Pfizer	●	●		●	●
Roche	●	●		●	●
Sanofi	●	●			●
Shionogi	●	●			●
Teva		●			●

\*In its analysis of Manufacturing & Production practices, the Benchmark uses global antibiotic sales volumes to inform its selection of companies to analyse.

## KEY FINDING 4

# Four companies move to decouple antibiotic sales volumes from sales agents' bonuses

The more that antibiotics are used, the faster they become ineffective.<sup>4</sup> One of the strategic pillars of the global effort to address antimicrobial resistance is therefore to ensure that antibiotics are used appropriately, only when needed, to prolong their effectiveness.

The more antibiotics that are sold, the more that are available, and this is thought to contribute to the problem

of overuse.<sup>5</sup> The Benchmark has found that four companies are changing the way they remunerate sales staff in ways that should remove the incentive to oversell antibiotics: GSK, Shionogi, Pfizer and Novartis report that bonuses are fully decoupled or that the company has taken steps towards adjusting incentives for its sales teams' bonuses from the volume of antibiotics they sell.

GSK has led in this area, having since 2013 separated pay from antibiotics sales volume for all its sales staff in every country in which it sells antibiotics. Shionogi also reports that it does not remunerate its sales teams based on antibiotic sales volume. Pfizer and Novartis are now following. In 2018, Pfizer will start working on pilots that aim to decouple the remuneration of its sales teams from sales volume. Novartis is starting to increase the weight of fixed pay in overall compensation for sales staff, while reducing the variable component.

At least one other company is taking a different approach at the product level. Johnson & Johnson's new anti-tuberculosis drug, bedaquiline (Sirturo®), is provided solely through national tuberculosis programmes and therefore does not require any marketing materials. The company reports that it does not deploy any sales organisations for the sale of Sirturo® in countries in scope.

**Figure 15. Decoupling sales volumes from sales agents' bonuses: four companies are taking action**

GSK, Novartis, Pfizer and Shionogi report that bonuses are fully decoupled from the volume of antibiotics they sell or that the company has taken steps towards adjusting incentives for its sales teams' bonuses.

## GSK

- Full decoupling
- All bonuses decoupled from sales volume
- Applies to all sales staff globally
- Changes made in 2013

## Shionogi

- Full decoupling
- Bonuses decoupled from antibiotic sales volume for all sales staff

## Pfizer

- Pilot
- All bonuses decoupled from sales volume
- Applies to sales staff in selected geographies
- Starts in 2018

## Novartis

- Adjusting incentives
- Lowering % of bonuses linked to sales volume

## REFERENCES TO THE KEY FINDINGS

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## PORTFOLIO ANALYSIS

# Antimicrobial portfolios: what medicines are on the market?

Antimicrobials must be used conservatively to preserve their useful lifespan. However, many people live without access to the antimicrobials they need, including for malaria, tuberculosis and

many bacterial infections.<sup>1</sup> Per product, it is critical that pharmaceutical companies, governments, donors and other stakeholders integrate and expand plans for conserving the effectiveness

of antimicrobials on the market, while also increasing people's ability to access antimicrobials when they need them.

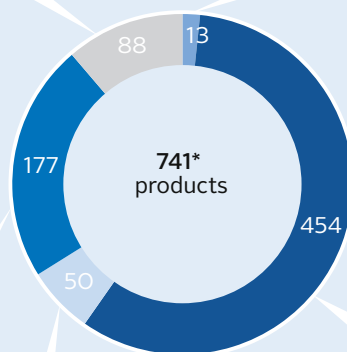
## 88 Antiprotozoals

- 24 Antiamebic and anti-giardiasis medicines
- 6 Antileishmaniasis medicines
- 45 Antimalarial medicines
- 9 Antipneumocystosis and antitoxoplasmosis medicines
- 0 Antitrypanosomal medicines
- 4 Multiple categories

Out of 88 antiprotozoals, 45 target malaria, including some older products that are redundant due to AMR. Most countries now rely on artemisinin-based antimalarials. Stewardship of these medicines and R&D into replacements is critical.<sup>2</sup> Other antiprotozoals target NTDs, such as leishmaniasis for which treatment is available but not widely accessible.

## Figure 16. Which antimicrobial medicines are available on the market?

The companies in scope have at least 741 antimicrobial medicines on the market – more than half of which (454) target bacterial infections. Resistance to different products emerges at different rates, with some products already being less effective.



## 13 Anthelmintics

- 7 Intestinal anthelmintics
- 0 Antifilarials
- 2 Antischistosomes and other antitrepanematode medicines
- 4 Multiple categories

1.5 billion people are infected with helminths, such as threadworms.<sup>3</sup> A sharp increase in anthelmintic resistance in livestock has raised concerns over the development of resistance in human helminths. Some countries have now restricted anthelmintics to prescription use only. In the last 30 years, only one new anthelmintic has been introduced.<sup>4</sup>

## 177 Antivirals

- 24 Antiherpes medicines
- 114 Antiretrovirals
- 6 Other antivirals
- 21 Antihepatitis medicines
- 12 Multiple categories

Out of 177 antivirals, most are antiretroviral therapies (ART) for HIV/AIDS. In 2010, almost 7% of people receiving ART had drug-resistant HIV. Increased use of ART will likely increase resistance.<sup>8</sup> This analysis includes 61 fixed-dose ART combinations, which reduce the pill burden for patients, improving patient adherence and limiting resistance.<sup>9</sup> New Direct Acting Antivirals for hepatitis C have shorter treatment regimens which also improve patient adherence.<sup>10</sup>

## 50 Antifungal medicines

Fungal infections now cause more deaths than malaria or tuberculosis. Resistance to antifungals has been described for almost all fungal pathogens including *Candida*.<sup>6</sup> However, fewer than 10 national surveillance programmes have been developed to monitor the resistance trends of fungal infections.<sup>7</sup>

## 454 Antibacterials

- 189 Beta-lactam antibacterials
- 180 Other antibacterials
- 1 Antileprosy medicines
- 55 Antituberculosis medicines
- 29 Multiple categories

More than half the products in the portfolio are antibacterials, including 189 beta-lactams. These remain important antibiotics for their broad-spectrum effectiveness. Ensuring access to these is a public health priority. A further 55 antibacterials target tuberculosis (TB). There has only been one new TB medicine introduced in 40 years. Stewardship of this medicine is being managed in national TB programmes.<sup>5</sup>

\*41 medicines are effective against pathogens in more than one of the five categories and were counted in all relevant categories.

## PORTFOLIO ANALYSIS

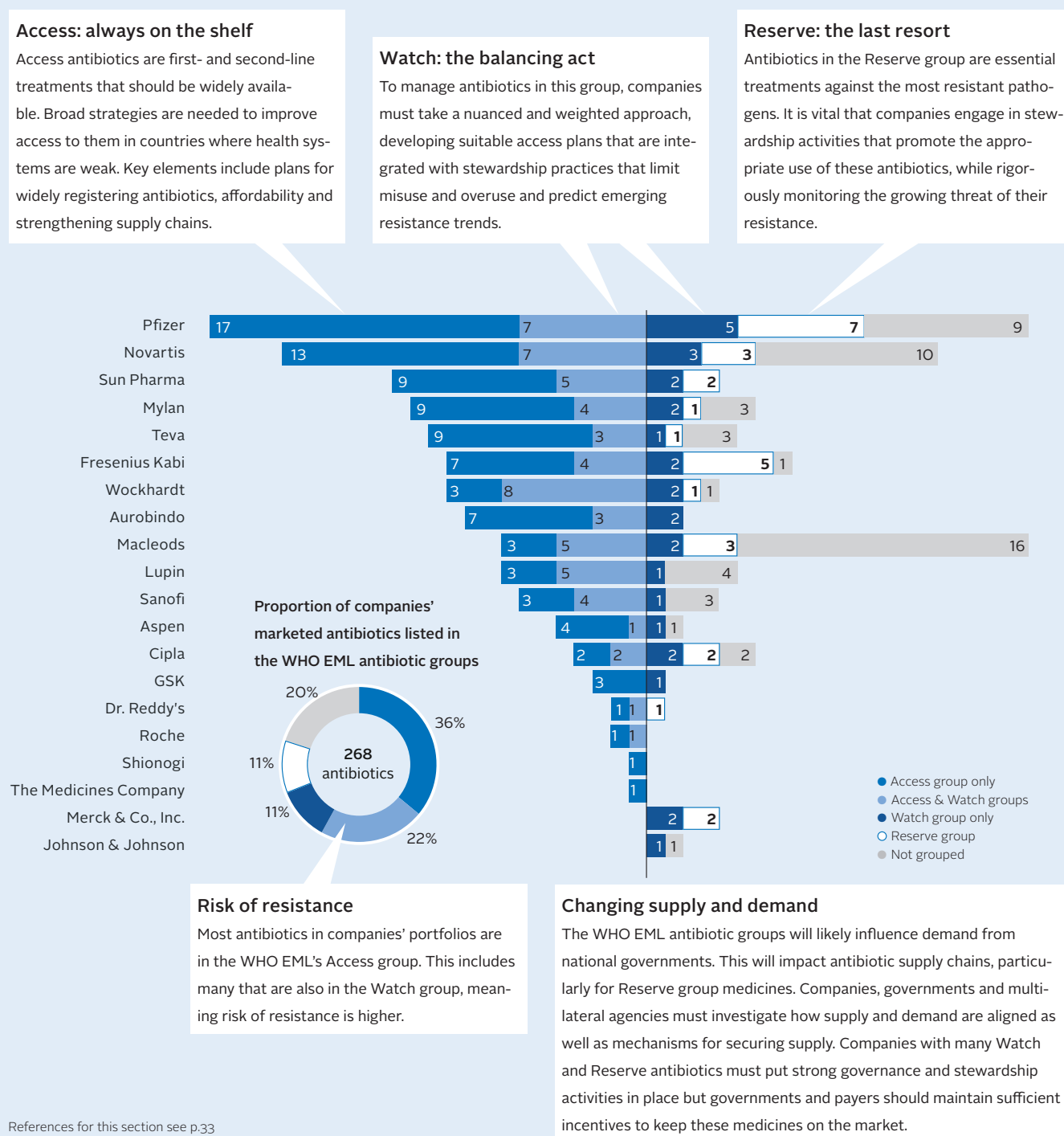
# Access is a leading priority for half of antibiotics on WHO EML

The Benchmark has compared companies' portfolios against Section 6 of the WHO Model List of Essential Medicines (EML). Out of 741 marketed products, 268 correspond to antibiotics on the

WHO EML. In 2017, the WHO EML categorised antibiotics into three groups – Access, Watch and Reserve. Companies have far more Access group antibiotics than ones in the Reserve group. Access

antibiotics should be widely available, affordable and quality assured. Reserve group antibiotics should only be used for the most severe cases when all alternative treatments have failed.<sup>11</sup>

Figure 17. Companies in scope have at least 268 antibiotics on the WHO EML (Section 6).



References for this section see p.33

## PORTFOLIO ANALYSIS

# Case studies: how three companies are addressing access and stewardship in tandem

Over the past 30 years, there has been a marked reduction in the global incidence of infectious diseases. This has been achieved in part due to increased access to antibiotics and is linked to the development of emerging economies and their health systems. Yet, infectious diseases are still among the most deadly, and access to lifesaving antibiotics in low- and middle-income countries remains limited.<sup>1</sup> At the same time human behaviour is stimulating the emergence of antimicrobial resistance among pathogens.

Today, the need to curb antimicrobial resistance is at the top of the global public health agenda. Achieving this aim depends on three inter-related issues:

- 1 the urgent need to develop new antibiotics and to conserve their effectiveness as they enter the market;
- 2 the equally pressing need to increase access to antimicrobials; and
- 3 the need to ensure existing antibiotics are used appropriately, in ways that delay the emergence of resistance.

Pharmaceutical companies have a role to play in addressing all three of these issues. On a per-product basis, companies are expected to take steps that support efforts to ensure access without promoting resistance.

The AMR Benchmark has examined the approaches pharmaceutical companies are taking to ensure access and also to address AMR. Here it presents three case studies of how pharmaceutical companies are balancing access to

treatment and stewardship. Bedaquiline (Sirturo®) from Johnson & Johnson is a new, on-patent medicine. Because it is being produced by only one company, the access programmes, coupled with tight stewardship controls, have a good chance of preventing drug-resistance. Amoxicillin/clavulanic acid, in this case sold by GSK as Augmentin™, is a much older, off-patent widely-used antibiotic. It must continue to be widely available – indeed access needs to increase – yet with multiple competitors in the market, stewardship is particularly complex. Cipla manufactures a wide range of antibiotics, such as the low-cost azithromycin and amoxicillin, which are both widely used for a variety of infections. The common thread running through these case studies is the balancing act of access and stewardship. The appropriate approach depends on two things: the application of each product as a first-, second- or third-line treatment and the nature of both the product and the market. Companies, governments and others must take these aspects into account as they seek to prevent or limit resistance.

In a situation where more incentives are needed to engage innovators to develop new antibiotics, there is also the need to ensure universal access to existing and newly introduced therapies, while avoiding the inappropriate use of these medicines. This is a challenging situation that affects not only companies, but also governments, health systems, patients, donors, etc. The lack of rigorous efforts to assure coverage of antibiotics increases the likelihood of resistance, but global efforts aimed at

stewardship and innovation cannot succeed without explicitly addressing the needs of the underserved.

The examples put forward are only a small snapshot of the different situations companies face to tackle this situation. All companies, independent of their business models, have a collective responsibility to preserve antibiotic effectiveness and promote universal access.

## CASE STUDY 1

Bedaquiline (Sirturo®), Johnson & Johnson

## CASE STUDY 2

Amoxicillin/clavulanic acid (Augmentin™), GSK

## CASE STUDY 3

Broad Generic Antimicrobial Portfolio, Cipla

**CASE 1: BEDAQUILINE (SIRTURO®), JOHNSON & JOHNSON**

## Access to new MDR-TB medicine is tightly controlled through national TB programmes and donations.

**NEW MILESTONE MDR-TB TREATMENT**

- First MDR-TB treatment to reach market in 40 years
- New mechanism of action (ATP Synthase Inhibitor)
- Only available for pulmonary MDR-TB with long-course regimens and shorter regimens

**CONTROLLED ACCESS**

- Restrictive access conditions require pharmacovigilance infrastructure, clinical monitoring
- Access provided through national programmes and donations via the USAID Bedaquiline Donation Programme.
- Equity-based inter-country tiered pricing approach in place
- Registered in 23 countries where access to medicine is likely limited

**STEWARDSHIP**

- Supports education for healthcare professionals on AMR, including on pharmacovigilance and TB-specific workshops
- No sales teams deployed
- Surveillance programme running (DREAM)

Tuberculosis (TB) poses a critical threat from AMR. In 2012, the U.S. Food & Drug Administration (FDA) gave fast-track accelerated approval, based on Phase II clinical studies, to the first innovative treatment for pulmonary multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) in 40 years: Johnson & Johnson's bedaquiline (Sirturo®).

Due to its accelerated approval, the medicine was not tested for long-term effectiveness and safety in larger populations. To further test the medicine and also to prevent acquired resistance from emerging, WHO issued a strict interim guideline on its use, monitoring and pharmacovigilance.<sup>2</sup> Countries with weaker health systems may be less likely to meet some of these criteria.

When filing bedaquiline for registration, Johnson & Johnson prioritised countries with high TB burdens. Russia was second to receive market approval, following the USA. Approval was granted in South Africa, the Philippines and Peru in 2014, the same year as in the European Union. These are countries with some of the highest MDR-TB burdens.

Today, bedaquiline is available via five routes: traditional reimbursement by national authorities, purchasing via the Global Drug Facility (GDF), equitable tiered pricing, institutional purchasing by international NGOs, and through a tightly controlled donation programme managed by USAID. In countries where

bedaquiline is not registered, access is possible with a WHO import waiver. Across the various access channels, 35,000 cumulative treatments have been delivered, mostly to India, Russia and South Africa. The donation programme was developed in 2015 with USAID to increase access in over 100 low- and middle-income countries. The company committed to donating 30,000 treatment courses in four years. According to Johnson & Johnson, 103 countries now have access, including 29 of the 30 countries with high MDR-TB burdens. The programme also includes specialist education on the use of bedaquiline and on activities to minimise risk, as well as technical support for establishing active pharmacovigilance. These capacity building activities are supported by USAID, national and local partners.

**Addressing the cost barrier**

To address affordability of bedaquiline, Johnson & Johnson has an equitable pricing strategy that sets prices according to a country's ability to pay. Its pricing tiers are based on criteria such as World Bank income classifications, GDP/GNI per capita and MDR-TB burden. Countries that do not meet the criteria or WHO's Guidelines, may receive additional technical support via other stakeholders, including the WHO and USAID.

**Stewardship measures**

Johnson & Johnson supports activities to raise awareness of TB and MDR-TB among healthcare professionals (HCPs) and achieve optimal clinical outcomes with bedaquiline. These include awarding unrestricted educational grants through the International Union Against TB for the design and delivery of MDR-TB HCP educational programmes in Ghana, Lesotho, Peru, South Africa, the Democratic Republic of Congo, and Rwanda. With USAID, Johnson & Johnson runs workshops on national pharmacovigilance programmes for staff of national TB programmes and national regulators in several low- and middle-income countries.

The company only provides bedaquiline under restricted access conditions – with no promotional activities or sales agents for the medicine, removing perverse incentives to oversell. Johnson & Johnson also supports efforts to track and predict the emergence of resistance to bedaquiline. Its DREAM surveillance programme (Drug Resistance Emergence Assessment in MDR-TB) runs in collaboration with National Tuberculosis Programmes and WHO's Supranational Reference Laboratories.

The Benchmark has assessed access and stewardship practices for 18 companies in relation to their antibiotics. The measures put in place by Johnson & Johnson for bedaquiline represent the most comprehensive of those specifically linked to a single product.

**CASE 2: AMOXICILLIN/CLAVULANIC ACID (AUGMENTIN™), GSK**

## Strategy aims to balance access and stewardship for off-patent widely-used antibiotic.

**OFF-PATENT ANTIBIOTIC**

- Multiple companies produce versions of amoxicillin/clavulanic acid
- Resistance has been noted in a range of pathogens including *Klebsiella* spp.
- Placed in WHO EML's Access group of antibiotics

**INCREASING ACCESS**

- Broad registration, now in 71 low- and middle-income countries
- Equitable pricing strategy, with different pricing tiers in-country
- Pricing strategy based on (e.g.) GNI, burden of disease, health system financing

**STEWARDSHIP**

- Continuing medical education programmes
- Marketing materials include information on AMR trends
- Decoupling of sales staff incentives from sales volume
- Antibiotic surveillance activities

Amoxicillin/clavulanic acid (Augmentin™) is a broad-spectrum antibiotic used to treat mild-to-moderate bacterial infections, including sinusitis, cellulitis, acute otitis media and community-acquired pneumonia. It was first introduced by GSK in 1981, following UK approval. It came off patent in 2002, triggering the arrival of many generic versions on the market. Of the 21 companies with marketed products in the Benchmark's scope, 13 report marketing at least one formulation of amoxicillin/clavulanic acid. Where there are more versions of a product available, the ability to control resistance decreases.

This broad-spectrum antibiotic is a widely-used treatment for a wide range of infectious diseases. As a result, it has been classified as an Access antibiotic by the WHO in its 2017 WHO Model List of Essential Medicines – meaning that it should be widely available, affordable and quality assured as a first- and second-line treatment for many infectious diseases.<sup>3</sup> However, as it is among the most commonly prescribed antibiotics worldwide, a wide range of different pathogens have developed high resistance rates to this medicine, including *Klebsiella* spp. (61% of isolates are resistant in Egypt, 33% in Brazil), and *Streptococcus pneumoniae* (17% resistant isolates in Vietnam).<sup>4</sup> While access remains a priority, the stewardship of this important medicine is also critical to ensure it can continue to be effective.

**Registration: the 1st step to availability**

GSK has filed to register amoxicillin/clavulanic acid in 71 of 106 low- and middle-income countries where access to medicine is likely limited. This makes it the most widely registered product in this group of countries analysed by the Benchmark. GSK has also developed an equitable pricing approach for setting prices at the national level, as well as for populations within countries. When setting prices for this medicine, GSK reports that it considers multiple socio-economic factors, including: a country's ability to pay, its burden of infectious diseases, how healthcare is financed, and its level of socio-economic inequality. There are many generic versions of amoxicillin/clavulanic acid that are lower in cost than GSK's version (Augmentin™).

**Appropriate promotion**

In parallel to its measures addressing affordability, GSK also runs stewardship activities for amoxicillin/clavulanic acid. These include the provision of medical education programmes regarding the appropriate use of the medicine. It also undertakes several practices for ensuring the product's appropriate promotion: it includes AMR-related information and trends in its marketing materials, and has completely separated the remuneration of its sales staff from the sales volume of antibiotics, including amoxicillin/clavulanic acid. GSK has also adapted some of its brochures to facilitate the appropriate use of the product

by patients. Looking across the data from the other 13 companies in scope that market amoxicillin/clavulanic acid, GSK performs well in balancing access and stewardship for this product. To maximise the effectiveness of GSK's actions, and extend the lifespan of this important antibiotic, other producers must meet or exceed the standard GSK sets.

Amoxicillin/clavulanic acid is a widely marketed off-patent product produced by multiple companies, which makes the challenge of expanding access while also protecting the product from resistance-promoting behaviour particularly complex. On the one hand, affordability and availability are easier to achieve due to competition from multiple generic medicine manufacturers. On the other hand, a wider number of producers means more actors that must adopt best practices for stewardship. It is vital that all producers of amoxicillin/clavulanic acid consider and implement stringent stewardship policies across all healthcare settings.

## CASE 3: BROAD GENERIC ANTIMICROBIAL PORTFOLIO, CIPLA

# Generic medicine manufacturer stands out for stewardship practices.

## GENERIC ANTIMICROBIALS

- Has more than 1500 products on the market
- Markets at least 25 antimicrobials, including 23 on Section 6 of the WHO EML

## INCREASING ACCESS

- One of only two generic medicine manufacturers with an equitable pricing approach
- Takes account of country's GNI when setting prices

## STEWARDSHIP

- Educational activities to educate HCPs on antibiotic stewardship
- Illustrates AMR trends in some marketing materials
- Adapts packaging to support rational use
- Engages in AMR surveillance

As a generic medicine manufacturer, Cipla uses a low-cost, high-volume model that allows it to specialise in developing generic versions or formulations of products such as amoxicillin and azithromycin after patent expiry. Across the industry, this business model has proven highly successful at expanding access to medicines in recent decades, particularly through price reduction. Yet it is seemingly at odds with the need to reduce the overuse of antibiotics. Looking ahead, generic medicine manufacturers have a clear responsibility to market their antibiotics appropriately.

Cipla has a presence in more than 80 countries, with 43 manufacturing facilities worldwide and markets more than 1,500 products across various therapeutic areas. This includes at least 25 antimicrobial medicines, 23 of which are listed on Section 6 of the WHO Model List of Essential Medicines (EML). It is one of only two generic medicine manufacturers in the scope of the Benchmark that reported an equitable pricing strategy that covers antimicrobials as well as multiple stewardship activities, particularly surveillance. Its inter-country equitable pricing strategy is based on countries' levels of income (gross national income (GNI) per capita).

## Stewardship activities

Cipla is the only generic medicine manufacturer in the scope of the Benchmark that engages in multiple activities to educate healthcare professionals (HCPs) on antibiotic stewardship. The company also implements brochure and packaging adaptations to facilitate appropriate use of antibiotics by patients. For example, it includes information about treatment duration on the strip of the box of the antibiotic azithromycin to help improve patient adherence to the treatment. It has conducted several AMR-related prevalence studies, delivering the results via conferences and peer-reviewed journals.

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## CROSS-CUTTING STORY

# Vaccines in the push to limit antimicrobial resistance

It is more than 30 years since researchers first discovered that bacteria producing extended-spectrum beta-lactamase (ESBL) enzymes were resistant to many penicillin and cephalosporin antibiotics, and to other types of antibiotics. Today, antimicrobial resistance (AMR) is recognised as a growing threat, emerging at a global level. It poses complex challenges to the treatment of infectious diseases, particularly in low- and middle-income countries<sup>1</sup> and in infections acquired in hospital settings.

Vaccines have the potential to play a significant role in helping to alleviate the problem of drug resistance. This role has been promoted by several organisations, such as Chatham House and the Sabin Vaccine Institute.<sup>2,3,4</sup> The potential has also been acknowledged in the final report of the UK-based Review on Antimicrobial Resistance<sup>5</sup>, the 2016 UN declaration on antimicrobial resistance<sup>6</sup>, the UN IACG Framework for Action<sup>7</sup> and the Davos Declaration.<sup>8</sup> While it is vital to develop new antibiotics to treat people who have a bacterial infection, it is equally vital to develop vaccines to prevent the incidence of infection. Vaccines can guard against major diseases such as tuberculosis and malaria, and can prevent viral infections (for which antibiotics are often wrongly prescribed). Vaccines do not just avert morbidity and mortality; they also reduce the need to use antibiotics. By limiting the use of antimicrobial medicines, they can, in turn, slow or curtail the emergence of resistance.

To combat AMR, vaccines constitute a clear and key line of defence. Yet, there is still much work to be done to explore and assess the range of health

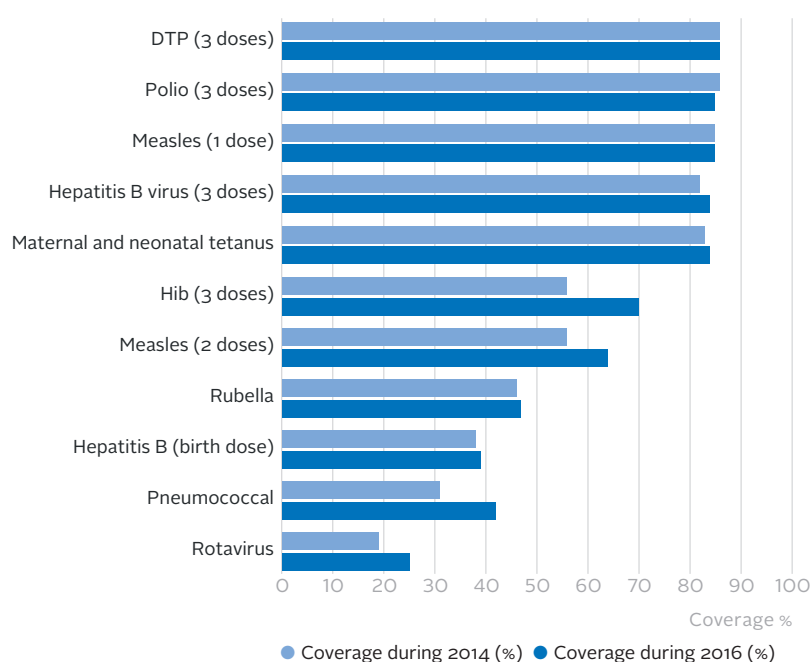
and economic benefits they can offer in this area. In this article, the Benchmark reports how companies are marketing and developing vaccines against pathogens with a critical level of resistance. This overview shows the pathogens and diseases for which the focus should be on improving immunisation coverage, on sustaining R&D efforts and/or on embarking on R&D in the very first place.

## PREVENTING INFECTION AND AVOIDING ANTIMICROBIAL MEDICINE MISUSE AND EXPOSURE

There is overwhelming evidence that immunisation programmes can have a profound impact on public health in general, and AMR more specifically. A recent notable example is the USA's introduction of the 13-valent pneumococcal vaccine in 2010, which has led to a significant reduction in disease in both vaccinated (direct protection) and unvaccinated (herd protection) children.<sup>9</sup> Between 1998 and 2008, use of pneumococcal vaccines in the USA has

**Figure 18. Global coverage of older vaccines exceeds 80% - for newer vaccines coverage remains relatively low**

In the period 2014 to 2016, global coverage of older vaccines remains stable at above 80%. For newer vaccines, global coverage is increasing but remains low.<sup>15</sup> (Source: WHO Immunization Coverage 2016)



been shown to reduce antibiotic-resistant infections in children by 64%, and in elderly patients by 45%.<sup>10</sup> Further, in geographic regions where vaccines for *S. pneumoniae* (pneumococcus) and *N. meningitidis* (meningococcus) have been introduced and widely deployed, resistant strains have been eliminated.<sup>11</sup> Similarly, use of the *H. influenzae* type b (Hib) conjugate vaccine, used to prevent Hib from causing meningitis and non-central nervous system infections has, in certain areas, almost eliminated ampicillin-resistant Hib.<sup>11</sup> Introduction of rotavirus vaccination in the USA in 2007 has led to more than an 80% decline in community-acquired rotavirus hospital admissions and more than a 60% decrease in hospital-acquired infections.<sup>12</sup> After introduction of a 7-valent pneumococcal vaccine in South Africa in 2009, rates of invasive pneumococcal disease dropped more than 50% in children younger than two years of age and more than 30% in adults 25 to 44 years of age between 2005 and 2012.<sup>13</sup>

Nevertheless, vaccines continue to have a huge untapped potential for improving public health. Millions of children around the world die from vaccine-preventable diseases before they reach the age of five. Overall, some two million of these deaths each year may be prevented if children receive the right vaccine. While immunisation coverage is increasing globally, in 2015 nearly one in five children did not receive the basic life-saving vaccines recommended by WHO for routine immunisation. The number of those not immunised with newer vaccines, such as those to prevent pneumococcal disease and rotavirus infection, is even higher (see figure 18).<sup>14,15,16</sup> WHO estimates that among children under five years old, there are 14.5 million episodes of serious pneumococcal infections each year worldwide, with more than 800,000 deaths<sup>17</sup> arising from pneumonia, meningitis, ear and sinus infections, and bloodstream infections.

Although pneumococcal vaccines are marketed and available, the worldwide immunisation rate of infants in

2016 was just 42% (figure 18). In general, the factors that deter or prevent vaccination include weaknesses in health systems and supply chains, insufficiencies in the supply of vaccines, challenges in financing and difficulties within communities in accepting vaccination. For newer vaccines, affordability and production capacity are among the key issues. The situation remains complex, but the impact of missed opportunities for immunisation is profound.

### Providing greater access to vaccines

The spread of disease in a community can be halted when enough people receive a vaccine, leaving too few susceptible individuals to infect. While it is often desirable to administer vaccines across large proportions of populations, these vaccines must first be purchased in considerable volumes. As immunisation programmes often aim to reach whole demographic groups, even small decreases in unit price can make large differences in the cost of each round of immunisation.

Affordability – particularly of newer vaccines – remains an issue. Affordability issues can become acute when a country's level of national income rises, and it moves from low-income up to lower-middle income status (as defined by the World Bank). Typically, it then loses access to pooled-procurement systems, putting pressure on the country's resources, especially for procuring more expensive vaccines (e.g., for human papillomavirus (HPV), rotavirus and pneumococcal infections).<sup>18</sup>

UNICEF\* and the Pan American Health Organization (PAHO)\*\* run pooled-procurement systems, as does Gavi, the Vaccine Alliance\*\*\*, a public-private global health partnership aiming to increase access to immunisation. These systems, which enable low- and middle-income countries to club together to buy vaccines in bulk, have been successful in helping countries to negotiate lower prices for vaccines. Companies that make and market vaccines need to develop and embed a

systematic approach to equitable pricing, particularly for countries that receive no Gavi support and cannot participate in pooled-procurement systems. They need to form clear strategies on pricing for all low- and middle-income countries, and share this global pricing information. This will help to facilitate negotiations and, by promoting a more competitive environment, help to ensure prices are fair. More broadly, in some countries, companies can improve the way they prioritise registration of vaccines according to public health needs.

In low- and middle-income countries, governments and other vaccine procurers need to invest further in regulatory systems and immunisation programmes. This investment is especially important for vaccines used to prevent infections caused by priority pathogens (see figure 19). Access to and wider use of these vaccines has the potential to curtail antibiotic resistance, and to avert 2.6 million deaths per year from infectious diseases, most of them (2.4 million) from tuberculosis and pneumonia worldwide.†

Global vaccine coverage against pneumococcal disease was estimated to potentially avert up to 11.4 million days of antibiotics for pneumonia caused by *S. pneumoniae* per year in children younger than five years of age.<sup>19</sup>

Supply, availability and affordability are closely interlinked. Multiple factors affect whether a population is able to obtain sufficient vaccine coverage, but an essential first step is to make high-quality, effective vaccines available and affordable, allowing procurers to purchase the quantities of vaccines necessary to immunise adequately the populations they target. As they work to create and guarantee a stable and affordable supply, all parties involved must recognise and reward effort, and pool resources wherever possible.

\* UNICEF is the world's largest supplier of vaccines to children and works with many stakeholders to increase demand for vaccines, including through pooled procurement.

\*\* PAHO is a UN public-sector procurement agency that has established a fund that enables member states to access lower vaccine prices.

\*\*\* Gavi brings together many key organizations in a single decision-making body regarding access to vaccines, and works to accelerate the introduction of new and underused vaccines in over 70 of the poorest countries.

† Data from Global Health Data Exchange, based on 2016 calculations for *H. influenzae* type b (48,000 deaths), pneumonia (1.2 million), tuberculosis (1.2 million) and typhoid fever (128,000).

## OVERVIEW OF COMPANIES IN SCOPE

The 2017 Access to Vaccines Index examined the actions taken by the world's largest manufacturers of vaccines to improve access to vaccines. It also assessed the factors that prompt

them to take action in this area.<sup>20</sup> This analysis discusses the practices of nine pharmaceutical companies. These include five of the large research-based companies that were also in the scope of the Access to Vaccines Index: GSK, Johnson & Johnson, Merck & Co., Inc., Pfizer and Sanofi.

The remaining four companies discussed here are all generic medicine manufacturers: Aurobindo, Mylan, Sun Pharma and Wockhardt. Other major producers of vaccines, such as Serum Institute of India, are not currently in the Benchmark's scope. The five large research-based pharmaceutical companies are all marketing and developing vaccines. They are each conducting vaccines R&D through one or more public-private partnerships. Of these, GSK is involved in three Product Development Partnerships (PDPs), while Johnson & Johnson and Sanofi are involved in one and two PDPs respectively. Mylan and Wockhardt have vaccines on the market. Aurobindo and Sun Pharma are developing vaccines.

### Figure 19. More research and development needed on vaccines against priority pathogens.

Five Benchmark companies (GSK, Johnson & Johnson, Merck & Co., Inc., Pfizer and Sanofi) market vaccines against four of 19 priority pathogens. To date, the companies are developing vaccines against 12 priority pathogens, with projects at various stages. None of the companies has vaccines either marketed or in development against seven remaining priority pathogens.

Priority pathogens	Marketed vaccines	Vaccines in preclinical development	Vaccines in clinical development
<b>Bacteria</b>			
Multidrug-resistant <i>Enterobacteriaceae</i> (incl. CRE and ESBL-producing)		1	1
Multidrug-resistant <i>Acinetobacter</i> spp. (incl. <i>A. baumannii</i> )			
Multidrug-resistant <i>Pseudomonas aeruginosa</i>			
<i>Neisseria gonorrhoeae</i>			1*
Drug-resistant <i>Campylobacter</i> spp.			
Vancomycin-resistant <i>Enterococcus</i> (VRE)			
Drug-resistant <i>Salmonella</i> spp.	4**	2	
Drug-resistant <i>Staphylococcus aureus</i>		2	1
Clarithromycin-resistant <i>Helicobacter pylori</i>			
Drug-resistant <i>Shigella</i> spp.		1	2
Drug-resistant <i>Streptococcus pneumoniae</i>	4†	1	4
Ampicillin-resistant <i>Haemophilus influenzae</i> (Hib)	14***		3†
Drug-resistant <i>Mycobacterium tuberculosis</i>	1 <sup>  </sup>	1	2
<i>Clostridium difficile</i>		1	2 <sup>§</sup>
Erythromycin-resistant group A <i>Streptococcus</i>			
Clindamycin-resistant group B <i>Streptococcus</i>		1	1
<b>Viruses</b>			
Human immunodeficiency virus (HIV)			3
<b>Protozoa</b>			
Multidrug-resistant <i>Plasmodium falciparum</i>		2	
<b>Fungi</b>			
Fluconazole-resistant <i>Candida</i> spp.			

\* Includes one adaptation

\*\* Targeting *S. enterica* ser. Typhimurium: GSK's Typherix and Hepatix; Sanofi's Typhim VI and Viatim

\*\*\* GSK's Hiberix / Vaxem Hib, Menitorix, MenHibrex, Infanrix Hexa, Infanrix Hib, Quinvaxem and Infanrix IPV Hib; Johnson & Johnson's Quinvaxem; Merck & Co., Inc.'s PedVax Hib and Vaxelis; Sanofi's ActHib, Hexaxim, Shang and Pentacel / Pentavac / Pentaxim

† Includes two adaptations

‡ GSK's Synflorix; Merck & Co., Inc.'s Pneumovax 23; Pfizer's Prevenar 13; Sanofi's Pneumo 23

§ Includes one candidate that was terminated after the period of analysis

<sup>||</sup> Merck & Co., Inc.'s BCG vaccine USP

### Are vaccines available for priority pathogens?

Of a total of 19 priority pathogens, companies in scope of the Benchmark have so far targeted 12 with vaccines that are either marketed already, or in development (see figure 19). The priority pathogens were identified based on the WHO priority pathogens list as of 25 February 2017 and 'CDC's US Biggest Threats as of April 2013'. For those pathogens, new innovative medicines and vaccines are highly needed.

The five large research-based pharmaceutical companies in scope (GSK, Johnson & Johnson, Merck & Co., Inc., Pfizer and Sanofi) market 23 vaccines that have the potential to prevent or reduce antibiotic-resistant infections caused by four priority pathogens: *H. influenzae* (Hib), *M. tuberculosis*, *S. pneumoniae* and *Salmonella enterica* ser. Typhimurium. In 2016, global immunisation coverage data showed 70% of infants were vaccinated against Hib and 42% against pneumonia. Rates of immunisation for TB and salmonella are not known.<sup>11</sup>

### Unaddressed priority gaps

Of the 19 priority pathogens overall, seven remain untargeted by companies in scope (see figure 19): multidrug-resistant *Acinetobacter* spp. (including *A. baumannii*), drug-resistant *Campylobacter* spp.,

vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant *P. aeruginosa*, erythromycin-resistant group A *Streptococcus*, clarithromycin-resistant *H. pylori* and fluconazole-resistant *Candida* spp. No company in scope has yet marketed a vaccine for these, or has an R&D project under development.

Companies in scope have yet to bring to market any vaccines to guard against 15 of the 19 identified priority pathogens (see figure 19). However, in addition to developing new vaccines for Hib, *M. tuberculosis*, *S. pneumoniae* and *Salmonella enterica* ser. Typhimurium, the five companies above are developing vaccines against an additional eight priority pathogens.

Attrition rates for R&D projects are high, and other organisations may be developing vaccines against these priority pathogens. Even so, it is important to incentivise large players – such as those in the scope of the Benchmark, which have the resources to develop and roll out vaccines effectively – to engage in developing vaccines that can prevent infection from these drug-resistant pathogens.

### Surveillance of vaccines

It is important to monitor the impact of vaccines on the emergence of resistance, so that efforts to curb AMR can be evaluated. To this end, pharmaceutical companies can support national and international efforts to run AMR surveillance programmes, which collect,

analyse and share data on infection rates and associated mortality rates. On top of 19 surveillance programmes on antibiotics assessed by the Benchmark, another programme monitors the effects of one or more vaccines. Pfizer's programme is notable, as it monitors the effects of vaccination as part of the wider effort to combat antimicrobial resistance. It is partnering with academic research groups around the world to look at epidemiological changes in disease caused by *S. pneumoniae*.

Using studies that focus on invasive pneumococcal disease, pneumonia, otitis media and nasopharyngeal carriage, Pfizer is examining how the introduction of pneumococcal conjugate vaccination in children and adults may change patterns of antimicrobial non-susceptibility. Through reports, conference presentations and peer-reviewed publications, Pfizer shares its results with regulatory agencies (as part of its regulatory commitments), public health authorities and the scientific community.

### THE WAY FORWARD: ENSURE VACCINES ARE ACCESSIBLE

The use and effectiveness of vaccines to address AMR remains understated and under-reported. Among options proposed to tackle the problem of AMR, vaccines comprise an important tool. By

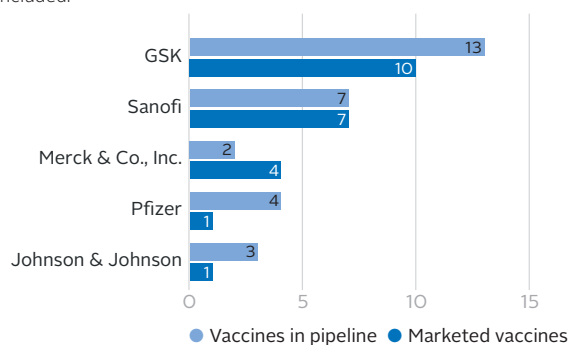
creating immunity and reducing infection, vaccines can eliminate the need for antimicrobial medicines. This helps to prevent the use of these medicines, averting the need for further interventions to conserve their utility. Several organisations – including the Bill & Melinda Gates Foundation<sup>25</sup>, Gavi, the Vaccine Alliance<sup>26</sup> and the Wellcome Trust<sup>27</sup> – are now advocating for vaccine development and higher rates of vaccination globally, not only to prevent disease but also as an essential intervention in tackling AMR.

Companies play an integral part in this intervention, as they have the means and responsibilities to make this a reality by: (1) responding to R&D gaps as identified by WHO and CDC to develop new vaccines; and (2) ensuring the accessibility, affordability and supply of these vaccines that make it to the market. The incentives put forward by major funders and other stakeholders involved must be aligned with these two responsibilities. Major funders can support companies' efforts in vaccine R&D and assist in the pooled procurement of vaccines to improve accessibility and affordability.

So far, five large research-based pharmaceutical companies in scope (GSK, Johnson & Johnson, Merck & Co., Inc., Pfizer and Sanofi) have vaccines on the market against four priority pathogens – with the potential to avert at least four million deaths per year globally.\* These same companies are now involved in R&D for the development of additional vaccines against twelve priority pathogens (including the four pathogens already targeted – see figure 20). GSK, Johnson & Johnson and Sanofi are developing some of these vaccines through PDPs. For candidate vaccines in the pipeline it is vital that companies work with stakeholders to ensure that affordable access and adequate supply are prioritised when these vaccines reach the market.

**Figure 20. Five companies market and develop vaccines for priority pathogens.**

A core group of five large research-based pharmaceutical companies, included in the Benchmark, targets priority pathogens for AMR with vaccines on the market or in development. The same companies have R&D projects for vaccines against 12 priority pathogens: these include 8 projects at preclinical stage and 21 projects at clinical stage. Projects provided on the basis of confidentiality were not included.



\* Data from Global Health Data Exchange (<http://ghdx.healthdata.org/gbd-results-tool>), based on 2016 calculations for *H influenzae* type B (48 thousand deaths), pneumonia (1.2 million), tuberculosis (1.2 million), typhoid fever (128 thousand), shigellosis (212 thousand), malaria (700 thousand) and HIV (1.0 million).

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# Analyses of industry activity

This section includes three analyses of industry performance, exploring how the 30 companies are addressing key AMR challenges. They are based on the Benchmark analysis of data submitted by the companies, contextualised against real-world constraints and stakeholder expectations where possible and appropriate.

Research Area	Analyses
Research & Development	<ul style="list-style-type: none"><li>- R&amp;D investments</li><li>- R&amp;D projects in the pipeline</li><li>- Partnerships</li><li>- Facilitating access and stewardship</li></ul>
Manufacturing & Production	<ul style="list-style-type: none"><li>- Environmental risk-management strategies</li><li>- Disclosure regarding environmental risk management</li></ul>
Appropriate Access & Stewardship	<ul style="list-style-type: none"><li>- Ensuring access</li><li>- Supporting stewardship through HCP education</li><li>- Appropriate promotion</li><li>- Brochure and packaging</li><li>- Surveillance</li></ul>

## MAIN FINDINGS

**Research & Development:** Leaders in R&D address global needs and plan ahead to ensure successful candidates are both accessible in low- and middle-income countries and used conservatively.

**Manufacturing & Production:** Most companies have environmental risk-management strategies in place that aim to minimise the impact of antibiotics discharged from manufacturing processes. However, the depth and breadth of these strategies differ widely regarding the different aspects evaluated by the Benchmark.

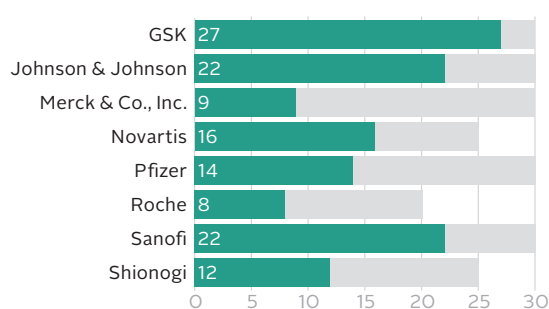
**Appropriate Access & Stewardship:** Leaders in this Research Area have access strategies in place regarding antimicrobial medicines in low- and middle-income countries, alongside their global stewardship of antibiotics.

## RESEARCH AREA: RESEARCH &amp; DEVELOPMENT

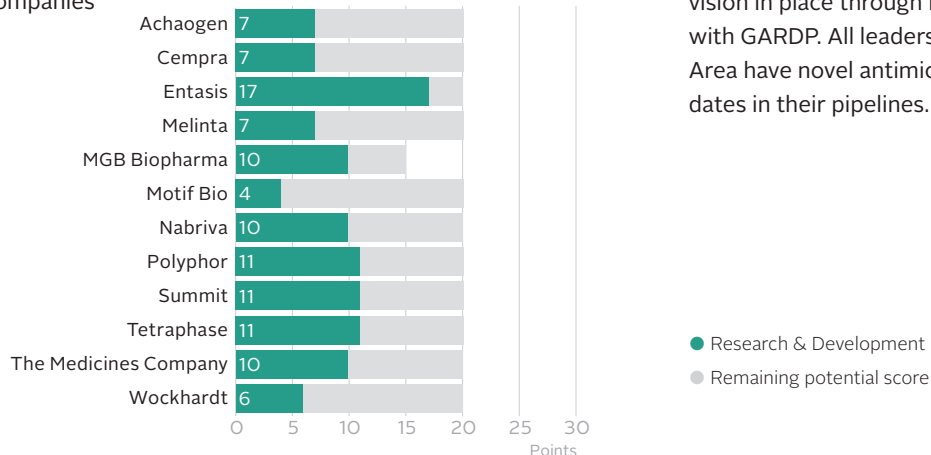
# What is in companies' antimicrobial pipelines?

Figure 21. Company performance: research &amp; development

## Large research-based pharmaceutical companies



## Biopharmaceutical companies



## THE LEADERS

In Research & Development, GSK is the leader amongst large research-based pharmaceutical companies, followed by Johnson & Johnson and Sanofi. GSK is the largest investor in the space of antimicrobial R&D and has a promising pipeline in terms of size as well as the number of vaccines and novel antimicrobial candidates. Among biopharmaceutical companies, Entasis leads. It has a novel antibiotic candidate in its pipeline, for which it has an access provision in place through its agreement with GARDP. All leaders in this Research Area have novel antimicrobial candidates in their pipelines.

## CONTEXT

As AMR increases, there is a pressing need for novel products to be developed to replace ineffective treatment options. Major scientific hurdles, along with technical and regulatory complexities, form significant disincentives to investing in such R&D. Nevertheless, investment is needed, including from those pharmaceutical companies that have resolved to remain in this sector. Certain pathogens pose a greater threat of resistance than others; the WHO and the US Centers for Disease Control and Prevention (CDC)

have both identified pathogens that are priorities for R&D into new medicines, vaccines and diagnostics.

Once a new antimicrobial medicine is approved, the challenge is to introduce it in a way that (a) ensures its rapid and appropriate accessibility for patients in need while (b) conserving its use to slow the inevitable emergence of resistance. Pharmaceutical companies are encouraged to engage with others to plan ahead, during the development process, to achieve these twin aims.

## WHAT THE BENCHMARK MEASURES

The Benchmark captures the antimicrobial pipelines of 20 companies active in this area of pharmaceutical R&D. It matches their pipelines with the WHO and CDC lists of priority pathogens, and reports on companies' plans to ensure access and stewardship of successful candidates. It also evaluates the scale of companies' investments in antimicrobial R&D.

## IN SUMMARY

### Majority of R&D projects for infectious diseases target priority pathogens

Of the 30 companies in scope,\* the Benchmark has identified 24 companies carrying out a total of 276 R&D projects that target infectious diseases. Of these, the majority (175) target pathogens identified as priorities for further R&D by the WHO and/or the CDC (referred to by the Benchmark as priority pathogens). Of the 175 R&D projects, 88 are in preclinical development, and 87 in clinical stage. Almost one third (54 out of 175) targets gram-negative bacteria, a critical target for AMR: over half of these are in the preclinical stages of development.

GSK has the fullest pipeline, with a large proportion of projects focussing on priority pathogens. It also has the highest number of vaccines in development that target priority pathogens. The pipelines of biopharmaceutical companies are comparatively smaller, as would be expected for companies of this type. These companies focus on R&D for priority areas.

### Over half of R&D projects targeting priority pathogens are conducted through partnerships

More than 50% of the 130 new R&D projects (excluding adaptations) are now being conducted in partnership. In 58 partnership-based projects, companies are working with public- or non-profit-sector partners only. In eight projects, companies' partners include both public- or non-profit- and private-sector entities. In the remaining seven projects, companies are working with other private-sector partners only.

Open collaborations, including PDPs, comprise a third of the overall number of project partnerships analysed by the Benchmark. Only one PDP (GARDP) is involved with the discovery and development of antibiotics against gram-negative (GNB) and/or gram-positive bacteria (GPB). Sanofi is developing half of the 16 new candidates targeting priority pathogens in its pipeline through open collaborations, which is comparatively high versus other companies assessed in this Research Area.

### Out of 28 antibiotics in late stages of clinical development, only two have both access and stewardship provisions in place

The Benchmark identified 56 R&D projects in late stages of clinical development targeting priority pathogens (out of 175 projects), including 28 antibiotics and 14 vaccines for bacterial infections (the other 14 candidates focus on HIV/AIDS and malaria). Of these 28 antibiotics, only two meet the standard of having plans in place to ensure both rapid access where needed and stewardship of the successful candidate: eravacycline, being developed by Tetraphase, targets a group of priority pathogens that cause complicated intra-abdominal and urinary tract infections; and paediatric bedaquiline for the treatment of tuberculosis, in development by Johnson & Johnson. Two other antibiotics – being developed by GSK for gonorrhoea and Pfizer for multidrug-resistant gram-negative bacterial infections – have stewardship provisions but no access plan, while three other antibiotics in the clinical pipeline (being developed by GSK, Entasis and Melinta) have an access plan in place but no stewardship provisions.

### Access provisions for late-stage candidates are varied

The most common access provisions for medicines and vaccines in late stages of development are: plans to register these products in countries where there is a high need (upon approval), plans for equitable and/or tiered pricing, and commitments to license IP to partners who work in geographic areas where access to medicine is likely limited. GSK, Johnson & Johnson, Pfizer and Sanofi have the most access provisions in place. The most predominant stewardship provision is the development of a surveillance programme for monitoring resistance.

\*This chapter reports on all R&D projects identified by the Benchmark for the 30 companies in scope. Please note, however, that generic medicine manufacturers were not scored in this research area to preserve comparability within that group of companies.

## RESEARCH & DEVELOPMENT METHODOLOGY: WHAT THIS RESEARCH AREA MEASURES

In this Research Area, the Benchmark assesses pharmaceutical companies engaged in antimicrobial R&D (i.e., in new antimicrobial drug development and/or the adapting of existing antimicrobial medicines and vaccines, including those in preclinical and clinical development, e.g., to develop new formulations or label extensions). It looks at the size of companies' pipelines, whether they are targeting priority pathogens identified by WHO and/or CDC, their R&D investments, R&D partnerships and how they plan ahead to ensure successful candidates are both accessible in low- and middle-income countries and used conservatively. Of the 30 companies in the scope of the Benchmark, this research area analyses 20: all eight large research-based pharmaceutical companies and

all 12 biopharmaceutical companies in scope. These companies have valiantly remained innovating in antimicrobials despite scientific, regulatory and commercial challenges. A key selection criterion for biopharmaceutical companies was that they are already developing at least one R&D project that targets a priority pathogen, as identified in WHO's report 'Antibacterial Agents in Clinical Development'.<sup>1</sup> The Benchmark does not assess the R&D activities of the 10 generic medicine manufacturers in scope so as to preserve the comparability of this group. However, the Benchmark highlights the product development activities of these companies where the information is available. Most companies in scope (24) have signed the Declaration by the Pharmaceutical, Biotechnology and

Diagnostics Industries on Combating Antimicrobial Resistance; ten have signed the Industry Roadmap for Progress on Combating Antimicrobial Resistance. In signing up to these industry-wide initiatives, companies reaffirm their commitment to investing in antimicrobial R&D.

The Benchmark analyses data collected through survey and from public sources. As far as possible, this data is clarified, cross-referenced and verified by the research team. How data is collected in the first instance depends on a company's level of engagement with the Benchmark research. All companies were surveyed, and data from public sources were analysed for all companies. Not all companies participated in the survey.

### INDICATORS

- A.1 R&D Investments
- A.2 R&D Projects
  - A.2.1 Pipeline size
  - A.2.2 Novelty of pipeline
  - A.2.3 Vaccines in pipeline
- A.3 R&D Collaborations
- A.4 Facilitating access and stewardship

Figure 22. Companies in scope

	Applicable indicators						
	A						
	1	2.1	2.2	2.3	3	4	
<b>Large research-based pharmaceutical companies</b>							
GSK	●	●	●	●	●	●	
Johnson & Johnson	●	●	●	●	●	●	
Merck & Co., Inc.	●	●	●	●	●	●	
Novartis	●	●	●		●	●	
Pfizer	●	●	●	●	●	●	
Roche	●	●	●		●		
Sanofi	●	●	●	●	●	●	
Shionogi	●	●	●		●	●	
<b>Biopharmaceutical companies</b>							
Achaogen	●	●		●	●		
Cempra	●	●		●	●		
Entasis	●	●		●	●		
Melinta	●	●		●	●		
MGB Biopharma	●	●		●			
Motif Bio	●	●		●	●		
Nabriva	●	●		●	●		
Polyphor	●	●		●	●		
Summit	●	●		●	●		
Tetraphase	●	●		●	●		
The Med. Company	●	●		●	●		
Wockhardt	●	●		●	●		

### ABOUT THIS CHAPTER

In this chapter, the Benchmark reports its findings in four sections, each relating to a separate indicator (the section on A.2 covers all sub indicators).

p43 A.1

p44 A.2.1–A.2.3

p49 A.3

p53 A.4

For a full listing of indicators and scoring eligibility see Appendix V.

Aurobindo, Cipla, Macleods and Mylan were not eligible for this Research Area. However, the companies are active in antimicrobial R&D and are mentioned in this Research Area where relevant.

## INVESTMENT

## INDICATOR

## A.1 R&amp;D Investments

# What approaches do companies take to invest in antimicrobial R&D?

As antimicrobial resistance increases, there is a pressing need for novel products to be developed to treat life-threatening infections. Yet there is little incentive for pharmaceutical companies to invest in antimicrobial R&D, not least because of the major scientific challenges involved in discovering and developing new antimicrobial classes, but also the regulatory hurdles of complex and divergent requirements to obtain market approval. The business model is also problematic, requiring considerable investment in R&D but low returns compared to alternative R&D areas, particularly as novel antibiotics must be used conservatively to limit the risk of resistance emerging. This makes high-volume, high-return markets less likely to develop, as well as undesirable from the perspective of AMR control.

Nevertheless, the pharmaceutical industry has a keen interest in the development of new antibiotics, as they are the basis of modern medicine. Even non-infectious diseases, such as many cancers, cannot be treated without the availability of effective antibiotics. Therefore, debate on the need for sustained push funding and pull incentives is critical, as it is important that sufficient investment is made into the development of new antimicrobials and vaccines.

In order to stimulate antimicrobial R&D, companies need to make and attract predictable and sustained investments, and follow clear plans to develop key products. Companies may be able to make use of existing push incentives (which reduce the costs of financial inputs for developers) and pull incentives (such as fast-track regulatory reviews and extended market exclusivity). Companies can also be involved in the debate and implementation of new industry incentives to spur antimicrobial R&D in the future.<sup>2</sup> These are essential

for maintaining profitability and a competitive edge in the market.

The Benchmark reports on the financial resources that companies' reportedly dedicated to antimicrobial R&D in the fiscal year 2016, including in-kind resources and contributions to collaborations. For both large research-based pharmaceutical companies and biopharmaceutical companies in scope, absolute amounts of investments are captured, however only large research-based pharmaceutical companies were scored in this area. Generic medicine manufacturers are not evaluated in this Research Area.

## LARGE DIFFERENCES IN WHAT COMPANIES INVEST IN ANTIMICROBIAL R&D

Five out of eight of the large research-based pharmaceutical companies evaluated reported their annual investments in antimicrobial R&D. Of all companies evaluated, GSK is the largest investor in antimicrobial R&D, followed by Johnson & Johnson. While these companies are the largest investors in absolute terms, Shionogi is the largest investor when comparing R&D investments with revenue. Large research-based pharmaceutical companies show large differences in what they earn from antimicrobials and in what goes back into antimicrobial R&D. Various companies state that specific revenue and R&D expenditure information cannot be reported in the area of antimicrobials.

Smaller biopharmaceutical companies are fully reliant on external funders as their only source of income. Their pipelines tend to be small and focussed on antibiotic drug discovery, on average including two clinical-stage antibiotic candidates. Across this group, investments in antimicrobial R&D vary

from USD 5 million to USD 80 million. The highest investments come from Cempre, Achaogen and Tetrphase, which all invest over USD 60 million.

Four out of 10 generic medicine manufacturers in scope (Aurobindo, Cipla, Macleods and Mylan) reported investments in R&D, directed toward adapting existing antimicrobial medicines.

## PIPELINE

## How many projects target priority pathogens?

## INDICATORS

A.2	R&D Projects
A.2.1	Pipeline size
A.2.2	Novelty of pipeline
A.2.3	Vaccines in pipeline

As resistance to current antimicrobials grows, the need for new and novel treatment options will become increasingly acute. New antibiotics that target resistant pathogens are particularly sought after, as are new vaccines. By preventing disease, vaccines remove the need for treatment, which in turn helps to preserve its effectiveness. New diagnostics are also needed, to ensure antibiotics are only used when they will actually work. New and existing products must be tied together in One Health approaches: strategies that encapsulate all aspects of protection, treatment, infection control and relapse prevention.

Existing antimicrobials and vaccines can also be improved through adaptations, for example, to qualify for additional indications or new fixed-drug combinations (FDCs). Such R&D can be useful in helping patients adhere to treatment guidelines and reduce any unnecessary exposure, e.g., by lowering the dosage or lessening the time-length of a treatment.<sup>3,4</sup> As adaptive R&D builds upon previous efforts, the therapies it yields may be ready for clinical trials more quickly and, if approved, be integrated more rapidly into healthcare.

To encourage and shape the direction of antimicrobial R&D, it is important to know what is already being developed. The Benchmark maps the pipelines of these companies against the priority pathogen lists published by WHO and the CDC, as well as HIV and *P. falciparum* (malaria) since these are AMR priority areas identified by WHO.<sup>1,5</sup>

In its pipeline analysis, the Benchmark evaluates 20 companies on the size and character of their pipelines. These include all eight large research-based pharmaceutical companies and 12 biopharmaceutical companies in scope. A key selection criterion for biopharmaceutical companies was that they are already developing at least one

R&D project that targets priority bacteria, as identified in a 2017 WHO report.<sup>1</sup> The Benchmark examines: the size of each company's R&D pipeline targeting priority pathogens; how many of its candidates are novel; and whether the company is engaged in vaccine R&D. The Benchmark does not assess the R&D activities of the 10 generic medicine manufacturers in its scope. Despite nine having R&D units, only four are observed to be active in the area of AMR.\*

### ALMOST TWO THIRDS OF R&D PROJECTS TARGET PRIORITY PATHOGENS

Of the 30 companies in scope\* the Benchmark has identified 24 companies carrying out a total of 276 R&D projects that target infectious diseases. Overall, there are 97 projects that focus on viral infections and 147 projects that target bacteria. Other classes of pathogens receive less attention, including fungi and helminths. The majority of projects identified (175 out of 276) target pathogens identified as priorities for further R&D by the WHO and/or the CDC (referred to by the Benchmark as priority pathogens): including 54 targeting gram-negative bacteria (GNB), 27 targeting gram-positive bacteria (GPB), 20 targeting both GNB & GPB, 29 targeting *M. tuberculosis*, 28 targeting HIV, 14 targeting *P. falciparum* and three targeting *Candida* spp.

The WHO and CDC prioritisation reports appear to be effective in directing company R&D activity toward specific pathogens. In the past, WHO and significant funders have focussed on HIV/AIDS, malaria and tuberculosis. They have helped to steer pharmaceutical companies to prioritise R&D in these areas and have provided incentives for engagement. Especially in the

preclinical pipeline there is a major focus on gram-negative bacteria including the four bacteria classified as 'critical' by WHO.

### Priority R&D: a breakdown

Of the 175 R&D projects targeting priority pathogens, 88 are in preclinical development and 87 in clinical stage. Almost one third (54 out of 175) targets gram-negative bacteria, a critical target for AMR: over half of these are in the preclinical stages of development.

In antibacterial R&D, gram-negative bacteria are an important target as they pose significant scientific challenges. Where gram-positive bacteria have a single cell membrane (enabling many types of antibiotic to enter the cell), gram-negative bacteria have a more complex cell wall as well as other mechanisms to expel toxic compounds.

Preclinical development involves projects that are in discovery and preclinical phases. Preclinical indicates a phase of research before a medicine is tested in humans, when researchers collect important data about feasibility, testing and drug safety. Projects in clinical development have reached at least Phase I, the first testing in human subjects. In its analysis of clinical stage projects, the Benchmark has also included five products that have been approved by regulatory agencies since 2016. Out of 87 clinical-stage projects targeting priority pathogens, 38 are new medicines, 17 new vaccines and 32 adaptations to existing medicines or vaccines. Looking only at the 38 new medicines, 29 target priority bacteria, with 26 being identified in WHO's 2017 report on 'Antibacterial agents in clinical development'.<sup>6</sup>

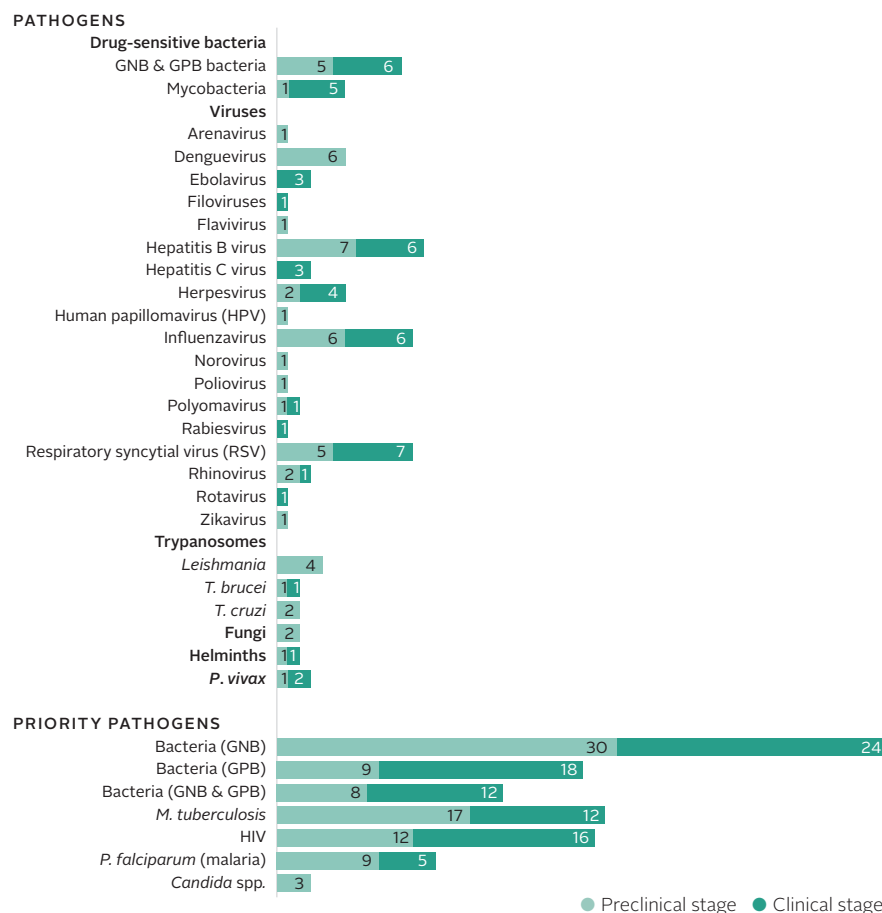
### The largest pipelines

GSK has the largest overall antimicrobial R&D pipeline (55 projects), and within this the largest number of projects targeting priority pathogens (40,

\* This chapter reports on all R&D projects identified by the Benchmark for the 30 companies in scope. Please note, however, that generic medicine manufacturers were not scored in this Research Area to preserve comparability within that group of companies.

**Figure 23. Antimicrobial pipelines contain 276 R&D projects.**

The companies in scope are developing 276 antimicrobial R&D projects. Of these, 136 are in clinical stages of development. Gram-negative bacteria (GNB) receive the most attention. Projects shown in this figure include adaptations.

**Figure 24. Criteria for WHO and CDC prioritisation of pathogens.**

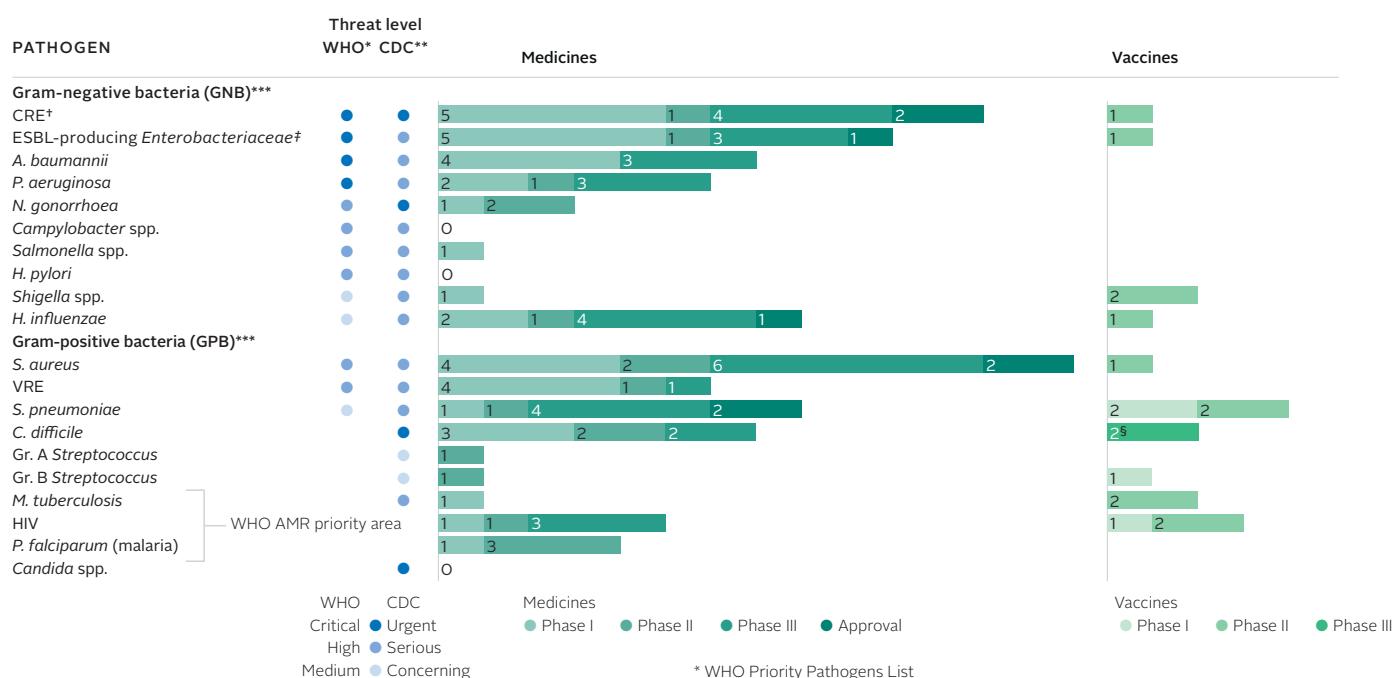
Priority pathogens identified by the Benchmark are drug-resistant pathogens as defined by the WHO R&D Priority List and by the CDC Biggest Threat List - priority lists to guide research and development.

	WHO	CDC
Mortality	●	●
Preventability	●	●
Transmissibility	●	●
Treatability	●	●
10-year projection of resistance	●	
Community burden	●	
Healthcare burden	●	
Existing R&D pipeline	●	
Prevalence of resistance	●	
10-year projection of incidence		●
Economic burden		●
Incidence		●

There are 175 projects targeting priority pathogens, including 87 clinical-stage candidates.

**Figure 25. Breakdown of the clinical pipeline for priority pathogens.**

Companies are focussing antimicrobial R&D efforts on high-priority pathogens<sup>§</sup> as identified by WHO and/or the CDC. Most attention is given to *Enterobacteriaceae* (CRE<sup>†</sup> and ESBL<sup>‡</sup>-producing), *S. aureus* and *S. pneumoniae*. Several pathogens receive little or no attention such as *Candida* spp., *Campylobacter* spp. and *H. pylori*. Projects shown in this figure exclude adaptations. At publication, this figure incorrectly grouped the pathogen VRE (vancomycin-resistant enterococcus) with gram-negative bacteria. This has been updated.



\* WHO Priority Pathogens List

\*\* CDC Biggest Threats list

\*\*\* Projects that target both GNB and GPB are included for each relevant pathogen

† CRE: carbapenem-resistant *Enterobacteriaceae*

‡ ESBL: Extended Spectrum  $\beta$ -Lactamase

§ One of these projects has been terminated after the period of analysis

constituting 70% of all its projects).<sup>\*</sup> Johnson & Johnson and Sanofi have the second and third largest antimicrobial pipelines, albeit with smaller proportions of projects that target priority pathogens. Of Johnson & Johnson's 48 projects, 15 target these pathogens.<sup>\*\*</sup> Of Sanofi's 32 projects, 18 target them.<sup>\*\*\*</sup> While Pfizer's antimicrobial pipeline is smaller than these companies, it focusses mainly on priority pathogens. It has seven projects in development in infectious diseases, six of these target priority pathogens, four of which are vaccine candidates.

The 12 biopharmaceutical companies in scope have smaller pipelines, but almost all of their antimicrobial R&D projects (40 out of 41) target priority pathogens. Among them, Entasis, Nabriva and Wockhardt have the largest pipelines targeting priority pathogens. Wockhardt has the most R&D projects in clinical-stage development (four new clinical-stage R&D projects and one adaptation).

#### Five companies active in vaccine R&D

The companies with the largest pipelines are also developing vaccines. Five companies are developing vaccines overall: GSK, Johnson & Johnson, Merck & Co. Inc., Pfizer and Sanofi are developing new vaccines (30 in total), for example, for the development for HIV and *S. pneumoniae*. The use of vaccines to prevent infectious diseases is valuable because it limits subsequent inappropriate use of antimicrobial medicines; which, in turn, can limit the emergence of resistance.

#### GENERIC MEDICINE MANUFACTURERS ACTIVE IN ADAPTIVE R&D

The R&D project pipeline that the Benchmark assesses includes 45 adapted medicines and vaccines. Adapting medicines and using them for a new purpose can help to curb antimicrobial resistance. For example, reducing the dosage or treatment duration can be useful to decrease exposure to unnecessarily high amounts

of antimicrobials, while also ensuring that the pathogen will be eliminated.<sup>7</sup> Eighteen companies in scope are adapting existing antimicrobials through R&D, including four generic medicine manufacturers.

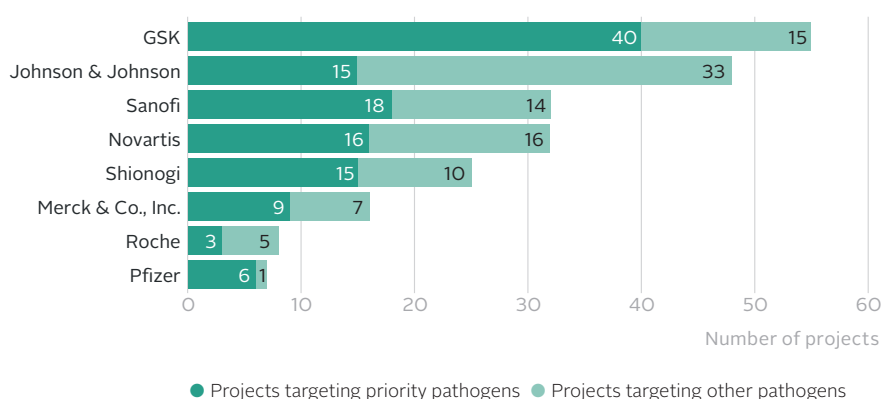
Johnson & Johnson is the large research-based pharmaceutical company with the most adaptations in its pipeline (six), including a paediatric formulation for bedaquiline and long-acting parenteral formulations for rilpivirine (for stand-alone use and in combination with cabotegravir, being developed in partnership with GSK). The long-acting formulation maintains viral suppression over a long period, and avoids the risk of patients not adhering to a

treatment regimen, which can occur more easily with oral regimens. GSK, Merck & Co., Inc., Pfizer and Sanofi are examples of other large research-based pharmaceutical companies involved in adapting existing agents. Notably, GSK is developing its meningococcal B vaccine (Baxsero®) for the prevention of gonorrhoea.

Four generic medicine manufacturers in scope are active in adaptive R&D for antimicrobials, accounting for 18 projects. For example, Cipla is developing a taste-masked four-in-one tablet formulation (abacavir/lamivudine/lopinavir/ritonavir) for the treatment of HIV/AIDS in children. Aurobindo, Macleods and Mylan are

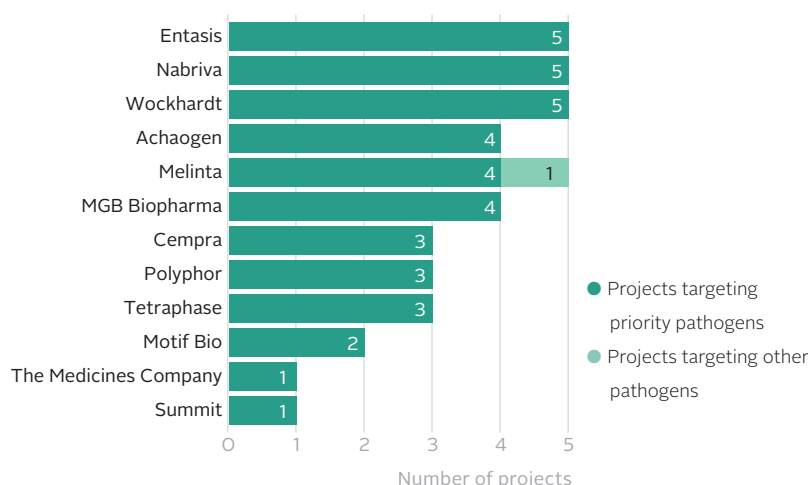
**Figure 26. GSK is developing the most projects that target priority pathogens.**

GSK directs approximately 70% of its antimicrobial R&D projects towards priority pathogens. The eight large research-based pharmaceutical companies that were analysed for this pipeline are developing 122 products targeting priority pathogens in total.



**Figure 27. Projects targeting priority pathogens by biopharmaceutical companies.**

The antimicrobial R&D pipelines of biopharmaceutical companies are smaller compared to large research-based pharmaceutical companies, but their R&D efforts are focussed almost exclusively on priority pathogens.



<sup>\*</sup> One project (GSK3342830) was terminated after the period of analysis

<sup>\*\*</sup> One project (Rilpivirine long-acting nanosuspension) was terminated after the period of analysis

<sup>\*\*\*</sup> One project (*C. difficile* vaccine) was terminated after the period of analysis

adapting antimicrobials that target HIV through new fixed drug combinations. Macleods is also investigating the effectiveness and tolerability of lower dosages or new formulations of anti-tuberculosis products for the use in children. The company is, for example, examining the effectiveness of a 150 mg dispersible tablet of linezolid, compared to the current recommended dose of 400 mg to 600 mg (as per the WHO Model List of Essential Medicines). Access to novel treatments will take time to establish. In the meantime, patients suffering from tuberculosis have much to gain from incremental R&D to regimens, e.g., reduction of treatment side effects.<sup>8,9</sup> This type of adaptive R&D is therefore encouraged. As generic medicine manufacturers, Aurobindo, Cipla, Macleods and Mylan are not scored in this Research Area.

#### Multidrug-resistant

##### ***Enterobacteriaceae* and *S. aureus* receive most attention**

There are 87 projects in clinical development targeting priority pathogens: the largest proportion antibiotics targeting *Enterobacteriaceae* (including carbapenem-resistant *Enterobacteriaceae* (CRE) and extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Enterobacteriaceae*) and *S. aureus*. Others focus on *S. pneumoniae*, *H. influenzae* type b (Hib) and *Acinetobacter* spp. While these pathogens are indeed priorities for R&D, there is also a great need for new antibiotics with a broad-spectrum activity against pathogens identified as 'Critical' by the WHO.<sup>1</sup>

Thirteen companies are involved in 17 clinical-stage candidates that target 'Critical' pathogens, mainly gram-negative bacteria, identified by WHO.<sup>1</sup> These include projects (16 antibiotic candidates and one vaccine) targeting *Enterobacteriaceae* (CRE and ESBL-producing), and multidrug-resistant *Acinetobacter* spp., including *A. baumannii*. The second most common target are gram-positive bacteria (*S. aureus*, *S. pneumoniae* and *C. difficile*) followed by HIV. Other priority gram-negative bacteria receive very

little R&D attention from the companies in scope: that includes *Campylobacter* spp., *Salmonella* spp., *Shigella* spp. and *H. pylori*. While Novartis has one medicine in clinical development (LYS228) that may be efficacious against *Salmonella* spp. and *Shigellae* spp., it is not developing the candidate for indications caused by these pathogens. Instead, this candidate is being developed for the treatment of complicated intra-abdominal infections and complicated urinary tract infections caused by drug-resistant gram-negative bacteria.

GSK has two clinical-stage vaccines for *Shigella sonnei* and *Shigella flexneri*, in addition to its preclinical development of two vaccines that cover non-typhoidal *Salmonella* and *S. enterica* ser. Typhimurium. Overall, however, companies in scope are giving no attention at clinical stage to some gram-negative bacteria, such as *H. pylori* and drug-resistant *Campylobacter* spp.

Merck & Co., Inc., MGB Biopharma and Shionogi are the only companies evaluated by the Benchmark to be investing in antifungal drug candidates that target fluconazole-resistant *Candida*; all in preclinical stage.

There are twice as many new drug candidates in clinical development (38) as there are new vaccine candidates (17). The likelihood of regulatory approval for vaccines is higher than for medicines: 16% of the vaccines in Phase I clinical development will receive approval initially, as compared with just 6% for a Phase I medicine.<sup>10</sup>

##### **How novel are new antimicrobials in the pipeline?**

Of the 38 medicines in clinical development, the Benchmark identifies 17 that can be considered novel. To qualify as novel, a candidate must fulfil one or more of the criteria defined by WHO<sup>6</sup>: it represents a new chemical class; aims at a new target; has a new mode of action; and/or has an absence of cross-resistance from existing antimicrobials. This includes nine novel antibiotics that target priority bacteria, including *M. tuberculosis* (also identified in the WHO report)<sup>6</sup>. These nine antibiotic candidates are being developed by eight



Inspecting bacterial growth at Novartis Institute for Biomedical Research.

companies: Entasis, GSK, Nabriva, MGB Biopharma, Polyphor, Roche, Summit and The Medicines Company (see figure 28).

Four of these companies have a product in development that meets all four of the WHO's criteria: Polyphor has murepavidin, a new antibiotic candidate that targets the cell membrane of drug-resistant *P. aeruginosa*; MGB Biopharma and Summit are developing compounds that target *C. difficile* (MGB Biopharma with MGB-BP-3, a DNA minor groove binder; and Summit with ridinilazole, a bisbenzimidazole)<sup>6</sup>; and Roche is developing a biological agent against *S. aureus* consisting of a monoclonal antibody that binds to the surface of the bacterium and releases rifamycin to kill it.

Of the remaining four companies, The Medicines Company has developed the  $\beta$ -lactamase inhibitor meropenem/vaborbactam (Vabomere<sup>TM</sup>); Nabriva is developing lefamulin, which belongs to a drug class that has been used in animals and in a topical formulation for humans, and for which levels of cross-resistance are yet unknown; GSK is developing gepotidacin; and Entasis is developing zoliflodacin. Gepotidacin and zoliflodacin both have novel chemical structures targeting existing functional targets, and to which cross-resistance has not emerged.

GSK is the only company developing novel medicines that treat tuberculosis and HIV/AIDS. Its clinical pipeline includes a novel anti-tuberculosis drug candidate and four novel agents that target HIV.

Novartis, Sanofi and Johnson & Johnson are developing novel anti-malaria medicines to target the

### Figure 28. What makes an antibiotic novel?

There are nine novel drug candidates in companies' clinical pipelines, five fulfilling all four criteria defined by the WHO.<sup>6</sup> A majority (six) of these are developed by biopharmaceutical companies.

Company	Antibiotic	Clinical phase	Pathogen	New drug class	New target	New MoA*	Absence of CR**
MGB Biopharma	MGB-BP-3	Phase I	<i>C. difficile</i>	●	●	●	●
Polyphor	Murepavadin (POL7080 iv)	Phase II	<i>P. aeruginosa</i>	●	●	●	●
Roche	Anti- <i>S. aureus</i> TAC (RG7861)***	Phase I	<i>S. aureus</i>	●	●	●	●
Summit	Ridinilazole	Phase II	<i>C. difficile</i>	●	●	●	●
GSK	GSK3036656	Phase I	<i>M. tuberculosis</i>	●	●	●	●
Entasis	Zoliflodacin (ETX0914) §	Phase II	<i>N. gonorrhoeae</i>	●		●	●
GSK	Gepotidacin §	Phase III	<i>N. gonorrhoeae</i>	●		●	●
Nabriva	Lefamulin §	Phase III	<i>S. aureus</i> , <i>H. influenzae</i>	●†		●	‡
The Medicines Company	Meropenem/vaborbactam (Vabomere™)	Approved	CRE	●			‡

\* Mode of action  
 \*\* Cross-resistance  
 \*\*\* New Biological Entity  
 § Broad-spectrum antibiotic candidate by nature

† First systemic formulation of this class for human use (currently used topically in humans and systemically in animals)  
 ‡ Data is inconclusive or agreement with the WHO advisory group was lacking.

drug-resistant *P. falciparum*. Working with Medicines for Malaria Venture (MMV), Novartis is developing two novel medicines, while Sanofi and Johnson & Johnson have one each.

While not considered novel according to WHO criteria, a further 21 antibiotic candidates at the clinical stage involve new agents within an existing chemical drug class, such as the  $\beta$ -lactam antibiotic class. These classes have been in use for some time (in most cases for decades) and resistance has emerged. As a result, the bacteria they target are more likely to have cross-resistance to new generations, and may adapt faster.

### TEN REPORTED BROAD-SPECTRUM ANTIBIOTICS IN THE PIPELINE

Of the 29 new antibiotic candidates in clinical development, ten are known to the Benchmark to be broad-spectrum, meaning that they act against both gram-positive and gram-negative bacteria. Seven companies are currently developing these broad-spectrum antibiotics with a focus on a single indication, albeit where public need for treatment is high. These companies could opt to develop these medicines for a wide selection of indications. Entasis, for example, decided to develop its broad-spectrum candidate zoliflodacin solely to treat gonorrhoea.

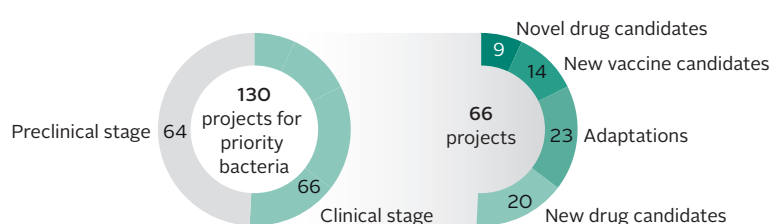
Other companies, such as Cempra and Melinta (merged in November 2017), are doing the opposite. They are broadening the reach of their antibiotic candidates to enlarge the number of patients these can treat, and are including multiple different indications – such

as complicated urinary tract infections (cUTI), community-acquired bacterial pneumonia (CABP) and hospital-acquired bacterial pneumonia (HABP), and acute bacterial skin and skin structure infections (ABSSSI) – caused by a wide set of pathogens.

Among broad- and narrow-spectrum antibiotics the range of bacteria against which they are active varies from very broad spectrum to very narrow spectrum and everything in the middle. Narrow-spectrum antibiotics are active against a selected group of bacterial types, for example gram-positive bacteria, or more specifically one species of gram-positive bacteria. These antibiotics have the benefit that they do not affect most other bacteria present in the body, which can prevent the emergence of resistance in other bacteria. For curbing AMR, they are best used in tandem with diagnostics tools that can quickly identify that the indicated bacteria are indeed causing the infection. Such point-of-care diagnostics are still lacking, which means it can take more than 16 hours to identify bacteria and their susceptibility profile to the antibiotic in question.<sup>11</sup> Broad-spectrum antibiotics are often empirically used to bridge the time period between diagnostic testing and the arrival of susceptibility results. However, this means exposing all bacteria in the body, increasing the chance of resistance

### Figure 29. Few novel clinical-stage projects targeting priority bacteria.

There are 130 projects targeting bacteria prioritised by WHO and/or CDC as AMR risks. Looking at the projects in clinical development, only nine are considered novel, e.g., they have a new mode of action or new target, meaning they have a lower risk that bacteria already show resistance.



emerging. Knowing this, researchers may choose to develop broad-spectrum antibiotics for use against only one indication with the intention of limiting its usage and decreasing the likelihood of resistance emerging.

The market for narrow-spectrum antibiotics is financially less attractive compared to broad-spectrum, as the target population is smaller. All antibody-based biologicals are narrow-spectrum: each targets a specific pathogen species. Biologicals are in turn also more costly to manufacture compared to synthetic

medicines.<sup>12</sup> Access may be restricted when biologicals reach the market due to affordability issues and the capacity to use and monitor treatments appropriately. One hurdle for the development of narrow-spectrum antibiotics is the challenge associated with traditional regulatory evaluation.<sup>13,14</sup> Clinical trials are designed to demonstrate non-inferiority, meaning a candidate medicine is at least as safe and effective as the current standard treatment.

However, demonstrating this non-inferiority for narrow-spectrum antibiotics can be more difficult, due to the

pathogenic heterogeneity of infections and therefore the need for costly – and often non-existent – diagnostics.<sup>14</sup> These complexities lead to the requirement of more patients, which in turn increases the time and cost of clinical trials. For example, a post hoc analysis of the effectivity of linezolid over vancomycin in HABP/VABP took five years to complete.<sup>15</sup> Polyphor is an example of a company developing a single-pathogen antibiotic (murepavadin); it started a timely process with EMA and FDA to develop a customised clinical trial design for murepavadin.

## PARTNERSHIPS

### Around half of R&D projects are being conducted in partnership

#### INDICATOR

A.3 R&D Collaborations

When pharmaceutical companies collaborate in R&D, they can reduce duplication, share risk, pool expertise, and stimulate innovation that leads to successful development. This can be achieved through various forms of partnership. Public-private partnerships can take various forms including: product development partnerships (PDPs) or partnerships with governments, NGOs or public institutes such as universities.

Public-private collaboration encourages open and collaborative sharing of intellectual property (IP), facilitates the rapid deployment of resources, and promotes the development of products.<sup>16</sup> Consequently, public-private partnerships are useful for targeting diseases that have a disproportionate effect on people living in low- and middle-income countries, for whom there is less commercial incentive to develop solutions.

For the last two decades, PDPs have proven particularly effective in this regard. PDPs take the form of centralised non-profit organisations that enable the public, private, academic, and philanthropic sectors to aggregate funding for (and pool the risk of) developing medicines, vaccines and other health tools. An example of such a partnership is the Medicines for Malaria

Venture (MMV), which has multiple partnerships with several companies. Much PDP funding comes from major global health donor organisations like the Bill & Melinda Gates Foundation and the Wellcome Trust.<sup>14</sup>

As an alternative to the PDP model, governments, private foundations and NGOs can also directly invest in companies' drug development. Such push incentives are used by governments and NGOs to stimulate need-based R&D. Examples of such partners include the Bill & Melinda Gates Foundation, Biomedical Advanced Research and Development Authority (BARDA), the European Commission (through the Innovative Medicines Initiative (IMI)) and the Wellcome Trust.

The Benchmark looks at the levels at which pharmaceutical companies engage in public-private R&D collaborations to discover and develop new medicines and vaccines that target priority pathogens. It looks for partnerships in three categories: (1) PDPs or open collaborations; (2) direct partnerships with governments and/or NGOs; (3) direct partnerships with public institutes such as universities. The Benchmark also presents an overview of the partners that the companies assessed in this research

area are working with in antimicrobial drug development.

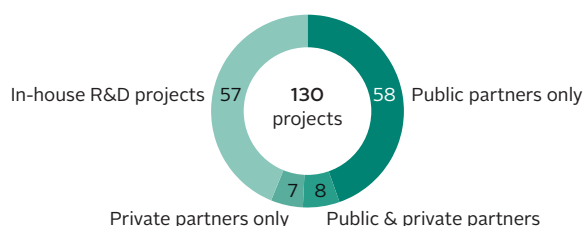
#### Over half of R&D projects targeting priority pathogens are conducted through partnerships

More than 50% of the 130 new R&D projects (excluding adaptations) are now being conducted in partnership. In 58 partnership-based projects, companies are working with public- or non-profit-sector partners only. In eight projects, companies' partners include both public- or non-profit and private-sector entities. In the remaining seven projects, companies are working with other private-sector partners only. (see figure 30).

In comparison, the 2016 Access to Medicine Index analysed the R&D projects being carried out by 20 of the world's largest research-based companies targeting a defined set of 51 high-burden diseases (including communicable and non-communicable diseases, neglected tropical diseases and maternal and neonatal health conditions): it found that a lower proportion, one third, of the 420 R&D projects identified were being carried out in partnership.

**Figure 30. Half of new R&D projects involve partnerships with public or non-profit partners.**

66 out of 130 R&D projects involving new medicines or vaccines targeting priority pathogens are carried out in partnerships with public or non-profit partners. These involve 27 PDPs or open collaborations, of which only two focus on new antibiotics for GNB and/or GPB – these are managed by GARDP and IMI. The remaining PDP projects are focussed on HIV/AIDS, malaria and tuberculosis.



The Benchmark finds that PDPs and open collaborations comprise a third of the overall number of project partnerships. These include 14 in preclinical-stage and 13 in clinical-stage development, as well as others that aim to develop novel fixed drug combinations (FDCs) using investigational agents

from different organisations. One example is the collaboration between Sanofi and MMV to formulate a new artefenomel/ferroquine antimalarial treatment for children. The majority of PDP projects focus on HIV/AIDS, malaria and tuberculosis and have been running since around 2000 when these diseases

began to be prioritised internationally.

A large proportion of the projects in the priority pathogen pipeline (excluding adaptations) that are for the treatment of HIV/AIDS, malaria and tuberculosis (19 out of 45) are in development with a PDP. Two out of 82 R&D projects that target priority GNB and/or GPB are collaborative efforts involving a PDP or open collaboration. The Innovative Medicines Initiative's New Drugs 4 Bad Bugs (ND4BB, launched in 2013) is a large multi-stakeholder research consortium focussed on the scientific, regulatory, and business challenges of AMR, and covers two R&D projects involving GSK, Pfizer and Sanofi.<sup>17</sup> The only PDP focussing on antibiotics against GNB and/or GPB is the Global Antibiotic Research and Development Partnership (GARDP), launched in 2016 as a joint initiative between WHO and the Drugs for Neglected Diseases Initiative (DNDi). PDPs in the field of antibiotic resistance are thus still in their infancy.

**Figure 31. Half of the partnering bodies are focussed on antibacterial R&D.**

This figure provides an overview of public partners (PDPs and funders) active in the space of AMR. Six organisations (Wellcome Trust, MMV, Bill & Melinda Gates Foundation, US NIH, BARDA and TB Alliance) are involved in most of the projects that target priority pathogens carried out in public-private partnerships.\*

Partner	Number of projects	Bacteria (GNB & GPB)	M. tuberculosis	HIV	P. falciparum (malaria)	Candida spp.	Companies involved**
Wellcome Trust	11	●	●		●		GSK, Merck & Co., Inc., Novartis, Polyphor, Summit, Tetrphase
MMV	10				●		Cipla, GSK, Johnson & Johnson, Novartis, Sanofi
Bill & Melinda Gates Foundation	8	●	●	●	●		Achaogen, GSK, Johnson & Johnson, Sanofi, Pfizer
US National Institutes of Health (NIH)	8	●		●			Achaogen, Entasis, GSK, Johnson & Johnson, Sanofi, Tetrphase
BARDA	7	●					Achaogen, Cempira, GSK, Pfizer, Roche, Tetrphase, The Medicines Company
TB Alliance	7		●				Macleods, Sanofi, Shionogi
US Ministry of Defence	5	●		●			GSK, Johnson & Johnson, Sanofi
Innovative Medicines Initiative (IMI)	3	●					GSK, Pfizer, Sanofi, Polyphor***
CARB-X	3	●					Achaogen, Entasis, Tetrphase
Aeras	2		●				GSK, Sanofi
PATH	2			●	●		GSK, Johnson & Johnson
HIV Vaccine Trials Network	2			●			Johnson & Johnson
GARDP	1	●					Entasis
DNDi	1			●			Cipla
IAVI	1			●			Johnson & Johnson
Pox-Protein Public & Private Partnership (P5)	1			●			GSK, Sanofi
Swiss Innovation Agency	1	●					Polyphor
European Vaccines Initiative	1				●		GSK

\* The public-private partnerships shown in this figure exclude partnerships with public research institutes.

\*\* The list of companies involved is not exhaustive as some details were provided on the basis of confidentiality.

\*\*\*After the Benchmark's period of analysis, Polyphor entered into collaboration with IMI.

Two PDPs focus on tuberculosis: TB Alliance for the development of new medicines and Aeras for the development of new vaccines.

The Benchmark finds that in addition to PDPs and open collaborations, 27 (20%) other R&D pipeline projects (excluding adaptations) assessed in this research area are funded by public organisations, including governments and NGOs. The most prominent funders, directly or indirectly (e.g., through initiatives such as the Combating Antibiotic Resistance Bacteria Biopharmaceutical Accelerator, or 'CARB-X'), are the US Biomedical Advanced Research and Development Authority (BARDA), the US National Institutes of Health and the Wellcome Trust.

### Public partners advocate global access

There are 18 public partners (see figure 31) involved in drug development focussed at priority pathogens with companies analysed. Eight of these require companies to make commitments regarding access provisions (plans and strategies for ensuring access to the approved product). The Benchmark finds that public partners can influence these provisions in two ways.

One way is to insert a clause into the funding agreement that requires a company to ensure access to the product in countries where need is high. If, following market approval, the company cannot prove within a specified amount of time that it is providing this access, the public or non-profit partner reserves the right to share its intellectual property (IP) with other partners who can provide access in specified countries. The Wellcome Trust is one such partner to use this measure.

Another way that public organisations ensure companies provide access through a PDP is to divide the IP rights for a product in development among countries where need is high. An example of this is seen in the agreement between GARDP and Entasis, to develop a potential new treatment, zoliflodacin, for drug-resistant gonorrhoea.



Research on HIV taking place in GSK's HIV Centre.

This gives GARDP the right to manufacture the drug worldwide and to sell or distribute it in 168 countries and territories outside the developed world.

As companies and partnerships develop antimicrobials, they need to link provisions for access with safeguards for stewardship. CARB-X is one public partner that requests stewardship plans from all biopharmaceutical companies in its portfolio. As yet, discussions are ongoing concerning how these plans should be designed.

### Innovative models: open-source drug discovery

In partnership with the MMV, GSK and Novartis have developed an innovative open-source drug discovery programme. This is accelerating progress in discovery by publishing raw data and results in the public domain, and encouraging scientists to make incremental contributions. Such a model helps keep down costs, and removes the ability to patent results, allowing others to build upon these discoveries.

In antimicrobial resistance, MMV applied the open-source drug discovery model in an initiative called the Malaria Box which was launched in 2011. Each Malaria Box assembled 400 diverse molecules active against *P. falciparum*, derived from an extensive screening of libraries held by GSK, Novartis, and the US-based St Jude Children's Research Hospital. Using an open data-sharing platform, MMV despatched more than 160 of these boxes, free of charge, to researchers in 27 countries, to help catalyse drug discovery and research. In December 2015, MMV launched a similar initiative: The Pathogen Box, filled with 400 diverse, drug-like molecules

active against a broader range of pathogens including *M. tuberculosis*.

### Which company does the most R&D in partnership?

Sanofi is comparatively more engaged in R&D partnerships: it is developing half of the 16 projects in its pipeline in scope through collaborative PDPs. GSK, Johnson & Johnson and Novartis are also active, with GSK engaging in nine PDPs out of 35 R&D projects eligible for this indicator (new candidates targeting priority pathogens).

Cipla and Macleods are the only two generic medicine manufacturers involved in collaborative public-private R&D. In collaboration with the Drugs for Neglected Diseases Initiative (DNDi), Cipla is developing an innovative new treatment for infants and children living with HIV/AIDS, to be delivered through taste-masked granules combining four antiretroviral ingredients (lopinavir, ritonavir, abacavir and lamivudine). Macleods collaborates with TB Alliance and UNITAID on the development of paediatric formulations of tuberculosis medicines.

Most of the biopharmaceutical companies (9 out of 12) in scope have no products on the market yet. As such, they do not gain revenue from sales and are fully dependent on external funding, such as private venture capital and research grants, to cover their R&D expenditures. Half of biopharmaceutical companies assessed in this research area receive public or NGO funds. Entasis is the only one involved in a PDP (with GARDP, established in 2016). The R&D projects in these pipelines are funded by BARDA, CARB-X, the Wellcome Trust and the National Institute of Allergy and Infectious Diseases (NIAID) among others. The remaining companies finance their R&D activities through private financing rounds or a stock exchange listing. Even so, it is encouraging that some private investors remain willing to invest in antibiotic development.

**PDPS IN ACTION: EXAMPLES OF LATE-STAGE CANDIDATES DEVELOPED THROUGH PARTNERSHIP****Case study 1****Toward a new combination treatment for malaria**

Partners: Sanofi &amp; Medicines for Malaria Venture (MMV)

Candidate: artefenomel/ferroquine

Start date: 2011

Ferroquine is a compound originated from and patented by University Lille 1. Sanofi, which has developed it for ten years, began to collaborate with MMV in 2011 to develop a combination of ferroquine and MMV's investigational compound artefenomel (OZ439). Five years previously, WHO guidelines recommended new treatments should combine two medicines with different mechanisms of action. Ferroquine is a novel ferrocene 4-aminoquinoline, while artefenomel exerts antimalarial activity via its peroxide bond (owing to its differing structure, it is likely to remain effective against artemisinin-resistant strains). Sanofi and MMV are developing this combination as a single-dose formulation, which may be preferable to the current 3-day ACT regimens. For the partnership, the main scientific challenges involve ensuring firstly that the formulation contains a sufficient amount of medicine and secondly that it can be absorbed optimally. MMV is contributing its extensive malaria research expertise, while Sanofi is sponsoring clinical trials, regulatory leadership, scientific engagement and manufacturing.

**Case study 2****Potential new treatment for drug-resistant gonorrhoea**

Partners: Entasis and GARDP

Candidate: zoliflodacin

Start date: 2017

GARDP aims to develop treatments for bacterial infections where drug resistance is present or emerging. Its first announced project, with Entasis, is to develop zoliflodacin to treat gonorrhoea. The partnership agreement makes GARDP responsible for pharmaceutical activities and clinical trials: this will include financing, managing, and coordinating Phase III trials to demonstrate the safety and efficacy of zoliflodacin in patients infected with gonorrhoea, comprising clinical safety, pharmacovigilance, and drug registration in countries where it has licensing rights. Entasis Therapeutics holds the patent for the active pharmaceutical ingredient (API) for zoliflodacin, and is working with GARDP on a clinical trial development strategy to ensure successful registration. It is responsible for sharing information to develop the drug candidate into Phase III, and for registering the drug candidate in its countries and territories; also for post-marketing pharmacovigilance in these, and maintaining a worldwide patient-safety database. Entasis has developed clinical plans and will work with GARDP to help implement these, and advise on execution.

As there is a geographical limitation to the license, Entasis has given GARDP an exclusive and royalty-free license for the medicine's use in the treatment of gonorrhoea. This licence includes sub-licensing rights for manufacturing worldwide and for the sale and/or distribution in 168 countries or territories outside the developed world.

In relation to any new IP rights generated during the development process, Entasis and GARDP agree to grant certain royalty-free exclusive licensing rights to each other, and the right to sub-license to enable registration and manufacturing.

## ACCESS &amp; STEWARDSHIP

## INDICATOR

## A.4 Facilitating access and stewardship

## Priority pathogens: few companies are planning ahead for access and/or stewardship of new antibiotics

Antimicrobial resistance is doubtlessly on the rise. Unchecked, it threatens many aspects of modern medicine. Nevertheless, more people die today through lack of access to existing antimicrobials than die due to drug-resistant infections. It is vital that new medicines are introduced in a way that (a) ensures its rapid and appropriate accessibility for patients in need while (b) conserving its use more broadly to slow the inevitable emergence of resistance. Pharmaceutical companies are encouraged to plan ahead, during the development process, to achieve these twin aims.

There are various mechanisms, such as licensing and affordability commitments, that can enhance access to newer medicines and vaccines in low- and middle-income countries where access to medicine is likely limited. For antimicrobial medicines, such mechanisms must be rolled out in tandem with complementary plans to ensure new products are used appropriately, only when needed.

Examples of access provisions include filing for registration, creating equitable pricing strategies (that take

some account of populations' varying ability to pay), gaining WHO prequalification and following a regulatory procedure known as Article 58 (European Medicines Agency; see inset), which helps companies to increase access to medicines and vaccines in low- and middle-income countries and improve public health. By developing access provisions during R&D, companies can substantially accelerate the speed at which they make new products available at an affordable price, and in sufficient volume.

For antimicrobial medicines, stewardship measures can include surveillance of antimicrobial resistance (AMR), activities to educate people and health-care professionals about AMR, and the introduction of more appropriate marketing practices (e.g., developing performance incentives for sales staff that are not linked to sales volumes).

The Benchmark looks at how companies plan to apply relevant stewardship strategies globally. As with access provisions, companies can develop plans for stewardship during product development.

The Benchmark assesses the access and stewardship provisions put in place during development by the 20 companies evaluated in this Research Area – looking only at projects targeting pathogens prioritised by WHO and/or CDC for R&D due to the threat of AMR. In scope are all eight large research-based pharmaceutical and 12 biopharmaceutical companies. It is expected that all large research-based pharmaceutical companies can use their often considerable logistical experience and capacity to facilitate access and stewardship for new products.

This analysis applies to (a) access provisions relating to new and adaptive antimicrobial candidates (medicines and vaccines) in late-stage development (clinical Phase II onwards) that target priority pathogens and are applied in any of the 106 low- and middle-income countries (countries where access to medicine is likely limited; see Appendix IV); and (b) stewardship provisions for the same medicines, excluding vaccines, with a global scope.

### What is WHO prequalification?

WHO prequalification entails the evaluation of quality, safety and efficacy of pharmaceutical products, based on information submitted by the manufacturers, and the inspection of the corresponding manufacturing and clinical sites. It is an important mechanism as many LMICs have weak or non-existent national regulatory authorities. The information is used by the UN and other procurement agencies to help make purchasing decisions. For example, UNICEF only procures prequalified vaccines to ensure acceptability, quality, safety and efficacy in target populations.

### What is EMA's article 58?

Article 58 was introduced by the European Medicines Agency (EMA) in 2004 to help increase access to medicines and vaccines in LMICs, while simultaneously strengthening the drug assessment capabilities of national regulatory agencies of these countries. It involves a pathway that combines EMA's scientific, clinical, and manufacturing review expertise with the local epidemiology and disease expertise of the WHO and LMIC national regulators to provide a scientific opinion for the corresponding LMICs. Seeking article 58 is useful for accelerating the introduction of a new medicinal product in low- and middle-income countries.

## TWO LATE-STAGE ANTIBIOTICS HAVE BOTH ACCESS AND STEWARDSHIP PROVISIONS IN PLACE

The Benchmark finds that of the 56 late-stage antimicrobial candidates that target priority pathogens, 14 are covered by an access provision. Out of the 40 medicines in late-stage development targeting priority pathogens, ten are covered by a stewardship provision. Only seven are covered by both access and stewardship strategies. Two are antibiotic candidates, and the other five are antivirals targeting HIV being developed by GSK, either alone (three) or in partnership with Johnson & Johnson (two).

Of the 28 antibiotics in late-stage development for priority pathogens, only two (eravacycline, Phase III; paediatric bedaquiline, Phase II) meet the standard of having provisions in place to ensure both rapid access where needed and stewardship of the successful candidate. Eravacycline, being developed by Tetrphase, targets a group of priority pathogens that cause complicated intra-abdominal and urinary tract infections caused by a range of pathogens. Bedaquiline (Sirturo®), conditionally approved for the treatment of multidrug-resistant tuberculosis (MDR-TB) in adults, is now being developed by Johnson & Johnson for the treatment of MDR-TB in children.

Two other antibiotics, being developed by GSK for gonorrhoea and Pfizer for multidrug-resistant gram-negative bacterial infections have stewardship provisions but no access plan, while three other antibiotics in the clinical pipeline have an access plan in place but no stewardship provisions, being developed by GSK, Entasis and Melinta.

### Few provisions for access and stewardship in place for late-stage antibiotic candidates

All but one large research-based pharmaceutical companies in scope (all except Roche) have clinical candidates targeting priority pathogens and thus relevant to this analysis. In total, they are developing 39\* such products in

clinical Phases II and III, or approved after 2016: 23 medicines and 16 vaccines. GSK accounts for the majority of late-stage candidates (15), and is followed by Johnson & Johnson (eight), Sanofi (six), Merck & Co., Inc. (five), Novartis (four), Pfizer (three) and Shionogi (one). Of these 39 projects, 13 have an access provision (7 drug and 6 vaccine candidates), the majority of which is indicated for HIV/AIDS.

Large research-based pharmaceutical companies report applying access provisions sporadically, including managed access programmes (i.e., managed with an NGO or a government), commercialisation via third parties in low- and middle-income countries, and non-profit business models (see figure 32).

GSK, Johnson & Johnson, Pfizer and Sanofi are the most mature in planning access. GSK has seven late-stage HIV candidates, including a vaccine. For all these, it has a tiered-pricing model and a needs-driven registration policy for countries with greater need of access. For most candidates, GSK commits to licensing, if the candidate is successful, which would allow generic medicine manufacturers to produce the patented medicine. In addition, GSK commits to making its vaccines available in 54 of the world's least-developed countries and reports having (but does not disclose) a tiered pricing strategy for vaccines.

GSK is, amongst other large research-based pharmaceutical companies, an advocate of a market entry reward for antibiotics (a potential pull incentive to stimulate antibiotic R&D), and is willing to participate in a pilot to facilitate this initiative. Questions remain over whether it will register its novel antibiotic (gepotidacin) in low- and middle-income countries.

Johnson & Johnson reports an access provision for its HIV vaccine in late-stage development, and the two FCDs (cabotegravir/rilpivirine; dolutegravir/rilpivirine (Juluca®)) for HIV/AIDS that are being developed with ViiV Healthcare. For the paediatric formulation of bedaquiline, Johnson & Johnson reports that it will use the same access and stewardship activities that are

currently in place for the adult formulation of bedaquiline (Sirturo®). This includes a managed access programme through the Global Drug Facility (GDF) and its own subsidiaries.

Sanofi plans to file for WHO pre-qualification and/or for the EMA article 58 appraisal for three of its vaccines in late-stage development. Pfizer has two vaccines in Phase II and III clinical development, for which it will apply an equitable pricing policy that is based on countries' ability to pay, while covering research and development costs.

Three large research-based pharmaceutical companies, GSK, Johnson & Johnson and Pfizer, have developed stewardship strategies for a total of nine late-stage antimicrobial medicines (six antiretroviral medicines and three antibiotics).

GSK has a stewardship plan in place for six antiretroviral candidates and its antibiotic candidate – gepotidacin. This plan entails educating healthcare professionals and other stakeholders about antimicrobial resistance and antibiotic stewardship, and decoupling sales force incentives from sales volumes. Johnson & Johnson reports to provide medical education for the use of bedaquiline (Sirturo®), and will expand this to paediatric healthcare professionals for the paediatric formulation.

For the avibactam/aztreonam combination, Pfizer plans to continue its AMR surveillance programmes, as well as launch educational initiatives regarding the risks of AMR and how vaccines could play a role in addressing this public health threat.

Overall, but especially for antibiotics, there is a lack of stewardship strategies. Moreover, while large research-based pharmaceutical companies are familiar with the need to provide access strategies for non-antibiotic antimicrobials, especially targeting HIV, they do not appear to be developing such plans for antibiotics.

\*Three projects are being developed in collaboration between multiple companies in scope.

**Figure 32. Almost half of the companies have at least one access and/or stewardship provision in place for a late-stage clinical candidate.**

Common access provisions include voluntary licensing, needs-based registration and equitable pricing. Stewardship provisions are focussed on surveillance programmes for monitoring resistance.

		Large research-based pharmaceutical companies						Biopharmaceutical companies				Total
		GSK	Johnson & Johnson	Novartis	Pfizer	Sanofi	Shionogi	Entasis	Melinta	Summit	Tetraphase	
Access	<b>Availability</b>											
	Voluntary licensing	●						●	●		●	4
	Needs-based registration	●	●		●							3
	EMA Article 58	●				●						2
	Affiliates in low- and middle income countries		●				●					2
	Managed Access programme with NGO and government(s)	●	●									2
	Commitment to NGO, with permission to exploit									●		1
	WHO prequalification					●						1
	<b>Affordability</b>											
	Equitable tiered pricing	●	●	●	●							4
	Non-profit business model	●										1
Stewardship	Resistance surveillance	●	●		●						●	4
	Educating healthcare professionals	●	●		●							3
	Decouple sales force incentives from volume sales	●										1

### GSK has access and stewardship plans in place for HIV candidates

GSK has reported it will market its HIV candidates through ViiV Healthcare (a joint venture between GSK, Pfizer and Shionogi), which has in place its own access-to-medicine policy. This includes several aspects, such as the priorities of needs-driven R&D and registration strategy, and a commitment to voluntary licensing to enable the generic manufacture and supply of medicines in low- and middle-income countries. ViiV Healthcare has a flexible pricing policy that it applies in middle-income countries. In addition, to improve affordability, it takes account of the gross domestic product (GDP) of each country and uses inter-country equitable pricing. It also considers the extent to which the HIV/AIDS epidemic has affected each country.

Regarding stewardship at a global level, ViiV Healthcare is supporting studies of HIV-1 drug resistance surveillance with RESPOND (the

International Cohort Consortium of Infectious Disease). It is also supporting regional and local investigators, including the Botswana Epidemiological ART Treatment (BEAT) Cohort Study.

### Fewer access and stewardship plans from biopharmaceutical companies

Biopharmaceutical companies have fewer candidates with an access provision. Typically, as these companies aim to be acquired by larger pharmaceutical companies or rely on partnerships, they do not establish business processes to commercialise their pharmaceuticals. Often, they seek third parties (such as regional pharmaceutical companies) to commercialise their products in other countries, and this may create a different attitude toward developing access strategies.

The biopharmaceutical companies evaluated have 17 antibiotics in late-stage development, all targeting priority pathogens. Only three, being developed by Entasis, Melinta and Tetraphase,

have an access provision. Entasis has agreed that its development partner, GARDP, will obtain the rights of the product developed within its partnerships in low- and middle-income countries. Melinta's Baxdela™, an antibiotic used to treat acute skin and skin structure conditions, was approved in June 2017. From 2015 onward, the company has been planning to contract partners to commercialise this product in Latin America, Asia-Pacific and various undisclosed countries in the Middle East and Africa.

In countries that do not have well-organised healthcare systems, stewardship can be hard to control. As weaknesses in healthcare systems increase the risk of resistance emerging, pharmaceutical companies can be reluctant to market their newest antimicrobials – especially antibiotics – in low- and middle-income countries. In general, the Benchmark finds that biopharmaceutical companies do not engage in planning stewardship; some state that

they see it as the responsibility of governments and hospitals.

Tetraphase is the exception. It leads in this area, being the only clinical-stage biopharmaceutical company to have both an access and stewardship provision in place for its most advanced candidate, eravacycline, used to treat complicated urinary tract infections (cUTI) caused by a range of pathogens: ESBL-producing *Enterobacteriaceae*, CRE, *A. baumannii*, *S. aureus*, VRE, *C. difficile*. The company actively seeks partners to develop and commercialise eravacycline in regions including Asia-Pacific, Eastern Europe, India, the Middle East and North Africa, and South America.

Its Antimicrobial Voluntary Evaluation Programme, or AVEP, provides strips and disks that enable hospitals to test susceptibilities of pathogens against the antibiotic. As eravacycline is now in clinical Phase III, it is not yet clear how Tetraphase will apply this susceptibility test after it gains market approval. In addition, through a third-party supplier, Tetraphase runs a global surveillance programme to monitor the susceptibility of hospitalised patients with bacterial infections for eravacycline on an annual basis. Substantial investments for both programmes have been made (more than USD 1 million to date).

Some governments or NGOs that fund companies' R&D projects put an access commitment into their funding agreements. The Wellcome Trust, for example, obtains the intellectual property rights to make arrangements for particular countries where specific public health needs are not met within a specific time frame. This has been the case for Summit's ridinilazole, an antibiotic for treating *C. difficile* infections.

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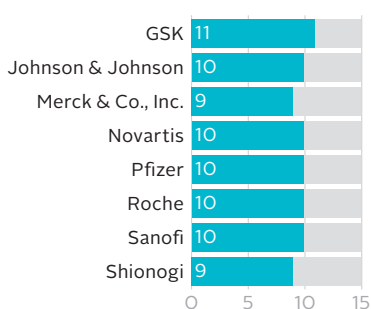
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## RESEARCH AREA: MANUFACTURING &amp; PRODUCTION

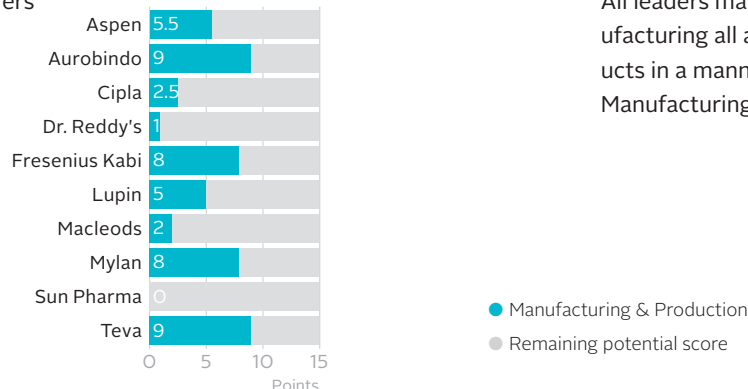
# How pharmaceutical companies ensure the production of antibiotics does not contribute to resistance

Figure 33. Company performance: Manufacturing &amp; Production

## Large research-based pharmaceutical companies



## Generic medicine manufacturers



## THE LEADERS

In Manufacturing & Production, the scores near the top are closely packed. Nevertheless, six companies pull ahead of other large research-based pharmaceutical companies and the generic medicine manufacturers: GSK, followed by Johnson & Johnson, Novartis, Pfizer, Roche and Sanofi. GSK undertakes every environmental risk-management activity that the AMR Benchmark examines, with the other five companies undertaking the majority of them. All leaders make a commitment to manufacturing all antibiotic drug products in a manner consistent with Good Manufacturing Practices (GMP).

## CONTEXT

The process for manufacturing and producing antibiotics by pharmaceutical companies can contribute to antimicrobial resistance (AMR) in two main ways: when companies release waste into the environment that includes antibiotics or antibiotic resistant bacteria<sup>1</sup>; and when they manufacture substandard antibiotics with sub-therapeutic levels of the active antibiotic ingredient.<sup>2</sup> Both routes can expose bacteria to levels of antibiotics that promote the emergence of resistance.

## WHAT THE BENCHMARK MEASURES

The Benchmark assesses specific policies and actions companies can take to uphold manufacturing practices in both areas. It evaluates how thorough their environmental risk-management strategies are, if companies take into account antibiotic discharge; how they apply these strategies to third-party suppliers; and their transparency regarding strategies, audit results, discharge levels, and the identities of third-party suppliers of active pharmaceutical ingredients (APIs) and drug products.

The Benchmark also looks at the mechanisms companies use to maintain high-quality standards in the production of antibiotics.

As this research area concerns manufacturing and production, the Benchmark evaluates only those companies with important sales volumes of antibiotic products.

## IN SUMMARY

### **Most companies have environmental risk-management strategies in place; depth and breadth of strategies vary**

The majority of companies analysed (15 of 18) show evidence of having some form of an environmental risk-management strategy that aims to minimise impact of antibiotics discharged from manufacturing processes. The depth and breadth of these strategies differ widely regarding the different aspects evaluated by the Benchmark. Six large research-based pharmaceutical companies (GSK, Johnson & Johnson, Novartis, Pfizer, Roche and Sanofi) lead the field, applying their environmental risk-management strategies most broadly, both to their own manufacturing sites and to those operated by third-party manufacturers of APIs and drug products. The performance of generic medicine manufacturers varies, with only the leaders focussing beyond their own manufacturing sites.

Fifteen companies have strategies for their own manufacturing sites, which most (14) also support with regular audits. Nearly half of those analysed (eight) report that they also apply their strategies to sites managed by third-party manufacturers of APIs and drug products. Six companies reported that they apply their strategies to external waste-treatment plants. Looking at auditing and the setting of discharge limits, 14 companies reported that they audit their own manufacturing sites, seven audit sites managed by third parties, and three audit external waste-treatment plants. Regarding discharge limits, eight companies set these for their own manufacturing sites, four for sites managed by third-party suppliers of APIs and drug products, and two for external waste-treatment sites.

### **Eight companies set discharge limits for antibiotics, but none discloses actual discharge levels**

Eight companies report that they have set limits on antibiotic discharge in wastewaters, but none discloses publicly its levels of actual discharges. This information is valuable and vital. Disclosing it could enhance the ability of governments, researchers and other stakeholders to understand the relationship between the discharge of active antibiotic ingredients into the environment and the development of antibiotic resistance. Four companies have set discharge limits for their own sites as well as those of third-party manufacturers of APIs and drug products, reporting that they also audit the implementation of their environmental risk-management strategies. One company (GSK) extends its discharge limits to both third-party manufacturers and external waste-treatment plants. GSK is also the only company that discloses predicted no-effect concentrations (PNEC) for resistance selection. It discloses these to the Benchmark, also giving reference to external sources for these PNECs. It does this for a subset of the antibiotics in its portfolio. The company publicly discloses safety data sheets for antibiotics, but doesn't publicly disclose PNECs.<sup>3</sup>

### **Only one company discloses names of third-party manufacturers**

The Medicines Company is the only company identified by the Benchmark that discloses the identities of its third-party manufacturers, making it an example of best practice in this area. In its 2016 annual report, it disclosed the identity of all third-party API and drug-product suppliers for its marketed branded antibiotics minocycline (Minocin® IV), oritavancin (Orbactiv®), and meropenem/vaborbactam (Vabomere™). It also disclosed suppliers for its generic medicines, azithromycin and clindamycin. Disclosing the identities of third-party suppliers enables governments, researchers and others to assess the impact of individual manufacturing chains on antibiotic resistance. Please note: The Medicines Company was not scored in this research area. As a biopharmaceutical company in scope, it is in scope for the R&D Research Area only.

## MANUFACTURING & PRODUCTION METHODOLOGY: WHAT THIS RESEARCH AREA MEASURES

In Manufacturing & Production, the Benchmark uses global antibiotic sales volumes to inform its selection of companies to analyse. It focusses on antibiotics (rather than all antimicrobial medicines). This is because antibiotic manufacturing and its potential impact on resistance is better described and understood than other areas of antimicrobial manufacturing. As such, it was possible to identify and develop metrics for this first iteration of the Benchmark.

Of the 30 companies in scope, the Benchmark analyses 18 companies that were included based on the importance of their antibiotics sales volumes.<sup>4,5</sup> The scale of these companies' sales volumes suggests they are the prominent players in multiple manufacturing chains with

reasonable influence on upstream suppliers. Consequently, their policies and practices may affect antimicrobial resistance more significantly than those of other companies.

Most companies in scope (24) have signed the Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance; ten have signed the Industry Roadmap for Progress on Combating Antimicrobial Resistance.<sup>6</sup> In signing up to these industry-wide initiatives, companies commit to support measures to reduce the impact on the environment from the production of antibiotics, and have installed a working group responsible for this topic.<sup>7</sup> Nine companies (GSK, Johnson & Johnson,

Merck & Co., Inc., Novartis, Pfizer, Roche, Sanofi, Shionogi and Teva) are also working together on environmental risk management in the Pharmaceutical Supply Chain Initiative (PSCI).<sup>8</sup>

The Benchmark analyses data collected through surveys and from public sources. As far as possible, this data is clarified, cross-referenced and verified by the research team. How data is collected in the first instance depends on a company's level of engagement with the Benchmark research. All companies were surveyed, and data from public sources were analysed for all companies. Not all companies contributed in the survey.

### INDICATORS

- B.1 Environmental risk-management strategy**
- B.2 Disclosure on environmental risk management**
- B.3 Manufacturing high-quality antibiotics**

Figure 34. Companies in scope

	Applicable indicators		
	B1	B2	B3
<b>Large research-based pharmaceutical companies</b>			
GSK	●	●	●
Johnson & Johnson	●	●	●
Merck & Co., Inc.	●	●	●
Novartis	●	●	●
Pfizer	●	●	●
Roche	●	●	●
Sanofi	●	●	●
Shionogi	●	●	●
<b>Generic Medicine Manufacturers</b>			
Aspen	●	●	●
Aurobindo	●	●	●
Cipla	●	●	●
Dr. Reddy's	●	●	●
Fresenius Kabi	●	●	●
Lupin	●	●	●
Macleods	●	●	●
Mylan	●	●	●
Sun Pharma	●	●	●
Teva	●	●	●

The Medicines Company did not meet the criteria used to select the two other company groups in scope, and was therefore not eligible for this Research Area. However, the company has notable activities in this area, which are mentioned in this Research Area where relevant.

### ABOUT THIS CHAPTER

In this chapter, the Benchmark reports its findings in two sections. The first relates to indicator B.1. The second relates to indicators B.2 and B.3.

p61 B.1

p63 B.2 & B.3

For a full listing of indicators and scoring eligibility see Appendix V.

## RISK-MANAGEMENT STRATEGIES

# How do companies manage environmental AMR risk during antibiotic manufacturing?

## INDICATOR

B.1 Environmental risk-management strategy

During antibiotic manufacturing, the release of wastewater can at times lead to the discharge of active antibiotic ingredients into the environment. Recent studies have shown that some environments around drug manufacturing sites contain high concentrations of antibiotics.<sup>1,9</sup> Once in the wider environment, active antibiotic ingredients can accelerate the development of antibiotic resistance in bacteria. This can happen when antibiotic levels are sufficiently high to enable natural selection for resistant strains of bacteria.

As research is being conducted to understand the impact of industrial discharges on antibiotic resistance, those working to understand the potential impact need greater insight about how often and under what circumstances such discharges are high, what levels of antibiotics impose an unacceptable risk, and how risks should best be managed. What is understood is that sometimes discharged levels of antibiotics are unacceptable, and pharmaceutical companies do have the technical ability to reduce such discharges, although awareness and sufficient incentives may not always be there.

As there is as yet a general paucity of specific regulations on antibiotics discharges, companies would need to set their own discharge limits below predicted no-effect concentrations (PNEC) for resistance selection.<sup>10</sup> It is important for combatting AMR that discharge limits are based on PNECs for resistance selection and not for, e.g., aquatic toxicity.

The AMR Benchmark examines which companies are setting such strategies, assessing three distinct areas: whether a company has a clear environmental risk-management strategy; whether it audits this strategy regularly; and whether its strategy includes limits on antibiotic discharge. Performance in

these areas is referred to as the 'depth' of strategies.

To manufacture antibiotics, most pharmaceutical companies rely at least partly on third parties to supply them with API and drug products. As API manufacturing units and formulation manufacturing sites are processing the active ingredients in antibiotics, there is a risk that these sites can discharge these active ingredients into the environment.

Some manufacturing sites have on-site wastewater-treatment plants, while others use external plants. Both on-site and off-site plants play a role in preventing the discharge of antibiotics into the environment.

Commonly, pharmaceutical companies that market antibiotics sit at the end of the manufacturing chain. As well as being able to control standards at their own sites, they may be able to exert considerable influence over the environmental risk management of their suppliers. To prevent antibiotics being discharged from manufacturing sites into the environment, those involved in the manufacturing chain must work together.

The Benchmark looks at whether companies are applying environmental risk-management strategies: to their own manufacturing sites; to third-party manufacturers of APIs and/or drug products; and to external waste-treatment plants. Performance in these areas is referred to as the 'breadth' of strategies.

There are also risks associated with discharges of antibiotic-resistant bacteria that may be the result of highly antibiotic-contaminated wastewaters with microbes. Disinfection of such wastewaters are important to prevent releases of generated antibiotic-resistant bacteria; however, this was not part

of the questionnaires or ranking of the companies this time.

## DEPTH AND BREADTH OF STRATEGIES VARY; SOME COMPANIES MEET MOST REQUIREMENTS

In this area, the Benchmark evaluated the 18 companies in its scope that make and market an important volume of antibiotics. Fifteen showed evidence of having an environmental risk-management strategy that aims to minimise risks for possible antibiotic discharges from manufacturing processes.

The depth and breadth of strategies differ widely (see figure 35). Most of these companies have strategies for their own manufacturing sites, supported by regular audits, and nearly half of those analysed (eight) could show they apply their strategies to sites managed by third-party manufacturers of APIs and drug products. Six gave evidence of how they apply their strategies to external waste-treatment plants.

Auditing follows a similar trend. Fourteen companies reported that they audit their own manufacturing sites and seven companies audit sites managed by third parties, but just three audit external waste-treatment plants. Regarding discharge limits, eight companies set these for their own manufacturing sites and four companies do so for sites managed by third-party suppliers of APIs and drug products, but only two set limits for external waste-treatment sites.

### Leaders expand focus beyond their own sites

Six companies lead in this area: GSK, Johnson & Johnson, Novartis, Pfizer, Roche and Sanofi.

All six have a clear strategy, and apply this both to their own manufacturing

sites and to the sites operated by third-party manufacturers of API and drug products. All strategies include audit plans for the companies' own sites and those of suppliers. In addition, all six companies set discharge limits for certain antibiotics (when manufactured at their own sites), though they have not yet developed limits for other antibiotics that are manufactured at their own sites or at third-party manufacturing sites.

Among these leaders, GSK stands out. It undertakes every environmental risk-management activity that the AMR Benchmark examines (see figure 35). The company applies its strategy, including audits, to its own manufacturing sites, to the sites of third-party API and drug-product manufacturers, and to external waste-treatment plants. GSK sets limits on antibiotic discharges and applies these not only to its own manufacturing sites, but also to the sites of third-party manufacturers and to waste-treatment plants. Taking responsibility for its manufacturing chain, GSK sets limits for all those directly involved in manufacture and discharge, including its direct suppliers.

Johnson & Johnson applies its environmental risk-management strategy to its own manufacturing sites, to the sites of third-party manufacturers, and to waste-treatment plants. At its own sites and those of third-party manufacturers, it performs audits and has set limits on antibiotic discharges.

Novartis has a risk-management strategy to minimise the environmental impact of antibiotic discharge from manufacturing. It applies this to its own facilities, to those of third-party manufacturers of API and drug products, and to external waste-treatment plants. Novartis performs audits at its own manufacturing sites and those of third-party manufacturers. It sets discharge limits for its own manufacturing sites and for external wastewater-treatment plants.

Roche has developed an environmental risk-management strategy that it applies – with audits and discharge limits – to its own sites and to those of third-party manufacturers of APIs and

**Figure 35. Depth and breadth of environmental risk-management strategies vary widely.**

The AMR Benchmark looks at where companies are applying environmental risk-management strategies (breadth), and whether these strategies include audits and limits on antibiotic discharge (depth). Six large research-based pharmaceutical companies are leading in this area by including the most elements in their strategy. Generic medicine manufacturers mainly focus their strategies on their own manufacturing sites.

	Breadth			Depth					
	Own manufacturing sites			Third party manufacturing sites of API and Drug Products			External waste-treatment plants		
	Strategy	Audits	Limits	Strategy	Audits	Limits	Strategy	Audits	Limits
<b>Large research-based pharmaceutical companies</b>									
GSK	●	●	●	●	●	●	●	●	●
Johnson & Johnson	●	●	●	●	●	●	●		
Merck & Co., Inc.	●	●		●	●				
Novartis	●	●	●	●	●		●		●
Pfizer	●	●	●	●	●	●			
Roche	●	●	●	●	●	●	●		
Sanofi	●	●	●	●	●		●	●	
Shionogi	●	●	●						
<b>Generic medicine manufacturers</b>									
Aspen	●	●							
Aurobindo	●	●					●	●	
Cipla									
Dr. Reddy's	●								
Fresenius Kabi	●	●							
Lupin									
Macleods	●	●							
Mylan	●	●							
Sun Pharma									
Teva	●	●	●	●					

drug products. It extends its strategy to cover external waste-treatment plants, but does not audit these or monitor discharge limits.

Sanofi has a risk-management strategy to minimise the environmental impact of antibiotic discharge from manufacturing. It applies this, with audits, to its own facilities, to those of third-party manufacturers, and to waste-treatment plants. Sanofi sets discharge limits for its own manufacturing sites, but it does not set limits for third-party manufacturers and external waste-treatment plants.

Pfizer has an environmental risk-management strategy that it applies to its own sites and those of third-party API and drug-product manufacturers. Its strategy includes limits

on discharge of antibiotics, and regular audits. As Pfizer's third-party manufacturers do not yet have a full set of antibiotic discharge limits, Pfizer engages with them to help set limits on discharge for antibiotics below PNEC for resistance. Pfizer's manufacturing sites include primary waste treatment plants. Secondary waste treatment occurs on and off site. Pfizer's environmental risk-management strategy does not apply to off-site waste-treatment plants.

Although not evaluated by the Benchmark, Pfizer has a public policy that includes a requirement for improvement plans or supplier exit if suppliers are unable to meet expectations.

## DISCHARGE LIMITS: NOT WIDELY REPORTED

Eight companies out of 18 report that they have set discharge limits. For half of these companies (four), these limits apply to both their own sites and those of third-party manufacturers. Two companies (GSK and Novartis) extend them to external waste-treatment plants.

GSK is the only company that reported PNECs for resistance selection to the Benchmark, also giving reference to external sources for these PNECs.<sup>10,11</sup> It does this for a subset of the

antibiotics in its portfolio. The company publicly discloses safety data sheets for antibiotics, but does not include PNECs in the safety data sheets.<sup>3</sup> Roche commits to disclosing PNECs publicly by the end of 2017. By sharing their PNEC information publicly, companies give governments, researchers, generic medicine manufacturers and others the opportunity to use this data in their work to minimise the impact of manufacturing discharge of antibiotics.

## No statement on environmental risk management

Three companies – Cipla, Lupin and Sun Pharma – have reported no evidence of a risk-management strategy to minimise the impact of their antibiotic manufacturing discharge on the environment. Cipla has, however, committed to develop an environmental risk-management strategy in 2018 in line with its commitments to the Industry Roadmap as a signatory. Lupin and Sun Pharma have not reported their intentions in this area to the Benchmark, nor have they done so publicly.

## MANUFACTURING HIGH-QUALITY ANTIBIOTICS

### What do companies disclose about environmental risk-management?

By disclosing their environmental risk-management practices – that is, the publication of strategies to minimise the discharge of antibiotics; details of manufacturing responsibilities and the management of active ingredients; and indications of strategy implementation – companies make it easier to share knowledge about good practice and ways to effectively manage discharge of antibiotics. For example, transparency about discharge levels can facilitate discussions about the scientific rationale behind the limits. Disclosure also enables independent organisations to review the practices of third-party manufacturers and waste-treatment plants, which may otherwise remain less transparent. By disclosing, companies enable others to hold them accountable for their policies and practices.

In this Research Area, the Benchmark assesses companies for transparency in five areas. These are: environmental risk-management strategy; audit results from their own manufacturing sites; audit results from the manufacturing sites of their third parties; antibiotic discharge levels; and the identities of third parties who supply antibiotic drug products, antibiotic APIs, and who treat waste.

Another step companies can take to reduce antimicrobial resistance is to maintain high manufacturing standards. They can do this by complying with GMP, which will help them to prevent substandard antibiotics from reaching patients, meaning the bacteria are exposed to a non-effective concentration, which can not only harm the patients taking these medicines to cure infections, but also accelerate the development of antibiotic resistance in bacteria by the selection of resistant strains.<sup>12</sup> In this section, the Benchmark captures the mechanisms companies report using to maintain high manufacturing standards.

## MAJORITY OF COMPANIES WITH A STRATEGY DISCLOSES THEIR STRATEGY

Out of 18 companies assessed in this area, 15 have put in place an environmental risk-management strategy. Of these, 12 disclose their strategies publicly. They are Aspen, Aurobindo, Fresenius Kabi, GSK, Johnson & Johnson, Merck & Co., Inc., Mylan, Novartis, Pfizer, Roche, Sanofi and Teva. All 12 disclose one or more documents

## INDICATORS

- B.2 Disclosure on environmental risk management
- B.3 Manufacturing high-quality antibiotics

(available on company websites) that describe their strategies to prevent the discharge of antibiotics into the environment. Making such disclosures is an important first step. It provides a measure of transparency, showing the willingness of pharmaceutical companies to adjust their manufacturing practices in order to minimise antibiotic resistance.

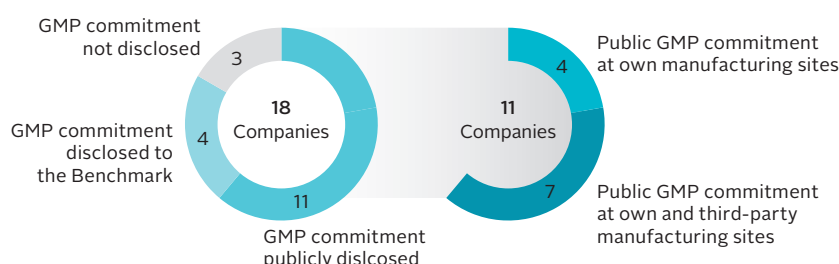
The remaining three companies with an environmental risk-management strategy are Shionogi, Dr. Reddy's and Macleods.

Shionogi engineer at its own manufacturing plant.



**Figure 36. More than half of companies publicly disclose GMP commitments.**

By publicly disclosing commitments to produce high-quality antibiotics, in compliance with GMP, companies demonstrate their efforts in preventing substandard antibiotics from reaching patients. These efforts can be strengthened by extending them to third-party manufacturing sites.



These three do not disclose their strategies publicly. However, Shionogi commits to disclosing its strategy in its 2017 environment, health and safety report.

**Only one company discloses the identities of third-party manufacturers**

Only one company – The Medicines Company\* – discloses the identities of third-party manufacturers, making it an example of best practice in this area. By disclosing this information, The Medicines Company acknowledges its share of responsibility for policies, practices and possible discharges at those sites.

In its 2016 annual report, this company disclosed the names of all third-party API and drug-product suppliers for its marketed branded products minocycline (Minocin® IV), oritavancin (Orbactiv®), and meropenem/vaborbactam (Vabomere™). It also disclosed suppliers for its generic medicines, azithromycin and clindamycin.

By disclosing the identities of third-party suppliers, The Medicines Company enables governments, researchers and others to assess the impact of its manufacturing chains on antibiotic resistance. The companies in scope are generally dominant players in their manufacturing chains — those with the most power to negotiate terms and influence standards and practices. This includes influence over the manufacturing and risk-management practices of third-party suppliers. Greater

public insight into how these chains are structured enables governments, NGOs and other stakeholders to analyse the environmental impact of specific/other companies along the supply chain.

No other company in scope has been transparent in this area. None has disclosed the identities of the third parties that manufacture their APIs and drug products, or of their third-party waste-treatment plants. Some companies comment that they consider this to be confidential business information.

Shionogi commits to disclosing its third parties in its 2017 environment, health and safety report.

**No public disclosures of discharge levels**

Manufacturing discharges are having an impact on antibiotic resistance. Researchers are currently studying the extent and nature of this impact.<sup>13</sup>

Ten companies in the Benchmark's scope signed the Industry Roadmap (see Appendix I). Through this, they

commit themselves to establishing science-driven targets for antibiotic discharge concentrations, and to standardising these.

Eight companies in scope for this research area report that they have set limits for antibiotic discharge. As yet, no company discloses publicly its levels of antibiotic discharge. This information is valuable. Disclosing it could enhance the ability of governments, researchers and other stakeholders to investigate and eventually better understand the relationship between industrial discharges of active antibiotic ingredients into the environment, and the development of antibiotic resistance. By disclosing their levels of discharged antibiotics, companies also enable others to hold them accountable for their discharges.

**BROAD COMMITMENT TO GOOD MANUFACTURING PRACTICE**

Pharmaceutical companies are expected to produce all their antibiotics using the highest quality standards, such as those of GMP. Using GMP standards helps companies avoid exposing patients to sub-therapeutic levels of antibiotics, and avoid aiding the spread of resistance. The Benchmark urges companies to make a public endorsement of GMP for all their manufacturing processes. It also encourages companies to share their insights and experiences of how, along their manufacturing

Pfizer assessors at supplier locations in India. (imaged used with permission)



\*Please note: The Medicines Company was not scored in this research area. As a biopharmaceutical company in scope, it is in scope for the R&D research area only.

chains, they are upholding GMP standards (see figure 36).

The Benchmark asked companies what mechanisms they have in place to ensure that their own and third-party production facilities manufacturing antibiotics maintain high-quality production standards.

Of the 18 companies the Benchmark assessed in this area, 13 commit to manufacturing all antibiotics and antibiotic drug products in a manner consistent with GMP. These companies are Aurobindo, Fresenius Kabi, GSK, Johnson & Johnson, Lupin, Merck & Co., Inc., Mylan, Novartis, Pfizer, Roche, Sanofi, Shionogi and Teva. Two further companies, Aspen and Cipla, commit to

maintaining a high quality of antibiotic production, consistent with GMP, only at their own manufacturing sites. They do not disclose a commitment to applying GMP at their third-party antibiotic drug-product manufacturers.

Three remaining companies (Dr. Reddy's, Macleods and Sun Pharma) do not provide any evidence of having mechanisms in place in this area — Dr. Reddy's and Sun Pharma do not publicly disclose this information while Macleods did not provide evidence to the Benchmark. They do not make any disclosure of commitments to maintain a high quality of antibiotic production consistent with Good Manufacturing Practice.

In 2017, three companies, Lupin, Mylan and Pfizer, received a warning letter by the FDA regarding significant violations of current good manufacturing practice regulations for finished pharmaceuticals. In 2017 EMA issued a statement of non-compliance with GMP for one company, Dr. Reddy's.

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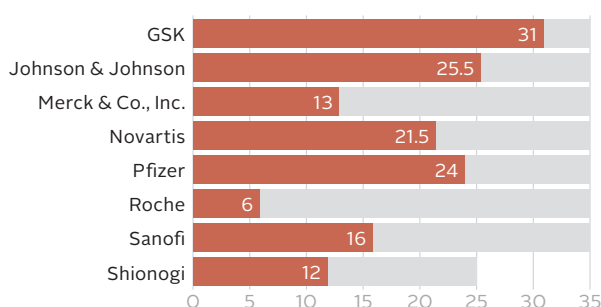
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## RESEARCH AREA: APPROPRIATE ACCESS &amp; STEWARDSHIP

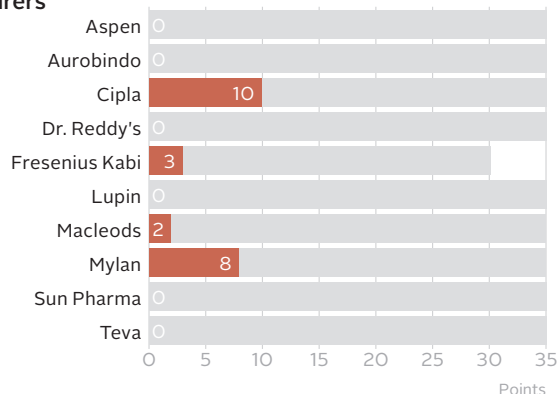
# How pharmaceutical companies approach access and stewardship for antibiotics

Figure 37. Company performance: Access &amp; Stewardship

## Large research-based pharmaceutical companies



## Generic medicine manufacturers



## THE LEADERS

Across this research area, four companies stand out: GSK, Pfizer, Novartis and Johnson & Johnson. All four demonstrate a range of activities across the indicators measured. Across access indicators, GSK leads, followed by Johnson & Johnson, Pfizer, Novartis and then Sanofi. All five companies have filed their newest antibiotics for registration in some countries in scope, and have considered the pricing and sustainable delivery of these medicines. In stewardship, GSK also leads, followed by Johnson & Johnson, Pfizer, and Novartis. Each of these companies provided evidence of stewardship in most areas, although Novartis lacks a surveillance programme.

## CONTEXT

Rising antimicrobial resistance (AMR) poses twin challenges: ensure their appropriate use (stewardship) while addressing the lack of access for millions globally.<sup>1,2</sup> Pharmaceutical companies can influence these two issues.<sup>3</sup> To ensure access, they can put in place strategies, relating to product registration, affordability and improving supply chains. Regarding stewardship, the role for pharmaceutical companies spans a range of areas such as education of healthcare professionals (HCPs), surveillance, and ensuring marketing practices take account of the risks of overuse and misuse.

## WHAT THE BENCHMARK MEASURES

The challenges of ensuring access to safe, effective, quality and affordable essential medicines and vaccines are significantly higher in poorer countries<sup>4</sup>; the Benchmark assesses companies' strategies to address access to antimicrobials in 106 low- and middle-income countries where access to medicine is likely limited (see Appendix III). It considers stewardship activities that specifically relate to antibiotics, with a global scope, looking at a range of areas such as education of HCPs, surveillance, and appropriate promotion practices. As this Research Area concerns activities relating to products

on the market, the Benchmark does not evaluate the biopharmaceutical companies in its scope. Most of these companies have no products on the market. However, the Benchmark highlights the relevant activities of these companies where possible.

## IN SUMMARY

### For the majority of newer antibiotics, registrations appear to be lower than for older ones

The Benchmark finds that newer antibiotics are currently registered in fewer countries than older products. To illustrate: 12 products in the analysis were introduced after 2011. These were (on average) filed for registration in fewer than five countries; the 24 products introduced before this point were (on average) filed for registration in almost 30 countries. Several products stand out, most notably Johnson & Johnson's bedaquiline – a long-awaited new medicine for tuberculosis. This is the only product introduced in the past five years, assessed by the Benchmark, that has been filed for registration in more than ten countries in scope – indeed, it has been filed in 23 countries. Products were included in this analysis where the year of their first global regulatory approval could be verified.

### Two of ten generic medicine manufacturers report an equitable pricing strategy

All large research-based pharmaceutical companies disclose an equitable pricing strategy that covers countries where access to medicine is likely limited. Equitable pricing strategies take some measures to ensure affordability. The quality of the strategies identified by the Benchmark varies; some are general strategies, whereas others are linked to specific products; some set prices at the national level, whereas others set prices for populations within countries. Out of ten generic medicine manufacturers analysed, Cipla and Mylan stand out for reporting an equitable pricing strategy. Generic medicine manufacturers generally price their medicines lower than those of their large research-based competitors. However, this practice on its own offers no guarantee that medicines will be affordable.

### The line between marketing and educational activities appears blurred

The Benchmark finds that the line between marketing and educational activities appears blurred. Companies generally lack clear educational targets, use similar content and goals for both marketing and educational purposes, and some programmes are reported as having both marketing and educational purposes. The Benchmark excluded some HCP education strategies from analysis for too closely resembling marketing tools, and offering little or no educational content. Several companies, conversely, stand out for their good practices in this area. GSK, Novartis and Pfizer show evidence of having content independently developed and using mechanisms to mitigate conflicts of interest (COI), including policies of not paying attendees or speakers in some cases and/or in some programmes. Companies generally use congresses and/or courses to deliver educational material.

### Range of mechanisms reported for mitigating conflict of interest in HCP education

Companies report several different mechanisms and processes to mitigate COI in their educational activities directed at HCPs. Out of 29 programmes, 21 give information about actions to mitigate COI; for most of these (18), content is developed independently; almost a third (13) run without branded materials; 11 do not require attendance payments for participants; and six have no commercial team involved in their development. In general, companies can develop clearer policies and protocols for mitigating COI. One very effective mechanism is to partner with a public organisation in the development and running of educational programmes. Both Johnson & Johnson and Pfizer are running educational programmes with public health organisations such as USAID, National TB programmes, hospitals and other health facilities.

### Nine companies are active in AMR surveillance programmes

Out of 19 companies (including Wockhardt), nine are active in AMR surveillance programmes, with a combined total of 19 active programmes. Ten of these have a national focus, while the remaining nine are international. Eleven programmes aim to measure long-term trends in antibiotic resistance. Almost half of programmes (eight) have run for fewer than three years, while six have run for more than ten years. Companies are running surveillance programmes across 147 countries, including 94 out of 106 countries where access to medicine is likely limited. Only three companies are conducting more than one surveillance programme (Cipla, Pfizer and Shionogi).

### Four companies take steps to adjust incentives for sales teams

Out of the 18 companies in scope, only four are taking steps to adjust sales teams' incentives. GSK demonstrates best practice in this area, decoupling all sales incentives for sales agents from volumes of sales. Shionogi does not remunerate its sales teams based on antibiotic sales volume. Two other companies are also working towards this. Novartis is taking steps to adjust incentives for its sales agents, reducing the variable portion in the overall compensation, while Pfizer will begin a pilot to fully decouple its agents' antimicrobial incentives from sales volumes.

At least one other company is taking a different approach at the product level. Johnson & Johnson's new anti-tuberculosis drug, bedaquiline (Sirturo®), is provided solely through national tuberculosis programmes and therefore does not require any marketing materials. The company reports that it does not deploy any sales organisations for the sale of Sirturo® in countries in scope.

## APPROPRIATE ACCESS AND STEWARDSHIP METHODOLOGY: WHAT THIS RESEARCH AREA MEASURES

In Appropriate Access & Stewardship, the Benchmark uses global antibiotic sales volumes to inform its selection of companies to analyse: the Benchmark assesses 18 companies in this research area.<sup>5,6</sup> These comprise all eight large research-based pharmaceutical companies in scope and all ten generic medicine manufacturers. The scale of these companies' sales volumes suggests that their policies and practices can likely have a significant impact on antimicrobial resistance. The Benchmark does not assess the activities of the 12 biopharmaceutical companies in scope so as to preserve the comparability of this group. Most of these companies have no products on the market. However, the Benchmark highlights the relevant activities of these companies where possible.

The 18 companies are evaluated on their access strategies and global stewardship interventions. Access strategies are evaluated where they relate to antimicrobials in 106 low- and middle-income countries (where access to medicine is likely limited; see Appendix III). It considers stewardship activities that specifically relate to antibiotics, with a global scope.

Most companies in scope (24) have signed the Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance; ten have signed the Industry Roadmap for Progress on Combating Antimicrobial Resistance. In signing up to these industry-wide initiatives, companies agreed to support efforts to increase AMR surveillance. Signatories commit to sharing

their data with public health bodies and healthcare professionals, to working to improve understanding of resistance trends, and to helping increase surveillance capabilities around the world.<sup>7</sup>

The Benchmark analyses data collected through survey and from public sources. As far as possible, this data is clarified, cross-referenced and verified by the research team. How data is collected in the first instance depends on a company's level of engagement with the Benchmark research. All companies were surveyed, and data from public sources were analysed for all companies. Not all companies participated in the survey.

### INDICATORS

- C.1 Registration of antibiotics
- C.2 Pricing of antimicrobials
- C.3 Ensuring efficient supply
- C.4 Supporting educational stewardship activities
- C.5 Appropriate promotion practices
- C.6 Brochure and packaging
- C.7 AMR surveillance
- C.8 Reducing uncontrolled use

Figure 38. Companies in scope

	Applicable indicators						
	C1	C2	C3	C4	C5	C6	C7
<b>Large research-based pharmaceutical companies</b>							
GSK	●	●	●	●	●	●	●
Johnson & Johnson	●	●	●	●	●	●	●
Merck & Co., Inc.	●	●	●	●	●	●	●
Novartis	●	●	●	●	●	●	●
Pfizer	●	●	●	●	●	●	●
Roche	●	●	●	●	●	●	●
Sanofi	●	●	●	●	●	●	●
Shionogi	●			●	●	●	●
<b>Generic Medicine Manufacturers</b>							
Aspen	●	●	●	●	●	●	●
Aurobindo	●	●	●	●	●	●	●
Cipla	●	●	●	●	●	●	●
Dr. Reddy's	●	●	●	●	●	●	●
Fresenius Kabi	●	●	●	●	●		●
Lupin	●	●	●	●	●	●	●
Macleods	●	●	●	●	●	●	●
Mylan	●	●	●	●	●	●	●
Sun Pharma	●	●	●	●	●	●	●
Teva	●	●	●	●	●	●	●

Wockhardt is a biopharmaceutical company that did not meet the criteria for evaluation in this Research Area. It does, however, have products on the market, and notable practices relevant to this area are mentioned.

### ABOUT THIS CHAPTER

In this chapter, the Benchmark reports its findings in six sections, each relating to separate indicators or a set of indicators. The indicators relating to access are covered together in the first section.

p69 C.1–C.3  
p73 C.4  
p77 C.5  
p78 C.6  
p78 C.7  
p81 C.8

For a full listing of indicators and scoring eligibility see Appendix V.

## ACCESS

# How do companies address the affordability of antibiotics?

## INDICATORS

- C.1 Registration of antibiotics
- C.2 Pricing of antimicrobials
- C.3 Ensuring efficient supply

Although AMR is a natural phenomenon, its development is being accelerated by human actions – including the misuse and overuse of antimicrobial medicines.<sup>8,9</sup> Yet, millions of people do not have access to antimicrobials, despite having potentially curable infections.<sup>10</sup> Low- and middle-income countries have a particular need for new strategies and programmes to increase access to antimicrobial medicines. Weak healthcare systems may limit access to antimicrobial medicines while also causing inappropriate use.<sup>11,12</sup>

Many of the global initiatives to address AMR aim to balance the need to enhance access where necessary with that of ensuring optimal and appropriate use of antimicrobial medicines through stewardship.<sup>8,13</sup> By stewardship, the Benchmark means a systematic and comprehensive process that aims to ensure that all aspects of prescription (e.g., drug, dose, duration), dispensing, and use of antibiotics follow the evidence available in order to minimise the emergence of resistance.

This section explores the strategies companies use to improve access to antimicrobial medicines in countries where access is likely limited. It examines access approaches from 18 companies: eight large research-based pharmaceutical companies and ten generic medicine manufacturers.

The Benchmark has identified 106 low- and middle-income countries whose populations are expected to have inadequate access to antimicrobial medicines. It evaluates access strategies across these countries and in relation to companies' newest\* and highest-volume antimicrobial medicines. It measures access approaches in three areas: registration, affordability and supply.

**Registration:** To make a new antimicrobial medicine available to the people that need it, a company must first

apply ('file') to register its medicine with a country's regulatory authority. Once approved, it can then be offered for sale. The Benchmark assesses companies on their efforts to register their five most recently introduced antibiotics on the WHO EML (Section 6) in countries in scope (see Appendices III and IV).

**Affordability:** This concerns both those needing to buy medicines on behalf of others (such as government agencies and other organisations) and individuals who need to buy medicines for personal or family use out of pocket. One of the main approaches that pharmaceutical companies can use to address affordability is 'equitable' pricing, which proactively considers the ability of a patient or healthcare system to afford specific prices for medicines. The Benchmark considers two types of equitable pricing strategies: inter-country, through which companies set prices per country at a national level (based on GDP, for example); and intra-country, through which companies set prices for different population segments within a country, taking into account the ability of those populations to pay. Both types of strategies aim to ensure affordability for the poorest population segments in both lower-income countries and countries with income inequality. For this measure, the Benchmark assesses companies' pricing practices for their highest-volume antimicrobial medicines (measured on global sales volume). This analysis, by including highest-volume antimicrobial medicines, does not include innovative antibiotics that have been approved in the last five years. These will probably not be sold in large volumes in the future, as public health systems should aim to keep new antibiotics in reserve in order to limit the emergence of resistance. Companies need to work closely with governments, NGOs and companies to develop a

pricing policy for such innovations. This must take account of affordability in low- and middle-income countries.

**Supply:** Companies share responsibility for maintaining and improving the efficiency of antimicrobial supply chains. This includes having measures in place to avoid stock-outs, and to improve how they forecast demand for their antimicrobial medicines. The Benchmark assesses the mechanisms companies have put in place to align supply and demand and to respond promptly to stock-outs.

## FIVE COMPANIES TAKE ACTION ACROSS REGISTRATION, AFFORDABILITY AND SUPPLY

The 18 companies the Benchmark assesses have a combined total of at least 710 antimicrobial medicines in their portfolios. Of these products, 437 correspond to medicines on the WHO's most recent model list of essential medicines, specifically in the section that profiles infectious diseases (Section 6, 2017 WHO Model List of Essential Medicines, or EML). Products on this list are considered, by WHO, as among the minimum medicine needs for a basic healthcare system to function.

The best performances come from a group of five companies: GSK, Johnson & Johnson, Novartis, Pfizer and Sanofi. These companies have filed their newest (i.e., most recently introduced) antibiotics for registration in at least some countries in scope, and have developed equitable pricing strategies for their highest-volume antimicrobial medicines. They also have supply-chain strategies to prevent or respond to stock-outs. A further six companies analysed in this area (Cipla, Fresenius Kabi, Macleods, Merck & Co., Inc., Mylan and Roche) demonstrate activities in at least one

\*Newest in this context refers to those medicines most recently introduced.

of these areas, but not in all three. One company, Shionogi, has not filed to register any antimicrobial medicines (nor markets any) in the countries in scope.

The remaining six companies (Aspen, Aurobindo, Dr. Reddy's, Lupin, Sun Pharma and Teva) do not disclose any information about their efforts to provide access to antimicrobial medicines in the 106 countries where access to medicine is likely limited. Together, these six companies have at least 216 antimicrobial medicines on the market, with 127 of them on the WHO EML (Section 6).

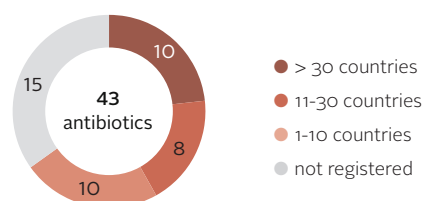
### ► REGISTRATION

#### Steady increase over time in geographic range of registrations per product

The Benchmark assesses the registration filings of 18 companies (eight large research-based pharmaceutical companies and ten generic medicine manufacturers). It looks at whether they have filed their five newest antibiotics for registration in 106 low- and middle-income countries. In evaluating companies in this metric, the Benchmark calculates the average number per company of countries in which it has filed to register its newest antibiotics. The 'newness' of a product refers to when it was first introduced to the market,

#### Figure 39. Almost 65% of antibiotics are registered in countries where access is less likely.

Eleven companies provided registration information about 43 antibiotics. GSK, Pfizer, Roche and Sanofi have the highest number of registration filings in countries in scope.



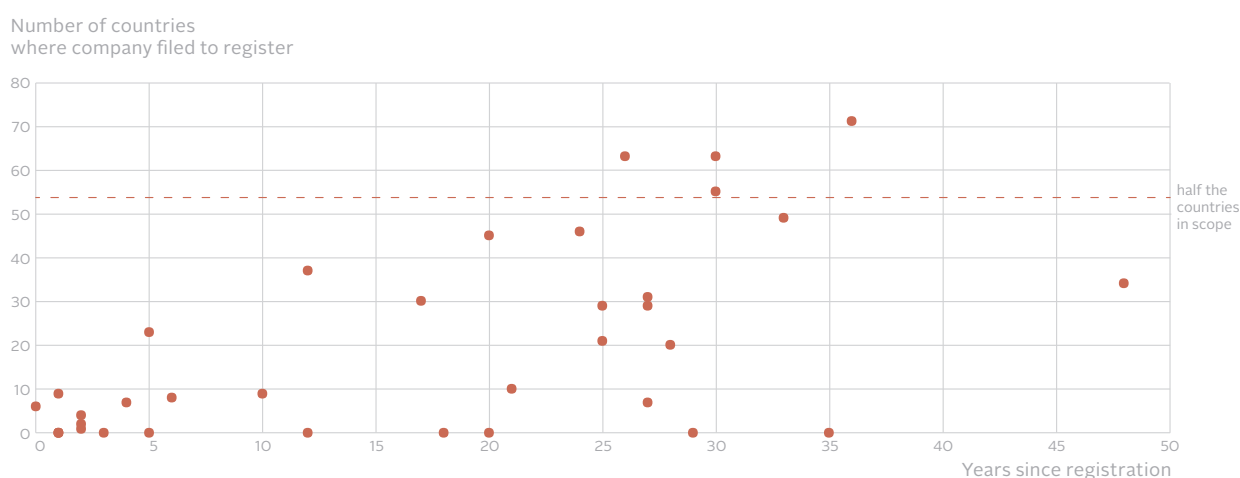
taken from the year of its first global regulatory approval.

Overall, the companies provided registration information about 43 antibiotic products. Fifteen have not been filed for registration in any country in scope, while 10 have been filed in up to 10 countries, and 18 have been filed in more than 10 countries (see figure 39). Of the 43 antibiotics for which registration details have been disclosed, the following have been filed for registration in the majority of countries in scope: amoxicillin/clavulanic acid (Augmentin™, GSK, 71 countries), azithromycin (Zithromax®, Zmax®, Pfizer, 63 countries), cefuroxime axetil (Ceftin®, Zinnat®, GSK, 63 countries) and mupirocin (Bactroban®, GSK, 55 countries).

Older antibiotics have been filed for registration in more countries than ones more recently introduced, with a steady increase in the number of filings of progressively older products (see figure 40). Products introduced in the past six years were, on average, filed for registration in fewer than five countries, whereas products introduced before this point were, on average, filed for registration in more than 25 countries. Products were included in this analysis only where the year of their first global regulatory approval could be verified. One company, Novartis, introduced its five newest antibiotics in 2011 or after (see figure 41).

#### Figure 40. Four antibiotics have been filed in more than half the countries in scope.

Products introduced\* since 2011 have been, on average, filed for registration in fewer than five countries, whereas older products have been filed in more than 25 countries. Four older antibiotics have been filed most widely, including the commonly used antibiotic amoxicillin/clavulanic acid (Augmentin™) by GSK. Johnson & Johnson's bedaquiline (Sirturo®) is the only new antibiotic (past five years) that has been filed for registration in more than 10 countries in scope.



\* Introduction refers to the year of approval by the US FDA, EMA or Japan's PMDA or the year a product was introduced as reported by the company. Products were included in this analysis only where the year of their first global regulatory approval was reported.

**Figure 41. Only three companies have registered new antibiotics in low- and middle-income countries this decade.**

Johnson & Johnson, Novartis and Teva are the only companies who have filed new antibiotics for registration this decade. Three companies (Shionogi, Cipla, Teva) who have disclosed their five newest antibiotics to the Benchmark have not registered any products in countries in scope. Products with the highest number of filings (bold) include some of the most commonly used antibiotics worldwide.

	Company	Most recently introduced products	Year of first registration	Number of countries where filed	
Large research-based pharmaceutical companies	GSK	<b>amoxicillin/clavulanic acid (Augmentin™)</b>	<b>1981 †</b>	<b>71</b>	GSK's Augmentin™ has the highest registration filings as it was first introduced in 1984 and is one of the most commonly used broad-spectrum antibiotics today.
		ceftazidime (Fortum®)	1990*	31	
		<b>cefuroxime axetil (Ceftin®, Zinnat®)</b>	<b>1987*</b>	<b>63</b>	GSK has filed to register three of its newest products in the majority of countries in scope.
		<b>mupirocin (Bactroban®)</b>	<b>1987*</b>	<b>55</b>	
		retapamulin (Altargo®)	2007**	9	
	Johnson & Johnson	bedaquiline (Sirturo®)	2012*	23	
		levofloxacin (Levaquin®)	1996*	10	
		ofloxacin (Floxin®)	1990*	7	
	Novartis	amoxicillin/clavulanic acid	2017 †	Not disclosed	
		linezolid	2015*	Not disclosed	
		meropenem	2011*	Not disclosed	
		moxifloxacin	2015 †	Not disclosed	
		tobramycin inhaler	2013*	Not disclosed	
	Pfizer	<b>azithromycin (Zithromax™, Zmax™)</b>	<b>1991*</b>	<b>63</b>	Pfizer has filed to register one of its newest products in the majority of countries in scope.
		linezolid (Zyvox®)	2000*	30	
		piperacillin/tazobactam (Tazosyn®, Zosyn®)	1993*	46	
		dalfopristin/quinupristin (Synercid®)	1999*	0	
		tigecycline (Tygacil®)	2005*	37	
	Roche	ceftriaxone (Rocephin®)	1984*	49	
		sulfamethoxazole/trimethoprim (Bactrim®)	1969†	34	
	Sanofi	cefixime (Oroken®)	1989*	20	Sanofi has filed to register all of its newest products in at least 20 countries in scope.
		cefepodoxime (Orelox®)	1992*	21	
		levofloxacin (Tavanic®)	1997**	45	
		roxithromycin (Rulid®)	1992 †	29	
		teicoplanin (Targocid®)	1990**	29	
	Shionogi	cefcapene (Flomox®)	1997***	0	
		doripenem (Finibax®)	2005***	0	
		flomoxef (Flumarin®)	1988***	0	
		latamoxef (Shiomarin™)	1982***	0	
		vancomycin	Not provided	0	
Generic medicine manufacturers	Cipla	clarithromycin	Not provided	0	
		fosfomycin	Not provided	0	
		minocycline	Not provided	0	
		polymyxin	Not provided	0	
	Macleods	isoniazid/pyrazinamide/rifampicin	Not provided	30	
		isoniazid/rifampicin	Not provided	30	
	Teva	daptomycin	2016*	0	
		linezolid	2012*	0	

\* Year of approval by the US FDA

\*\* Year of approval by the EMA (or the Netherlands MEB)

\*\*\* Year of approval by Japan's PMDA

† Year of approval by Australia's TGA

‡ Year when the company reported the product was introduced

Johnson & Johnson's bedaquiline (Sirturo®) is the only product introduced in the past five years that has been filed for registration in more than 10 countries in scope. Indeed, it has been filed in 23 such countries. It is also worth noting that through the Global Drug Facility, more than 70 countries have approved importation of bedaquiline prior to regulatory approval.

#### **Leaders file for registration in >25 countries**

Of the large research-based pharmaceutical companies in scope, the best performers in this area have filed to register their five newest products in more than 25 countries on average. These companies are GSK, Pfizer and Sanofi. GSK has filed to register three of the antibiotics it has introduced most recently in the majority of countries in scope. Its most widely filed antibiotic, amoxicillin/clavulanic acid (Augmentin™), is also the most widely filed antibiotic of all products analysed; it has been filed for registration in 71 of the 106 countries in scope. GSK has filed to register the two other of its newest antibiotics in up to half of the countries concerned. Its five newest antibiotics were introduced between 1981 and 2007.

Pfizer has filed to register its five newest antibiotics, introduced between 1991 and 2005, in 35 countries on average. Of these, azithromycin (Zithromax®) was filed for registration in 63 countries, but dalfopristin/quinupristin (Synercid®) has not been filed in any country in scope. Pfizer did not report filing information about newer antibiotics acquired recently (i.e., from AstraZeneca in 2016 and from Basilea in 2017), as these products are still being integrated into Pfizer's portfolio (i.e., ongoing MAA transfer processes in several markets).

Sanofi has filed to register five of its newest antibiotics, introduced between 1989 and 1997, in 29 countries (on average). All of its newest antibiotics were filed in at least 20 countries in scope.

Generic medicine manufacturers, because of the nature of their business, launch more medicines per year

than large research-based pharmaceutical companies. Generally, as a result, a generic medicine manufacturer's five newest antibiotics are likely to have been introduced much more recently than a large research-based pharmaceutical company's five newest antibiotics. This difference in chronology means that the newest antibiotics from generic medicine manufacturers are often registered less widely than the newest products from large research-based pharmaceutical companies (see figure 41). Generic medicine manufacturers Fresenius Kabi and Macleods disclosed registration details of their antibiotics. Macleods has filed to register two of its newest products in 30 countries. Other generic medicine manufacturers did not disclose details of their efforts to register their newest antibiotics in those countries in greatest need of access, and this information is not publicly available.

#### **► AFFORDABILITY**

##### **Two of ten generic medicine manufacturers report an equitable pricing strategy**

The Benchmark assesses companies on the equitable pricing strategies they have developed for the five antibiotics and antimicrobial medicines with the highest volumes of sales (it does not consider specific price points). The Benchmark also evaluates whether companies address the needs of different population segments by taking into account affordability among and within countries in scope.

All the large research-based pharmaceutical companies in scope disclose – publicly or to the Benchmark – an equitable pricing strategy for the 106 countries where access to antimicrobial medicines is likely limited. The quality of these strategies varies according to whether they are general or product-specific, and whether they relate to pricing within a country, among countries or both. Two of the ten generic medicine manufacturers in scope – Cipla and Mylan – reported to the Benchmark an equitable pricing strategy (details below). While generic medicine manufacturers may use a business

model that prices medicines lower than do large research-based pharmaceutical companies, this does not guarantee affordability. As they set prices, it is important these manufacturers show how pricing strategies take account of socio-economic factors, and the abilities of patients or healthcare systems to afford medicines.

#### **Leaders apply inter- and intra-country equitable pricing**

GSK, Novartis and Johnson & Johnson lead in the area of equitable pricing for antimicrobial medicines. All are large research-based pharmaceutical companies, and all apply inter-country equitable pricing strategies to the antibiotics and antimicrobial medicines in their portfolios that have the largest global sales volumes. They also have product-specific intra-country equitable pricing strategies for at least some products. GSK is the leading company. It commits to applying a product-specific equitable pricing strategy, among and within countries, to the majority of its highest-volume antimicrobial medicines in more than half of the countries in scope. These products are amoxicillin/clavulanic acid (Augmentin™), amoxicillin (Amoxil®), albendazole (Zentel™), dolutegravir (Tivicay®)\*, abacavir/lamivudine (Epzicom®, Kivexa®)\*, abacavir (Ziagen®)\* and lamivudine/zidovudine (Combivir®)\*.

Novartis commits to applying an equitable pricing strategy among countries to all its highest-volume antibiotics and non-antibiotic antimicrobial medicines. As part of its partnership established with the WHO in 2001, in which Novartis committed to making artemether/lumefantrine (Coartem®) available without profit to the public sector of malaria-endemic countries, it applies equitable pricing models within countries, for more than half of the 106 countries in scope. Originally a ten-year agreement, the company continues this commitment.

Johnson & Johnson commits to applying a product-specific equitable pricing strategy among countries to bedaquiline (Sirturo®), darunavir (Prezista®) and simeprevir (Olysio®).

\* This product is marketed via ViiV Healthcare

It also commits to applying product-specific equitable pricing within countries to bedaquiline (Sirturo®), mebendazole (Vermox®) and simeprevir (Olysio®), three of its highest-volume antimicrobial medicines.

Shionogi has no antimicrobial medicines registered in countries in scope, so does not disclose a pricing strategy. Roche reports that it has no strategy in place.

Cipla commits to improving affordability by applying a general equitable pricing strategy among countries using income, whereas Mylan commits to improving affordability by applying a general equitable pricing strategy within countries, to the antimicrobial medicines they sell in the highest volumes.

Other generic medicine manufacturers in scope (Aspen, Aurobindo, Dr. Reddy's, Fresenius Kabi, Lupin, Macleods, Sun Pharma and Teva) do not disclose equitable pricing strategies for

the antimicrobial medicines they sell in the highest volumes publicly, nor to the Benchmark.

#### ► SUPPLY

##### **Leaders engage with others to align supply and demand, prevent stock-outs**

The Benchmark has examined companies' mechanisms for preventing stock-outs and improving demand forecasting for their highest-volume antimicrobials. Only eight companies disclosed supply and demand information for their highest-volume antibiotics and antimicrobial medicines. Six of the eight strategies were eligible for scoring in this indicator, because information was specific to antimicrobial medicines. GSK, Johnson & Johnson and Mylan lead in this area. They engage with stakeholders such as government health ministries, The Global Fund and WHO to align forecasting of supply and demand for

their antimicrobial medicines, and this helps to prevent or minimise stock-outs. The three companies have mechanisms (such as internal workflows, safety stocks and supply chain management systems) that enable them to respond efficiently to stock-outs in countries in scope. Mylan is engaging in global serialisation efforts to improve traceability of products along the supply chain. GSK and Johnson & Johnson hold a portion of safety stock in their warehouses across the globe to balance out changes in demand and variation.

No other companies demonstrate engagement with relevant stakeholders to improve the efficiency of their supply chains. A lack of engagement may lessen their ability to prevent stock-outs and continue to deliver sustainably to those 106 countries where access to medicine is likely limited.

## EDUCATION

# Do companies educate healthcare professionals about AMR and stewardship?

The consumption of antibiotics, including the misuse and overuse of antibiotics for human and animal purposes, is driving the emergence of AMR.<sup>9</sup> To change this behaviour, one of the first steps is to raise awareness of AMR while also building knowledge about how to prevent resistance from emerging.<sup>3,8</sup> Pharmaceutical companies have a rich depth of knowledge and expertise about antimicrobial resistance (AMR) and can play an important role in changing prescribing behaviours among healthcare professionals (HCPs). The scale and geographic reach of many companies' operations gives them a major opportunity to educate a large number of HCPs. Such programmes can focus on how and why antimicrobials must be used appropriately, namely by prescribing the right drug, at the right time, at the right dose and for the right duration.

At the same time, companies need to be held accountable for their influence over HCPs and healthcare delivery. Transferring gifts, meals, travel offers, payments and other forms of influence has been documented across the industry as companies seek to build relationships with HCPs. These practices are often legal, but are acknowledged to represent conflicts of interest for the companies and HCPs involved. At stake are the prescribing behaviours that should ensure patients receive only the medicines they need. As companies create and implement HCP educational programmes, they must take care to mitigate these and other conflicts of interest (COIs).<sup>14</sup>

The Benchmark looks at the educational programmes reported by companies aimed at healthcare professionals relating to AMR. It looks at how companies mitigate conflicts of interest

that arise from their programmes. The Benchmark also examines how pharmaceutical companies develop the content of their educational programmes, specifically to assess whether and how commercial teams or external experts are involved in that process.

## LINE BETWEEN MARKETING AND EDUCATION IS BLURRED

The Benchmark finds that, in this area, the line between marketing and education activities is blurred. Companies' programmes regarding AMR generally appear to lack clear educational targets and use similar content and goals for both marketing and educational purposes. Some programmes are reported as having both marketing and educational purposes. The blurring of this line means that even when a company

## INDICATOR

### C.4 Supporting educational stewardship activities

has the ability to reach a large number of healthcare professionals, marketing-based approaches can compromise the value of educational programmes to curb AMR. As a result, the Benchmark took the step of excluding from its analysis some HCP education strategies that too closely resemble marketing tools, offering little or no educational content.

GSK, Novartis and Pfizer perform best when it comes to providing educational content that is independently developed and supports stewardship activities. These companies report five, three and seven educational programmes respectively that support stewardship activities. They show evidence of independently developing content and using mechanisms to mitigate conflicts of interest, for example, not paying speakers or attendees. They generally use congresses and/or courses to deliver educational material.

## EDUCATIONAL PROGRAMMES FOCUS ON THREE TOPICS

### AMR stewardship

Of all programmes submitted to the Benchmark for analysis, almost 90% have content that deals with issues of AMR awareness and stewardship, and offers ways to increase awareness of AMR among healthcare professionals. Companies such as Merck & Co., Inc. and Pfizer focus on the implementation of surveillance and stewardship programmes (i.e., programmes that monitor the rise and spread of

resistance, and programmes aimed at conserving the efficacy of antimicrobials). Examples include Pfizer's collaborations with the University of Dundee and the British Society for Antimicrobial Chemotherapy (BSAC), and Merck & Co., Inc.'s collaboration with the National Quality Forum to develop guidelines for implementing stewardship programmes in hospital settings (National Quality Partners Playbook: Antibiotic Stewardship in Acute Care). Other companies use data from surveillance programmes to build expertise: examples include GSK's Surveillance of Antibiotic Resistance (SOAR) programme of webcasts and meetings, where the company shares and disseminates up-to-date information about the treatment of community-acquired respiratory tract infections, to spread awareness on AMR.

### Rational use of antibiotics

WHO defines rational use as 'patients receiving medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.'<sup>15</sup> In company programmes, topics within this theme include appropriate diagnosis and prescription, improved adherence to treatment guidelines, and appropriate use of antibiotics to avoid unnecessary consumption. Linked to the paragraph before, GSK's SOAR programme consists of meetings to educate HCPs on appropriate prescribing and updated guidelines to improve appropriate use by patients; or Novartis' work with the Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy in Russia, sponsoring congresses covering topics such as appropriate diagnosis and treatment of multidrug resistant microorganisms.

### Disease-specific education

Content and activities in this theme include the sharing and updating of new treatment guidelines, and outlines of clinical cases that focus on a specific disease or groups of diseases. Johnson & Johnson, for example, has developed

educational programmes about multi-drug-resistant tuberculosis, including the MDR-TB New Drug Introduction and Protection (NDIP) programme in China, which provides conferences and training courses on clinical management and infection control, in combination with a donation programme for bedaquiline (Sirturo®).

## COMPANIES SHOW A PREFERENCE FOR ACTIVE LEARNING

The Benchmark evaluated 29 educational programmes run by 18 companies (see figure 42).

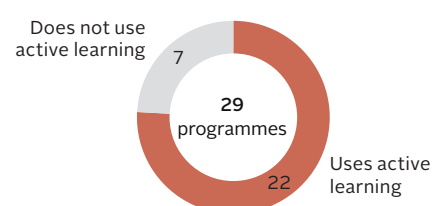
Twenty-two of the programmes deliver content through active learning channels such as courses, trainings, meetings and congresses; and twelve use passive learning (usually text-based) methods such as books, leaflets and webpages. Methods such as webcasts are in between, with both active and passive examples. Active learning methods are generally defined as those where attendees receive direct feedback from an instructor, as an integral part of the lesson; passive learning is typified by the traditional lecture, where the student does not interact with the instructor.<sup>16</sup>

Of the 29 programmes assessed, more than half (17) include meetings and congresses as a way of delivering educational content (see figure 43). Other frequently used methods are courses and trainings (in 11 programmes), as well as more passive tools such as leaflets, books and webpages (12). Webcasts are the least recurrent option, with only six activities delivered through this channel.

In reality, most companies combine both modes of learning and various types of delivery channel. Johnson & Johnson and Novartis, for example, use training sessions and meetings in half of their programmes, while other companies prefer delivering contents through leaflets or webpages combined with courses (Shionogi & Co., Merck & Co., Inc.). Pfizer, on the other hand, chooses

**Figure 42. Companies prefer active learning techniques to educate HCPs.**

Active learning techniques include courses, trainings, meetings and congresses.



courses and trainings in most of the programmes submitted.

More active methods of learning may be the most successful in changing the behaviour of target audiences, and may prompt participants to seek further education through, for example, training courses, massive open online courses (MOOCs), and continuing medical education (CME).<sup>17</sup>

Most programmes do not have a clear target audience; 'healthcare professionals' is the most commonly stated audience (for 20 programmes), a term that can cover highly specialised professionals to healthcare technicians operating in rural areas. 'Doctors' are targeted by 15 programmes (with some directing their contents to different specialists, including paediatricians, gynaecologists and infectious disease specialists). Three programmes target pharmacists, and one is for dentists. Pfizer is the only company to focus on policy makers, with the content in many of its educational AMR programmes covering the implementation of stewardship initiatives.

## MANAGING CONFLICTS OF INTEREST

The Benchmark evaluates all companies on their approaches to mitigating conflicts of interest (COI) within and arising from AMR educational activities. It considers the approaches and evaluates what companies are using to reduce the impact of such conflicts, and whether these are general, or particular to an individual programme. Companies report several different mechanisms and processes to mitigate COI in their educational activities directed at healthcare professionals. Out of 29 programmes, 21 give information about actions to mitigate conflicts of interest; most of these (18) report that content is developed independently; almost a third (13) run without branded materials; 11 do not include attendance payments for participants; and six have no commercial team involved in their development (see figure 45). It should be noted that the data do not allow

the Benchmark to conclude that the remaining programmes are in fact linked to such practices, only that there is no evidence that they are not.

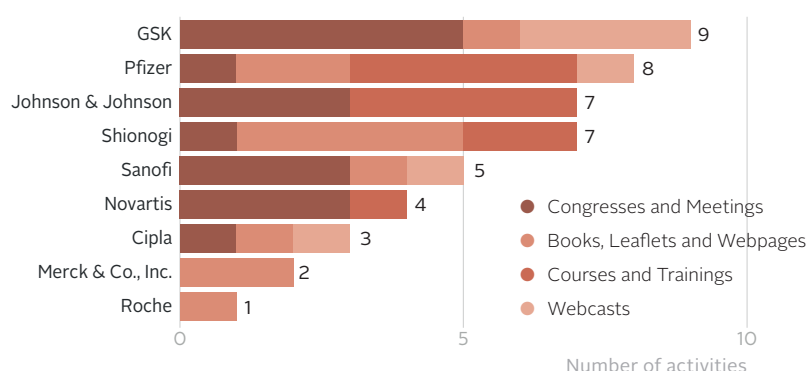
In general, companies can develop clearer policies and protocols for mitigating COI. One very effective mechanism is to partner with a public

organisation in the development and running of educational programmes. Both Johnson & Johnson and Pfizer are running educational programmes with public organisations.

GSK is a leader in the Benchmark's measure of COI mitigation, which evaluates approaches, not outcomes. Of all

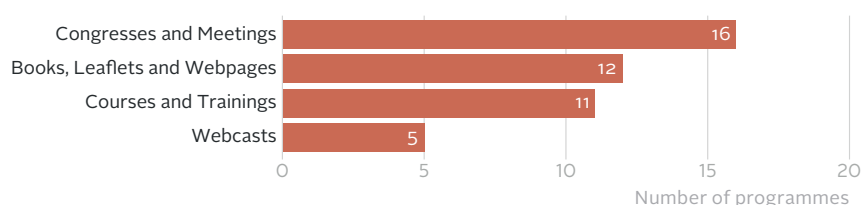
**Figure 43. Companies deliver AMR-related content through a mix of activities.**

Pharmaceutical companies support the education of HCPs on AMR stewardship via different activities, with a preference for congresses and meetings to involve students more directly in the discussion.



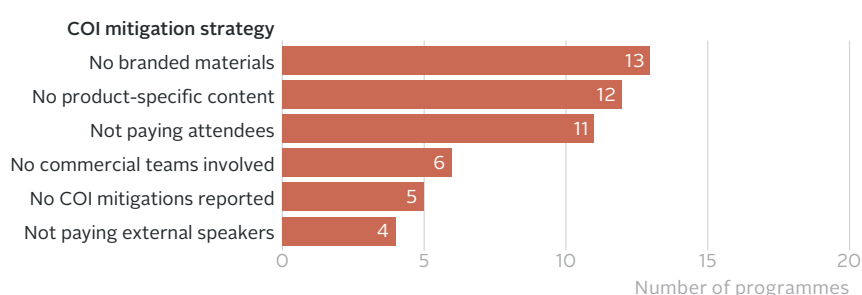
**Figure 44. Only five of the 29 programmes run educational webcasts.**

Of the 29 programmes assessed, 16 include congresses and meetings as a way of delivering contents. Other active learning methods (courses and trainings) are less popular, with 11 of the programmes using them to deliver content. Other options are books, leaflets and webpages. Only five of the 29 programmes run educational webcasts - a cost-effective and easy to use, universal medium.



**Figure 45. Non-branded educational materials are the most common conflict of interest (COI) mitigation techniques.**

Abstaining from branded materials and product-specific contents in educational materials are the two most common measures used by companies to mitigate COIs in AMR-related educational programmes. Not paying programme participants is also a relatively common measure, whereas not paying external speakers is relatively rare.



the companies evaluated, GSK makes the strongest commitment to reducing COI in its educational programmes, and provides evidence of a clear policy to address COI, applicable to all units. Under this policy, it no longer pays healthcare professionals to speak to other prescribers about prescription medicines and vaccines, and now uses an external body to select healthcare professionals for sponsorship to attend congresses. Most educational programmes are not product-specific, and GSK's commercial teams are, in some cases, not involved in developing materials. It also commits to disclosing payments to organisations and healthcare professionals.

Novartis and Pfizer perform strongly, too. Novartis develops and provides programmes without the involvement of commercial teams. Its compliance, medical and legal teams review programmes to help address and avoid conflicts of interest, and activities are non-promotional. Pfizer's programmes have a similar internal review process to ensure compliance. In addition, both companies reduce the risk of conflicts of interest by partnering with universities and scientific societies to run several of their programmes.

Johnson & Johnson operates most of its programmes in partnership with stakeholders who collaborate in developing content. Merck & Co., Inc., has created, through a subsidiary, a medical reference website called Univadis, which provides direct links to high-quality information and educational resources on AMR, ensuring independence. Where Merck & Co., Inc. participates as a partner in other educational programmes, it uses no company logos or branded products.

Shionogi delivers educational programmes without branding or product-specific contents.

Sanofi runs educational activities in France, China, Vietnam and India, using round tables and conferences and focussing on infectious disease management and appropriate use of antibiotics. While it does not provide evidence of a clear COI mitigation strategy and independent content development,

it has created the website Antibio-Responsible, giving information about the responsible use of antibiotics, and providing data about susceptibility and resistance.

Roche provides information solely for Roche China. The company reported that its China Headquarters provides on-demand educational materials on rational use of antibiotics for self-learning purposes, but stated that due to limited resources, it does not initiate educational programmes independently. Roche develops its own content but does not give clear details of strategies to mitigate COI and ensure independence.

Cipla is the only generic medicine manufacturer that reports different approaches to educate HCPs on AMR. Cipla's main focus is mostly on round tables, congresses and awareness campaigns to the general public. However, the company does not provide any information for mitigating conflict of interest (COI), or information on the content development. While not assessed in this Research Area, notably, Wockhardt's approach to AMR-related education is to improve patient knowledge through mobile clinics that provide free primary healthcare to rural populations in India (operated by the Wockhardt Foundation).

### **Mechanisms to mitigate COI**

Companies use several different mechanisms and processes to ensure they mitigate conflicts of interest. One very effective mechanism is to partner with a public organisation. Through this, companies can mitigate conflicts of interest by, for example, enabling public health authorities to educate healthcare professionals.

Johnson & Johnson and Pfizer are taking fresh, constructive approaches. More typically, pharmaceutical companies continue to run educational programmes that comprise congresses, meetings and symposia in which experts present and discuss a variety of topics. These programmes risk (and may be criticised for) conflicts of interest in multiple areas: how they develop content, use branded products, and

offer attendees economic and material incentives, for example.

Johnson & Johnson is running an educational programme in South Africa in conjunction with The International Union Against Tuberculosis and Lung Disease and the country's National Tuberculosis Program. Johnson & Johnson contributes unrestricted educational grants, enabling the Union to develop and deliver medical educational programmes about multidrug-resistant tuberculosis (MDR-TB) and the appropriate use of anti-tuberculosis drugs. Its 'train the trainers' approach enables a cascade of knowledge, heightening the programme's reach. The mechanism of funding the programme through unrestricted grants helps to ensure that content is developed independently, and to mitigate conflict of interest.

Another example is Pfizer's collaboration with the University of Dundee and the British Society for Antimicrobial Chemotherapy (BSAC). Together, the three organisations run a Massive Open Online Course (MOOC) on the subject of antimicrobial stewardship. The course's content, available in six languages, is developed by the University of Dundee and the BSAC, and spans a general view of the global impact of antimicrobial resistance through to specifics about how to implement stewardship programmes. It does not use branded materials.

By collaborating in this way, Pfizer reduces the risk of COI. In providing a relevant programme with independently developed content, it can make a positive impact to influence and change the behaviour of healthcare professionals. The three-way partnership also plans to publish an interactive book about antimicrobial stewardship, focusing on how to implement and evaluate programmes.

## STEWARDSHIP

# What steps are companies taking to ensure antimicrobials are promoted appropriately?

## INDICATOR

## C.5 Appropriate promotion practices

One of the main factors that contributes to the emergence of antibiotic resistance is the misuse and overuse of these medicines.<sup>8,10</sup> Examples of this include a healthcare professional deciding to prescribe antibiotics to treat a viral infection, or the sharing of antibiotics among friends and family members without recommended medical advice. Companies whose business models rely on making a high volume of sales can sometimes promote the misuse and overuse of antibiotics through their marketing practices. For example, rewarding sales staff for achieving high sales volumes works against conservation efforts designed to ensure antibiotics are used only when appropriate.<sup>18,19</sup> This can contribute to the emergence of antibiotic resistance. Similarly, materials used to market antimicrobials present an opportunity to raise awareness of the risks of AMR.

The industry is therefore encouraged to establish new business models with stakeholders to ensure access to new antibiotics, while supporting appropriate use, as recognised in the Industry Roadmap on AMR.

The Benchmark evaluates the promotional practices that companies develop to advance the appropriate use of antibiotics and to incentivise their sales representatives to market antibiotics in an appropriate way.

## EIGHT COMPANIES ARE CHANGING MARKETING PRACTICES IN FAVOUR OF STEWARDSHIP

Of the 18 companies assessed, nine commit to strengthening their promotion practices in relation to the stewardship of antimicrobials. Eight out of the 18 companies already use their marketing materials to highlight the risks of increasing resistance.

All large research-based pharmaceutical companies in scope have made a commitment to review their promotional activities in order to strengthen antimicrobial stewardship and promoting the appropriate use of antibiotics. Cipla is the only generic medicine manufacturer in scope that commits to appropriate promotion practices, while Cipla and Fresenius Kabi are the only generic medicine manufacturers that include resistance trends in marketing materials (see figure 46).

The most frequently identified marketing practice is a process known as decoupling — separating volume of sales-based incentives from sales-force remuneration. Four companies

take steps to adjust incentives for sales teams.

GSK demonstrates best practice in this area. Since 2013, the company has decoupled all sale incentives for sales agents from volumes of sales. The company now remunerates its sales force based on their technical knowledge, and the quality of service they deliver through in-clinic evaluation and monitoring. Shionogi has also fully decoupled its sales force's performance incentives from antibiotic sales volume. It does not remunerate its sales teams based on antibiotic sales volume.

Two other companies are also taking steps towards adjusting sales incentives. Novartis is adjusting incentives

**Figure 46. Nine companies commit to reviewing promotional activities.**

Four companies are taking steps to decouple performance incentives for sales teams from antibiotic sales volume. GSK and Shionogi have fully decoupled these incentives.

Company	Commits in the Industry Roadmap to reviewing promotional activities	Reflects AMR trends in marketing materials	Takes steps to adjust incentives for sales teams	Fully decouples sales force's incentives from antibiotic sales volume
<b>Large research-based pharmaceutical companies</b>				
GSK	●	●	●	●
Johnson & Johnson	●	●		
Merck & Co., Inc.	●			
Novartis	●	●	●	
Pfizer	●	●	●	
Roche	●			
Sanofi	●	●		
Shionogi	●	●	●	●
<b>Generic medicine manufacturers</b>				
Aspen				
Aurobindo				
Cipla	●	●		
Dr. Reddy's				
Fresenius Kabi		●		
Lupin				
Macleods				
Mylan				
Sun Pharma				
Teva				

for its sales teams around the world increasing the weight of fixed pay in overall compensation to reduce the variable component. Pfizer will begin a pilot to fully decouple its agents' antimicrobial incentives from sales volumes. Its materials and sales force training are reviewed by medical experts to ensure

they are aligned with antibiotic stewardship principles.

At least one other company is taking a different approach at the product level. Johnson & Johnson's new anti-tuberculosis drug, bedaquiline (Sirturo®), is provided solely through national tuberculosis programmes and therefore does

not require any marketing materials. The company reports that it does not deploy any sales organisations for the sale of Sirturo® in countries in scope.

All the other companies the Benchmark measures in this area show no evidence of developing or adopting appropriate promotion practices.

## BROCHURE AND PACKAGING

### Are companies adapting brochures and packaging to facilitate stewardship?

#### INDICATOR

C.6 Brochure and packaging

Brochure and packaging materials can be designed to improve both access (if understood as the combination of accessibility, availability, acceptability and quality) and stewardship: to support access, companies can address language and literacy rates, and ensure materials take account of cultural context and sensitivities; to support stewardship, companies can include information about using the medicine only when prescribed and for the entire treatment course, for example.

From the 18 companies assessed, eight companies provided information of possible brochure and packaging adaptations for evaluation. Of

these, six received some credit for their adaptations.

Most reported adaptations addressing stewardship comprise additional information brochures on, e.g., AMR and appropriate use. Two reported adaptations that aim to improve access for illiterate populations – neither has yet been implemented. Another example of a packaging adaptation is a blister pack for bedaquiline (Sirturo®) developed by Johnson & Johnson, which aims to ensure the quality of the product as well as improve adherence. Other adaptation for bedaquiline (Sirturo®) is a six-month presentation that can help improve adherence in places where DOTs strategies are taking place.

The other is from Novartis, which has created a dosing tool to indicate the correct dose of antibiotics in children. No company reports adapting brochures or packaging materials for language requirements, including into languages of specific regions within countries.

Cipla adapts its packaging to facilitate appropriate use of antibiotics by patients, by providing information on treatment duration. This can help to improve patient adherence to treatment. Mylan adapts its packaging with symbols and pictograms illustrating the necessary dosage schedule for patients. This adaptation can also improve adherence for illiterate populations.

## SURVEILLANCE

### How are companies supporting the surveillance of drug resistance?

#### INDICATOR

C.7 AMR surveillance

Antimicrobial resistance (AMR) is a global issue. Dealing with it effectively requires information about where it is emerging and spreading. In turn, this means taking a collaborative approach to making assessments, gaining the right information to take good decisions, and providing evidence for taking particular courses of action. In addition, all parties need to use harmonised standards to collect, analyse and share data about resistance.

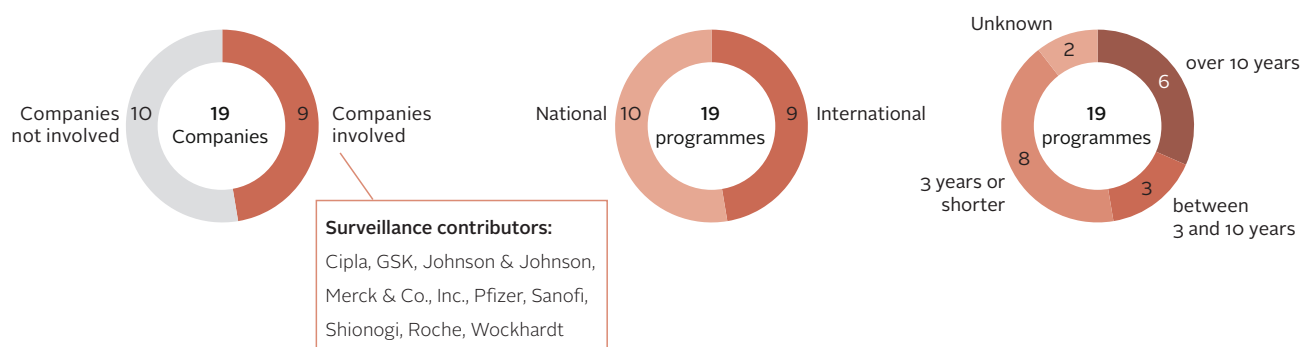
Using a comprehensive approach, national governments, international public health organisations (WHO), non-governmental organisations, industry and those in academia should work together to generate knowledge about AMR. Translating this knowledge into practice should help to promote the development of a global AMR surveillance network to closely observe and research antimicrobial resistance in every field of human medicine. Building such a network requires a large

amount of effort. National and international surveillance systems are now beginning to collect, analyse and share AMR data at all levels: patient, clinic and hospital. The World Health Organisation (WHO) is using its Global Antimicrobial Resistance Surveillance System (GLASS) to support its global action plan on AMR<sup>3,20</sup>, and to standardise procedures and foster collaboration.

Many pharmaceutical companies signed the 2016 Industry Roadmap for Progress in Combating Antimicrobial

**Figure 47. AMR surveillance: Number, geographical scope and length of surveillance programmes.**

The Benchmark found that nine of the 19 companies mentioned on surveillance activities (seven large research-based pharmaceutical companies, Cipla and Wockhardt) are running or supporting 19 AMR surveillance programmes across 147 countries.



Resistance, including 10 companies in the scope of the Benchmark. In doing so, they agreed to support efforts to increase the surveillance of AMR. Signatories commit to sharing their data with public health bodies and healthcare professionals, to working to improve understanding of resistance trends, and to helping increase surveillance capabilities around the world.<sup>7</sup>

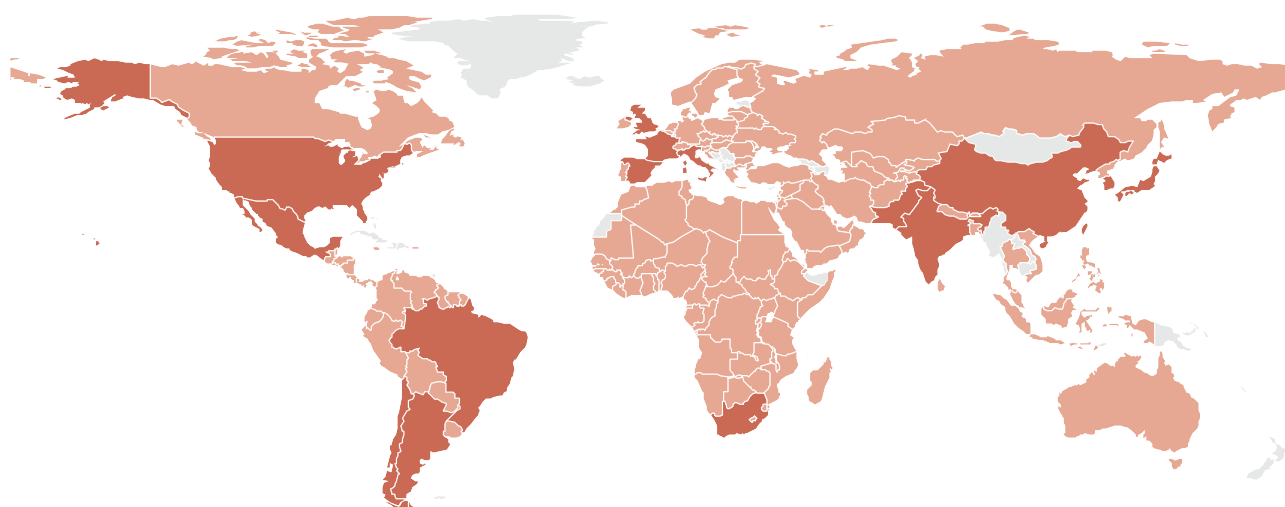
As antibiotic manufacturers, pharmaceutical companies have the material and economic means, as well as the technical expertise and experience, to undertake surveillance activities. Surveillance data is also useful for companies in different aspects. From an R&D perspective, surveillance shows

trends of how resistance spreads and provides data on new targets for new medicines, and data on new mechanisms of resistance. It can also help to identify unmet needs for new antibiotics or diagnostics. From a marketing perspective, it allows to model future resistance trends, and conduct pre- and post-launch surveillance programmes and establish products' lifecycles. This data can help fill in the gaps for many countries where health systems do not have the technical expertise.

The Benchmark assesses companies on their efforts to build a collaborative international AMR surveillance network. As part of this, it evaluates how they are working with academic institutions and public health authorities to enable the sharing of data and increase transparency. Eighteen companies have been analysed in this area as they have marketed antibiotics. Although not eligible for this area, Wockhardt is also mentioned due to its activity in surveillance programmes.

**Figure 48. AMR surveillance programmes are being conducted in 147 countries worldwide.**

Nine companies assessed by the Benchmark are engaged in surveillance programmes, active in 75% of countries in the world.



## OF THE 19 COMPANIES MENTIONED, ONLY NINE ARE ACTIVE IN AMR SURVEILLANCE PROGRAMMES

These companies – Cipla, GSK, Johnson & Johnson, Merck & Co., Inc., Pfizer, Sanofi, Shionogi, Roche and Wockhardt – contribute to 19 programmes. GSK, Johnson & Johnson, Wockhardt, Roche and Sanofi are running one programme each. The other four companies (Cipla, Pfizer, Merck & Co., Inc., and Shionogi) are running more than one surveillance activity.

Companies run surveillance activities in 147 countries, including 94 out of 106 countries identified by the Benchmark as those with the greatest need of access (see figure 48). Of the 94 countries, most have 1–2 programmes running (69), and India has the most with five programmes. Of all countries globally, Japan has the highest number of programmes in progress, with six surveillance activities in total.

Ten programmes have a national scope (Sanofi's programme in France, Shionogi's four surveillance programmes in Japan, Roche's research grants in China, Pfizer's LEADER and CHINET programmes in the US and China, respectively, and Cipla and Wockhardt's programmes in India), while the remaining nine are international in scope. Eleven programmes aim to measure long-term trends in antimicrobial resistance, but almost half of the programmes (8) are fewer than three years old, while six have run for more than ten years.

Only two companies publish the results of their surveillance programmes in full: Pfizer with its ATLAS (Antimicrobial Testing Leadership and Surveillance) programme, and Merck & Co., Inc. with its SMART (Study for Monitoring Antimicrobial Resistance Trends). A further five of the 19 programmes share their data with public health authorities, engaging in further AMR-related actions (such as the implementation of antimicrobial stewardship plans, or increasing the scope of the surveillance system, etc.). Most programmes (14) share their data through

articles in peer-reviewed journals and presentations at congresses.

GSK, Johnson & Johnson, Pfizer and Merck & Co., Inc. have international programmes for AMR surveillance. Seven of the programmes, both national and international, run in hospitals that offer secondary and tertiary care, and in operating rooms.

Only one programme (the SENTRY Programme, managed by JMI Labs and partnered with Pfizer) reports on AMR surveillance activities carried out at the community level. This means countries with less specialised health networks have less representative data, at least from the companies in scope, which constitutes a big gap. It will be important to help build surveillance networks in countries whose health systems cannot do this alone.

GSK demonstrates best practice with The Survey of Antibiotic Resistance, or SOAR, an international programme that focusses on observing AMR in respiratory tract infections. SOAR shares its results through peer-reviewed journals and congresses, and collaborates with public health authorities to develop and update therapeutic guidelines. Sanofi, Johnson & Johnson, Pfizer and Merck & Co., Inc. are doing similar things; however, GSK, together with the Wellcome Trust and the Open Data Institute, is working to develop an industry-sponsored surveillance database with open-source anonymised data sets. This would harmonise and open AMR surveillance data from companies to different stakeholders.

Sanofi, Johnson & Johnson, Pfizer and Merck & Co., Inc. have programmes to monitor resistance trends, sharing the results with public health agencies. Merck & Co., Inc. runs the SMART programme, while Pfizer runs ATLAS. These programmes have many similarities. Both have run for more than a decade, and both have a global scope in monitoring patterns of resistance. Results from both programmes are available publicly on webpages.

Both SMART and ATLAS report playing a supportive role for public health authorities. Pfizer reports engaging in many other programmes, such

as the Linezolid Efficacy and Accurate Determination or Resistance (LEADER), and the European Surgical Site Infections Epidemiology Study (EUPJI Network). One of its programmes, based in Latin America, reports looking at trends in antibiotic resistance and at the burden of disease due to *S. aureus*. As this region has a high need for surveillance systems, Pfizer's programme fills a gap, helping public health authorities to develop measures to prevent resistance.

Johnson & Johnson, through its Drug Resistance Emergence Assessment in MDR-TB (DREAM) programme, focusses on resistance to anti-tuberculosis drugs, such as its own product Sirturo (bedaquiline). It collaborates with WHO Supranational Reference Laboratories and national TB reference laboratories in 11 countries, providing funding through individual clinical study agreements. Johnson & Johnson shares its surveillance results in peer-reviewed journals, and with national TB programmes.

Sanofi partners with public health institutions to monitor AMR trends in France, for example. The company does not own the data, and depends on its partners to publish results in journals or at congresses.

While the generic manufacturing industry has a global market presence, Cipla is the only generic manufacturing company to run an AMR surveillance programme. Similarly, Wockhardt is the only company in the biopharmaceutical arena reporting a surveillance programme. Both operate programmes in India, where Cipla is involved in surveys and prevalence studies. Wockhardt runs a surveillance programme there, which works with hospitals and laboratories to monitor resistance trends. Roche China takes a different approach. The company awards grants to researcher-led projects, without imposing conditions on how the research is carried out. These grants are focussed on antibiotic susceptibility in China. Both Roche and Wockhardt publish results from their programmes in peer-reviewed journals.

## SALES CONTROL

# Are companies taking steps to reduce non-prescription (over-the-counter) sales?

## INDICATOR

## C.8 Reducing uncontrolled use

(Indicator not scored, due to data quality and availability)

While it is often considered the role of the government to track and control non-prescription or over-the-counter (OTC) sales, ten companies that have signed the Industry Roadmap, have committed to collaborate with governments and other stakeholders to reduce uncontrolled antibiotic purchases, including OTC sales. Some of these companies are putting practices in place to facilitate the appropriate use of antibiotics.

Pfizer reported its commitment to supporting government initiatives to reduce uncontrolled consumption of antibiotics. This is aligned with the Industry

Roadmap on AMR that some companies in scope have signed, where they committed to 'Collaborate with governments, their agencies and other stakeholders to reduce uncontrolled antibiotic purchase, such as via over-the-counter and non-prescription internet sales.' In practice, very little has been done, and most companies don't know where to start. While some companies are developing tools to track and trace products, it will not necessarily reduce OTC sales unless they share the data with authorities, collaborating to monitor OTC and non-prescription sales in pharmacies.

GSK's main approach to avoid OTC sales is educating pharmacists to reduce non-prescription sales, and other companies include AMR-related topics in the sales agents' educational contents, so they can sensitise pharmacists and retailers to reduce OTC.

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# Company Report Cards

The 2018 Antimicrobial Resistance Benchmark includes 30 company report cards, which each provide a contextualised analysis of one company's performance in the 2018 Benchmark. This includes a summary of its performance (both overall and per Research Area). Each report card includes overviews of the company's portfolio and pipeline, and identifies tailored opportunities for it to increase access to antimicrobial medicines, while ensuring their appropriate use. The report cards are divided into five areas:

## **Performance**

This section explains the relevance of the company for the Antimicrobial Resistance Benchmark and its overall performance. It covers:

- Drivers behind its scores
- Main areas where the company scores well or poorly compared to peers

## **Sales and Operations**

This section provides a general description of the company's global operations, including recent changes in its business (e.g., acquisitions or divestments), focussing on its antimicrobial business.

For biopharmaceutical companies with no products on the market, this section is called 'Operations'.

## **Antimicrobial Portfolio**

This provides a description of the number and type of antimicrobial medicines the company markets as of September 2017 and the proportion included on the WHO EML (Section 6).

## **Opportunities**

This section outlines opportunities for the company to do more to ensure access to antimicrobials and ensure their appropriate use. The opportunities take into account company-specific characteristics as far as possible.

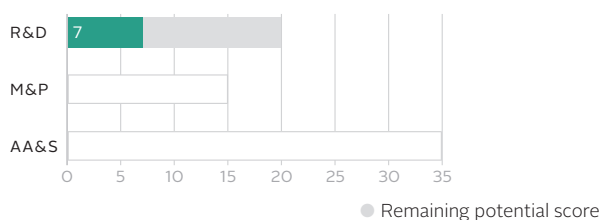
## **Performance by Research Area**

These three sections summarise company performance for each of the Research Areas, by indicator. The paragraphs describe the company's performance and highlight (where available) relevant examples of its activities.

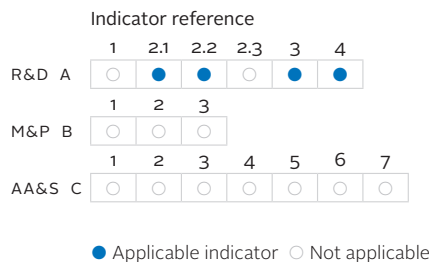
# Achaogen, Inc.

Stock exchange: XNAS • Ticker: AKAO • HQ: South San Francisco, CA, USA • Employees: 106 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Achaogen was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Achaogen is a biopharmaceutical company, selected for having a pipeline that targets priority pathogens. It was evaluated in the area of Research & Development only. The company's R&D investment in antibiotic drug development in 2016 amounts to USD 74 million, which is high compared to other biopharmaceutical companies in the Benchmark. Achaogen is a mid-performing company compared to the biopharmaceutical companies in scope. It has

four projects in its antimicrobial R&D pipeline, all targeting priority pathogens. The company engages in numerous public-private partnerships and agreements with various organisations to develop its antibiotic candidates. Achaogen has one R&D project in late-stage clinical development. It reported no information about whether this project is supported by access or stewardship provisions.

## OPERATIONS

Achaogen, founded in 2002, is a biopharmaceutical company focussing on the development of antibiotics to treat multidrug-resistant gram-negative bacterial infections. The company's most advanced drug candidate, plazomicin, is currently awaiting FDA approval following the completion of two successful Phase III trials: one in bloodstream infections caused by carbapenem-resistant Enterobacteriaceae (CRE) and the other in complicated urinary tract infection and

acute pyelonephritis. The company has a collaboration with Thermo Fisher Scientific, Inc. to develop and commercialise an assay to measure plazomicin levels in the blood, in order to ensure safe and effective dosing during treatment. Achaogen has no products on the market. To date, it has received financial support from various funders for the development of its pipeline, including BARDA, the US National Institute of Allergy and Infectious Diseases (NIAID), CARB-X

and the Bill & Melinda Gates Foundation. It was listed on the NASDAQ stock exchange in 2014, having raised approximately USD 72 million from shareholders such as Domain Partners, Venrock, Wellcome Trust and ARCH Venture Partners, among others. In 2016, it raised USD 25 million from a private placement (led by New Enterprise Associates).

## ANTIMICROBIAL PORTFOLIO

Achaogen does not have any products on the market.

## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Achaogen is developing one antibiotic candidate (plazomicin) in late-stage clinical development. Achaogen can ensure access and stewardship provisions are in place for plazomicin (e.g., through partnerships).

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT	Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	4 projects 4 target priority pathogens
		○	●	●	○	●	●		

### A.2.1-2.2 Four R&D projects that target priority pathogens.

Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. Achaogen invested USD 74 million in antibiotic drug development in 2016. The company is developing four projects that target gram-negative bacteria. Three of these projects involve the development of new drug candidates, while the remaining R&D project is an adaptation. Plazomicin, currently awaiting FDA approval, is Achaogen's most advanced candidate. Plazomicin is an aminoglycoside with activity against carbapenem-resistant Enterobacteriaceae, but is vulnerable to cross-resistance with other aminoglycosides such as gentamicin and amikacin. The two other R&D projects are candidates in preclinical stage and both target multidrug-resistant gram-negative bacteria: one investigates LpxC inhibitor compounds and the other monoclonal antibodies. The company is also developing C-Scape, a combination of a  $\beta$ -lactam and  $\beta$ -lactamase inhibitor, both already on the market and off-patent.

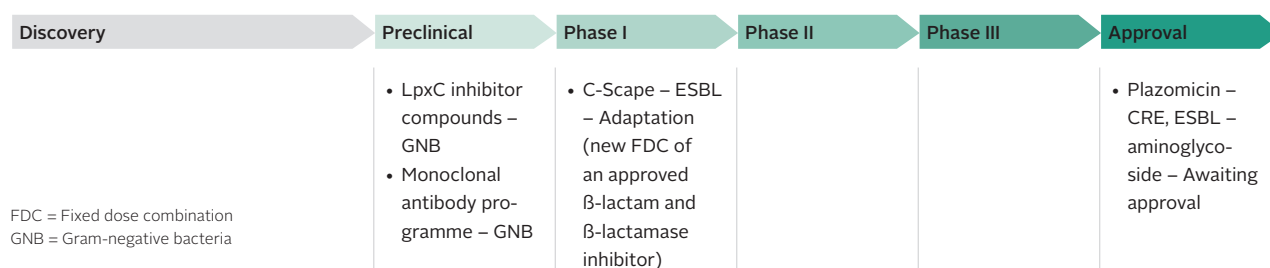
### A.3 Three R&D projects being developed with public partners.

Achaogen is developing two R&D projects in its priority pathogen pipeline through public-private partnership. It has funding agreements with four public partners for the development of three R&D projects in its priority pathogen pipeline. It has received financial support from BARDA for the development of plazomicin ( $\leq$ USD 123.8 million). The company also has a contract for  $\leq$ USD 5 million with the NIAID and recently received a CARB-X award to support its LpxC inhibitor programme for the treatment of bacterial infections, currently in preclinical stage. Furthermore, in May 2017, the company announced it would receive  $\leq$ USD 10.5 million in grant funding (along with a USD 10 million equity investment) from the Bill & Melinda Gates Foundation to further its preclinical R&D research on antibody candidates against gram-negative bacteria, including those that cause neonatal sepsis. Achaogen has also received BARDA funding for the development of C-Scape ( $\leq$ USD 18 million).

### A.4 No information on access or stewardship provisions.

Achaogen reports no information on access or stewardship provisions for its antibiotic candidate in late-stage development. It has signed the Davos Declaration, which includes a general commitment to ensuring access to antimicrobial medicines and vaccines, and to support the appropriate and responsible use of these products.

### Pipeline targeting priority pathogens



## MANUFACTURING & PRODUCTION

As a biopharmaceutical company with no products on the market, Achaogen was not eligible for this Research Area.

## APPROPRIATE ACCESS & STEWARDSHIP

As a biopharmaceutical company with no products on the market, Achaogen was not eligible for this Research Area.

## ANIMAL HEALTH & DIAGNOSTICS

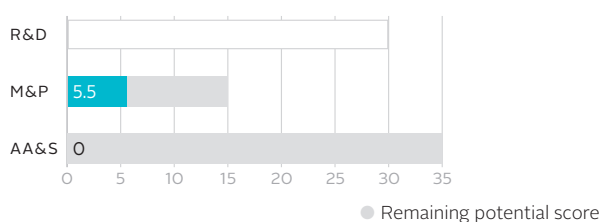
*Activities in this area are not scored by the Benchmark. This information is provided given the importance of animal health and diagnostics on the topic of AMR.*

Achaogen is developing a diagnostic assay for therapeutic drug management of plazomicin in a partnership with Thermo Fisher Scientific. This diagnostic platform monitors the levels of plazomicin in the blood in order to ensure safe and effective dosing during treatment.

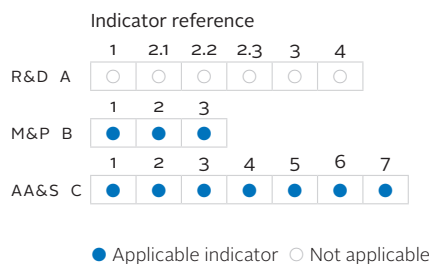
# Aspen Pharmacare Holdings Limited

Stock exchange: XJSE • Ticker: APN • HQ: Durban, South Africa • Employees: 10,204 • Signatory to Davos Decl.: No • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Aspen was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Aspen is a prominent producer of antibiotics globally by sales volume. As a generic medicine manufacturer, Aspen was evaluated in Manufacturing & Production and Appropriate Access & Stewardship only. It reported no information to the Benchmark, and publicly available information is limited. Although the company's performance in the Benchmark is lower compared to most other generic medicine manufacturers in scope, it reports a set of environmental risk-management principles that include an auditing process. There was

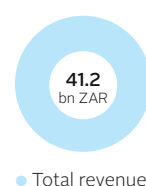
no evidence, however, that these principles are applied to its third-party suppliers of antibiotic APIs and drug products. It reports mechanisms for maintaining high quality of antibiotic production at its own manufacturing sites. The company reports no information regarding an equitable pricing approach, or where it files products for registration. Aspen does not report any involvement in stewardship activities that promote appropriate antibiotic use.

## SALES AND OPERATIONS

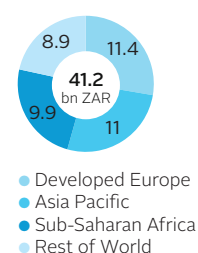
Aspen is a global supplier and manufacturer of generic pharmaceutical products and active pharmaceutical ingredients, as well as infant nutritional and consumer health products. The company has a substantial presence in low- and middle-income countries in regions such as Latin America, Russia, Eastern Europe, sub-Saharan Africa (SSA) and South Asia, with 25 manufacturing facilities worldwide. Throughout SSA, it is a market leader in the antibiotics, respiratory, pain, cough and cold segments. Its primary therapeutic focus areas are thrombosis, anaesthetics, cytotoxics, and infant nutritional.

In 2016, Aspen acquired GSK's portfolio of anaesthetic products (five medicines), as well as exclusive rights to commercialise AstraZeneca's anaesthetics portfolio (seven medicines) in 100 countries worldwide (including, e.g., China, but excluding, e.g., the USA). In 2009, Aspen and GSK formed the "GSK Aspen Healthcare for Africa" collaboration in SSA, which came to an end in January 2017, with GSK paying Aspen GBP 45 million.

## Revenues by product<sup>§</sup>



## Revenues by region<sup>§</sup>

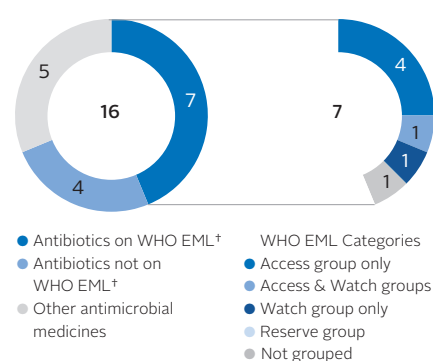


## ANTIMICROBIAL PORTFOLIO

According to publicly available data, Aspen markets at least 16 antimicrobial medicines, ten of which are listed on the WHO EML (Section 6). Eleven of the company's antimicrobials are antibiotics, with seven on the WHO EML (Section 6), including ceftazidime, in the EML's Watch group,

and ciprofloxacin, in both the Access and Watch groups. The remainder (five) of the company's portfolio includes antifungals, antiprotozoals and the anthelmintic albendazole. The company also markets an antiseptic face wash containing triclosan.

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Net revenue; FYE 30 June 2017

## OPPORTUNITIES

**Engage in antimicrobial stewardship.** Aspen can engage in stewardship activities, e.g., through surveillance activities, educational activities for healthcare professionals on AMR (while mitigating conflicts of interest), and engage in appropriate promotion practices.

**Expand environmental risk-management strategy.** Aspen can ensure its antibiotic discharge limits are applied to its environmental risk-management strategy. It can also extend this strat-

egy to the sites of third parties that manufacture antibiotic APIs and drug products on its behalf, as well as to external waste-treatment sites. Aspen currently discloses a general environmental risk-management strategy that it applies to its own manufacturing sites.

**Ensure affordability and registration plans for new and existing antimicrobials.** Aspen can seek to improve access in low- and middle-income countries through registration of new and

existing antimicrobials, and ensure that they are priced affordably. Currently, the company does not disclose such information.

## PERFORMANCE BY RESEARCH AREA

### RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Aspen's main focus is the manufacturing of generic products and as such was not in scope for this Research Area.

### B MANUFACTURING & PRODUCTION

Indicators scored on 1 2 3

#### B.1 Environmental risk-management principles for own sites.

Aspen has set environmental risk-management principles to minimise the impact of antibiotic manufacturing discharge. These apply to its own manufacturing sites and include auditing. There is no evidence that they are applicable to third-party manufacturers of antibiotic APIs and drug products or to external waste-treatment plants. The company reports no information about setting discharge limits.

#### B.2 Limited transparency regarding environmental risk management.

Aspen publishes its environmental risk-management principles in its annual report. It does not disclose audit results, or the discharge levels of antibiotics. The company also does not share the identities of its third-party suppliers of antibiotic APIs and drug products or external waste-treatment plants.

#### B.3 Commits to following GMP.

Aspen reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites, but the company does not report any commitment relating to how GMP standards apply to its third-party suppliers of antibiotic drug products.

### C APPROPRIATE ACCESS & STEWARDSHIP

Indicators scored on 1 2 3 4 5 6 7

#### C.1 No information on filing for registration.

Aspen reports no information on where it has filed its newest antibiotics for registration in countries in scope.\* This information is not otherwise publicly available.

#### C.2 No disclosure on equitable pricing approach.

Aspen does not disclose an equitable pricing approach for its highest-volume antibiotics and/or antimicrobial medicines.

#### C.3 No insight into steps addressing supply chain efficiency.

Aspen does not disclose how it works with stakeholders (e.g., governments, procurers) to align supply and demand for antimicrobial medicines, specifically to prevent or minimise stock-outs in countries in scope.\* The company also does not report on whether it has processes in place to respond to stock-outs in countries in scope.\*

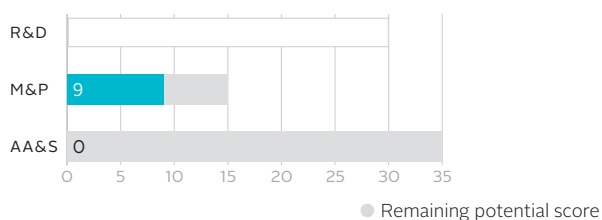
#### C.4-C.7 No apparent involvement in stewardship activities.

Aspen does not report any involvement in stewardship activities (from education to surveillance to appropriate promotion practices) that promote appropriate antibiotic use.

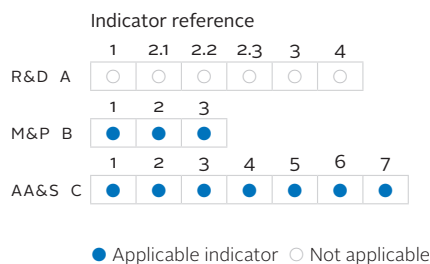
# Aurobindo Pharma Limited

Stock exchange: XNSE • Ticker: AUOPHARMA • HQ: Hyderabad, India • Employees: 13,982 • Signatory to Davos Decl.: No • Signatory to Industry Roadmap: No\*\*

## Performance by Research Area



## How Aurobindo was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Aurobindo is a prominent producer of antibiotics globally by sales volume. As a generic medicine manufacturer, Aurobindo was evaluated in Manufacturing & Production and Appropriate Access & Stewardship only. The company performs well when compared with the other generic medicine manufacturers in scope. It performs well in Manufacturing & Production, but falls behind in Appropriate Access &

Stewardship. Aurobindo discloses a comprehensive environmental risk-management strategy, which is applied to external waste-treatment plants. The company reports that it has mechanisms in place for maintaining high quality of antibiotic production. Aurobindo does not report any involvement in stewardship activities that promote appropriate antibiotic use.

## SALES AND OPERATIONS

Aurobindo is a manufacturer of active pharmaceutical ingredients (APIs) and oral and injectable generic formulations. Its portfolio covers seven major therapeutic areas, including antibiotics, antiretrovirals (ARVs) and cardiovascular and central nervous systems. It has nine manufacturing units for APIs and intermediate products and seven for formulations, as well as R&D centres in India and the USA. Aurobindo markets its products in more than 150 countries worldwide, with a focus on the USA and Europe. It sells antimicrobial medicines in at least 92 countries, at least 50 of which are low- and middle-income countries.\* In the fiscal year 2016,

it sold 1.45 billion units (DDDs) of antimicrobial medicines. Within its antimicrobial business, the company is currently focussing on developing its manufacturing capacity of penems — broad-spectrum antibiotics used for multi-drug-resistant infections. In 2017, Aurobindo entered a multilateral agreement to provide a new class of ARVs (developed within a licensing agreement with Gilead Sciences Inc. and ViiV Healthcare) to low- and middle-income countries. In return for guaranteed minimum sales volumes, Aurobindo will supply a generic FDC of dolutegravir/lamivudine/tenofovir for a maximum price of about USD 75 per patient per year.

## ANTIMICROBIAL PORTFOLIO

Aurobindo markets at least 40 antimicrobial medicines, 28 of which are listed on the WHO EML (Section 6). Eighteen of the company's antimicrobial medicines are antibiotics, with 12 listed on the WHO EML (Section 6), includ-

ing five on the EML's Watch group. The remainder (22) of the company's portfolio comprises 20 antivirals (16 of which target HIV) and two antifungals.

## OPPORTUNITIES

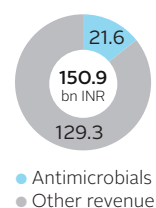
**Engage in antimicrobial stewardship.** Aurobindo can engage in stewardship activities, e.g., through surveillance activities, educational activities for healthcare professionals on AMR (while mitigating conflict of interest), and engage in appropriate promotion practices.

**Ensure affordability and registration plans for new and existing antimicrobials.** Aurobindo can seek to improve access in low- and middle-income countries through the registration of new and existing antimicrobials, and ensure that they are priced affordably. Currently, the company

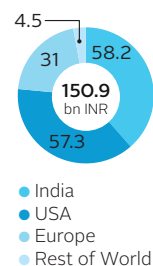
does not disclose such information.

**Ensure transparency regarding environmental risk management.** Aurobindo can share more information on how it manages environmental risk (e.g., the company can publish the results of audits carried out on its environmental risk-management strategy and the identities of external waste-treatment plants). After the period of analysis, the company disclosed the identities of external waste-treatment plants to the Benchmark.

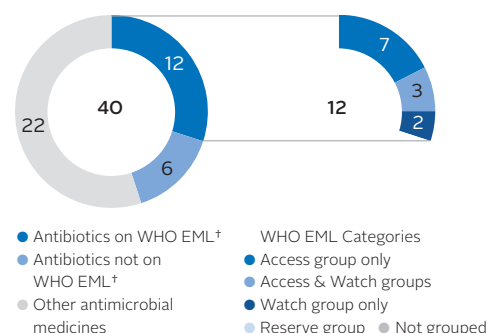
## Revenues by product<sup>§</sup>



## Revenues by region<sup>§</sup>



## Antimicrobial portfolio breakdown



**Expand environmental risk-management strategy.** Aurobindo can set and apply discharge limits for antibiotic manufacturing. It currently has an environmental risk-management strategy that applies to its own manufacturing sites and external waste-treatment sites.

**Increase engagement in R&D innovation.** Aurobindo is currently engaged in developing a new fixed dose combination of antiretroviral medicines. It can continue to engage in incremental R&D, and ensure access and stewardship provisions are in place for these projects.

\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Revenue from operations; FYE 31 March 2017

\*\* Company states it has applied to be a signatory

## PERFORMANCE BY RESEARCH AREA

### A RESEARCH & DEVELOPMENT

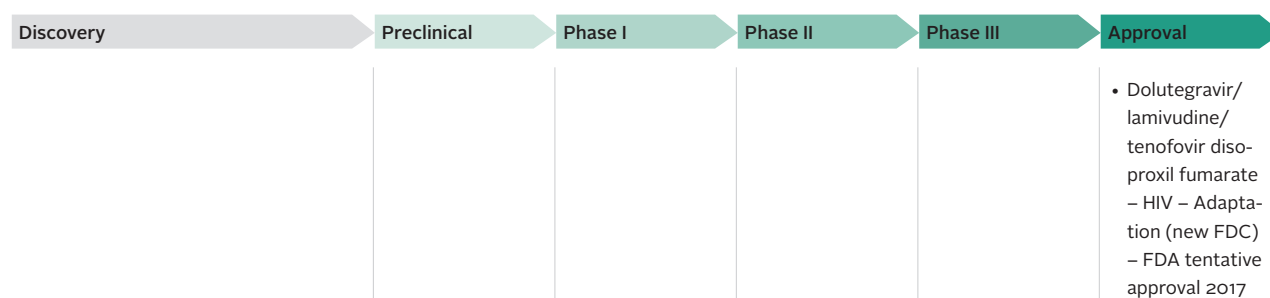
As a generic medicine manufacturer, Aurobindo was not eligible for this Research Area. However, the company is active in antimicrobial R&D.

#### One fixed dose combination for HIV/AIDS.

On reviewing publicly available information, the Benchmark found that Aurobindo has one project in its antimicrobial R&D pipeline that targets HIV. This involves dolutegravir/lamivudine/tenofovir disoproxil fumarate, a new FDC for

the treatment of HIV/AIDS. In 2017, Aurobindo received FDA tentative approval for this FDC, as it consists of patented antiretrovirals from Gilead Sciences Inc., Bristol-Myers Squibb Co. and ViiV Healthcare.

#### Pipeline targeting priority pathogens



FDC = Fixed dose combination

### B MANUFACTURING & PRODUCTION

Indicators scored on 1 2 3  
● ● ●

#### B.1 Environmental risk-management strategy for own and external sites.

Aurobindo has an environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge. The strategy includes auditing and applies to its own sites and external waste-treatment plants. For a subset of sites, Aurobindo follows a Zero-Liquid Discharge process (ZLD, a water treatment process in which all wastewater is cleaned and reused); for others it deactivates antibiotics prior to external waste treatment. The company reports no infor-

mation about setting discharge limits. Aurobindo states that it does not use third-party suppliers for the manufacturing of antibiotic drug products.

#### B.2 Limited transparency regarding environmental risk management.

Aurobindo publishes its environmental risk-management strategy in its annual report. It does not disclose audit results, or the discharge levels of antibiotics. The company does not share the identities of its external waste-treatment plants.

After the period of analysis the company disclosed the identities of external waste-treatment plants to the Benchmark.

#### B.3 Commits to following GMP.

Aurobindo reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards.

### C APPROPRIATE ACCESS & STEWARDSHIP

Indicators scored on 1 2 3 4 5 6 7  
● ● ● ● ● ● ●

#### C.1 No information on filing for registration.

Aurobindo reports no information on where it has filed its newest antibiotics for registration in countries in scope.\* This information is not otherwise publicly available.

#### C.2 No disclosure on equitable pricing approach.

Aurobindo does not disclose an equitable pricing approach for its highest-volume antibiotics and/or antimicrobial medicines. The company states that its approach to affordability is through tenders.

#### C.3 No insight into steps addressing supply chain efficiency.

Aurobindo does not disclose how it works with stakeholders (e.g., governments, procurers) to align supply and demand for antimicrobial medicines, specifically to prevent or minimise stock-outs in countries in scope.\* The company also does not report on whether it has processes in place to respond to stock-outs in countries in scope.\*

#### C.4-C.7 No apparent involvement in stewardship activities.

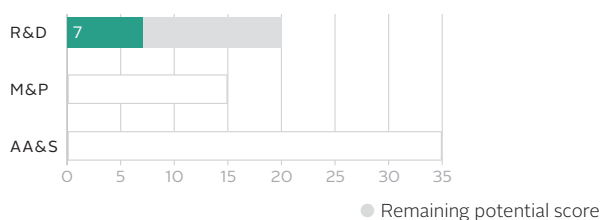
Aurobindo does not report any involvement in stewardship activities (from education to surveillance to appropriate promotion practices) that promote appropriate antibiotic use.

# Cempra, Inc.

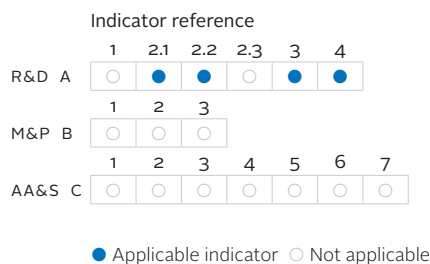
Merged with Melinta Therapeutics, Inc. in 2017

Stock exchange: XNAS • Ticker: CEMP • HQ: Chapel Hill, NC, USA • Number of employees: 45 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Cempra was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Cempra is a biopharmaceutical company that has recently merged with Melinta, selected for having a pipeline that targets priority pathogens. It was evaluated in the area of Research & Development only. Its R&D investment in antibiotic drug development in 2016 amounted to USD 82 million. It is a mid-performing company compared to the biopharmaceutical companies in scope. Cempra's pipeline consists of one novel drug candidate and one adaptation, both in clin-

ical-stage development. The company engages in public-private partnerships and agreements with various organisations to develop its antibiotic candidates. Cempra reported no information on having any access or stewardship provisions in place for its late-stage clinical R&D projects.

## OPERATIONS

Cempra, founded in 2006, was a biopharmaceutical company focussing on the development of differentiated anti-infectives for acute and community care settings. In 2017, the company announced it would merge with Melinta Therapeutics, Inc., a biopharmaceutical company also in scope of the Benchmark. The merger was completed in November 2017.

Cempra was formed by in-licensing Optimer Pharmaceuticals' macrolide programme, with the aim of developing a superior macrolide, with less toxic properties than the recently introduced telithromycin—the first ketolide antibi-

otic to enter clinical use. This led to solithromycin, currently in clinical stage of development, in both intravenous and oral formulations, for the treatment of community-acquired bacterial pneumonia and gonorrhoea.

Prior to merging with Melinta, Cempra had no products on the market. In 2013, it received five-year funding from the Biomedical Advanced Research and Development Authority (BARDA) for approximately USD 60 million to develop solithromycin. The company was considering additional indications for this compound, for example, for the treatment of malaria, tuberculosis, *H. pylori* gastritis and various infections in

cystic fibrosis patients. The company was also investigating compounds from its macrolide platform, which have the potential to treat bacteria typically responsible for human skin and lung infections, as well as respiratory disease in animal health.

Cempra was listed on the NASDAQ stock exchange in 2012, raising approximately USD 47.7 million. Prior to this, between 2006 and 2009, company investors included Intersouth Partners, Aisling Capital, Optimer Pharmaceuticals and Quaker Bioventures, among others.

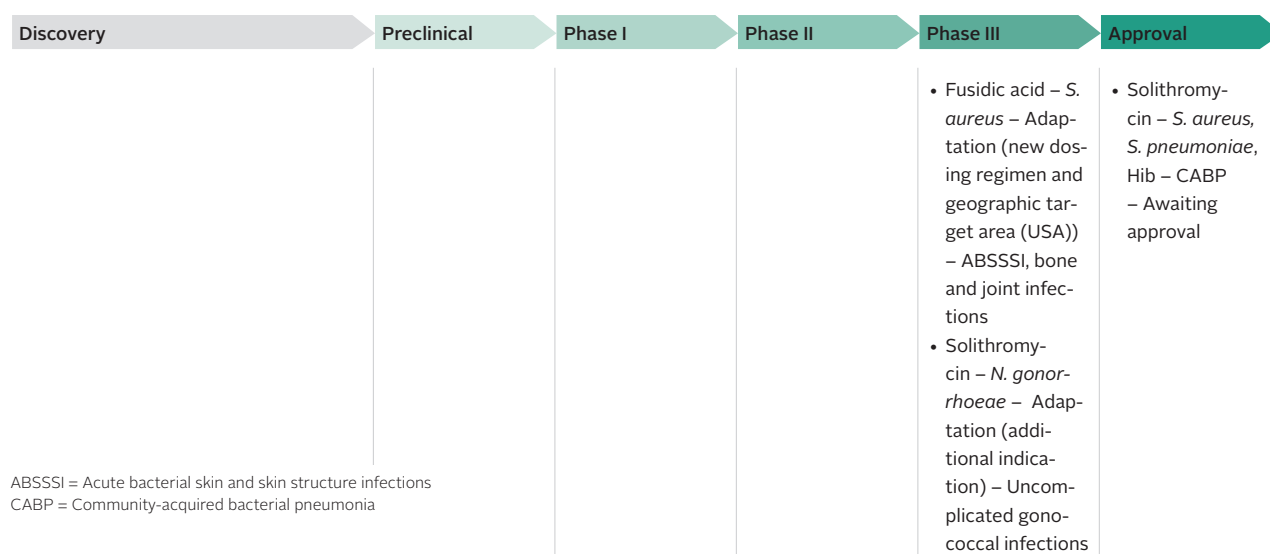
## ANTIMICROBIAL PORTFOLIO

Cempra does not have any products on the market.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT		Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	3 projects 3 target priority pathogens
<p><b>A.2.1-2.2 One new medicine and two adaptations in the pipeline.</b></p> <p>Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. Cempira invested USD 82 million in antibiotic drug development in 2016. The company has three projects in its antimicrobial R&amp;D pipeline, all targeting priority bacteria. Its antibiotic candidate, solithromycin, is a macrolide developed for community-acquired bacterial pneumonia (CABP). The medicine was submitted to the FDA in 2016 for market approval, but was rejected due to inadequate characteristics of liver toxicity, and detected deficiencies in the manufacturing facilities of the company's manufacturing contractors (Wockhardt Limited and Hospira, Inc.). A similar EMA application has subsequently been withdrawn. Additionally, solithromycin is in Phase III clinical development for the treatment of gonorrhoea. Cempira is also developing a new and proprietary regimen of fusidic acid (Taksta™), an existing antibiotic with activity against methicillin-resistant <i>S. aureus</i> (MRSA).</p>			○	●	●	○	●	●		
<p><b>A.3 One R&amp;D project being developed with public partners.</b></p> <p>Cempira is developing one R&amp;D project in its priority pathogen pipeline through public-private partnership. It has received financial support from BARDA for the development of solithromycin. This began in 2013 and will last for five years. The BARDA grant provides Cempira with funding for the clinical development of the compound for the treatment of bacterial infections in paediatric populations. The most recent funding instalment (March 2016 to mid-2018) amounted to USD 25.5 million, for the conclusion of Phase II/III studies on intravenous, oral capsule and oral suspension formulations for paediatric patients with community-acquired bacterial pneumonia (CABP).</p>										
<p><b>A.4 No information on access or stewardship provisions.</b></p> <p>Cempira reports no information on access or stewardship provisions for its two antibiotic candidates in late-stage development. It has signed the Davos Declaration, which includes a general commitment to ensuring access to antimicrobial medicines and vaccines, and to support the appropriate and responsible use of these products.</p>										

## Pipeline targeting priority pathogens



## B MANUFACTURING &amp; PRODUCTION

As a biopharmaceutical company with no products on the market, Cempira was not eligible for this Research Area.

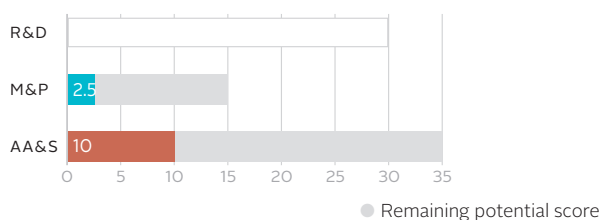
## C APPROPRIATE ACCESS &amp; STEWARDSHIP

As a biopharmaceutical company with no products on the market, Cempira was not eligible for this Research Area.

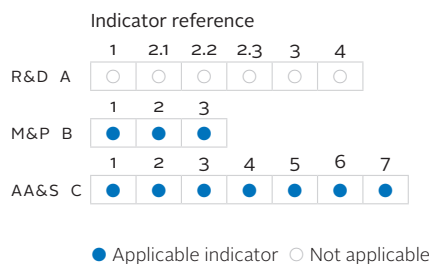
# Cipla Limited

Stock exchange: XNSE • Ticker: CIPLA • HQ: Mumbai, India • Number of employees: 23,043 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: Yes

## Performance by Research Area



## How Cipla was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Cipla is a prominent producer of antibiotics globally by sales volume. As a generic medicine manufacturer, Cipla was evaluated in Manufacturing & Production and Appropriate Access & Stewardship only. The company is among the top performing generic medicine manufacturers. It performs strongly in Appropriate Access & Stewardship but falls behind in Manufacturing & Production. Cipla has no environmental risk-management strategy; however, it reports having mecha-

nisms in place for maintaining a high quality of antibiotic production at its own manufacturing sites. The company reports that it has not filed its five newest antibiotics for registration in countries in scope.\* It reports equitable pricing strategies for its five highest-volume antimicrobial medicines. Cipla's performance in stewardship is driven by its engagement in a number of stewardship activities including AMR surveillance programmes.

## SALES AND OPERATIONS

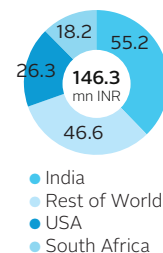
Cipla is an Indian-based generic medicine manufacturer founded in 1935. Its pharmaceuticals segment develops, manufactures and markets generic medicines, as well as active pharmaceutical ingredients (APIs). Cipla (including associates) is present in over 80 countries, has 43 manufacturing facilities worldwide and markets over 1,500 products across various therapeutic areas, with a major focus on respiratory health, API development and Global Access. Its business areas are: respiratory health, APIs and Cipla Global Access. Cipla Global Access is an international tender-based institutional business that concentrates on five key therapy areas: HIV/AIDS, malaria, multidrug-resistant tuberculo-

sis, hepatitis C and reproductive health. In 2016, Cipla completed the acquisition of US-based Exelan Pharma and InvaGen Pharmaceuticals, which expanded the company's portfolio in the USA, along with its manufacturing and R&D capabilities. In early 2017, it divested its animal health business (operated by subsidiaries Cipla Agrimed SA and Cipla Vet SA, primarily in sub-Saharan Africa (SSA)) to Ascendis Pharma. Cipla sells antimicrobial medicines in Australia, India, South Africa and the USA, as well as in low- and middle-income countries\* such as Sri Lanka, Nepal, Myanmar, and in some regions of the Middle East, Latin America and SSA.

## Revenues by product<sup>§</sup>



## Revenues by region<sup>§</sup>

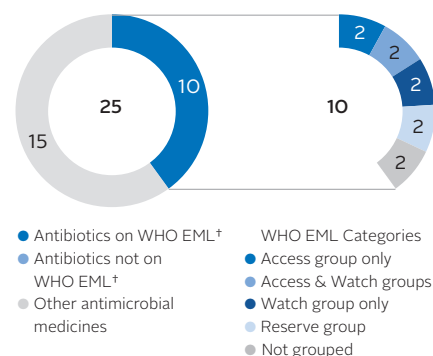


## ANTIMICROBIAL PORTFOLIO

Cipla markets at least 25\*\* antimicrobial medicines, 23 of which are listed on the WHO EML (Section 6). The remaining two medicines are the antivirals lamivudine and efavirenz/lamivudine/tenofovir (listed on the EML with different doses than those marketed by Cipla). All ten of the company's antibiotics appear on the WHO EML (Section 6), including two antibiotics in the EML's Reserve group (colistin and linezolid). The

remainder of the company's portfolio comprises 13 antivirals (indicated for HIV/AIDS, hepatitis B or hepatitis C) and two antiprotazoals indicated for the treatment of malaria.

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

\*\* Cipla provided only a sample of its global antimicrobial portfolio

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Revenue from operations; FYE 31 March 2017; regional breakdown by business unit provided by company

## OPPORTUNITIES

**Develop an environmental risk-management strategy.** Cipla has stated a commitment to develop and implement an environmental risk-management strategy. It can ensure its strategy includes discharge limits and auditing processes, which apply to the company's own manufacturing sites, to the sites of third-party suppliers and to external waste-treatment sites.

**Increase engagement in antimicrobial stewardship.** Cipla can engage in appropriate promotion activities. It can ensure that current AMR edu-

cational activities for HCPs include conflict of interest mitigations. Cipla has conducted several AMR surveys, and can engage in the development of long-term AMR surveillance programmes.

**Improve access through the registration of antibiotics in more countries.** Cipla can file its new and existing antimicrobials for registration in more low- and middle-income countries. Cipla has reported that it has not filed its newest antibiotics for registration in countries in scope.\*

**Increase engagement in R&D innovation.** Cipla is currently engaged in adapting generic antimicrobial medicines. For example, the company is currently engaged in developing new formulations for HIV/AIDS and for malaria in collaboration, respectively, with the Drugs for Neglected Diseases Initiative (DNDi) and the Medicines for Malaria Venture (MMV). It can continue to engage in incremental R&D, and ensure access and stewardship provisions are in place for these projects.

## PERFORMANCE BY RESEARCH AREA

### A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Cipla was not eligible for this Research Area. However, the company is active in antimicrobial R&D.

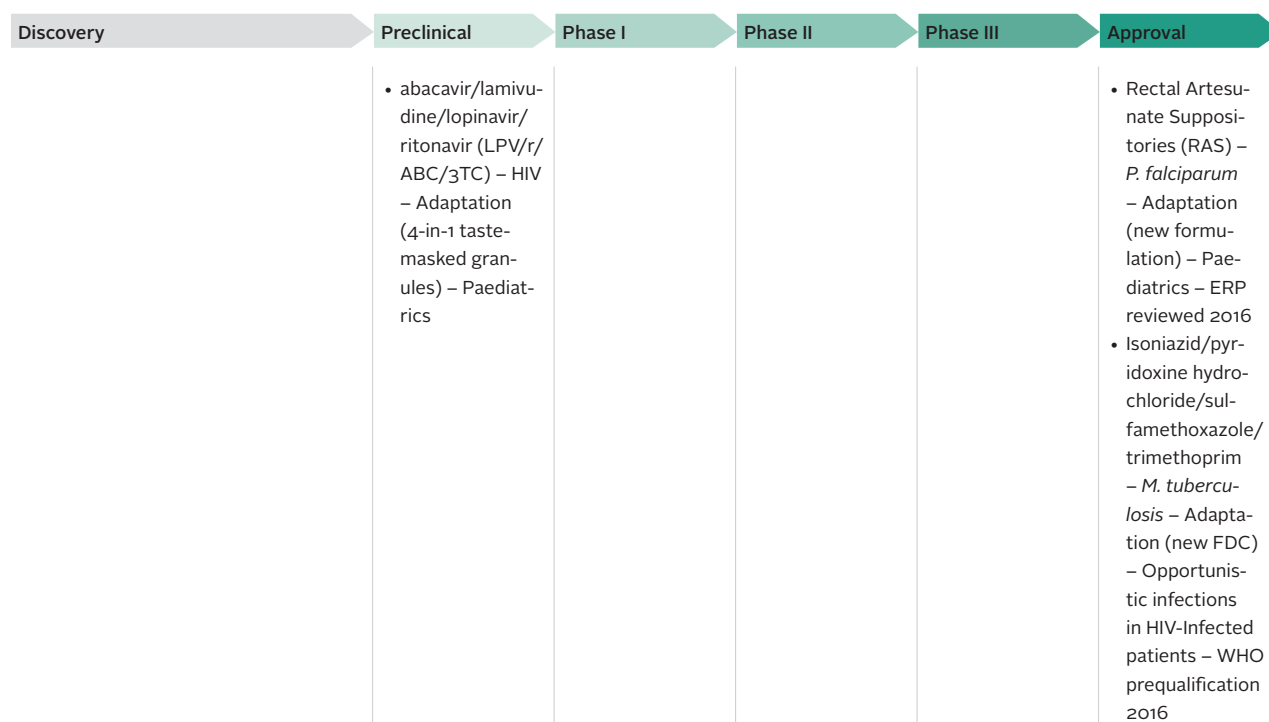
#### Three R&D projects, most being developed with public partners.

The company reports that it has three antimicrobial R&D projects, targeting HIV, *P. falciparum* (malaria) and *M. tuberculosis*. Regarding R&D collaborations with public partners, Cipla is

developing taste-masked granules of an abacavir/lamivudine/lopinavir/ritonavir combination for paediatric patients with HIV/AIDS in collaboration with DNDi. This project is currently in pre-clinical stage. The company has developed its Rectal Artesunate Suppositories (RAS) together with MMV. The Global Fund's Expert Review Panel (ERP) authorized procurement of RAS for pre-referral management of severe malaria in 2016 and the medicine is moving through its

final stages in WHO prequalification. Cipla aims to make RAS available to rural areas in Africa and to national community health programmes, with the support of international donors that have already pledged to procure it. Cipla is also the first generic medicine manufacturer to develop a combination of isoniazid/pyridoxine hydrochloride/sulfamethoxazole/trimethoprim, which received WHO prequalification in 2016 for preventing tuberculosis in HIV/AIDS patients.

#### Pipeline targeting priority pathogens



B MANUFACTURING & PRODUCTION		Indicators scored on	1	2	3
<b>B.1 Commits to developing environmental risk-management strategy.</b> Cipla currently has no environmental risk-management strategy in place to minimise the impact of antibiotic manufacturing discharge. Notably, however, it has committed to developing one in 2018 in an effort to be in line with the commitments in the Industry Roadmap.			●	●	●
<b>B.2 No transparency on environmental risk management.</b> Cipla does not publish any element looked for by the Benchmark, namely: antibiotic discharge levels, audit results, and the identities of its third-party suppliers of antibiotic APIs and drug products, or of its external waste-treatment plants. It has, however, committed to develop an environmental risk-management strategy in 2018 in line with its commitments as a signatory to the Industry Roadmap.					
<b>B.3 Commits to following GMP.</b> Cipla reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites but the company does not report any commitment relating to how GMP standards apply to its third-party suppliers of antibiotic drug products.					

C APPROPRIATE ACCESS & STEWARDSHIP		Indicators scored on	1	2	3	4	5	6	7
<b>C.1 Newest antibiotics not filed for registration.</b> Cipla reports that it has not filed its five newest antibiotics for registration in countries in scope.*			●	●	●	●	●	●	●
<b>C.2 Inter-country equitable pricing for antimicrobials.</b> Cipla discloses inter-country equitable pricing approaches, taking gross national income (GNI) into account, for its five highest-volume antimicrobial medicines. These pricing approaches reportedly apply in all countries in scope* where Cipla markets these products. This covers Latin America, sub-Saharan Africa and a subset of other countries.									
<b>C.3 General commitment to ensuring supply chain efficiency.</b> Cipla has made a general commitment to improve supply chain efficiency. During the period of analysis, the Benchmark identified no information on how Cipla works with stakeholders (e.g., governments, procurers) to align supply and demand for antimicrobial medicines, specifically to prevent or minimise stock-outs in countries in scope. The company also did not then									



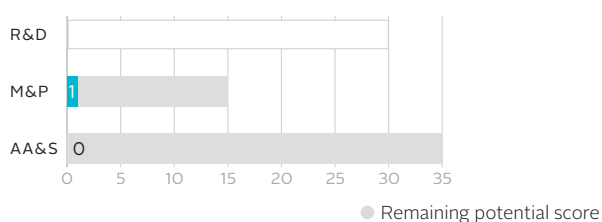
# Dr. Reddy's Laboratories Ltd.

Stock exchanges: XNSE; XNYS • Tickers: DRREDDY; RDY • HQ: Hyderabad, India • Employees: 22,681

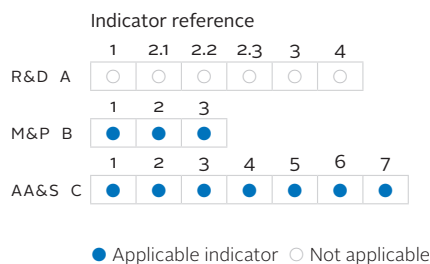
Signatory to Davos Decl.: No

Signatory to Industry Roadmap: No

## Performance by Research Area



## How Dr.Reddy's was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Dr. Reddy's is a prominent producer of antibiotics globally by sales volume. As a generic medicine manufacturer, Dr. Reddy's was evaluated in Manufacturing & Production and Appropriate Access & Stewardship only. Its performance is low compared to most other generic medicine manufacturers in scope. It reported no information to the Benchmark, and publicly available information is limited, specifically regarding its approach to manufacturing high quality antibiotics, its

approach to equitable pricing, where it has filed antibiotics for registration, its actions to ensure efficient supply and its involvement in stewardship activities. However, Dr. Reddy's has an environmental risk-management strategy that is based on a zero-liquid discharge (ZLD) process at all its manufacturing sites, including manufacturing sites for antibiotics.

## SALES AND OPERATIONS

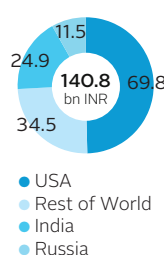
Dr. Reddy's is a generic medicine manufacturer founded in 1984, with commercial presence in 26 countries. Its core therapeutic areas include oncology, gastroenterology, cardiovascular health, diabetes and anti-infectives. The company's Global Generics segment manufactures and markets prescription and over-the-counter (OTC) medicines (generics and medicines manufactured in its biologics unit). Its Proprietary Products segment develops and manufactures differentiated formulations in dermatology and neurology. It has 25 manufacturing facilities: 18 in India (including seven for active pharmaceutical ingredients), three in the USA, two in the UK and one each in China and Mexico. It has ten

R&D facilities: six in India, two in the USA and two in Europe. In 2015, Dr. Reddy's acquired several established brands from UCB for the territories of India, Nepal, Sri Lanka and Maldives, covering dermatology, respiratory diseases, ear, nose and throat disorders, and paediatrics. In 2016, it completed the acquisition of eight products from Teva's US portfolio. In 2017, it signed a global licensing pact with CHD Bioscience (USA), to develop and commercialise CHD's Phase III clinical candidate DFA-02 for USD 30 million. DFA-02 is a gentamicin/vancomycin extended-release gel indicated for the prevention of surgical site infection following non-emergency, elective colorectal surgery.

## Revenues by product<sup>§</sup>



## Revenues by region<sup>||</sup>

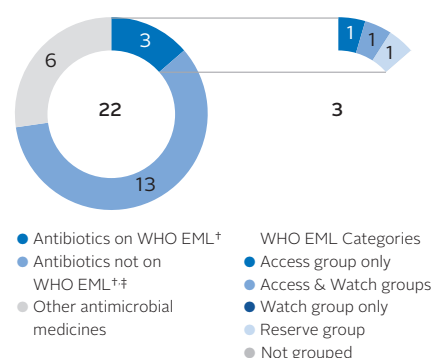


## ANTIMICROBIAL PORTFOLIO

According to publicly available data, Dr. Reddy's markets at least 22 antimicrobial medicines, seven or more of which are listed on the WHO EML (Section 6). Sixteen of the company's antimicrobial medicines are antibiotics, with at least three listed on the WHO EML (Section 6), including one antibiotic in the EML's Reserve

group (linezolid). The remaining six medicines are three antivirals and three antifungals. The company also markets an influenza vaccine in Germany, via its subsidiary Betapharm.

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.

† EML Section 6: Anti-Infective Medicines

‡ Includes antibiotics whose formulation or dose could not be determined

§ Revenue from operations; FYE 31 March 2017

|| Sales (inc. excise duty), license fees, and service income; excluding other operating income; FYE 31 March 2017

## OPPORTUNITIES

### Engage in antimicrobial stewardship.

Dr. Reddy's can engage in stewardship activities, e.g., through surveillance activities, educational activities for healthcare professionals on AMR (while mitigating conflict of interest), and engage in appropriate promotion practices.

**Improve transparency on environmental risk management.** Dr. Reddy's can share information on how it manages environmental risk, e.g.,

information on discharge limits for its own and third-party manufacturers' sites. The company currently discloses its environmental risk-management activities in its corporate sustainability report.

**Ensure affordability and registration plans for new and existing antimicrobials.** Dr. Reddy's can seek to improve access in low- and middle-income countries through the registration of new

and existing antimicrobials, and ensure that they are priced affordably. Currently, the company does not disclose such information.

**Engage in R&D innovation.** Dr. Reddy's can engage in incremental R&D innovation to address resistance, improve adherence and the appropriate use of antimicrobial medicines.

## PERFORMANCE BY RESEARCH AREA

### A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Dr. Reddy's main focus is the manufacturing of generic products and, as such, was not in scope for this Research Area.

### B MANUFACTURING & PRODUCTION

Indicators scored on 1 2 3 ● ● ●

#### B.1 Follows Zero-Liquid Discharge at own sites.

Dr. Reddy's environmental risk-management approach is based on following a zero-liquid discharge (ZLD) process at all its manufacturing sites, including manufacturing sites for antibiotics. Dr. Reddy's reports no information about setting discharge limits or auditing this process. It does not appear to have extended this approach to its third-party manufacturers of antibiotic APIs and drug products, or to external waste-treatment plants.

#### B.2 No transparency on environmental risk management.

Dr. Reddy's does not disclose its strategy to minimise the impact of manufacturing discharge of antibiotics. It does not publish any element looked for by the Benchmark, namely: antibiotic discharge levels, audit results, and the identities of its third-party suppliers of antibiotic APIs and drug products, or of its external waste-treatment plants.

#### B.3 No statement on how antibiotic quality is maintained.

Dr. Reddy's makes no statement regarding how it ensures high quality antibiotic production following international manufacturing standards accepted by recognised national and international authorities (such as GMP).

### C APPROPRIATE ACCESS & STEWARDSHIP

Indicators scored on 1 2 3 4 5 6 7 ● ● ● ● ● ● ●

#### C.1 No information on filing for registration.

Dr. Reddy's reports no information on where it has filed its newest antibiotics for registration in countries in scope.\* This information is not otherwise publicly available.

#### C.2 No disclosure on equitable pricing approach.

Dr. Reddy's does not disclose an equitable pricing approach for its highest-volume antibiotics and/or antimicrobial medicines.

#### C.3 No insight into steps addressing supply chain efficiency.

Dr. Reddy's does not disclose how it works with stakeholders (e.g., governments, procurers) to align supply and demand for antimicrobial medicines, specifically to prevent or minimise stock-outs in countries in scope.\* The company also does not report on whether it has processes in place to respond to stock-outs in countries in scope.\*

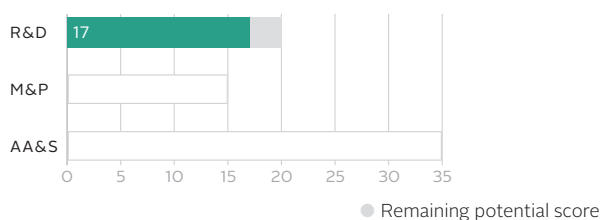
#### C.4-C.7 No apparent involvement in stewardship activities.

Dr. Reddy's does not report any involvement in stewardship activities (from education to surveillance to appropriate promotion practices) that promote appropriate antibiotic use.

# Entasis Therapeutics Inc.

Stock exchange: Privately held • HQ: Waltham, MA, US • Number of employees: 30 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Entasis was evaluated: applicable indicators

		Indicator reference						
		1	2.1	2.2	2.3	3	4	
R&D	A	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	
		1	2	3				
M&P	B	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>				
		1	2	3	4	5	6	7
AA&S	C	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Entasis is a biopharmaceutical company, selected for having a pipeline that targets priority pathogens. It was evaluated in the area of Research & Development only. Entasis invested USD 10-20 million in antibiotic drug development in 2016. The company is the leader among other biopharmaceutical companies in scope. It has five projects in its antimicrobial R&D pipeline, all targeting priority pathogens, including one novel

antibiotic candidate. Entasis engages in numerous public-private partnerships and agreements with various organisations to develop its antibiotic candidates. Entasis has one R&D project in late-stage clinical development, for which it has an access provision and stewardship commitment in place.

## OPERATIONS

Entasis is a privately held US-based biopharmaceutical company established in 2015 with start-up funding from AstraZeneca and full rights to a subset of its small-molecule anti-infectives pipeline. The company focusses on creating innovative medicines to treat diseases caused by drug-resistant gram-negative bacteria. Its pipeline includes both clinical and pre-clinical small-molecule antibacterials, target-

ing, among others, *N. gonorrhoeae*, *P. aeruginosa* and *A. baumannii*. The company's most advanced drug candidate is zoliflodacin, indicated for the treatment of uncomplicated gonorrhoea. Entasis has no products on the market. In 2016, the company raised USD 50 million in a Series B financing round, which was led by Clarus and included Frazier Healthcare Partners, Novo Holdings A/S and Eventide Fund. This

was extended in September 2017 by an additional USD 31.9 million from Pivotal bioVenture Partners, Sofinnova Ventures and TPG Biotech.

## ANTIMICROBIAL PORTFOLIO

Entasis does not have any products on the market.

## OPPORTUNITIES

### Develop stewardship plan for zoliflodacin.

Entasis has signed a licensing agreement to ensure access and the responsible use of its antibiotic candidate (zoliflodacin) in late-stage clinical development, that covers 168 countries. It can develop a plan for ensuring appropriate use of the product, on approval, in remaining territories.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT	Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	5 projects 5 target priority pathogens
		○	●	●	○	●	●		

**A.2.1–2.2 One novel antibiotic in the clinical pipeline.**

Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. Entasis invested USD 10–20 million in antibiotic drug development in 2016. The company has five projects in its antimicrobial R&D pipeline targeting priority pathogens, largely focussing on gram-negative bacteria. Its novel antibiotic candidate zoliflodacin is an innovative bacterial topoisomerase II inhibitor with a new mode of action, for which no cross-resistance has been described. Although zoliflodacin has broad-spectrum activity, it is currently in development for the treatment of gonorrhoea only. Entasis is seeking to optimize the medicine's dosing regimen for this indication, as well as limit its widespread use for other indications to prevent emergence of resistance. Additionally, Entasis has particular expertise in the structure and function of bacterial  $\beta$ -lactamases, and is involved in the development of new and improved  $\beta$ -lactamase inhibitors in combination with existing  $\beta$ -lactams. ETX2514 is a broad-spectrum  $\beta$ -lactamase inhibitor, which is being developed in two different

combinations: with sulbactam and with imipenem. ETXo282 is a combination of cefpodoxime with a broad-spectrum class A and C  $\beta$ -lactamase inhibitor.

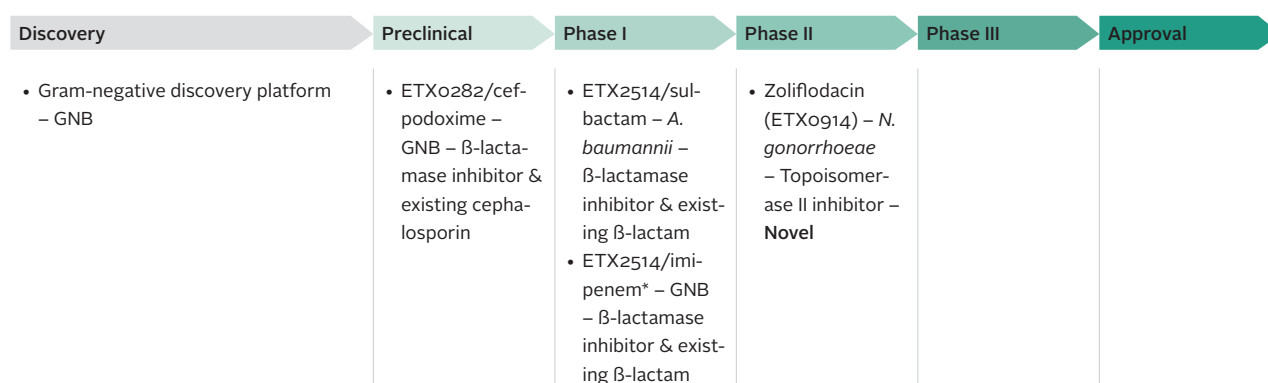
**A.3 Three R&D projects being developed with public partners, including one PDP.**

Entasis is developing three R&D projects in its priority pathogen pipeline through public-private partnership. In July 2017, the company announced a collaboration with Global Antibiotic Research & Development Partnership (GARDP) for the clinical development of zoliflodacin after successfully finishing Phase II studies that were funded and conducted by the US National Institute of Allergy and Infectious Diseases (NIAID). Through this PDP, GARDP is responsible for the clinical trials, including financing, managing, and coordinating Phase III trials, pharmacovigilance and drug registration in the countries where it has licensing rights. Entasis retains commercial rights in the majority of mature markets, and grants GARDP an exclusive and royalty-free licence (for the treatment of gonorrhoea) with sublicensing rights for global manufacturing and sale and distribution in 168 countries or

territories. In March 2017, Entasis received funding from CARB-X to develop ETXo282/cefepodoxime through Phase I clinical development. The company also received a second CARB-X award in October 2017 to progress its discovery-stage penicillin-binding protein inhibitor programme from lead optimization through Phase I clinical trials.

**A.4 Access provision and stewardship commitment in place for zoliflodacin.**

Entasis reports that it has an access provision in place and stewardship commitment for its antibiotic in late-stage development. The access provision for its investigational antibiotic (zoliflodacin) has been developed through its collaboration with GARDP. GARDP is responsible for providing access and promoting the responsible use of zoliflodacin in their respective territories (168 countries identified by GARDP where access to medicine is likely limited). Entasis is committed to developing stewardship programmes, as well as affordable and equitable pricing, in order to ensure access in mature markets.

**Pipeline targeting priority pathogens**

GNB = Gram-negative bacteria

\* This project is considered as an adaptation for scoring, as ETX2514 is considered as a new project in the ETX2514/sulbactam combination.

**B MANUFACTURING & PRODUCTION**

As a biopharmaceutical company with no products on the market, Entasis was not eligible for this Research Area.

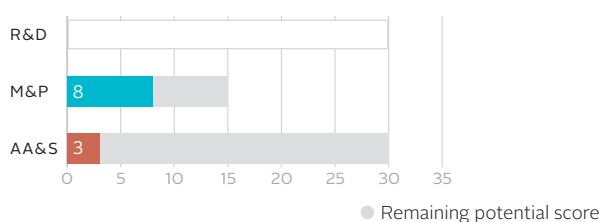
**C APPROPRIATE ACCESS & STEWARDSHIP**

As a biopharmaceutical company with no products on the market, Entasis was not eligible for this Research Area.

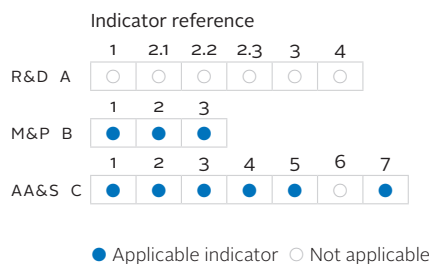
# Fresenius Kabi AG

Stock exchange: XFRA • Ticker: FRE • HQ: Bad Homburg, Germany • Employees: 34,917 • Signatory to Davos Decl.: via MFE • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Fresenius Kabi was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Fresenius Kabi is a prominent producer of antibiotics globally by sales volume. As a generic medicine manufacturer, Fresenius Kabi was evaluated in Manufacturing & Production and Appropriate Access & Stewardship only. The company is among the top performing generic medicine manufacturers. It discloses an environmental risk-management strategy for its own sites. Fresenius Kabi reports mechanisms for maintaining a high quality of antibiotic production and also requires its third-party suppliers of drug products to apply the same

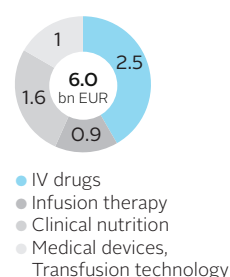
quality standards to their production facilities. Fresenius Kabi reports information on where it files antibiotics for registration; however, there is no information available regarding the company's approach to equitable pricing for its highest-volume antimicrobial medicines. Regarding stewardship, the company reflects AMR trends in its marketing materials through leaflets on AMR-related topics for its top marketed products.

## SALES AND OPERATIONS

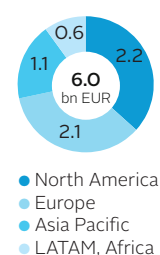
Fresenius Kabi is a wholly owned subsidiary of Fresenius SE & Co. KGaA, and specialises in medicines and technologies for infusion, transfusion and clinical nutrition in the field of critical and chronic care. It has four business segments: intravenous (IV) drugs; infusion therapy; clinical nutrition; and medical devices & transfusion technology. Its IV drugs segment includes anti-infectives. In 2017, Fresenius Kabi announced that it would acquire Akorn Inc., a US-based manufacturer and marketer of prescription and over-the-counter ophthalmic,

injectable and specialty sterile and non-sterile pharmaceuticals. Also in 2017, the company completed the acquisition of Merck KGaA's biosimilars business, whose product pipeline focussed on oncology and autoimmune diseases. Fresenius Kabi markets its antimicrobial medicines in 34 countries globally, six of which are low- or middle-income countries.\* All of the company's antimicrobial medicines are infusion or powder-for-injection formulations.

## Revenues by product§



## Revenues by region§

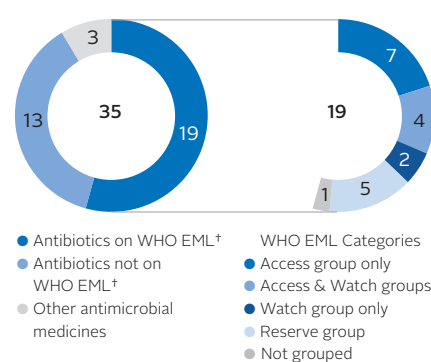


## ANTIMICROBIAL PORTFOLIO

Fresenius Kabi markets at least 35 antimicrobial medicines, 21 of which are listed on the WHO EML (Section 6). Thirty-two of the company's antimicrobial medicines are antibiotics, with 19 listed on the WHO EML (Section 6), including five in the EML's Reserve group (aztreonam, cefepime, daptomycin, linezolid and tigecycline).

The remaining three medicines are an antifungal (fluconazole) and the antivirals aciclovir and ganciclovir, indicated for infections caused by herpes virus and cytomegalovirus, respectively.

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

† EML Section 6: Anti-Infective Medicines

§ Sales, FYE 31 December 2016

## OPPORTUNITIES

**Increase engagement in antimicrobial stewardship.** Fresenius Kabi adopts some appropriate promotion practices through leaflets on AMR-related topics for its top marketed products. It can engage in more stewardship activities, e.g., through surveillance activities, educational activities for healthcare professionals on AMR (while mitigating conflict of interest), and expand on appropriate promotion practices.

**Improve access to new and existing antimicrobials.** Fresenius Kabi can file its new and existing antimicrobials for registration in more countries. Fresenius Kabi has filed two of its newest antibiotics for registration in countries in scope.\*

The company can also seek to improve access in low- and middle-income countries by ensuring its new and existing antimicrobials are priced affordably.

**Improve transparency regarding environmental risk management.** Fresenius Kabi can share more information on how it manages environmental risk, e.g., the company can publish the results of audits carried out on its environmental risk-management strategy. Fresenius Kabi already discloses environmental risk principles.

**Expand its environmental risk-management strategy.** Fresenius Kabi can ensure its environ-

mental risk-management strategy is extended to the sites of third parties who manufacture antibiotic APIs and drug products on its behalf. Fresenius Kabi currently has an environmental risk-management strategy, that includes auditing processes, and is applied to its own manufacturing sites.

**Engage in R&D innovation.** Fresenius Kabi can engage further in incremental R&D innovation to address resistance and improve appropriate use of antimicrobial medicines. The company already engages in incremental R&D directed at improving usability of its medicines by HCPs.

## PERFORMANCE BY RESEARCH AREA

### A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Fresenius Kabi's main focus is the manufacturing of

generic products and, as such, was not in scope for this Research Area.

### B MANUFACTURING & PRODUCTION

Indicators scored on 1 2 3

#### B.1 Environmental risk-management strategy for own sites.

Fresenius Kabi has a general environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge. This applies to its own manufacturing sites and includes audits. There is no information suggesting that the strategy is applicable to third-party manufacturers of antibiotic APIs and drug products or to external waste-treatment plants. The company reports no information about setting discharge limits.

#### B.2 Limited transparency regarding environmental risk management.

Fresenius Kabi publishes its environmental risk-management principles in its annual report. It does not disclose audit results, or the discharge levels of antibiotics. The company also does not share the identities of its third-party suppliers of antibiotic APIs and drug products, or external waste-treatment plants.

#### B.3 Commits to following GMP, including at 3rd-party sites.

Fresenius Kabi reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. Fresenius Kabi requires its third-party suppliers to apply the same quality standards to their production facilities.

### C APPROPRIATE ACCESS & STEWARDSHIP

Indicators scored on 1 2 3 4 5 6 7

#### C.1 Some newest antibiotics filed in some countries in scope.

Fresenius Kabi reports information about where it has filed some of its newest antibiotics for registration in some countries in scope.\* However, the Benchmark is not able to publish further information, as all details were provided on the basis of confidentiality.

#### C.2 No information available on equitable pricing approach.

There is no information available regarding Fresenius Kabi's approach to equitable pricing for its highest-volume antibiotics and/or antimicrobial medicines.

#### C.3 No insight into steps addressing supply chain efficiency.

Fresenius Kabi does not disclose how it works with stakeholders (e.g., governments, procurers) to align supply and demand for antimicro-

bial medicines, specifically to prevent or minimise stock-outs in countries in scope.\* The company also does not report on whether it has processes in place to respond to stock-outs in countries in scope.\*

#### C.4 No information on AMR-related education.

There is no information available regarding Fresenius Kabi's involvement in AMR-related educational activities for HCPs.

#### C.5 Adopts some appropriate promotion practices.

The Benchmark measures how companies address stewardship through appropriate promotion practices. Fresenius Kabi is one of two generic medicine manufacturers that reports taking action in this regard by reflecting AMR trends in its marketing materials. For example, the company created, for its top marketed

products, leaflets aimed at informing HCPs on AMR-related topics. These leaflets include AMR-related information under the "Special Warnings and Precautions for Use" section. There is no information available on decoupling of the company's sales force's incentives from volume of antibiotic sales.

#### C.6 No antibiotics dispensed directly to patients.

Fresenius Kabi is not eligible for this indicator as it does not have any antibiotics in its portfolio that are directly dispensed to patients. All of its antibiotics are administered in the hospital.

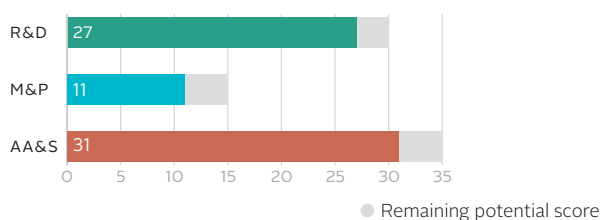
#### C.7 No information regarding AMR surveillance programmes.

There is no information available regarding Fresenius Kabi's efforts to engage in AMR surveillance programmes.

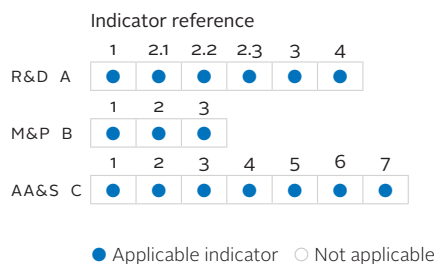
# GlaxoSmithKline plc

Stock exchange: XLON • Ticker: GSK • HQ: Brentford, UK • Employees: 99,300 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: Yes

## Performance by Research Area



## How GSK was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

GSK performs well in all three Research Areas, and is one of the leaders when compared with other large research-based pharmaceutical companies in scope. GSK has the largest antimicrobial R&D pipeline of all large research-based pharmaceutical companies in scope: 55<sup>†</sup> projects, of which 40<sup>†</sup> target priority pathogens, including several novel candidates and 12 new vaccine candidates. It has access and/or stewardship provisions in place for most late-stage candidates. GSK discloses the most comprehensive environmental risk-management strategy of all companies evaluated, which includes discharge limits and reportedly applies to all GSK's third-party suppliers of antibiotic APIs and drug products, as well as to

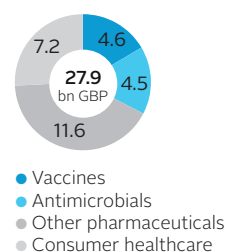
external waste-treatment plants. GSK has filed its five newest antibiotics for registration in many countries in scope.\* It also reports a comparatively broad inter- and intra-country equitable pricing approach for antimicrobial medicines, as well as multiple steps to improve supply chain efficiency. In stewardship, GSK reports that it engages in several AMR education programmes aimed at healthcare professionals, taking action to mitigate conflict of interest in these programmes. It has ceased remunerating sales staff based on sales volume. It engages in AMR surveillance and collaborates and shares its data with public health authorities.

## SALES AND OPERATIONS

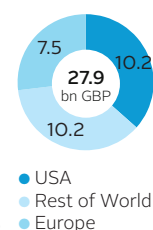
GSK is a large research-based pharmaceutical company with three divisions: pharmaceuticals, vaccines and consumer healthcare. In 2016, GSK sold the largest volume of antibiotics of all companies in scope of the Benchmark. During 2016, the company's leading antibiotics were sold in 126 countries, 57 of which were low- and middle-income countries\*. In 2009, GSK and Pfizer established ViiV Healthcare, a joint venture solely focussed on the development of HIV/

AIDS medicines. Shionogi joined ViiV Healthcare in 2012. Equity positions in ViiV Healthcare are GSK: 76.5%, Pfizer: 13.5% and Shionogi: 10%. In 2015, GSK completed the acquisition of Novartis' vaccine business (excluding influenza vaccines) and in return divested its marketed oncology portfolio to Novartis. In the same year, GSK sold two of its meningococcal vaccines to Pfizer (Mencevax® and Nimenrix®).

## Revenues by product<sup>§</sup>



## Revenues by region<sup>§</sup>

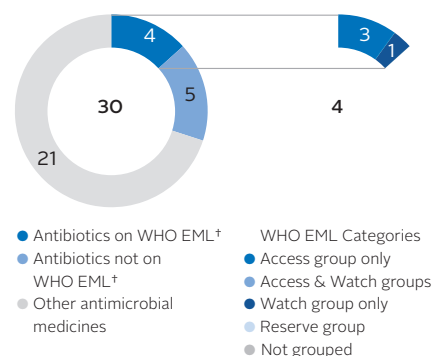


## ANTIMICROBIAL PORTFOLIO

GSK markets at least 30 antimicrobial medicines, 14 of which are included in the WHO EML (Section 6). The majority of the company's antimicrobial medicines are established products. Nine of its medicines are antibiotics, including the amoxicillin/clavulanic acid formulation Augmentin™, a 35-year old top-selling antibiotic (by volume). The remainder (21) of the company's portfolio includes antiprotazoals and anthel-

minthics, as well as 15 antivirals (12 of which target HIV). The company also markets a chlorhexidine antiseptic gel for umbilical cord care in neonates and has a large and diverse vaccines portfolio, which includes the vaccines Hiberix®, targeting *Haemophilus influenzae* type B, and Synflorix®, targeting *S. pneumoniae*.

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.

\*\* GSK is involved in the COMBACTE-CDI network, a recently launched project within the IMI COMBACTE research consortium.

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Group turnover; FYE 31 December 2016

## OPPORTUNITIES

**Develop access plans for gepotidacin.** GSK has a stewardship plan in place for its antibiotic candidate (gepotidacin) in late-stage clinical development. GSK can ensure that access plans are also in place for this candidate.

**Improve transparency regarding environmental risk management.** GSK can build on its current level of transparency, e.g., by adding its Predicted No Effect Concentrations (PNECs) for resistance selection to its safety data sheets. It can also work with suppliers to publish PNECs that apply to its third-party manufacturers of antibiotic APIs and drug products. The company currently publishes several policy docu-

ments regarding its environmental risk-management strategy, as well as its safety data sheets. It has also disclosed its PNECs to the Benchmark under a non-disclosure agreement.

**Expand on stewardship activities.** GSK has established its SOAR surveillance programme for monitoring resistance trends in respiratory tract infections. It can expand this programme to include other diseases and territories, and integrate its activities within existing structures such as WHO's GLASS programme. GSK has adapted its brochures in South Africa to facilitate the appropriate use of antibiotics by patients. It can expand this practice to more countries in scope\*

and take further language and literacy needs into consideration.

**Expand practices for aligning supply and demand.** GSK can work with relevant stakeholders (e.g., suppliers, procurers and payers) to align supply and demand for all antimicrobials, especially for its antibiotics, in countries in scope.\* GSK has a general mechanism in place for aligning demand and supply, as well as product-specific mechanisms for five products including albendazole (Zendel®).

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT	Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	55 projects 40 target priority pathogens
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### A.1 Comparatively high antimicrobial R&D investments.

GSK reports investments in antimicrobial R&D in 2016, which are high compared to other large research-based pharmaceutical companies in the Benchmark. However, the Benchmark is not able to publish further information, as all details were provided on the basis of confidentiality.

### A.2.1-2.3 Largest priority pathogens pipeline, including six novel clinical candidates.

GSK has 55<sup>†</sup> antimicrobial R&D projects in its

pipeline, 28<sup>†</sup> of which are in clinical stage development. Forty<sup>†</sup> of the company's projects target priority pathogens. It has the largest pipeline of the large research-based pharmaceutical companies assessed by the Benchmark, and the highest number of projects that focus on priority pathogens (for both medicines and vaccines). In antimicrobial R&D, GSK's major focus is on HIV and gram-negative bacteria and, to a smaller extent, *M. tuberculosis* and gram-positive bacteria. Six out of seven<sup>†</sup> of GSK's investigational medicines in clinical development (exclud-

ing adaptations) are considered novel, making the company's clinical pipeline the most innovative among large research-based pharmaceutical companies included in the Benchmark. GSK has 11 antimicrobial vaccines in clinical development (excluding adaptations), six of which are developed against diseases caused by a priority pathogen, including HIV, *Shigella* spp. and non-typeable *H. influenzae* (for which no vaccines currently exist). GSK is also investigating the development of a meningococcal vaccine (Bexsero®) for protection against gonorrhoea.

### Pipeline targeting priority pathogens

Discovery	Preclinical	Phase I	Phase II	Phase III	Approval
<ul style="list-style-type: none"> <li>Active Transport project – GNB – In partnership with Sanofi</li> <li>FimH inhibitors – GNB</li> <li>Antibiotics early discovery project – GNB</li> <li>Phenotypic screening and target-based programme for NMT and ProRS – <i>P. falciparum</i></li> <li>► Malaria next generation vaccine – <i>P. falciparum</i></li> </ul>	<ul style="list-style-type: none"> <li>Confidential project – GNB &amp; GPB</li> <li>► <i>Salmonella</i> INTS vaccine – non-typhoidal <i>Salmonella enterica</i></li> <li>► Enteric fever bivalent conjugate vaccine – <i>Salmonella enterica</i> Typhi &amp; Paratyphi A</li> <li>► <i>C. difficile</i> vaccine</li> <li>► <i>S. aureus</i> vaccine</li> <li>GSK3488917 – HIV</li> <li>Confidential project – HIV</li> <li>Confidential project – HIV</li> <li>► pfATP4 inhibitors – <i>P. falciparum</i></li> <li>Malaria drug discovery programme – <i>P. falciparum</i></li> </ul>	<ul style="list-style-type: none"> <li>GSK3342830 ‡ – <i>Enterobacteriaceae</i>, <i>P. aeruginosa</i>, <i>A. baumannii</i></li> <li>GSK3036656 – <i>M. tuberculosis</i> – Novel</li> <li>MI254 – HIV – Novel</li> </ul>	<ul style="list-style-type: none"> <li>Gepotidacin – <i>N. gonorrhoea</i>, GPB – Gonorrhoea, ABSSI – Novel</li> <li>► <i>S. pneumoniae</i> next generation vaccine</li> <li>► COPD vaccine – Hib</li> <li>► <i>Shigella</i> GMMA vaccine – <i>S. sonnei</i></li> <li>► <i>Shigella</i> conjugates vaccine – <i>S. flexneri</i></li> <li>► <i>M. tuberculosis</i> vaccine</li> <li>GSK2838232 – HIV – Novel</li> <li>► HIV vaccine – In partnership with Sanofi</li> </ul>	<ul style="list-style-type: none"> <li>Dolutegravir/lamivudine – HIV – Adaptation (new FDC)</li> <li>Cabotegravir/rilpivirine long-acting – HIV – Adaptation (new formulation) – In partnership with Johnson &amp; Johnson</li> <li>Fostemsavir – HIV – Novel</li> <li>Cabotegravir long-acting (PrEP) – HIV – Novel</li> <li>► <i>N. gonorrhoea</i> vaccine – Adaptation (additional indication of Bexsero®)</li> </ul>	<ul style="list-style-type: none"> <li>Dolutegravir/rilpivirine (Juluca®) – HIV – Adaptation (new FDC) – In partnership with Johnson &amp; Johnson – FDA approval 2017</li> <li>Chlorhexidine (Umbipro) – antiseptic – GNB &amp; GPB – Adaptation (new formulation for umbilical cord infection) – EMA approval 2016</li> </ul>
<b>Stage: not published</b> <ul style="list-style-type: none"> <li><i>M. tuberculosis</i></li> <li><i>M. tuberculosis</i></li> <li><i>M. tuberculosis</i></li> <li><i>M. tuberculosis</i></li> <li>HIV</li> <li>HIV</li> <li>► Gr. B <i>Streptococcus</i> hexavalent vaccine</li> </ul>					

► Vaccine

GNB = Gram-negative bacteria

GPB = Gram-positive bacteria

FDC = Fixed dose combination

‡ GSK3342830 has been terminated after the period of analysis.

### A.3 Twenty-four R&D projects being developed with public partners, including eight PDPs.

GSK is developing 24 R&D projects in its priority pathogen pipeline through public-private partnership.\*\* The company is involved in eight PDPs and one open research consortium, the highest number reported among all companies assessed by the Benchmark. Of these nine projects, seven are in preclinical stage and two are in clinical stage. For the development of its Phase II HIV vaccine, GSK partners with the Pox-Protein Public Private Partnership (P5), a project that includes the US National Institute of Allergy and Infectious Diseases (NIAID), the Bill & Melinda Gates Foundation, the South African Medical Research Council, the HIV Vaccine Trials Network (HVTN), the US Military HIV Research Program and Sanofi. The company also collaborates with Aeras, a non-profit biotechnology organisation, on the development of its tuberculosis vaccine, currently in Phase II clinical development. GSK's antibiotic candidate gepotidacin

is partially funded by both BARDA and the US Defense Threat Reduction Agency under "Other Transaction Authority" (OTA) agreements, which are cost-sharing reimbursement contracts.

### A.4 Access and/or stewardship provisions in place for most late-stage candidates.

GSK reports that it has access and/or stewardship provisions in place for most of its R&D candidates targeting priority pathogens in late-stage development. It has access provisions for 11 out of its 15 antimicrobial candidates in late-stage development. GSK states that it will market its HIV candidates via ViiV Healthcare, which has a general access to medicine policy that includes a commitment to voluntary licensing to allow supplies of generic versions of its products in least-developed, low- and lower-middle income countries and all sub-Saharan African countries. In addition, the policy includes a flexible pricing procedure in middle-income countries that factors in the gross domestic product (GDP) and impact of the epidemic in each coun-

try to improve affordability. Furthermore, the company has stewardship provisions in place for seven out of eight of its medicines in late-stage development. Stewardship for GSK's HIV candidates will be managed by ViiV Healthcare, which sponsors HIV drug resistance surveillance studies that are executed via several independent consortia. Moreover, GSK has a company-wide commitment to decouple sales force incentives from volume of sales, an important stewardship incentive in combating AMR. Only one out of seven of its vaccine candidates has an access provision, while three have an access commitment. For example, the agreement with the non-profit biotechnology organisation Aeras, for the development of an anti-tuberculosis vaccine includes a global access commitment clause, and WHO prequalification is foreseen. For this indicator, countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.

## B MANUFACTURING & PRODUCTION

Indicators scored on 1 2 3

### B.1 Most comprehensive environmental risk-management strategy.

GSK is the only company in the Benchmark to undertake every environmental risk-management activity that the Benchmark examines. Namely, the company applies an environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge. It includes auditing and limits on antibiotic discharge, for its own manufacturing sites, third-party manufacturers of antibiotic APIs and drug products, and external waste-treatment plants.

### B.2 Limited transparency regarding environmental risk management.

GSK publishes several of its environmental risk-management policy documents on its website. It does not disclose audit results, or the discharge levels of antibiotics. The company also does not share the identities of its third-party suppliers of antibiotic APIs and drug products or external waste-treatment plants.

### B.3 Commits to following GMP, including at 3rd-party sites.

GSK reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. GSK requires its third-party suppliers to apply the same quality standards to their production facilities.

## C APPROPRIATE ACCESS & STEWARDSHIP

Indicators scored on 1 2 3 4 5 6 7

### C.1 Filed five newest antibiotics in countries in scope.

GSK leads in this area, as it reports that it has filed its five newest antibiotics for registration in up to 71 countries in scope.\* Three of its most recently introduced antibiotics were filed for registration in more than half of the countries in scope.\* Its amoxicillin/clavulanic acid antibiotic (Augmentin™) was filed for registration in the highest number of countries in scope\* (71). Another two of its antibiotics were registered in nine and 31 countries in scope.\* GSK's five newest antibiotics were introduced between 1981 and 2007.

### C.2 Leader in inter- and intra-country equitable pricing.

GSK discloses that it applies an equitable pricing strategic framework to all products including antimicrobials. In addition, it discloses product-specific inter- and intra-country equitable pricing approaches for seven out of nine of its

highest-volume antimicrobial medicines. These approaches cover >50% of countries in scope.\* For albendazole (Zentel™), GSK has committed to applying intra- and inter-country equitable pricing (including donations) in endemic countries in scope.\*

### C.3 Taking multiple steps to improve supply chain efficiency.

GSK engages with WHO and various Ministries of Health of countries in scope\* to align supply and demand forecasting for albendazole (Zentel™), aiming to ensure a continuous exchange of information on, e.g., outbreaks. For five of its nine highest-volume antimicrobials, GSK has mechanisms in place to respond efficiently in the event of stock-outs in countries in scope.\* These mechanisms include inter-market (e.g., country-level) stock transfers, and for cefazidime (Fortum®) the prioritisation of emerging markets over established markets.

### C.4 Multiple activities in AMR-related educational programmes.

GSK reports that it is involved in educational programmes for healthcare professionals (HCPs) that include AMR stewardship and rational use of antibiotics, with conflicts of interest (COI) mitigation measures in place. Programmes such as "Surveillance of Antibiotic Resistance" (SOAR) deliver content through 'active learning channels' (e.g., conferences and courses) to a broad spectrum of HCPs, such as doctors, pharmacists, and microbiologists. A general COI mitigation policy applies to all of the company's programmes. Under this policy, GSK no longer pays HCPs to participate in its educational programmes, and uses an external body to select HCPs for sponsorship to attend congresses. Most educational programmes are not product specific. GSK's commercial teams are, in some cases, not involved in developing materials.

**C.5 Comprehensive involvement in appropriate promotion practices.**

The Benchmark measures how companies address stewardship through appropriate promotion practices. GSK reports that it takes action in this regard: it reflects AMR trends in its marketing materials and has decoupled all sales force incentives from sales volumes for all its products. This approach is unique in the industry. The company now remunerates its sales force based on their technical knowledge, and the quality of service they deliver through in-clinic evaluation and monitoring.

**C.6 Implements brochure and/or packaging adaptations to facilitate appropriate use.**

GSK has adapted its brochures in South Africa to facilitate appropriate use of antibiotics by patients. The company is also developing a digital solution that provides product information to patients, taking illiteracy into account.

**C.7 International programme for AMR surveillance.**

GSK runs one international programme, focussed on AMR trends for community-acquired respiratory tract infections. The company shares the results with public health authorities, through conferences and multiple peer-reviewed journals. Additionally, the company is collaborating with other organisations (such as the Open Data Institute and the Wellcome Trust) to explore the possibility of developing a single industry-sponsored antibiotic surveillance database, with harmonised measurements and results.

**ANIMAL HEALTH & DIAGNOSTICS**

*Activities in this area are not scored by the Benchmark. This information is provided given the importance of animal health and diagnostics on the topic of AMR.*

GSK does not market antibiotics for animal use. It has a public policy in place which, states that the company will not license its new antibiotics for agricultural use.

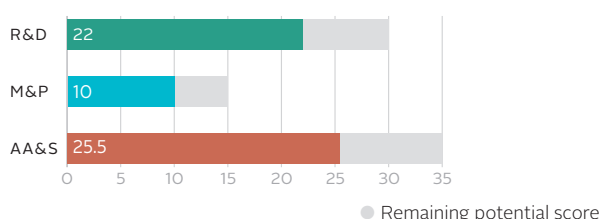
While GSK does not have its own diagnostics division, the company reports that it works with third parties to complement AMR product development with diagnostic tests whenever possible. Additionally, the company reports that it provides scientific advice and seed-funding for public-private partnerships and for awards for the development of point-of-care diagnostics to be used in conjunction with antibiotics. GSK also supports COMBACTE-CARE, a European net-

work that addresses the diagnostic challenges for the epidemiological and clinical studies of carbapenem-resistant bacteria.

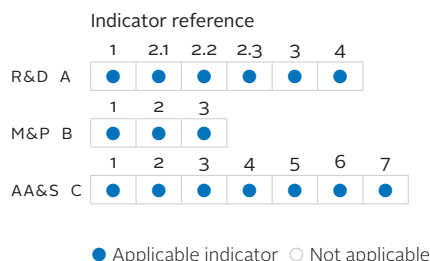
# Johnson & Johnson

Stock exchange: XNYS • Ticker: JNJ • HQ: New Brunswick, NJ, US • Employees: 127,100 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: Yes

## Performance by Research Area



## How Johnson & Johnson was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Johnson & Johnson is one of the leaders when compared with other large research-based pharmaceutical companies in scope, driven by strong performances in Research & Development, Manufacturing & Production and Appropriate Access & Stewardship, largely centred around tuberculosis-related activities. The company has one of the largest antimicrobial R&D pipelines of the large research-based pharmaceutical companies in scope: 48\*\* projects, of which 15\*\* target priority pathogens, including one novel antimalarial candidate and at least three new vaccine candidates. It has access and stewardship provisions in place for some late-stage candidates. The company discloses a comprehensive

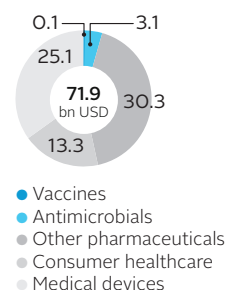
environmental risk-management strategy, which includes discharge limits and reportedly applies to all Johnson & Johnson's third-party suppliers of antibiotic APIs and drug products. It has filed its three newest antibiotics for registration in some countries in scope.\* It also reports equitable pricing strategies for some antibiotics, as well as multiple steps to improve supply chain efficiency. In stewardship, Johnson & Johnson engages in several tuberculosis-related educational programmes aimed at healthcare professionals, taking action to mitigate conflict of interest in these programmes. It engages in tuberculosis-related surveillance programmes, and collaborates and shares its data with public health authorities.

## SALES AND OPERATIONS

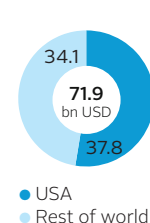
Johnson & Johnson is a large research-based pharmaceutical company with operations in three segments: consumer healthcare, pharmaceuticals and medical devices. Its pharmaceuticals segment focusses on therapeutic areas such as cardiovascular health and metabolism, immunology, infectious diseases and vaccines, neuroscience and oncology. The company sells antimicrobial medicines or vaccines in 108 countries globally, 38 of which are low- to middle-income countries.\* Johnson & Johnson's vaccines are

developed and produced by Janssen Vaccines & Prevention BV (part of Janssen Pharmaceutical Companies), which divested its oral typhoid and oral cholera vaccines to PaxVax and Valneva in 2014 and 2015 respectively.

### Revenues by product<sup>§</sup>



### Revenues by region<sup>§</sup>

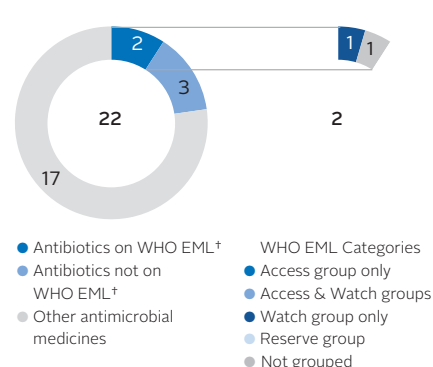


## ANTIMICROBIAL PORTFOLIO

Johnson & Johnson markets at least 22 antimicrobial medicines, seven of which are listed on the WHO EML (Section 6). Five of the company's antimicrobial medicines are antibiotics. This includes levofloxacin (Elequine®, Levaquin®), listed on the EML's Watch group, and bedaquiline (Sirturo®), included in the EML's complementary list of reserve second-line drugs for the treatment of multidrug-resistant tuberculosis. Out of the remaining 17 medicines, six target

HIV, two are used in the treatment of hepatitis C, five are antifungals and four are anthelmintics or antiprotozoals. The company has two vaccines on the market: Quinvaxem®, indicated for protection against five major childhood infectious diseases, and Hepavax-Gene®, a recombinant vaccine against hepatitis B. Johnson & Johnson reports that these are being phased out, citing availability of other products.

### Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

† EML Section 6: Anti-Infective Medicines

§ FYE 1 January 2017

## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Johnson & Johnson has stated a commitment to ensure access and stewardship plans are in place for all of its candidates in the pipeline. It can ensure that this commitment is followed through with specific plans applying to all of its candidates in late-stage clinical development.

**Improve transparency regarding environmental risk management.** Johnson & Johnson can share more information on how it manages envi-

ronmental risk, e.g., the company can publish information regarding the levels of antibiotic discharge. Currently Johnson & Johnson discloses several policy documents regarding its environmental risk-management strategy.

**Expand on stewardship activities.** Johnson & Johnson engages in the DREAM surveillance programme, covering first- and second-line anti-tuberculosis medicines. The company can consider to expand this to more countries, e.g., in sub-Saharan Africa, and ensure data from

such programmes is made publicly available. The company does not report stewardship activities for other antibiotics and can consider such activities for these antibiotics as well.

**Improve access through the registration of new antibiotics.** Johnson & Johnson can improve access in low- and middle-income countries\* by filing its antimicrobials, particularly bedaquiline (Sirturo®) for registration in these countries. Johnson & Johnson has currently filed to register this product in 23 countries in scope.\*

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT	Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	48 projects 15 target priority pathogens
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### A.1 Comparatively high antimicrobial R&D investments.

Johnson & Johnson reports investments in antimicrobial R&D in 2016, which are high compared to other large research-based pharmaceutical companies in the Benchmark. However, the Benchmark is not able to publish further information, as all details were provided on the basis of confidentiality.

#### A.2.1-2.3 Fifteen R&D projects that target priority pathogens, including one novel clinical antimalarial medicine.

Johnson & Johnson has 48\*\* antimicrobial R&D projects in its pipeline, 23\*\* of which are in clinical-stage development. Fifteen\*\* of the company's projects target priority pathogens. Ten of these are in clinical-stage development, making it the second-largest clinical-stage pipeline that targets priority pathogens, among the large research-based pharmaceutical companies assessed by the Benchmark. These ten projects

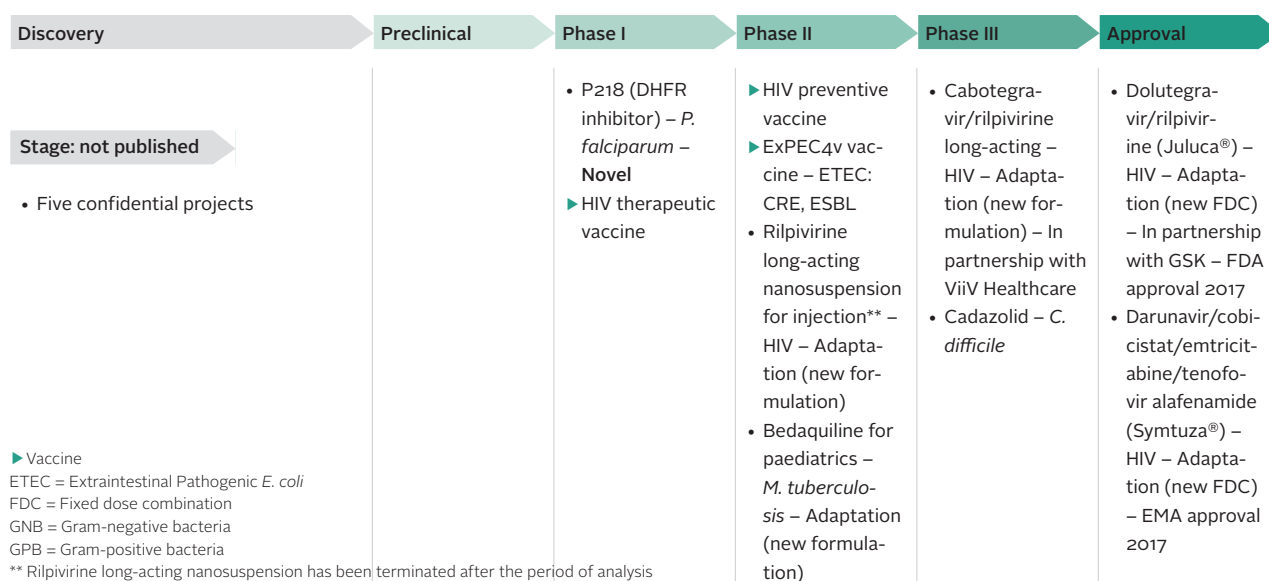
consist of two medicines, three vaccines and five\*\* adaptations to existing pharmaceuticals, including the adaptation of its anti-tuberculosis medicine bedaquiline (Sirturo®) for paediatric use. One of the investigational medicines is the antibiotic cadazolid, an oxazolidinone-quinolone hybrid targeting *C. difficile*, which was adopted through the acquisition of Actelion in 2017 and is now in Phase III of clinical development. The other is a novel antimalarial medicine, a dihydrofolate reductase inhibitor, in Phase I clinical development. The company is collaborating with ViiV Healthcare on the combination of its HIV/AIDS medicine rilpivirine (Edurant®) with ViiV Healthcare's HIV/AIDS medicines: dolutegravir (Tivicay®)/rilpivirine (Edurant®) combination, as well as a cabotegravir/rilpivirine (Edurant®) long-acting nanosuspension for injection. The company has two vaccines in clinical development targeting HIV, and a third vaccine targeting multidrug-resistant extra-intestinal *E. coli* (specifically, targeting the four most prevalent sero-

types resistant to at least three antibiotics). No vaccines currently exist for either pathogen.

### A.3 Three R&D projects being developed with public partners, including two PDPs.

Johnson & Johnson is developing three R&D projects in its priority pathogen pipeline through public-private partnership. The company is developing an HIV vaccine in clinical stage through a consortium of partners, including, the National Institutes of Health (NIH), the Bill & Melinda Gates Foundation, the International AIDS Vaccine Initiative (IAVI), the United States Military HIV Research Program (MHRP) and the Beth Israel Deaconess Medical Center (BIDMC), among others. Additionally, the company is developing an antimalarial medicine through a PDP with the Medicines for Malaria Venture (MMV).

### Pipeline targeting priority pathogens



#### A.4 Access and stewardship provisions in place for some late-stage candidates.

Johnson & Johnson reports that it commits to having access and stewardship provisions in place for all its candidates in development before regulatory approval. To the Benchmark, the company reports that it will expand the access and stewardship activities currently in place for bedaquiline (Sirturo®) to its paediatric formulation in Phase II development. This

entails a managed access programme through the Global Drug Facility and its own subsidiaries, and medical education on the use of bedaquiline (Sirturo®) to paediatric healthcare professionals. In addition, Johnson & Johnson has access provisions in place for three other R&D candidates targeting priority pathogens in late-stage development, including its HIV vaccine candidate and the antiretroviral combinations, developed in collaboration with ViiV Healthcare.

Johnson & Johnson is responsible for delivery of the long-acting injectable cabotegravir/rilpivirine (Edurant®) regimen to developing countries. Only one of the remaining four candidates in late-stage development (ExPEC4v vaccine) has an access commitment in place. For this indicator, countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.

## B MANUFACTURING & PRODUCTION

Indicators scored on 1 2 3

### B.1 Comprehensive environmental risk-management strategy.

Johnson & Johnson undertakes almost all environmental risk-management activities that the Benchmark examines. Namely, it applies an environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge. It includes auditing and limits on antibiotic discharge, for its own manufacturing sites and those of third-party manufacturers of antibiotic APIs and drug products. Johnson & Johnson states that its strategy applies to external waste-treatment plants, yet it also reports that it

does not set discharge limits for these plants nor audits implementation of the strategy.

### B.2 Limited transparency regarding environmental risk management.

Johnson & Johnson publishes elements of its environmental risk-management strategy on its website. It does not disclose audit results, or the discharge levels of antibiotics. The company also does not share the identities of its third-party suppliers of antibiotic APIs and drug products or external waste-treatment plants.

### B.3 Commits to following GMP, including at 3rd-party sites.

Johnson & Johnson reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. Johnson & Johnson requires its third-party suppliers of drug products to apply the same quality standards to their production facilities.

## C APPROPRIATE ACCESS & STEWARDSHIP

Indicators scored on 1 2 3 4 5 6 7

### C.1 Filed three newest antibiotics in some countries in scope.

Johnson & Johnson reports that it has filed its three newest antibiotics for registration in some countries in scope\* (between 7–23 countries). Two of these antibiotics are licensed from Daiichi Sankyo for sale in Latin America only. Johnson & Johnson has filed these two antibiotics (introduced in 1990 and 1996) for registration in seven and ten of the countries in scope\* in Latin America. Johnson & Johnson's bedaquiline (Sirturo®) is the only product introduced in the past five years (2012) that has been filed for registration in more than ten countries in scope\*. Indeed, it has been filed in 23 such countries. It is also worth noting that through the Global Drug Facility, more than 70 countries have approved importation of bedaquiline prior to regulatory approval.

### C.2 Product-specific equitable pricing.

Johnson & Johnson discloses equitable pricing approaches for four of its seven highest-volume antimicrobial medicines: bedaquiline (Sirturo®), darunavir (Prezista®), mebendazole (Vermox®) and simeprevir (Olysio®). It applies inter-country equitable pricing to three of these (not mebendazole), and intra-country equitable pricing to bedaquiline, mebendazole and simeprevir. Its inter-country pricing policy for bedaquiline reflects countries' ability to pay (measured by GNI per capita) and disease burden (of multidrug-resistant tuberculosis).

### C.3 Taking multiple steps to improve supply chain efficiency.

Johnson & Johnson engages with PAHO, the Global Drug Facility, WHO and others to align supply and demand forecasting for three of its seven highest-volume antimicrobial medicines: bedaquiline (Sirturo®), darunavir (Prezista®) and mebendazole (Vermox®). It also has mechanisms in place (i.e., it maintains safety stocks) to respond efficiently in the event of stock-outs in countries in scope.\* These mechanisms cover bedaquiline (Sirturo®), darunavir (Prezista®) and simeprevir (Olysio®).

### C.4 Multiple activities in tuberculosis-related educational programmes.

Johnson & Johnson has provided tuberculosis-related stewardship information only. The company reports that it is involved in tuberculosis educational programmes for HCPs that include AMR stewardship and rational use of antibiotics, with conflicts of interest (COI) mitigation measures in place. The company collaborates with third parties such as the International Union against Tuberculosis and Lung Disease and USAID on the appropriate use of anti-tuberculosis drugs, pharmacovigilance and multi-drug-resistant tuberculosis management. The company supports these initiatives with unrestricted educational grants, which ensures independent content development.

### C.5 No active promotion of bedaquiline.

The Benchmark measures how companies

address stewardship through appropriate promotion practices. Johnson & Johnson's new anti-tuberculosis drug, bedaquiline (Sirturo®), is provided solely through national tuberculosis programmes and therefore does not require any marketing materials. The company reports that it does not deploy any sales organisations for the sale of Sirturo® in countries in scope.\*

### C.6 Implements packaging adaptation for bedaquiline to facilitate appropriate use.

The company collaborated with Stop TB Partnership to adapt bedaquiline (Sirturo®) packaging by creating a six-month presentation and a blister preparation of the medicine. The former aims to improve patient adherence to treatment in Directly Observed Treatment (DOT) programmes, while the latter aims to facilitate usage in different environmental conditions.

### C.7 Engages with WHO reference laboratories and national tuberculosis programmes.

Johnson & Johnson runs one multi-country surveillance programme, focussed on tuberculosis resistant trends. It engages numerous laboratories to support the surveillance of tuberculosis resistance trends via the Drug Resistance Emergence Assessment in multidrug-resistant tuberculosis programme (DREAM). Although results are to be published in peer-reviewed journals, the company is also sharing data with national tuberculosis programmes.

## ANIMAL HEALTH &amp; DIAGNOSTICS

*Activities in this area are not scored by the Benchmark. This information is provided given the importance of animal health and diagnostics on the topic of AMR.*

Johnson & Johnson reports that it is developing bedaquiline sensitivity diagnostic plates and panels that are to be deployed on the Becton Dickinson and Thermo Fisher Scientific Inc. lab

infrastructure. In December 2015, Johnson & Johnson and the Foundation of Innovative New Diagnostics (FIND) entered into a collaboration for the discovery of point-of-care diagnostics for tuberculosis case detection, including multidrug-resistant strains.

The company has also formed a partnership with Cue Inc. to develop an HIV viral load test on Cue's Lab-In-A-Box molecular diagnostic plat-

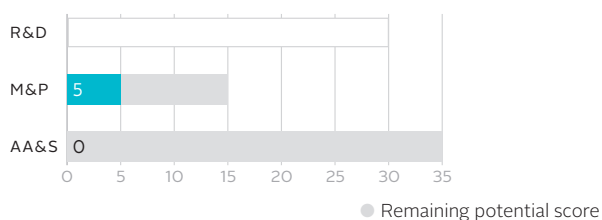
form. The technology is aimed to improve routine viral load testing of HIV/AIDS patients on antiretroviral therapy.

# Lupin Limited

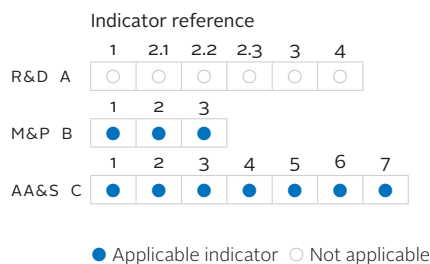
Stock exchange: XNSE • Ticker: LUPIN • HQ: Mumbai, India • Number of employees: 16,792 •

Signatory to Davos Decl.: via MFE  
Signatory to Industry Roadmap: No

## Performance by Research Area



## How Lupin was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Lupin is a prominent producer of antibiotics globally by sales volume. As a generic medicine manufacturer, Lupin was evaluated in Manufacturing & Production and Appropriate Access & Stewardship only. The company's performance in the Benchmark is lower compared to most other generic medicine manufacturers in scope. Lupin does not report having an environmental risk-management strategy. The company

reports that it has mechanisms in place for maintaining a high quality of antibiotic production and requires its third-party suppliers to apply the same quality standards to their production facilities. Lupin does not report any information on its access strategies regarding antimicrobial medicines, or its involvement in stewardship activities that promote appropriate antibiotic use.

## SALES AND OPERATIONS

Lupin is an Indian-based generic medicine manufacturer founded in 1968. It produces active pharmaceutical ingredients (APIs), as well as generic medicines. The company develops advanced drug-delivery systems and has a highly differentiated pipeline. It has operations in more than 100 countries, with key markets for finished drug products in the USA, India, Japan, Europe, South Africa, Philippines and Australia. The company focusses on cardiovascular health, diabetes and anti-infectives, with a strong history in anti-tuberculosis medicines and cephalosporin antibiotics. Its anti-tuberculosis formulations are sold globally. Within the company's India business (contributing approx. 22% to global revenues), the anti-infectives and anti-tuberculosis business segments made up 18% of revenues in 2016 (fiscal year). Lupin (and subsidiaries) have

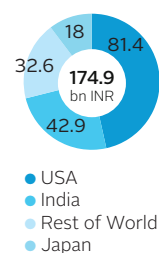
18 manufacturing facilities across India, Japan, the USA, Mexico and Brazil (five for active pharmaceutical ingredient production). The company invests in R&D for biosimilars, mainly in immunology, endocrine health and oncology. It has nine R&D facilities, in India and elsewhere, including the USA, Japan and the Netherlands. In 2016, Lupin acquired Gavis Pharmaceuticals, whose portfolio includes cardiovascular, central nervous system (CNS) and anti-infective medicines, among others. Also in 2016, Lupin reached an agreement with Shionogi to acquire 21 branded products coming off-patent in Japan, for approx. USD 150 million. These cover therapeutic areas such as the CNS, oncology and anti-infectives.

## Revenues by product<sup>§</sup>



● Total revenue

## Revenues by region<sup>§</sup>

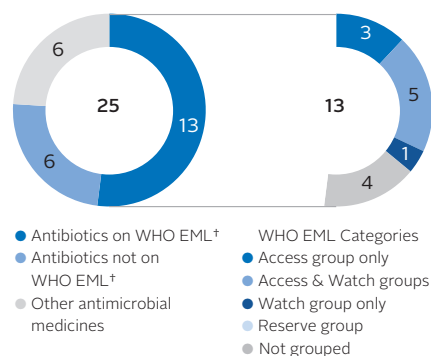


## ANTIMICROBIAL PORTFOLIO

According to publicly available data, Lupin markets at least 25 antimicrobial medicines, 18 of which are listed on the WHO EML (Section 6). Nineteen of the company's antimicrobial medicines are antibiotics, with 13 listed on the WHO EML (Section 6), including six in the EML's Watch group. The remainder (six) of the compa-

ny's portfolio comprises the antifungal voriconazole, listed on the WHO EML (Section 6) for the treatment of aspergillosis, the antiprotazoal tinidazole and four medicines containing the antiretroviral lamivudine.

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Revenue from operations; FYE 31 March 2017

## OPPORTUNITIES

**Engage in antimicrobial stewardship.** Lupin can engage in stewardship activities, e.g., through surveillance activities, educational activities for healthcare professionals on AMR (while mitigating conflicts of interest), and engage in appropriate promotion practices.

**Ensure transparency regarding environmental risk management.** Lupin can share information on how it manages environmental risk, e.g., the

company can publish information regarding the levels of antibiotic discharge. Currently the company does not demonstrate evidence of having an environmental risk-management strategy in place.

**Ensure affordability and registration plans for new and existing antimicrobials.** Lupin can seek to improve access in low- and middle-income countries through the registration of new and

existing antimicrobials, and ensure that they are priced affordably. Currently, the company does not disclose such information.

**Engage in R&D innovation.** Lupin can engage in incremental R&D innovation to address resistance, improve adherence and the appropriate use of antimicrobial medicines.

## PERFORMANCE BY RESEARCH AREA

### A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Lupin's main focus is the manufacturing of generic products and, as such, was not in scope for this Research Area.

### B MANUFACTURING & PRODUCTION

Indicators scored on 1 2 3

● ● ●

#### B.1 Reports no environmental risk-management strategy.

Lupin does not report having an environmental risk-management strategy in place to minimise the environmental impact of manufacturing discharge of antibiotics.

#### B.2 No transparency on environmental risk management.

Lupin does not disclose its strategy to minimise the impact of manufacturing discharge of antibiotics. It does not publish any element looked for by the Benchmark, namely: antibiotic discharge levels, audit results, and the identities of its third-party suppliers of antibiotic APIs and drug products, or of its external waste-treatment plants.

#### B.3 Commits to following GMP, including at 3rd-party sites.

Lupin reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. Lupin requires its third-party suppliers to apply the same quality standards to their production facilities.

### C APPROPRIATE ACCESS & STEWARDSHIP

Indicators scored on 1 2 3 4 5 6 7

● ● ● ● ● ● ●

#### C.1 No information on filing for registration.

Lupin reports no information on where it has filed its newest antibiotics for registration in countries in scope.\* This information is not otherwise publicly available.

#### C.2 No disclosure on equitable pricing approach.

Lupin does not disclose an equitable pricing approach for its highest-volume antibiotics and/or antimicrobial medicines.

#### C.3 No insight into steps addressing supply chain efficiency.

Lupin does not disclose how it works with stakeholders (e.g., governments, procurers) to align supply and demand for antimicrobial medicines, specifically to prevent or minimise stock-outs in countries in scope.\* The company also does not report on whether it has processes in place to respond to stock-outs in countries in scope.\*

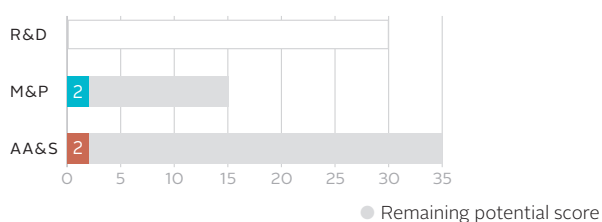
#### C.4-C.7 No apparent involvement in stewardship activities.

Lupin does not report any involvement in stewardship activities (from education to surveillance to appropriate promotion practices) that promote appropriate antibiotic use.

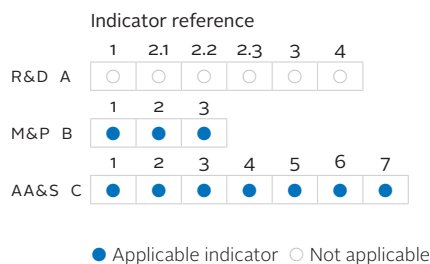
# Macleods Pharmaceuticals Ltd.

Stock exchange: Privately held • Ticker: - • HQ: Mumbai, India • Employees: > 13,500 • Signatory to Davos Decl.: No • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Macleods was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Macleods is a prominent producer of antibiotics globally by sales volume. As a generic medicine manufacturer, Macleods was evaluated in Manufacturing & Production and Appropriate Access & Stewardship only. Although the company's performance in the Benchmark is lower compared to most other generic medicine manufacturers in scope, it discloses an environmental risk-management strategy for its own sites, which includes an auditing process. It does not

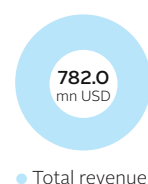
report its approach to assuring high quality antibiotic production consistent with international standards. Macleods has provided information on where it has filed two of its newest antibiotics for registration, but does not disclose an equitable pricing approach for its antibiotics and antimicrobial medicines, or actions to ensure efficient supply. The company does not report any involvement in stewardship activities that promote appropriate antibiotic use.

## SALES AND OPERATIONS

Macleods is an Indian-based privately-held manufacturer of generic medicines focussing on essential pharmaceuticals. The company is present in more than 100 countries worldwide, including in Southeast Asia, Africa and North America. It has a total of 14 manufacturing facilities: one for active pharmaceutical ingredients (APIs) and 13 for drug products. Current drug formulations include tablets, hard and soft gelatine capsules and dry powder injections. The company is actively seeking to expand its manufacturing capabilities to include, among other things, metered dose inhalation products and liquid injectables. Macleods' products cover a

wide range of therapeutic indications, including tuberculosis, malaria, bacterial infections, diabetes and respiratory and cardiovascular diseases. The company has an in-house bioequivalence centre and an R&D centre, and it is active in the development of incremental innovations for antimicrobial medicines. Its antimicrobial medicines are sold in over 52 countries globally, 43 of which are low- or middle-income countries.\* According to publicly available data, revenues for the fiscal year 2016 amounted to USD 782 million.

## Revenues by product<sup>§</sup>

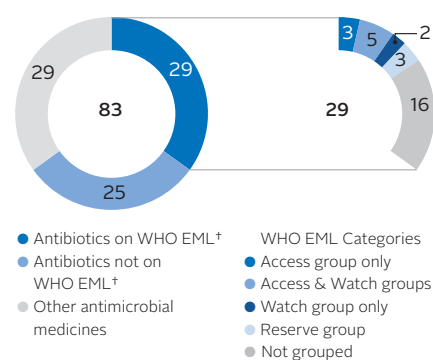


## ANTIMICROBIAL PORTFOLIO

Macleods markets at least 83 antimicrobial medicines, 51 of which are listed on the WHO EML (Section 6). Fifty-four of the company's antimicrobial medicines are antibiotics, with 29 listed on the WHO EML (Section 6), including three in the EML's Reserve group (cefepime, colistin and linezolid). The remainder (29) of the company's

portfolio comprises eight antimalarials (all listed on the WHO EML) and 21 antivirals (including 19 indicated for HIV/AIDS).

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Turnover 2016-2017

## OPPORTUNITIES

**Engage in antimicrobial stewardship.** Macleods can engage in stewardship activities, e.g., through surveillance activities, educational activities for healthcare professionals on AMR (while mitigating conflicts of interest), and engage in appropriate promotion practices.

**Ensure transparency regarding environmental risk management.** Macleods can share information on how it manages environmental risk, e.g., by disclosing its environmental risk-management strategy and the levels of antibiotic discharge.

**Improve access through the affordability and**

**registration of new and existing antimicrobials.** Macleods has filed two of its newest anti-tuberculosis medicines for registration in 30 countries in scope.\* It can seek to improve access in low- and middle-income countries through the registration of more antimicrobials, and ensure that these are priced affordably.

**Expand environmental risk-management strategy.** Macleods can ensure that antibiotic discharge limits are added to its environmental risk-management strategy. It can also extend this strategy to the sites of third parties who manufacture antibiotic APIs and drug products

on its behalf, as well as to external waste-treatment sites. Macleods currently has a general environmental risk-management strategy that it applies to its own manufacturing sites.

**Increase engagement in R&D innovation.** Macleods is currently engaged in adapting generic antimicrobial medicines. For example, the company is developing paediatric formulations containing lower doses of anti-tuberculosis medicines (in collaboration with the TB Alliance). It can continue to engage in incremental R&D, and ensure access and stewardship provisions are in place for these projects.

## PERFORMANCE BY RESEARCH AREA

### A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Macleods was not eligible for this Research Area. However, the company is active in antimicrobial R&D.

**Several R&D projects being developed with public partners.**

Macleods reports that it has twelve projects in

its antimicrobial R&D pipeline targeting priority pathogens. This includes ten lower-dose formulations of tuberculosis medicines for paediatric use and an additional indication for clofazimine, currently indicated for leprosy. The company collaborates with TB Alliance and UNITAID on the development of these formulations. TB Alliance

has a general access to medicine policy that includes global adoption, availability and affordability. Macleods is also developing a dolutegravir/lamivudine/tenofovir fixed dose combination for the treatment of HIV/AIDS.

### Pipeline targeting priority pathogens

Stage unknown	Preclinical	Phase I	Phase II	Phase III	Approval
<ul style="list-style-type: none"> <li>• Clofazimine – <i>M. tuberculosis</i> – Adaptation (Additional indication)</li> <li>• Ethambutol – <i>M. tuberculosis</i> – Adaptation (new formulation: dispersible tablets 100 mg) – Paediatrics</li> <li>• Linezolid – <i>M. tuberculosis</i> – Adaptation (new formulation: dispersible tablets 150 mg) – Paediatrics</li> <li>• Isoniazid – <i>M. tuberculosis</i> – Adaptation (new formulation: dispersible tablets 100 mg) – Paediatrics</li> <li>• Dolutegravir/lamivudine/tenofovir disoproxil fumarate – HIV – Adaptation (new FDC)</li> </ul>					<ul style="list-style-type: none"> <li>• Cycloserine – <i>M. tuberculosis</i> – Adaptation (new formulation: capsules 125 mg) – Paediatrics – ERP reviewed</li> <li>• Ethionamide – <i>M. tuberculosis</i> – Adaptation (new formulation: dispersible tablets 125 mg) – Paediatrics – WHO prequalified 2017</li> <li>• Levofloxacin – <i>M. tuberculosis</i> – Adaptation (new formulation: dispersible tablets 100 mg) – Paediatrics – ERP reviewed</li> <li>• Moxifloxacin – <i>M. tuberculosis</i> – Adaptation (new formulation: dispersible tablets 100 mg) – Paediatrics – ERP reviewed</li> <li>• Pyrazinamide – <i>M. tuberculosis</i> – Adaptation (new formulation: dispersible tablets 150 mg) – Paediatrics – WHO prequalified 2016</li> <li>• Rifampicin/isoniazid – <i>M. tuberculosis</i> – Adaptation (new formulation: dispersible tablets 75 mg + 50 mg) – WHO prequalified 2017</li> <li>• Rifampicin/isoniazid/pyrazinamide – <i>M. tuberculosis</i> – Adaptation (new formulation: dispersible tablets 75+50+150 mg) – WHO prequalified 2017</li> </ul>

FDC = Fixed dose combination  
ERP = Expert Review Panel

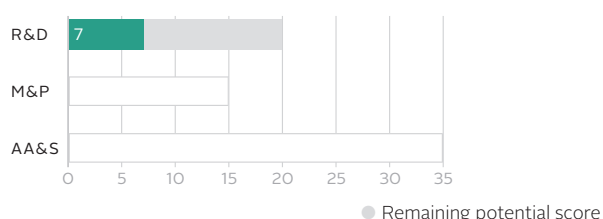
B MANUFACTURING & PRODUCTION		Indicators scored on	1	2	3
<b>B.1 Environmental risk-management strategy for own sites.</b> Macleods has an environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge. This applies to its own manufacturing sites and includes auditing. There is no evidence that the strategy is applicable to third-party manufacturers of antibiotic APIs and drug products or to external waste-treatment plants. The company reports no information about setting discharge limits.			●	●	●
<b>B.2 No transparency on environmental risk management.</b> Macleods does not disclose its strategy to minimise the impact of manufacturing discharge of antibiotics. It does not publish any element looked for by the Benchmark, namely: antibiotic discharge levels, audit results, and the identities of its third-party suppliers of antibiotic APIs and drug products, or of its external waste-treatment plants.					
<b>B.3 No statement on how antibiotic quality is maintained.</b> Macleods makes no statement regarding how it ensures high quality antibiotic production following international manufacturing standards accepted by recognised national and international authorities (such as GMP).					

C APPROPRIATE ACCESS & STEWARDSHIP		Indicators scored on	1	2	3	4	5	6	7
<b>C.1 Filed two newest antibiotics in some countries in scope.</b> Macleods has provided filing information on two of its newest antibiotics: isoniazid/rifampicin and isoniazid/pyrazinamide/rifampicin. These two products both target tuberculosis and have now been filed for registration in 30 countries in scope,* mainly in sub-Saharan Africa.			●	●	●	●	●	●	●
<b>C.2 No disclosure on equitable pricing approach.</b> Macleods does not disclose an equitable pricing approach for its highest-volume antibiotic and/or antimicrobial medicines. The company states that its approach to affordability is through tenders.									
<b>C.3 No insight into steps addressing supply chain efficiency.</b> Macleods does not disclose how it works with stakeholders (e.g., governments, procurers) to align supply and demand for antimicrobial medicines, specifically to prevent or minimise stock-outs in countries in scope.* The company also does not report on whether it has processes in place to respond to stock-outs in countries in scope.*									
<b>C.4-C.7 No apparent involvement in stewardship activities.</b> Macleods does not report any involvement in stewardship activities (from education to surveillance to appropriate promotion practices) that promote appropriate antibiotic use.									

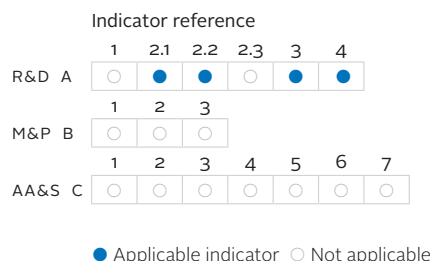
# Melinta Therapeutics, Inc.

Stock exchange: XNAS • Ticker: MLNT • HQ: New Haven, CT, USA • Number of employees: 11-50 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Melinta was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Melinta is a biopharmaceutical company, selected for having a pipeline that targets priority pathogens. At the end of 2017, Melinta merged with Cemptra and, in January 2018, acquired The Medicines Company's infectious disease business. The company was evaluated in the area of Research & Development only. It is a mid-performing company compared to the biopharmaceutical companies in scope. The com-

pany has five projects in its antimicrobial R&D pipeline, four of which target priority pathogens. Melinta has one antibiotic approved by the FDA for the treatment of acute bacterial skin and skin structure infections (ABSSSI), and has licensed the commercialisation and co-development rights of this product to partners in various geographic areas.

## SALES AND OPERATIONS

Melinta is a US-based biopharmaceutical company focussing on the development of antibiotics for infections caused by drug-resistant bacteria. The company was founded in 2000 (as Rib-X Pharmaceuticals), by Yale University faculty, including a co-winner of the 2009 Nobel Prize for Chemistry for studies on the function of the ribosome, a cellular structure responsible for protein synthesis. Based on these studies, the company's drug discovery platform allows for atomic-level analysis of interactions between drug candidates and their bacterial targets at the ribosome, thereby aiding the design of antibiotics capable of bypassing resistance mechanisms. Melinta has used this platform to estab-

lish its preclinical research programme targeting the 'ESKAPE' pathogens: *E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacteriaceae*. The company's only antimicrobial medicine on the market, delafloxacin (Baxdela™), was acquired from Wakunaga Pharmaceutical in 2006 and approved by the FDA for the treatment of ABSSSI in 2017. It is available in both intravenous and oral formulations. The latter is expected to offer advantages in terms of administration and reduced hospital admission rates. Recent funding rounds for the company have been led by Vatera Holdings LLC (e.g., USD 67 million in 2015), together with Quadrant Capital Advisors, Inc., Arisaph

Pharmaceuticals, Inc. and Malin Corporation plc. At the end of 2017, Melinta merged with Cemptra and announced the acquisition of the infectious disease business of The Medicines Company, both biopharmaceutical companies in scope of the Benchmark. The latter acquisition was completed in January 2018 and included three antimicrobial medicines marketed by The Medicines Company: the recently launched meropenem/vaborbactam (Vabomere™) and established products oritavancin (Orbactiv®) and minocycline (Minocin®). On merging with Cemptra, Melinta became listed on the NASDAQ stock exchange with ticker MLNT.

## ANTIMICROBIAL PORTFOLIO

Melinta has one antibiotic on the market, delafloxacin (Baxdela™), currently not included in the WHO EML (Section 6). Delafloxacin was approved by the US FDA in June 2017 for the treatment of acute bacterial skin and skin struc-

ture infections (ABSSSI) and is available in both intravenous and oral formulations. The oral formulation is expected to offer advantages in terms of ease of administration and reduced hospital admission rates.

## OPPORTUNITIES

**Develop access and stewardship plans for products on the market.** Regarding products on the market, e.g., meropenem/vaborbactam (Vabomere™), part of The Medicines Company's acquisition, Melinta can plan for access and stewardship provisions, e.g., through partnerships. Regarding delafloxacin (Baxdela™),

Melinta has signed licensing agreements to help ensure access to a range of countries in scope.\* Melinta can develop a strategy for ensuring appropriate use of the product in all countries.

**Plan ahead for access and stewardship during R&D.** Melinta merged with Cemptra in 2017 and

now has a total of three antibiotic candidates in late-stage clinical development. The company can ensure access and stewardship provisions are in place for these candidates, for example, through partnerships.

\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT	Indicators scored on	Antimicrobial pipeline
	1 2.1 2.2 2.3 3 4 ○ ● ● ○ ● ●	5 projects 4 target priority pathogens

**A.2.1-2.2 Four R&D projects that target a priority pathogen.**

Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. Melinta has five projects in its antimicrobial R&D pipeline, four of which target priority bacteria. Its antibiotic, delafloxacin (Baxdela™), is a fluoroquinolone targeting both gram-negative and gram-positive bacteria (including methicillin-resistant *S. aureus*), many of which are resistant to other quinolones. The compound was approved by the FDA in 2017 for the treatment of ABSSSI, in both oral and intravenous formulations. It is currently in Phase III clinical trials for community-acquired bacterial pneumonia. Additionally, Melinta has two preclinical R&D projects for the development of new drug classes (such as pyrrolocytosines) through its ESKAPE pathogen programme, and one macrolide discovery programme.

**A.3 No public-private partnerships reported.**

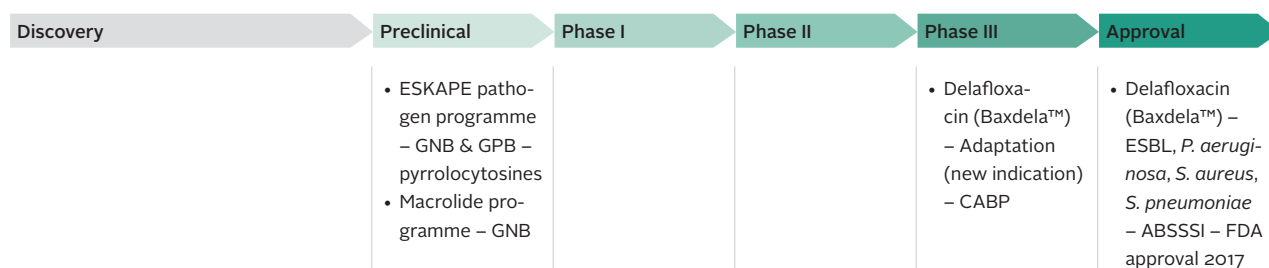
Melinta conducts R&D in-house and with private-sector partners. It does not participate in public-private partnerships, or in partnerships with non-profit organisations, for antimicrobial R&D.

**A.4 Access provision in place, but no information regarding stewardship.**

Melinta reports that it has an access provision in place for its recently approved antibiotic, but reports no information on stewardship provisions. In 2017, Melinta licensed the commercialisation and co-development rights of delafloxacin (Baxdela™) to the Menarini Group in 68 countries in Europe, Asia-Pacific, and the Commonwealth of Independent States (CIS). Additionally, Melinta and Malin Corporation plc entered into an agreement for the commercialisation and distribution of the drug in certain countries in the Middle East and Africa. The company has also entered into a similar agree-

ment with Eurofarma Laboratórios, one of the largest pharmaceutical companies in Brazil, for the development and commercialisation of the medicine in Brazil and other Latin American countries where Eurofarma operates. For this indicator, countries in scope are 106 low- and middle-income countries where access to medicine is likely limited. Regarding stewardship provisions, Melinta signed the Davos Declaration, which includes a general commitment to support the appropriate and responsible use of antimicrobial medicines and vaccines.

## Pipeline targeting priority pathogens



ABSSSI = Acute bacterial skin and skin structure infections

CABP = Community-acquired bacterial pneumonia

GNB = Gram-negative bacteria

GPB = Gram-positive bacteria

## B MANUFACTURING &amp; PRODUCTION

Melinta is a biopharmaceutical company that did not meet the criteria for evaluation in this Research Area. It does, however, have products on the market.

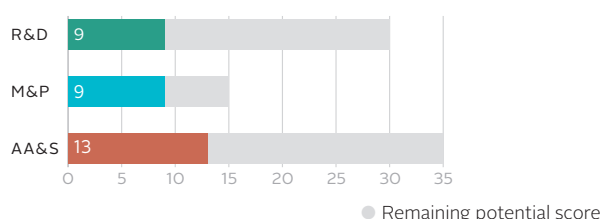
## C APPROPRIATE ACCESS &amp; STEWARDSHIP

Melinta is a biopharmaceutical company that did not meet the criteria for evaluation in this Research Area. It does, however, have products on the market.

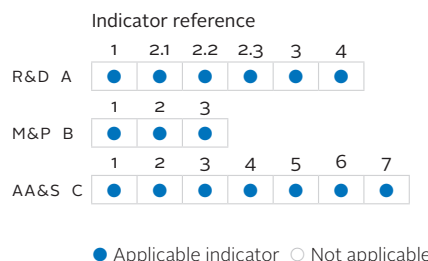
# Merck & Co., Inc.

Stock exchange: XNYS • Ticker: MRK • HQ: Kenilworth, NJ, US • Employees: 68,000 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: Yes

## Performance by Research Area



## How Merck & Co., Inc. was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Merck & Co., Inc. is active in many important areas related to AMR, reflected in its good performance in certain areas of the Benchmark. Due to a lack of publicly available information and engagement with the Benchmark, it performs less well in areas evaluating depth of engagement in AMR. The company has a relatively small antimicrobial R&D pipeline: 16 projects of which nine target priority pathogens, including two new vaccine candidates. The company discloses an environmental risk-management strategy that reportedly also applies to all Merck & Co., Inc.'s third-party suppliers of antibiotic

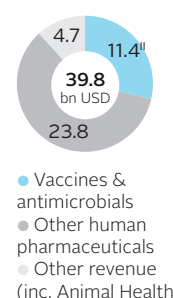
APIs and drug products. The company reports no information about setting discharge limits. Regarding access, Merck & Co., Inc. has not publicly disclosed where it has filed its newest antibiotics for registration. It has, however, publicly committed to engaging in equitable pricing for some antimicrobials. Regarding stewardship, the company reports that it engages in several AMR educational activities aimed at healthcare professionals. It has also established a long-running AMR surveillance programme.

## SALES AND OPERATIONS

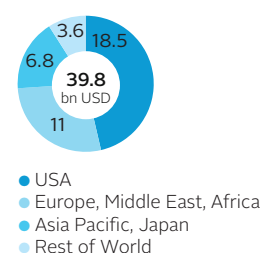
Merck & Co., Inc. (known as MSD outside of the US and Canada) is a large research-based pharmaceutical company with three business segments: pharmaceuticals, vaccines and animal health. The company sells its products in more than 140 countries worldwide. Its core therapeutic areas include infectious diseases and vaccines. In 2015, Merck & Co., Inc. acquired Cubist Pharmaceuticals for USD 9.5 billion, a company

specialising in the development and supply of antibiotics to treat infections arising in acute care settings, frequently caused by drug-resistant bacteria. At the end of 2016, Merck & Co., Inc. and Sanofi Pasteur ended their vaccines joint venture in Europe (Sanofi Pasteur MSD, established 1994) to independently manage their product portfolios.

## Revenues by product<sup>§</sup>



## Revenues by region<sup>§</sup>

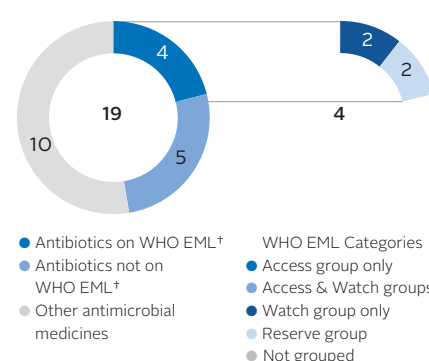


## ANTIMICROBIAL PORTFOLIO

According to publicly available data, Merck & Co., Inc. markets at least 19 antimicrobial medicines, nine of which are listed on the WHO EML (Section 6). Nine of the company's antimicrobials are antibiotics, with four listed on the WHO EML (Section 6), including two in the EML's Reserve group: daptomycin (Cubicin®) and ceftolozane/tazobactam (Zerbaxa®). Out of the remaining ten medicines, seven are antivirals used for treating HIV/AIDS or hepatitis C, two are antifungals, and one is an anthelmintic.

The company also markets an antibody, bezlotumab (Zinplava®), indicated, in conjunction with antibacterial therapy, to reduce recurrence of *C. difficile* infections. The company's vaccines portfolio includes both traditional childhood immunisations (such as a measles, mumps and rubella combination vaccine) and newer additions, such as Gardasil®/ Gardasil®9 for use against certain strains of human papillomavirus (HPV), and RotaTaq® for use against rotavirus.

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> FYE 31 December 2016

<sup>||</sup> For 16 top-selling products

## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Merck & Co., Inc. discloses no information regarding access and stewardship provisions for its candidates. Merck & Co., Inc. can develop and implement access and stewardship plans for all its candidates in late-stage clinical development.

**Expand environmental risk-management strategy.** Merck & Co., Inc. can ensure that it sets and applies discharge limits for antibiotic manufacturing. The company publishes its environmental risk-management policies that it applies to both

its own and third-party manufacturing sites.

**Improve access through the registration and affordability of new and existing antimicrobials.** Merck & Co., Inc. discloses information on its registration approach for six antimicrobials, including antimicrobial medicines and vaccines. It can seek opportunities to ensure greater access in more low- and middle-income countries through the registration of new and existing antimicrobials, and ensure that these are priced affordably.

**Expand on stewardship activities.** Merck & Co., Inc. engages in educational activities for health-care professionals on AMR globally. It also developed the SMART surveillance programme, which has been measuring resistance trends globally since 2002. The company can collaborate with public health authorities, and can ensure that the data is made publicly available via an open database. Merck & Co., Inc. can also engage in improving appropriate promotion practices.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT		Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	16 projects 9 target priority pathogens
			●	●	●	●	●	●		
A.1 No information on antimicrobial R&D investments.		adaptation of the existing medicines ceftolozane/tazobactam (Zerbaxa™) and tedizolid (Sivextro®) for Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HABP/VABP). Its clinical-stage projects consist of a next-generation HIV/AIDS medicine, a β-lactamase inhibitor targeting gram-negative bacteria, and a vaccine against <i>S. pneumoniae</i> .							the company collaborates with the University of Granada and the regional government of Andalusia, Spain, in a research alliance called Medina Discovery, which focusses on the screening and validation of drug targets for infectious diseases. Merck & Co., Inc. also collaborates with Rutgers University, USA, for the discovery of novel antimicrobial medicines, with funding from the National Institutes of Health (NIH).	
A.2.1-2.3 Nine candidates targeting priority pathogens.		A.3 Some preclinical R&D projects being developed with public partners.							A.4 Access and stewardship commitment in place.	
Merck & Co., Inc. does not publicly report information on candidates in Phase I development. According to publicly available information, the company has 16 antimicrobial R&D projects in its pipeline, including ten projects in clinical-stage development. Nine of the company's projects target priority pathogens. Although its priority pathogen pipeline is relatively small compared to other large research-based pharmaceutical companies assessed by the Benchmark, eight of the nine projects that target priority pathogens are focussed on multidrug-resistant bacteria (the remaining project targets HIV). This includes the		Merck & Co., Inc. is developing three preclinical R&D projects in its priority pathogen pipeline through public-private partnerships (including non-profit organisations). It is developing a vaccine for shigellosis through its joint venture with the Wellcome Trust called Hilleman Laboratories. Hilleman Laboratories focusses on developing affordable vaccines and addressing R&D gaps for low-resource settings. In addition,							Merck & Co., Inc. has a Global AMR Action Plan which describes the company's commitment to support access and stewardship for its novel antimicrobials portfolio. It has signed the Davos Declaration, which includes a general commitment to ensuring access to antimicrobial medicines and vaccines, and to support the appropriate and responsible use of these products.	

### Pipeline targeting priority pathogens

Discovery	Preclinical	Phase I	Phase II	Phase III	Approval
<ul style="list-style-type: none"> <li>Discovery programmes through Medina Discovery – GNB, <i>P. falciparum</i>, <i>M. tuberculosis</i></li> <li>Partnership with Orchid Pharma, India – Bacteria &amp; fungi</li> <li>Partnership with Rutgers University – Bacteria</li> </ul>	<ul style="list-style-type: none"> <li>► <i>Shigella</i> vaccine</li> </ul>		<ul style="list-style-type: none"> <li>► <i>S. pneumoniae</i> conjugate vaccine V114</li> </ul>	<ul style="list-style-type: none"> <li>Cilastatin/imepenem/relebactam (MK7655A) – <i>P. aeruginosa</i>, CRE – cIAI, cUTI, HABP/VABP</li> <li>Ceftolozane/tazobactam (Zerbaxa™) – GNB – Adaptation (Additional indication) – HABP/VABP</li> <li>Tedizolid phosphate (Sivextro®) – GPB – Adaptation (Additional indication) – HABP/VABP</li> <li>Doravirine (MK1439) – HIV</li> </ul>	

► Vaccine

cIAI = Complicated intra-abdominal infections

cUTI = Complicated urinary tract infections

FDC = Fixed dose combination

GNB = Gram-negative bacteria

GPB = Gram-positive bacteria

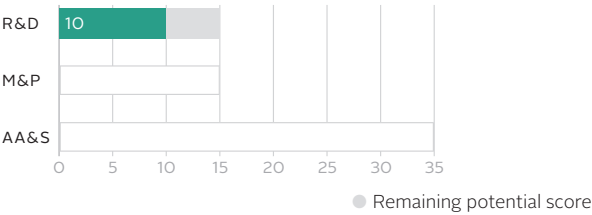
HABP/VABP = Hospital-acquired/Ventilator-associated bacterial pneumonia

B MANUFACTURING & PRODUCTION		Indicators scored on	1	2	3				
<b>B.1 Environmental risk management at own and external sites.</b> Merck & Co., Inc. has an environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge. The strategy applies to its own manufacturing sites and to third-party manufacturers of antibiotic APIs and drug products. The company commits to auditing the implementation of this strategy at both types of site. There is no evidence of the strategy being applicable to external waste-treatment plants. The company reports no information about setting discharge limits.			●	●	●				
<b>B.2 Limited transparency regarding environmental risk management.</b> Merck & Co., Inc. publishes elements of its environmental risk-management strategy on its website. It does not disclose audit results, or the discharge levels of antibiotics. The company also does not share the identities of its third-party suppliers of antibiotic APIs and drug products or external waste-treatment plants.									
<b>B.3 Commits to following GMP, including at 3rd-party sites.</b> Merck & Co., Inc. reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. Merck & Co., Inc. requires its third-party suppliers of drug products to apply the same quality standards to their production facilities.									
C APPROPRIATE ACCESS & STEWARDSHIP		Indicators scored on	1	2	3	4	5	6	7
<b>C.1 Some newest antibiotics filed in some countries in scope.</b> Merck & Co., Inc. has filed some of its newest antibiotics, cilastatin/imipenem (Primaxin®) and ertapenem (Invanz®), for registration in some countries in scope.* However, further details are not publicly available.		tries in scope.	●	●	●	●	●	●	●
<b>C.2 Makes general commitment to equitable pricing.</b> Merck & Co., Inc. discloses a general (not product-specific) inter- and intra-country equitable pricing approach covering countries in scope.*									
<b>C.3 Some insight into approach to supply chain efficiency.</b> Merck & Co., Inc. does not disclose how it works with stakeholders (e.g., governments, procurers) to align supply and demand for its highest-volume antimicrobial medicines, specifically to prevent or minimise stock-outs in countries in scope.* It does, however, publish a set of Supply Chain Standards, including the capacity to respond to changing demand. The company also does not report on whether it has processes in place to respond to stock-outs in countries in scope.									
<b>C.4 Multiple activities in AMR-related educational programmes.</b> Merck & Co., Inc. is involved in educational programmes for HCPs that include AMR stewardship and rational use of antibiotics, with conflicts of interest (COI) mitigation measures in place. Programmes include its recently launched knowledge platform that provides direct links to high-quality information and educational resources on AMR. The company also reports working with relevant stakeholders (e.g., CDC and a Colombian public health institute) to develop stewardship guidelines and programme metrics and support antimicrobial stewardship programmes in hospitals.									
<b>C.5-C.6 No information regarding brochure and/or packaging adaptations, or appropriate promotion practices.</b> Merck & Co., Inc. does not report any language, cultural or literacy adaptations made to its brochures or packaging that would promote appropriate use. Furthermore, the company does not report any appropriate promotion practices in its marketing materials or decoupling its sales force's incentives from volume of antibiotic sales.									
<b>C.7 International programme for AMR surveillance.</b> Merck & Co., Inc. runs a global surveillance programme focussed on AMR trends, namely the “Study for Monitoring Antimicrobial Resistance Trends” (SMART), which has a global scope and has been measuring resistance trends in intra-abdominal samples since 2002. The data has been published in several peer-reviewed publications over the years. The company also publicly commits to providing updated data by country and region. The company also engages in two other AMR-related surveillance programmes, the Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) and Surveillance of Tedizolid Activity and Resistance (STAR).									
ANIMAL HEALTH & DIAGNOSTICS									
<i>Activities in this area are not scored by the Benchmark. This information is provided given the importance of animal health and diagnostics on the topic of AMR.</i>			develop alternatives to antibiotics for animal use and to facilitate the appropriate use of antibiotics in animals. Merck & Co., Inc. runs a surveillance programme that monitors the emergence of bacterial resistance to Merck & Co., Inc. Animal Health antibiotics. Additionally, the company reports that it provides veterinarians, commercial production operations, farmers, ranchers			and feed companies with guidelines on resistance management, appropriate dosage, and length of usage to support the appropriate use of antibiotics.			
Merck & Co., Inc. is the only company in scope that is involved in antibiotics for use in animal health. The company conducts research to									

# MGB Biopharma

Stock exchange: Privately held • Ticker: - • HQ: Bellshill, Scotland, UK • Employees: 2-10 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: No

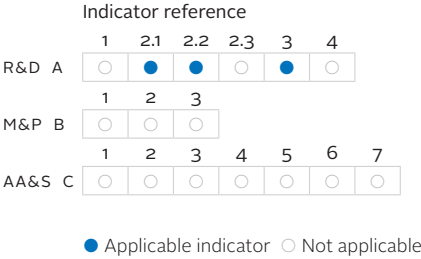
Performance by Research Area



## PERFORMANCE

MGB Biopharma is a biopharmaceutical company, selected for having a pipeline that targets priority pathogens. It was evaluated in the area of Research & Development only. The company performs well compared to other biopharmaceutical companies in scope. MGB Biopharma has four projects

How MGB Biopharma was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## OPERATIONS

MGB Biopharma, founded in 2010, is a biopharmaceutical company focussing on a new class of anti-infectives, the DNA Minor Groove Binders (MGBs), which interact with microbial cell DNA and interfere with its replication. MGBs were originally developed at the University of Strathclyde in Glasgow, which licensed the technology to MGB Biopharma, granting the company exclusive global rights in all fields except cancer. The company's most advanced drug can-

didate, MGB-BP-3, is active against gram-positive bacteria and has recently completed a Phase I clinical safety study in the oral treatment of *C. difficile* infection. The compound is an analogue of the naturally occurring antibiotic (and antiviral) distamycin. MGB Biopharma has plans to extend the therapeutic indications of this compound and is currently developing MGBs that are active against viruses, fungi and parasites. The University of Strathclyde remains a close partner

of the company in the development of its MGB pipeline. MGB Biopharma has no products on the market. In 2017, the company closed a USD 1 million financing round to fund the development and production of MGB-BP-3 for a Phase II clinical study in *C. difficile* infection. The financing round was led by Archangel Investors Limited and included contributions from TRI Capital Ltd, Barwell plc and Scottish Investment Bank.

## ANTIMICROBIAL PORTFOLIO

MGB Biopharma does not have any products on the market.

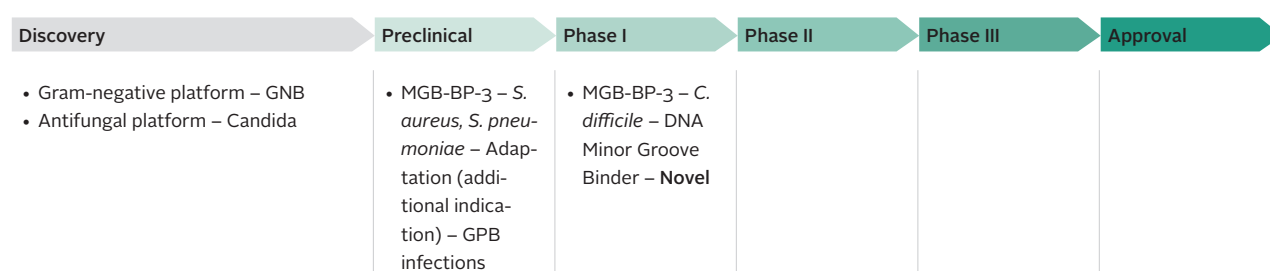
## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** MGB Biopharma has one antibiotic candidate (MGB-BP-3) in clinical development, currently in Phase I. MGB Biopharma is encouraged to implement access and stewardship plans for this candidate as it moves into Phase II clinical development.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT		Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	4 projects 4 target priority pathogens
<b>A.2.1-2.2 One novel antibiotic in the clinical pipeline.</b> Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. MGB Biopharma has four projects in its antimicrobial R&D pipeline, all targeting priority pathogens. MGB Biopharma is currently developing its MGB-BP-3 antibiotic for the treatment of <i>C. difficile</i> infections. MGB-BP-3's antimicrobial activity is based on a new mode of action, namely its activity as a DNA Minor Groove Binder (MGB). Despite being in development for treatment of <i>C. difficile</i> infections, MGB-BP-3 is		also active against other gram-positive bacteria, such as methicillin-resistant <i>S. aureus</i> (MRSA), vancomycin-resistant <i>Enterococcus</i> (VRE) and Streptococci. The company is also developing intravenous and topical formulations of the compound in preclinical stages, and has discovery platforms for gram-negative bacteria and fungi.	○	●	●	○	●	○	<b>A.4 No R&amp;D candidates in late-stage development.</b> MGB Biopharma is not eligible for this indicator as it does not have any R&D candidates in late-stage development.	
<b>A.3 All R&amp;D projects being developed with public partner.</b> MGB Biopharma is developing all three R&D projects in its priority pathogen pipeline in collaboration with the University of Strathclyde.										

### Pipeline targeting priority pathogens



GNB = Gram-negative bacteria

GPB = Gram-positive bacteria

## B MANUFACTURING & PRODUCTION

As a biopharmaceutical company with no products on the market, MGB Biopharma was not eligible for this Research Area.

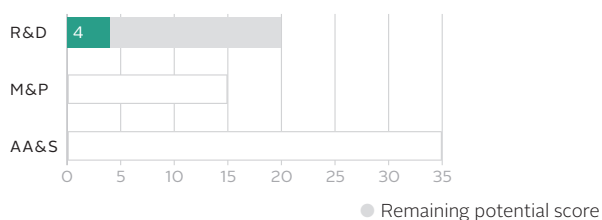
## C APPROPRIATE ACCESS & STEWARDSHIP

As a biopharmaceutical company with no products on the market, MGB Biopharma was not eligible for this Research Area.

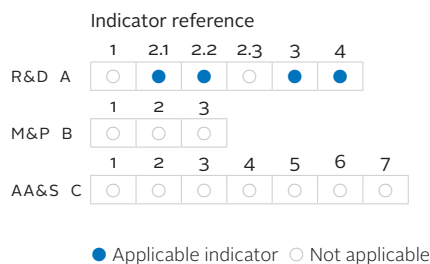
# Motif Bio plc

Stock exchanges: XLON; XNAS • Ticker: MTFB • HQ: London, United Kingdom • Employees: 7 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Motif Bio was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Motif Bio is a biopharmaceutical company, selected for having a pipeline that targets priority pathogens. It was evaluated in the area of Research & Development only. Motif Bio invested USD 35 million in antibiotic drug development in 2016. Its performance in the Benchmark is low compared with other biopharmaceutical companies in scope. It has two projects in its antimicrobial R&D pipeline, both targeting priority pathogens.

During the period of analysis, the company did not engage in public-private partnerships but conducted R&D in-house and/or with private-sector partners to develop its candidate compounds. Motif Bio has one R&D project in late-stage clinical development, and reports that it has both an access and stewardship commitment in place for this candidate.

## OPERATIONS

Motif Bio is a biopharmaceutical company which specialises in developing novel antibiotics against infections caused by multidrug-resistant bacteria. The company's most advanced antibiotic drug candidate, iclaprim, is active against gram-positive bacteria. It is currently being developed for the treatment of acute bacterial skin and skin structure infections and hospital-acquired pneumonia, including infections caused by methicillin-resistant *S. aureus* (MRSA) and multidrug-resistant *S. pneumoniae*. The compound was acquired from Nuprim Inc.

in 2015 following the merger of the two companies. In 2017, it was granted 'orphan drug' status by the FDA (for developing a drug or biological product to treat a rare disease or condition) for treating *S. aureus* lung infections in patients with cystic fibrosis. The company aims to collaborate with universities and other pharmaceutical companies to expand its pipeline of antibiotics against gram-positive and gram-negative bacteria. Motif Bio is a member of the BEAM alliance, a group of biopharmaceutical companies addressing the regulatory and commercial envi-

ronments in Europe regarding R&D, approval and market viability of products combating antimicrobial resistance. Motif Bio has no products on the market. In 2016, the company raised USD 25 million from UK and US investors through a NASDAQ IPO.

## ANTIMICROBIAL PORTFOLIO

Motif Bio does not have any products on the market.

## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Motif Bio has stated a commitment to ensure access and stewardship provisions are in place for its antibiotic candidate (iclaprim) in late-stage clinical development. It can ensure that these provisions are applied and implemented accordingly.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT	Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	2 projects 2 target priority pathogens
		○	●	●	○	●	●		

### A.2.1-2.2 Two candidates targeting priority pathogens.

Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. Motif Bio invested USD 35 million in antibiotic drug development in 2016. The company has two projects in its antimicrobial R&D pipeline targeting priority pathogens, both in development for the treatment of gram-positive bacterial infections. The company's most advanced antibiotic candidate is iclaprim, an antibiotic designed to be effective against bacteria that are resistant to other antibiotics, including trimethoprim, a commonly used antibiotic with the same mechanism of action. Iclaprim is an antibiotic of the dihydrofolate reductase (DHFR) inhibitor class that is active against methicil-

lin-resistant *S. aureus* (MRSA). Iclaprim is currently in Phase III clinical development and is being developed for acute bacterial skin and skin structure infections (ABSSSI) and hospital-acquired bacterial pneumonia (HABP). Motif Bio is also developing another antibiotic in the preclinical stage, targeting MRSA.

### A.3 No public-private partnerships reported during the period of analysis.

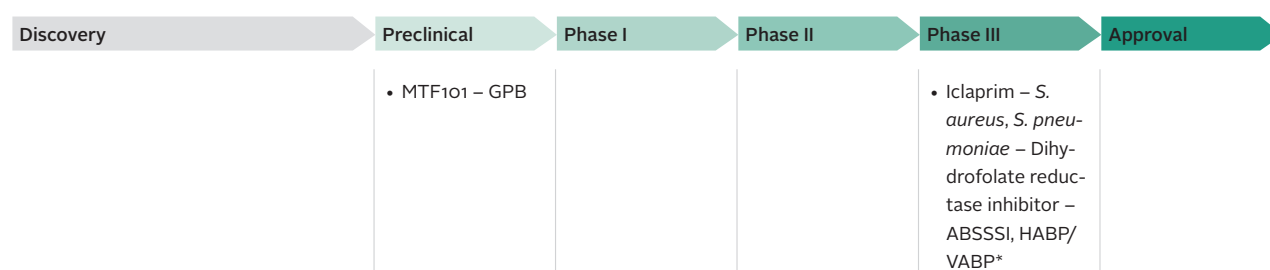
Motif Bio conducts R&D in-house and/or with private-sector partners. During the period of analysis, it did not participate in public-private partnerships, or in partnerships with non-profit organisations, for antimicrobial R&D. After the period of analysis, the company announced *in vitro* testing of iclaprim's activity against various

strains of *Burkholderia*, *Stenotrophomonas* and *Achromobacter*, in partnership with the Cystic Fibrosis Foundation.

### A.4 Access and stewardship commitments for iclaprim.

Motif Bio reports that it has both an access and a stewardship commitment in place for its antibiotic candidate in late-stage development. The company commits to filing iclaprim for registration based on public health needs and disease prevalence. It also commits to ensuring access to its product in low- and middle-income countries, with pricing strategies that take affordability into account. For this indicator, countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.

### Pipeline targeting priority pathogens



ABSSSI = Acute bacterial skin and skin structure infections

GPB = Gram-positive bacteria

HABP/VABP = Hospital-acquired/Ventilator-associated bacterial pneumonia

\* After the period of analysis, Motif Bio stated that Phase III trials for iclaprim in patients with HABP/VABP have started

## B MANUFACTURING & PRODUCTION

As a biopharmaceutical company with no products on the market, Motif Bio was not eligible for this Research Area.

## C APPROPRIATE ACCESS & STEWARDSHIP

As a biopharmaceutical company with no products on the market, Motif Bio was not eligible for this Research Area.

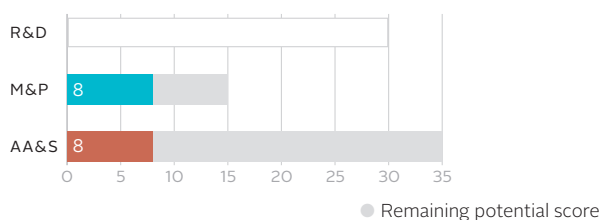
# Mylan NV

Stock exchange: XNAS • Ticker: MYL • HQ: Canonsburg, PA, US • Number of employees: > 35,000

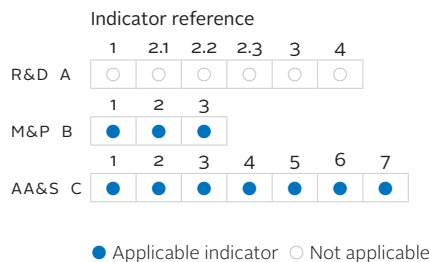
Signatory to Davos Decl.: Yes

Signatory to Industry Roadmap: No

## Performance by Research Area



## How Mylan was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Mylan is one of the largest producers of antibiotics globally by sales volume. As a generic medicine manufacturer, Mylan was evaluated in Manufacturing & Production and Appropriate Access & Stewardship only. It has the highest performance among generic medicine manufacturers in scope. The company discloses an environmental risk-management strategy that is applied to its own manufacturing sites. Mylan reports mechanisms for maintaining a high quality of antibiotic production and also requires its third-party suppliers to apply

the same quality standards to their production facilities. The company reports no information on where it files products for registration; however, it discloses a general intra-country equitable pricing approach. The company also engages in stakeholder engagement to ensure efficient supply. Regarding stewardship, Mylan adapts its packaging with symbols and pictograms illustrating the necessary antibiotic dosage schedule for patients.

## SALES AND OPERATIONS

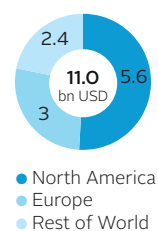
Mylan, founded in 1961, is a US-based global provider of generic and specialty pharmaceuticals. The company produces and markets innovative and generic medicines, active pharmaceutical ingredients and consumer healthcare products in approximately 165 countries and territories worldwide. The company's key therapeutic areas include cardiovascular, CNS and anaesthesia, infectious disease, immunology, respiratory and allergy, dermatology and oncology. In 2017, Mylan announced a multilateral agreement to provide a new class of antiretrovirals (ARVs) to low- and middle-income countries. This agreement includes the South African government, the Kenyan government, the Joint United Nations Programme on HIV/AIDS

(UNAIDS), the Clinton Health Access Initiative and the Bill & Melinda Gates Foundation (BMGF), among others. Under the agreement, the company will supply a generic fixed dose combination of dolutegravir/lamivudine/tenofovir disoproxil fumarate (developed as part of a licensing agreement with Gilead Sciences Inc. and ViiV Healthcare) for a maximum price of about USD 75 per patient per year. In return, the BMGF will guarantee minimum sales volumes of the drug. Since 2015, Mylan has made several large acquisitions, including those of Meda, Abbott's non-US developed markets specialty and branded generics business and the non-sterile, topicals-focused specialty and generics business of Renaissance Acquisition Holdings.

## Revenues by product<sup>§</sup>



## Revenues by region<sup>||</sup>

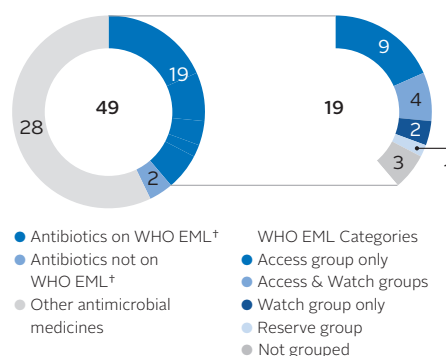


## ANTIMICROBIAL PORTFOLIO

Mylan markets at least 49 antimicrobial medicines, 38 of which are listed on the WHO EML (Section 6). Twenty-one of the company's antimicrobial medicines are antibiotics, with 19 listed on the WHO EML (Section 6), including one on the EML's Reserve group (linezolid).

The remainder (28) of the company's portfolio comprises two antifungals and 26 antivirals, including 22 indicated for HIV/AIDS, the largest anti-HIV portfolio in the Benchmark.

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Net sales and other revenues from third-parties; FYE 31 December 2016

<sup>||</sup> Third-party net sales; FYE 31 December 2016

## OPPORTUNITIES

**Expand engagement in antimicrobial stewardship.** Mylan adapts its packaging with symbols and pictograms illustrating the necessary dosage schedule for patients. It can expand this practice to more countries in scope\* and take further language and literacy needs into consideration. Mylan can engage in more stewardship activities, e.g., through surveillance activities, educational activities for healthcare professionals on AMR (while mitigating conflict of interest), and engage in appropriate promotion practices.

**Expand environmental risk-management strategy.** Mylan can ensure antibiotic discharge limits are added to its environmental risk-management strategy. It can also extend this strategy to the sites of third parties who manufacture antibiotic APIs on its behalf, as well as to external waste-treatment sites. Mylan has a general environmental risk-management strategy that it applies to its own manufacturing sites.

**Ensure affordability and registration plans for new and existing antimicrobials.** Mylan disclosed its approach to equitable pricing specifi-

cally for its antiretrovirals. It can seek to improve access in low- and middle-income countries through registration of new and existing antimicrobials, and ensure that more products are priced affordably.

**Increase engagement in R&D innovation.** Mylan is currently engaged in developing new fixed dose combinations of antiretroviral medicines. It can continue to engage in incremental R&D, and ensure access and stewardship provisions are in place for these projects.

## PERFORMANCE BY RESEARCH AREA

### A RESEARCH & DEVELOPMENT

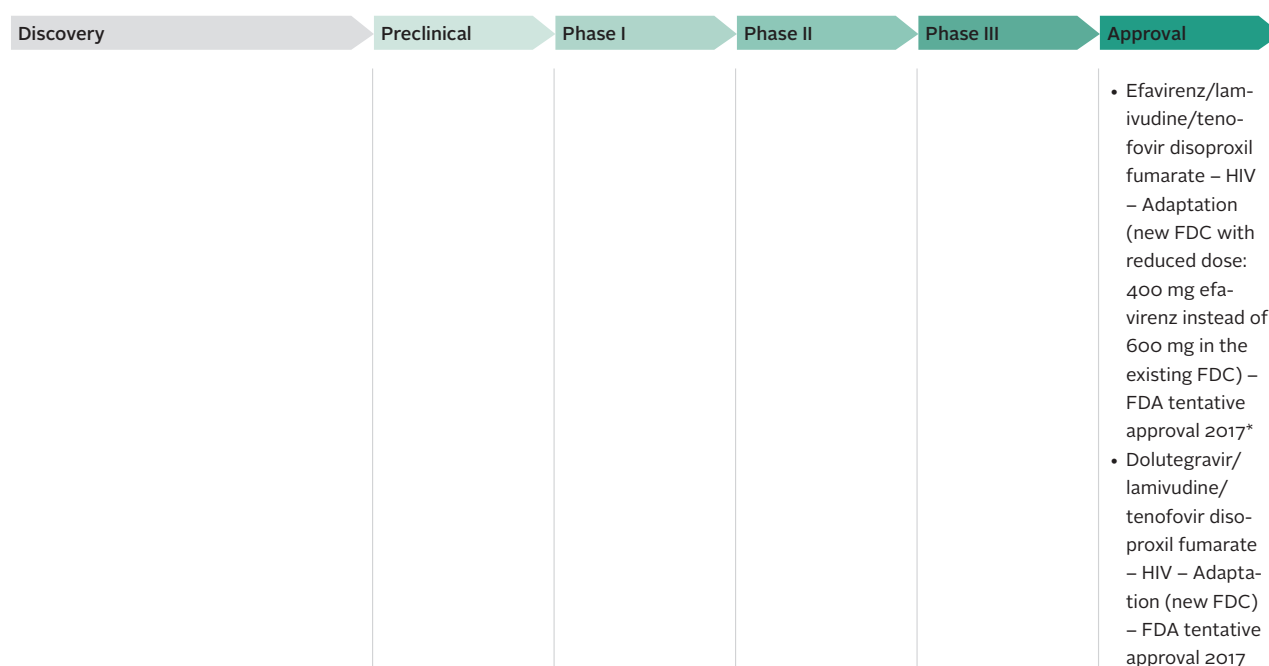
As a generic medicine manufacturer, Mylan was not eligible for this research area. However, the company is active in antimicrobial R&D.

**Two new fixed dose combinations for HIV/AIDS.** Mylan reports that it has two projects in its antimicrobial R&D pipeline targeting a priority pathogen, namely HIV. One project involves a dose reduction to efavirenz (600 mg to 400 mg), in

the Fixed Dose Combination (FDC) efavirenz/lamivudine/tenofovir disoproxil fumarate, which has been shown to be non-inferior while containing a reduced drug dose, and can be sold at a lower price. The other project involves dolutegravir/lamivudine/tenofovir disoproxil fumarate, a new FDC for the treatment of HIV/AIDS. In 2017, Mylan received FDA tentative approval for both of these FDCs, as they consist of patented

antiretrovirals from Gilead Sciences Inc., Bristol-Myers Squibb Co. and ViiV Healthcare. Mylan commits to pricing these generics affordably. In particular, Mylan has announced a new agreement with UNAIDS and other partners to make the dolutegravir/lamivudine/tenofovir disoproxil fumarate combination available to public sector purchasers in low- and middle-income countries at around USD 75 per person, per year.

Pipeline targeting priority pathogens

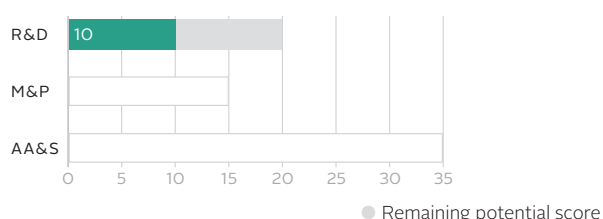


B MANUFACTURING & PRODUCTION	Indicators scored on	1 2 3
<b>B.1 Environmental risk-management strategy for own sites.</b>	<b>B.2 Limited transparency regarding environmental risk management.</b>	<b>B.3 Commits to following GMP, including at 3rd-party sites.</b>
<p>Mylan has an environmental risk-management strategy that includes minimising the impact of antibiotic manufacturing discharge. The strategy applies to its own sites and includes auditing. At a number of sites in India, Mylan follows a Zero-Liquid Discharge process (ZLD, a water treatment process in which all wastewater is cleaned and reused). The company's environmental risk-management strategy has not been extended to Mylan's third-party manufacturers of antibiotic APIs and drug products, or to external waste-treatment plants. The company reports no information about setting discharge limits.</p>	<p>Mylan reports some of its environmental risk-management initiatives in its Global Sustainability Report, published on its website. It does not disclose audit results, or the discharge levels of antibiotics. The company also does not share the identities of its third-party suppliers of antibiotic APIs and drug products, or of external waste-treatment plants.</p>	<p>Mylan reports that it has mechanisms for maintaining a high quality of pharmaceutical production that includes antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. Mylan requires its third-party suppliers to apply the same quality standards to their production facilities.</p>
C APPROPRIATE ACCESS & STEWARDSHIP	Indicators scored on	1 2 3 4 5 6 7
<b>C.1 No information on filing for registration.</b>	<b>C.3 Taking multiple steps to improve supply chain efficiency.</b>	<b>C.4-C.7 Some involvement in AMR stewardship activities.</b>
<p>Mylan reports no information on where it has filed its newest antibiotics for registration in countries in scope.* This information is not otherwise publicly available.</p> <p><b>C.2 Intra-country equitable pricing for antimicrobials.</b></p> <p>Mylan discloses a general (not product-specific) intra-country equitable pricing approach. It reports that this applies to at least its 5 highest-volume antimicrobial medicines (all HIV/AIDS medicines) in countries in scope.* Under this general approach, the lowest prices are reserved for Global Fund, PAHO and PEPFAR.</p>	<p>Mylan engages with the Global Fund, PEPFAR and the South African government to align supply and demand forecasting for five of its highest-volume antimicrobials. These are all HIV/AIDS medicines. The company also has response mechanisms in place for its HIV/AIDS medicines in order to respond efficiently in the event of stock-outs in countries in scope.* These mechanisms are designed to enable Mylan to anticipate and respond to competing suppliers' stock-outs.</p>	<p>Mylan adapts its packaging with symbols and pictograms illustrating the necessary dosage schedule for patients. This can help to improve patient adherence to treatment. However, it does not report of any activities in HCP education, appropriate promotion practices, or surveillance programmes.</p>

# Nabriva Therapeutics plc

Stock exchange: XNAS • Ticker: NBRV • HQ: Dublin, Ireland • Number of employees: 66 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Nabriva was evaluated: applicable indicators

		Indicator reference						
		1	2.1	2.2	2.3	3	4	
R&D	A	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	
		1	2	3				
M&P	B	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>				
		1	2	3	4	5	6	7
AA&S	C	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Nabriva is a biopharmaceutical company, selected for having a pipeline that targets priority pathogens. It was evaluated in the area of Research & Development only. Nabriva has invested USD 48 million in antibiotic drug development in 2016. The company performs well compared to other biopharmaceutical companies in scope. Nabriva's R&D pipeline consists of five projects, all of which target priority pathogens, including one novel antibiotic candidate. The company

does not provide evidence of engaging in public-private partnerships and agreements to develop and commercialise its candidate compounds. Nabriva has no access or stewardship provisions in place for its late-stage clinical antimicrobial candidates.

## OPERATIONS

Nabriva is a biopharmaceutical company engaged in research and development of novel antibiotics to treat bacterial infections, with a focus on the pleuromutilin class of antibiotics. Pleuromutilins were discovered in the 1950s and have since been used systemically in animals and topically in humans. In 2006, Nabriva was incorporated as a spin-off from the Sandoz GmbH Antibiotics Research Institute in Austria.

The company then became public in 2015. In 2017, it relocated its corporate headquarters to Ireland. Nabriva is currently developing lefamulin, a semi-synthetic compound that inhibits the synthesis of bacterial protein. Lefamulin has recently completed a Phase III trial evaluating its safety and efficacy in patients with CABP. Nabriva is a member of the BEAM alliance, a group of biopharmaceutical companies

addressing the regulatory and commercial environments in Europe regarding R&D, approval and market viability of products combating antimicrobial resistance. Nabriva has no products on the market. In 2016, the company had USD 6.5 million worth of revenues from research premiums and grants.

## ANTIMICROBIAL PORTFOLIO

Nabriva does not have any products on the market.

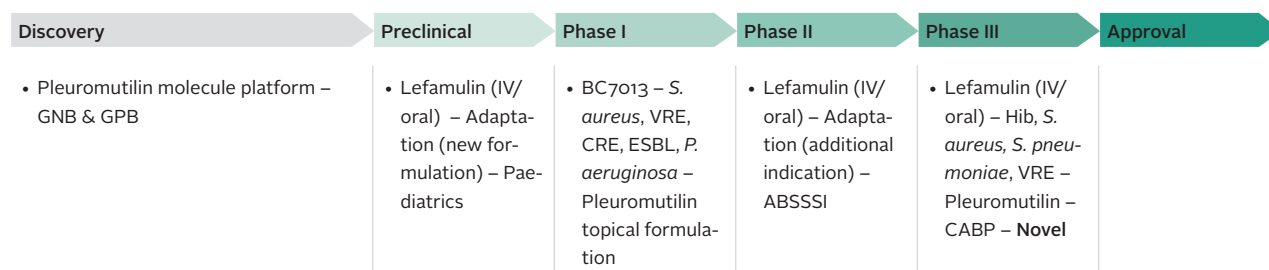
## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Nabriva is developing one antibiotic candidate (lefamulin) in late-stage clinical development. Nabriva can ensure access and stewardship provisions are in place for lefamulin, e.g., through partnerships.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT	Indicators scored on 1 2.1 2.2 2.3 3 4 ○ ● ● ○ ● ●	Antimicrobial pipeline 5 projects 5 target priority pathogens
<p><b>A.2.1-2.2 Pipeline focussed on pleuromutilin antibiotics.</b></p> <p>Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. Nabriva invested USD 48 million in antibiotic drug development in 2016. The company has five projects in its antimicrobial R&amp;D pipeline, all targeting priority pathogens, including one topical formulation. Currently, Nabriva has one systemic pleuromutilin antibiotic (lefamulin) in Phase III clinical trials to evaluate the safety and efficacy of intravenous to oral lefamulin in patients with CABP. Nabriva intends to develop lefamulin for additional indications, including for the treatment of acute bacterial skin and skin structure infections (ABSSSI)</p>	<p>and for paediatric use. Lefamulin is seen by WHO as a new innovative antibiotic, as this is the first pleuromutilin for systemic use in humans. Additionally, Nabriva is developing a pleuromutilin in topical form (BC7013) for the treatment of uncomplicated skin and skin structure infections (uSSSI). The company also owns a pleuromutilin discovery platform.</p> <p><b>A.3 No public-private partnerships reported.</b></p> <p>Nabriva conducts R&amp;D in-house and/or with private-sector partners. It does not participate in public-private partnerships, or in partnerships with non-profit organisations, for antimicrobial R&amp;D.</p>	<p><b>A.4 No information on access or stewardship provisions.</b></p> <p>Nabriva reports no information on access or stewardship provisions for its antibiotic candidate in late-stage development. It has signed the Davos Declaration, which includes a general commitment to ensuring access to antimicrobial medicines and vaccines, and to support the appropriate and responsible use of these products.</p>

## Pipeline targeting priority pathogens



ABSSSI = Acute bacterial skin and skin structure infections

CABP = Community-acquired bacterial pneumonia

GNP= Gram-negative bacteria

GPB = Gram-positive bacteria

## B MANUFACTURING &amp; PRODUCTION

As a biopharmaceutical company with no products on the market, Nabriva was not eligible for this Research Area.

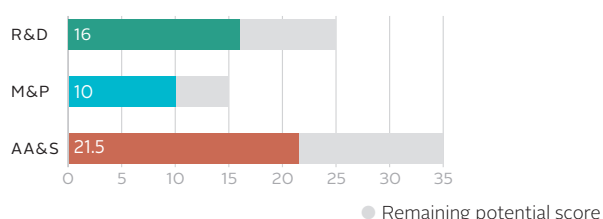
## C APPROPRIATE ACCESS &amp; STEWARDSHIP

As a biopharmaceutical company with no products on the market, Nabriva was not eligible for this Research Area.

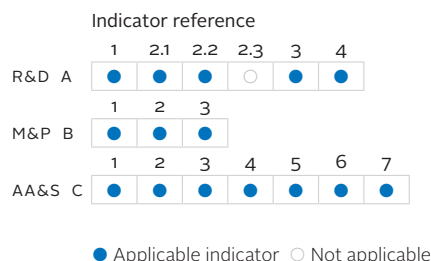
# Novartis AG

Stock exchange: XSWX • Ticker: NOVN • HQ: Basel, Switzerland • Employees: 118,393 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: Yes

## Performance by Research Area



## How Novartis was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Novartis is among the top performing large research-based pharmaceutical companies, following close behind the leaders. This is driven by strong performance in Manufacturing & Production and Appropriate Access & Stewardship. Its performance in Research & Development is on par with the average for this group of companies. The company has an antimicrobial R&D pipeline of 32\*\* projects, of which 16 target a priority pathogen, including two novel antimalarial candidates. It has an access commitment in place for four of its R&D candidates. The company discloses a comprehensive environmental risk-management strategy, which includes discharge limits and reportedly applies to all Novartis' third-party suppliers of antibiotic APIs and drug products. Novartis has filed

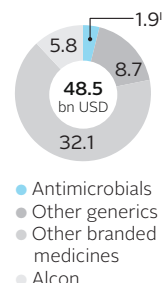
its newest antibiotics in some countries in scope\* and commits to engaging in inter-country equitable pricing for its antimicrobials. The company reports that it widely applies intra-country equitable pricing for one product. It also reports engaging with local healthcare facilities to align supply and demand. Regarding stewardship, Novartis engages in numerous AMR educational activities aimed at healthcare professionals, taking steps to mitigate conflict of interest, and is currently adjusting incentives for its sales teams to increase the weight of fixed pay in overall compensation and to reduce the variable component. In contrast to other large research-based pharmaceutical companies in scope, Novartis does not report engaging in antibiotic-specific AMR surveillance programmes.

## SALES AND OPERATIONS

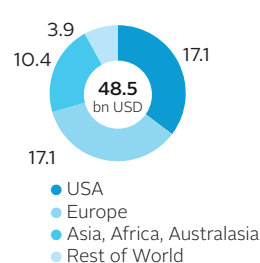
Novartis is a large research-based pharmaceutical company with three divisions: Innovative Medicines, Alcon (eye-care products) and Sandoz (generic medicines). The Innovative Medicines division has two business units: pharmaceuticals (primary care and specialty medicines) and oncology. The bulk of antimicrobial medicines in the company's portfolio are marketed by Sandoz. Sandoz markets antimicrobials in about 140 countries globally, of which 71 or more are low- or middle-income countries.\*

Sandoz also sells other drug products, pharmaceutical intermediates and active pharmaceutical ingredients (APIs). It sold and/or donated 2,425 million doses of antimicrobial medicines during the fiscal year 2016. In 2015, Novartis divested its vaccine business (excluding influenza vaccines) to GSK in an asset swap that included the acquisition of GSK's marketed oncology portfolio. The influenza vaccines unit ceased operation in 2014 and was finally acquired by CSL Limited in 2015 (including its development pipeline).

## Revenues by product<sup>§</sup>



## Revenues by region<sup>§</sup>

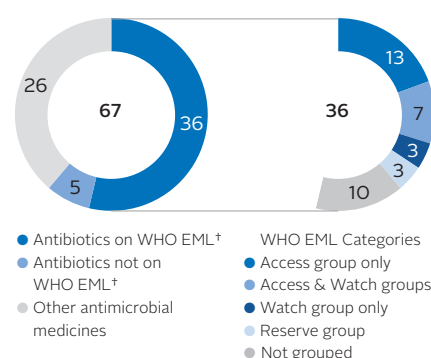


## ANTIMICROBIAL PORTFOLIO

Novartis markets at least 67 antimicrobial medicines, the second largest reported antimicrobial portfolio among the large research-based pharmaceutical companies assessed by the Benchmark. Sixty of these 67 medicines are listed on the WHO EML (Section 6). The bulk of the company's antimicrobial medicines are classical fermentation-derived antibiotics (penicillins, cephalosporins and macrolides), marketed

by its generics division Sandoz. Of 41 antibiotics on the market, 36 are listed on the WHO EML (Section 6), including three antibiotics in the EML's Reserve group (cefepime, daptomycin and linezolid). The remainder (26) of the company's portfolio includes antivirals, antifungals, antiparasitics and anthelmintics, the majority of which are listed on the WHO EML (Section 6).

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Net sales; FYE 31 December 2016

<sup>||</sup> Approximately

## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Novartis has a general registration procedure in place for candidates that reach Phase III clinical development, and has specifically stated a commitment to apply this to its late-stage candidates. Novartis can ensure that this procedure is applied, while also implementing further access and stewardship plans for all its candidates in late-stage clinical development.

**Improve transparency regarding environmental risk management.** Novartis can share more information on how it manages environmental risk, e.g., the company can disclose the levels

of antibiotic discharge. Currently, Novartis discloses several elements of its environmental risk-management strategy.

**Expand environmental risk-management strategy.** Novartis can apply its antibiotic discharge limits to third parties who manufacture antibiotic APIs on its behalf. Novartis has set discharge limits for its own manufacturing sites and external waste-treatment plants as part of its environmental risk-management strategy.

**Engage in more stewardship activities.** Novartis engages in several stewardship activities. The company can engage in antibiotic resistance surveillance programmes, collaborate with public health authorities and ensure that data is made publicly available through open databases.

**Expand its SMS for Life programme to more countries.** Novartis can expand its SMS for Life (2.0) programme, a public-private partnership between Novartis and local public health facilities to track medicines stock levels, to more countries in scope.\* The programme is already operating in six African countries.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT	Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	32 projects 16 target priority pathogens
		●	●	●	○	●	●		

**A.1 Average antimicrobial R&D investments.** Novartis reports investments in antimicrobial R&D in 2016, which are average compared to other large research-based pharmaceutical companies in the Benchmark, however the exact amount is confidential. These investments cover antimicrobial medicines only, as Novartis is not involved in vaccine development.

### A.2.1-2.2 Pipeline focussed on gram-negative bacteria and malaria.

Novartis has 32\*\* antimicrobial R&D projects in its pipeline, seven of which are in clinical stage development. Sixteen of the company's projects target priority pathogens. It has an average-sized pipeline compared to other large research-based pharmaceutical companies assessed by the Benchmark. The company has a strong focus on malaria and bacteria, mostly gram-negative. It has nine drug candidates in preclinical development (eight of which target bacteria), and four drug candidates in clinical development. Novartis' clinical pipeline consists of four investigational medicines including: two novel

antimalarial medicines (both imidazolopiperazines); LFF571 (an antibiotic targeting *C. difficile* in Phase II development); and LYS228 (an antibiotic with activity against carbapenem-resistant *Enterobacteriaceae* spp. (CRE), currently starting Phase II clinical trials). Additionally, Novartis is awaiting approval for the inclusion of tuberculosis as an additional indication for its leprosy medicine, clofazimine (Lamprene®).

### A.3 Six R&D projects being developed with public partners, including two PDPs.

Novartis is developing six R&D projects in its priority pathogen pipeline through public-private partnership (including non-profit organisations). Two antimalarial candidates, cipargamin and KAF156/lumefantrine, are being developed through PDPs with the Medicines for Malaria Venture (MMV). Development of KAF156/lumefantrine is co-funded by the Bill & Melinda Gates Foundation and development of cipargamin is co-funded by the Wellcome Trust. The other four projects are in preclinical stage and involve public research institutes.

### A.4 Access commitment in place, but no information regarding stewardship.

Novartis reports that it has an access commitment in place for its four R&D candidates targeting priority pathogens in late-stage development, but reports no information on stewardship provisions. In the 2016 Access to Medicine Index, Novartis was a leader in registering products in countries in scope.\* The company commits to applying the same strategy to its late-stage investigational candidates. For example, the PDP funding agreements for its antimalarial candidates include clauses to ensure broad access. Regarding stewardship provisions, Novartis signed the Davos Declaration, which includes a general commitment to support the appropriate and responsible use of antimicrobial medicines and vaccines. After the period of analysis, Novartis stated its practice of initiating global surveillance for potential resistance to its novel antimicrobial agents a minimum of four years prior to expected launch (in line with FDA recommendations).

### Pipeline targeting priority pathogens

Discovery	Preclinical	Phase I	Phase II	Phase III	Approval
<ul style="list-style-type: none"> <li>Inhibitors/modulators of bacterial outer membrane biogenesis – GNB</li> <li>Bacterial cell wall inhibitors – GNB</li> <li>Inhibitors/modulators of bacterial cell envelope biogenesis and function – GNB</li> <li>Phenotypic screening of natural products – GNB</li> <li>Discovery of new combinations of existing and new chemical entities – GNB</li> <li>Uncomplicated malaria – <i>P. falciparum</i></li> </ul>	<ul style="list-style-type: none"> <li>JA-43-AO00 – GNB &amp; GPB</li> <li>EE-67-VB84 – <i>P. aeruginosa</i></li> <li>FB-11-AR48 – GNB &amp; GPB</li> <li>Cipargamin (KAE609) – <i>P. falciparum</i> – Adaptation (new formulation: intravenous)</li> <li>Confidential project – GNB – Adaptation (new formulation)</li> </ul>	<ul style="list-style-type: none"> <li>LYS228† – GNB</li> </ul>	<ul style="list-style-type: none"> <li>LFF571 – <i>C. difficile</i>, <i>S. aureus</i>, VRE</li> <li>KAF156/lumefantrine – <i>P. falciparum</i> – Novel</li> <li>Cipargamin (KAE609) – <i>P. falciparum</i> – Novel</li> </ul>		<ul style="list-style-type: none"> <li>Clofazimine (LAM320) – <i>M. tuberculosis</i> – Adaptation (additional indication) – Awaiting approval</li> </ul>

GNB = Gram-negative bacteria

GPB = Gram-positive bacteria

† This candidate moved to Phase II clinical development after the period of analysis.

\*\* After the period of analysis, Novartis submitted an adaptive project of tobramycin for the treatment of bronchiectasis-related *Pseudomonas*, including the assessment of resistance.

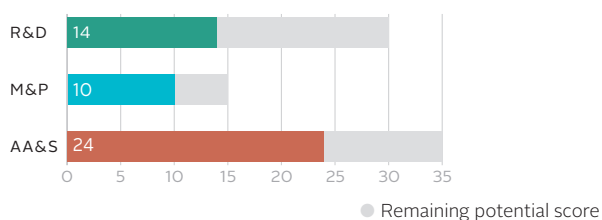
B MANUFACTURING & PRODUCTION		Indicators scored on	1	2	3
<b>B.1 Comprehensive environmental risk-management strategy.</b> Novartis undertakes almost all environmental risk-management activities that the Benchmark examines. Namely, it applies an environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge. This includes auditing at its own manufacturing sites and those of third-party manufacturers of antibiotic APIs and drug products. Novartis sets limits on antibiotic discharge for its own manufacturing sites and external waste-treatment plants, yet not to third-party manufacturers of antibiotic APIs and drug products.			●	●	●
<b>B.2 Limited transparency regarding environmental risk management.</b> Novartis publishes elements of its environmental risk-management strategy on its website. It does not disclose audit results, or the discharge levels of antibiotics. The company also does not share the identities of its third-party suppliers of antibiotic APIs and drug products or external waste-treatment plants.					
<b>B.3 Commits to following GMP, including at 3rd-party sites.</b> Novartis reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. Novartis requires its third-party suppliers of drug products to apply the same quality standards to their production facilities.					

C APPROPRIATE ACCESS & STEWARDSHIP		Indicators scored on	1	2	3	4	5	6	7
<b>C.1 Filed newest antibiotics in some countries in scope.</b> Novartis reports information about where it has filed five of its newest antibiotics for registration in some countries in scope* (between one and eight countries). These products were introduced between 2011 and 2017.			●	●	●	●	●	●	●
<b>C.2 Inter- and intra-country equitable pricing.</b> Novartis discloses a general (not product-specific) commitment to applying inter-country equitable pricing to its highest-volume antimicrobials including antibiotics. It applies intra-country equitable pricing approaches for artemether/lumefantrine (Coartem®) in the majority of countries in scope.* This approach was first developed and implemented in partnership with WHO in 2001. Novartis has independently extended this approach beyond its initial ten-year term.									
<b>C.3 Local engagement to align supply and demand.</b> Novartis engages with primary and local health-care facilities to align supply and demand forecasting for two of its highest-volume antimicrobial medicines: artemether/lumefantrine (Coartem®) and efavirenz. This applies in the following countries in scope*: Cameroon, the Democratic Republic of Congo, Ghana, Kenya,									
<b>C.4 Multiple activities in AMR-related educational programmes.</b> Novartis reports that it is involved in educational programmes for HCPs that include AMR stewardship and rational use of antibiotics, with conflicts of interest (COI) mitigation measures in place. Programmes include topics on diagnosis, treatment and management of multidrug-resistant bacterial infections. The company provides a protocol to mitigate COI. All educational activities reported were developed in collaboration with third parties.									
<b>C.5 Comprehensive involvement in appropriate promotion practices.</b> The Benchmark measures how companies address stewardship through appropriate promotion. Novartis reports that it takes action in this regard: it reflects AMR trends in its marketing materials and is currently adjusting incentives for its sales teams around the world. For									
<b>C.6 Implements brochure and/or packaging adaptations to facilitate appropriate use</b> Novartis has adapted several brochures (to include demographic and literacy considerations) to facilitate appropriate use of antibiotics by patients. For example, paediatric brochures have been incorporated to illustrate the appropriate dosage of amoxicillin, and the packaging for its penicillin G antibiotic in Africa has been adapted for patients who may be illiterate.									
<b>C.7 No apparent involvement in surveillance programmes.</b> Novartis reports no involvement in antibiotic resistance-specific programmes aimed at increasing global surveillance capabilities.									

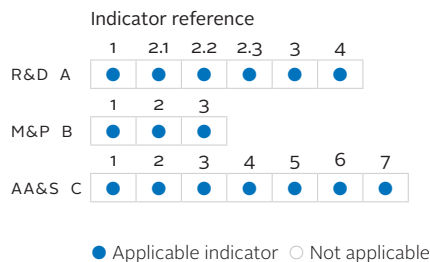
# Pfizer Inc.

Stock exchange: XNYS • Ticker: PFE • HQ: New York, NY, US • Employees: 96,500 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: Yes

## Performance by Research Area



## How Pfizer was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Pfizer\*\* is among the top performing large research-based pharmaceutical companies, following close behind the leaders. It performs well in Manufacturing & Production and Appropriate Access & Stewardship, achieving an average performance in Research & Development. The company does not report its antimicrobial R&D investments and its R&D pipeline is comparatively small compared to other large research-based pharmaceutical companies assessed by the Benchmark: seven antimicrobial projects. Notably, six of these target priority pathogens, including four vaccines. It has access provisions in place for its vaccines in late-stage development.

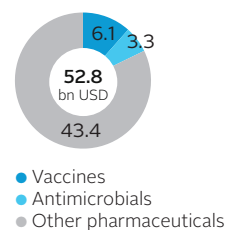
Pfizer discloses a comprehensive environmental risk-management strategy, which includes discharge limits and reportedly applies to all Pfizer's third-party suppliers of antibiotic APIs and drug products. Pfizer has filed four of its five newest antibiotics in countries in scope.\* It also reports having mechanisms in place for responding efficiently to stock-outs in countries in scope.\* Regarding stewardship, Pfizer is engaged in a number of AMR educational and training activities for healthcare professionals, taking steps to mitigate conflicts of interest, as well as engaging in established AMR surveillance programmes that have an emphasis on data-sharing.

## SALES AND OPERATIONS

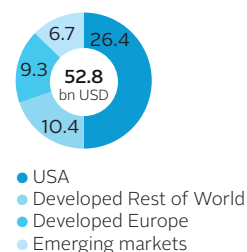
Pfizer is a large research-based pharmaceutical company with two business segments: Pfizer Essential Health and Pfizer Innovative Health, which includes vaccines. Pfizer sells antimicrobial medicines in at least 122 countries globally, of which 53 or more are low- to middle-income countries.\* In 2016, the company sold more than 160 million doses of vaccines, including 61 million doses of Prevnar 13® in partnership with Gavi, the Vaccines Alliance. In 2009, GSK and Pfizer established ViiV Healthcare (GSK: 76.5%, Pfizer: 13.5% and Shionogi: 10%), a joint venture solely focussed on the development of HIV/AIDS medicines. In 2015, Pfizer completed the acquisition of Hospira — a provider of generic injectable medicines (including antimicrobials)

and biosimilars. In 2016, the company acquired AstraZeneca's small-molecule anti-infectives business and late-stage pipeline, including commercialisation rights to avibactam/ceftazidime (Zavicefta™).\*\* In 2017, Pfizer and Basilea Pharmaceutica Ltd. entered into an agreement whereby Pfizer was granted exclusive rights to develop and commercialise the antifungal isavuconazole (Cresemba®) in several European countries, China and 16 Asian-Pacific countries (exc. Japan).\*\* Pfizer purchased two meningococcal vaccines, Mencevax® and Nimenrix®, from GSK in 2015. It had previously purchased from Baxter, in 2014, the vaccines NeisVac-C® and FSME-IMMUN®/TicoVac®, indicated for meningitis and tick-borne encephalitis, respectively.

## Revenues by product<sup>§</sup>



## Revenues by region<sup>§</sup>

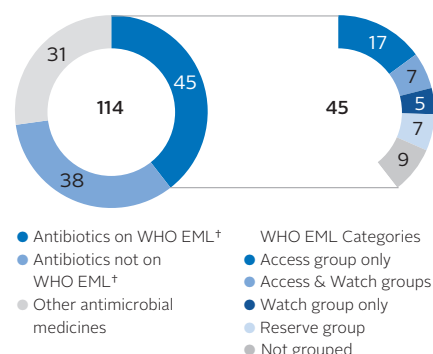


## ANTIMICROBIAL PORTFOLIO

Pfizer markets at least 114 antimicrobial medicines, the largest reported antimicrobial portfolio among the large research-based pharmaceutical companies assessed by the Benchmark. Sixty of these 114 medicines are listed on the WHO EML (Section 6). Eighty-three of the company's antimicrobial medicines are antibiotics, with 45 listed on the WHO EML (Section

6), including seven in the EML's Reserve group. The remainder (31) of the company's portfolio includes antifungals (systemic and topical), antiprotazoals and anthelmintics, as well as eight antivirals. Pfizer also markets two antiseptic irrigation solutions and six vaccines, including Prevnar 13® for pneumococcal pneumonia, and four meningococcal vaccines.

## Antimicrobial portfolio breakdown



\*\* Assets, specifically marketed products, acquired from AstraZeneca in 2016, and Basilea in 2017, remain subject to integration into the Pfizer portfolio (including MAA transfer process in several markets). These assets have therefore been excluded from this analysis.

\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.

† EML Section 6: Anti-Infective Medicines

§ FYE 31 December 2016

## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Pfizer has registration and affordability plans in place for all of its vaccine candidates. It also has stewardship plans in place for its antibiotic candidate (avibactam/aztreonam) in the form of AMR surveillance programmes and educational activities for HCPs. Pfizer can ensure that access plans are also in place for avibactam/aztreonam.

**Improve transparency regarding environmental risk management.** Pfizer can share more information on how it manages environmental risk, e.g., the company can disclose the levels of anti-

biotic discharge, and publish the identities of third parties who manufacture antibiotic APIs and drug products on its behalf. Currently, Pfizer discloses several policy documents on its environmental risk management.

**Expand environmental risk-management strategy.** Pfizer has set discharge limits for its own manufacturing sites and third parties who manufacture antibiotic APIs and drug products as part of its environmental risk-management strategy. It can ensure these antibiotic discharge limits are applied to external waste-treatment sites.

**Ensure access to more antimicrobials.** Pfizer is currently committed to engaging in inter-country equitable pricing for its antimicrobial medicines. Pfizer can expand its affordability strategy by engaging in intra-country equitable pricing for its antimicrobial medicines, and improving access to recently acquired assets from AstraZeneca and Basilea such as avibactam/ceftazidime (Zavicefta®) and isavuconazole (Cresemba®).

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT		Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	7 projects 6 target priority pathogens
<b>A.1 No information on antimicrobial R&amp;D investments.</b>										
Pfizer reports no information on its antimicrobial R&D investments.										
<b>A.2.1-2.3 Six R&amp;D projects focussed on priority pathogens.</b>										
Pfizer has seven antimicrobial R&D projects in its pipeline, six of which are in clinical stage development. Six of the company's projects target priority pathogens. Although Pfizer has a smaller pipeline compared to leaders in this area, all of its projects focus on multidrug-resistant bacterial infections. Pfizer has one project in pre-clinical development that focusses on new fixed dose combinations (FDCs) of existing β-lactam and β-lactamase inhibitors. Pfizer is involved in the clinical development of new vaccines and new FDCs of existing antibiotics. This includes the development of a new combination of the existing β-lactam aztreonam and the β-lactamase inhibitor avibactam, a project that was obtained with the acquisition of AstraZeneca's antibiotics division, in collaboration with Allergan. Pfizer has no new chemical entities in its pipeline. Nevertheless, it has four vaccines in										
<b>A.3 Two R&amp;D projects being developed with public partners.</b>										
Pfizer is developing two R&D projects in its priority pathogen pipeline through public-private partnerships (including non-profit organisations).*** After acquiring avibactam from AstraZeneca in 2016, Pfizer continued the development of avibactam/aztreonam in collaboration with Allergan, currently in Phase II clinical development, through the COMBACTE-CARE programme (IMI's New Drugs 4 Bad Bugs consortium). The project also includes funding from BARDA. In 2016, Pfizer received funding from the Bill and Melinda Gates Foundation to conduct a Phase I/II clinical trial to evaluate the investigational group B <i>Streptococcus</i> (GBS) vaccine in South Africa. Moreover, Pfizer is part of a public-private consultation group led by WHO on group B <i>Streptococcus</i> vaccine development, which aims to develop standardised antibody assays to identify correlates of protection.										
<b>A.4 Access provisions in place for its vaccines in late-stage development.</b>										
Pfizer reports that it has access provisions in place for both of its vaccines in late-stage development. It reports that it has a stewardship provision in place for its antibiotic candidate in late-stage development, and commits to plan access plans during R&D but does not provide information on details of such action plans. For its two vaccines in Phase II and III clinical stage, it will apply an equitable pricing policy that is based on countries' ability to pay, while covering research and development costs. It is unknown if this policy applies to its avibactam/aztreonam combination. Furthermore, Pfizer plans to continue its AMR surveillance programmes, as well as launch educational initiatives regarding the risks of AMR and how vaccines could play a role in addressing this public health threat. For this indicator, countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.										

### Pipeline targeting priority pathogens

Discovery	Preclinical	Phase I	Phase II	Phase III	Approval
<p>► Vaccine</p> <p>cIAI = Complicated intra-abdominal infection</p> <p>FDC = Fixed dose combination</p> <p>GNB = Gram-negative bacteria</p> <p>GPB = Gram-positive bacteria</p> <p>HABP/VABP = Hospital-acquired/Ventilator-associated bacterial pneumonia</p> <p>MBL = metallo-β-lactamase</p> <p>† This candidate moved to Phase III clinical development after the period of analysis.</p>	<ul style="list-style-type: none"> <li>Discovery of FDCs with existing small molecules – GNB – Adaptation (new FDC)</li> </ul>	<ul style="list-style-type: none"> <li>► Pneumococcal conjugate 20-valent vaccine (PFO6482077) – <i>S. pneumoniae</i></li> <li>► Group B <i>Streptococcus</i> 6-valent conjugate vaccine (PFO6760805)</li> </ul>	<ul style="list-style-type: none"> <li>► <i>S. aureus</i> 4-antigen vaccine (PFO6290510)</li> <li>• Avibactam/aztreonam (PFO6947387) – MBL – cIAI, HABP/VABP – Adaptation (new FDC) – In partnership with Allergan plc†</li> </ul>	<ul style="list-style-type: none"> <li>► <i>C. difficile</i> vaccine (PFO6425090)</li> </ul>	<p>*** Pfizer is involved in the COMBACTE-CDI network, a recently launched project within the IMI COMBACTE research consortium.</p>

**B MANUFACTURING & PRODUCTION**Indicators  
scored on 1 2 3**B.1 Comprehensive environmental risk-management strategy.**

Pfizer undertakes many of the environmental risk-management activities that the Benchmark examines. Namely, it applies an environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge. It includes auditing and limits on antibiotic discharge, at its own manufacturing sites and those of third-party manufacturers of antibiotic APIs and drug products. Pfizer's manufacturing sites include primary waste treatment. Secondary waste treatment occurs on- and off-site. The environmental risk-management strategy does not apply to off-site waste-treatment plants.

**B.2 Limited transparency regarding environmental risk management.**

Pfizer publishes elements of its environmental risk-management strategy on its website. It does not disclose audit results, or the discharge levels of antibiotics. The company also does not share the identities of its third-party suppliers of antibiotic APIs and drug products or external waste-treatment plants.

**B.3 Commits to following GMP, including at 3rd-party sites.**

Pfizer reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. Pfizer requires its third-party suppliers of drug products to apply the same quality standards to their production facilities.

**C APPROPRIATE ACCESS & STEWARDSHIP**Indicators  
scored on 1 2 3 4 5 6 7**C.1 Filed four of five newest antibiotics in countries in scope.**

Pfizer reports that it has filed four of its five newest antibiotics, introduced in 1991-2005, for registration in countries in scope\* (between 30-63 countries). The fifth antibiotic, introduced in 1999, has not been filed for registration in any country in scope.\* Pfizer did not report filing information about newer antibiotics acquired recently (i.e., from AstraZeneca in 2016 and from Basilea in 2017), as these products are still being integrated into the Pfizer portfolio (e.g., ongoing MAA transfer processes in several markets).

**C.2 Makes general commitment to equitable pricing.**

Pfizer discloses a general (not product-specific) commitment to applying inter- and intra-country equitable pricing to antimicrobials in countries in scope.\* Pfizer is also committed to long-term public-private donation programmes for azithromycin (Zithromax®) and fluconazole (Diflucan®).

**C.3 Mechanisms in place to respond to stock-outs.**

Pfizer reports that it has mechanisms in place for responding efficiently to stock-outs of all of its antimicrobial medicines and vaccines in countries in scope.\* These are based on a set of demand and supply principles, such as ensuring supplies are distributed equitably between countries, sharing information on shortages with purchasers, and assigning additional resources in the event of delays. Pfizer does not disclose how it works with stakeholders (e.g., governments,

procurers) to align supply and demand for antimicrobial medicines, specifically to prevent or minimise stock-outs in countries in scope.\* It has launched a website on supply status of injectables, including antimicrobial medicines such as piperacillin/tazobactam (Zosyn®).

**C.4 Multiple activities in AMR-related educational programmes.**

Pfizer reports that it is involved in educational programmes for HCPs that include AMR stewardship and rational use of antibiotics, with conflict of interest (COI) mitigation measures in place. Programmes such as "Sharing Hospital Anti-infectives Perspectives and Experience" (SHAPE) and the "Infectious Disease Education and Learning" (IDEAL) support the implementation of local antimicrobial stewardship programmes. Its COI mitigation strategy consists of external content development and SOPs to review content and potential COIs. The company participates in various interactive courses and massive open online courses (MOOCs) in collaboration with third parties, aiming at changing the behaviour of HCPs in stewardship and resistance.

**C.5 Comprehensive involvement in appropriate promotion practices.**

The Benchmark measures how companies address stewardship through appropriate promotion. Pfizer reports that it takes action in this regard: it reflects AMR trends in its marketing materials and is currently working on a pilot project to decouple the remuneration of its sales

force from sales volume. In addition to providing AMR-related trends in its marketing materials, Pfizer's materials are reviewed by medical experts to ensure they are aligned with antibiotic stewardship principles. Moreover, sales force training includes topics such as challenges in AMR and stewardship.

**C.6 Provides information on treatment duration.**

Pfizer adapts its packaging to facilitate appropriate use by providing information on treatment duration. This can help to ensure that patients complete the treatment course.

**C.7 Open source surveillance programme.**

Pfizer reports that it is involved in several surveillance programmes, focussed on AMR trends. Pfizer's ATLAS programme stands out among all AMR surveillance programmes identified by the Benchmark, as it is completely accessible to the public. The company is highly active in surveillance activities globally, some of which have been running for over 14 years. Pfizer reports that it collaborates with public health agencies for its surveillance programme in Latin America.

**ANIMAL HEALTH & DIAGNOSTICS**

*Activities in this area are not scored by the Benchmark. This information is provided given the importance of animal health and diagnostics on the topic of AMR.*

Pfizer does not market antimicrobials for use in animals.

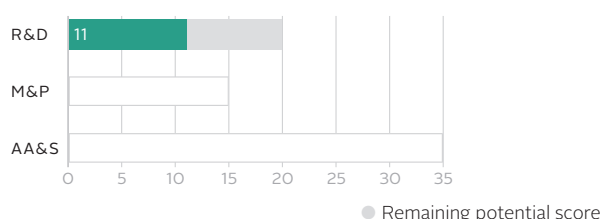
Pfizer supports COMBACTE-CARE, a European network that addresses the diagnostic challenges for the epidemiological and clinical stud-

ies of carbapenem-resistant bacteria. The company has also entered into collaborations with diagnostic manufacturers to support commercial availability of susceptibility tests for its new antibiotics.

# Polyphor Ltd.

Stock exchange: Privately held • Ticker: - • HQ: Allschwil, Switzerland • Employees: approx. 100 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Polyphor was evaluated: applicable indicators

		Indicator reference						
		1	2.1	2.2	2.3	3	4	
R&D	A	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	
		1	2	3				
M&P	B	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>				
		1	2	3	4	5	6	7
AA&S	C	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Polyphor is a biopharmaceutical company, selected for having a pipeline that targets priority pathogens. It was evaluated in the area of Research & Development only. It invested more than USD 5 million in antibiotic drug development in 2016. The company performs well when compared with other biopharmaceutical companies in scope. It has three projects in its antimicrobial R&D pipeline, all targeting priority pathogens.

Polyphor engages in public-private partnerships to develop its candidate compounds. The company has one R&D project in late-stage clinical development, but reports no information on access or stewardship provisions for this candidate.

## OPERATIONS

Polyphor, founded in 1996, is a privately-held Swiss-based biopharmaceutical company, focusing on the development of macrocycle drugs that address antibiotic resistance and severe pulmonary diseases. Polyphor discovered a new class of antibiotics effective against gram-negative bacteria, the Outer Membrane Protein Targeting Antibiotics (OMPTA). The most advanced drug candidate is murepavadin, indicated for the treatment of infections caused by *P. aeruginosa*. Murepavadin recently entered Phase III clinical studies, after showing encouraging results in a Phase II study in patients with ventilator-associated bacterial pneumonia (VABP), when co-administered with stand-

ard-of-care treatment. Polyphor also develops an inhaled formulation of murepavadin for cystic fibrosis as part of a consortium, funded by the Innovative Medicines Initiative (IMI), a public-private partnership of EFPIA and the EU. While murepavadin is selective for *P. aeruginosa*, the next generation of OMPTAs are broad-spectrum antibiotics, which target most important gram-negative pathogens, including extensively drug-resistant (XDR) and multidrug-resistant (MDR) strains. In early 2017, Polyphor received a CHF 2.3 million award from the Wellcome Trust to advance the development of its broad-spectrum, gram-negative preclinical candidates. The company has a proprietary macrocycle discovery

platform, frequently used in research collaborations with other pharmaceutical companies. Polyphor is a member of the BEAM alliance, a group of biopharmaceutical companies addressing the regulatory and commercial environments in Europe regarding R&D, approval and market viability of products combating antimicrobial resistance. Polyphor has no products on the market. In 2017, the company announced that it had successfully completed a CHF 40 million private financing round, 98% of which came from existing investors, with substantial contributions from Varuma AG and Ingro Finanz AG.

## ANTIMICROBIAL PORTFOLIO

Polyphor does not have any products on the market.

## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Polyphor is developing one antibiotic candidate (murepavadin) in late-stage clinical development. Polyphor can ensure access and stewardship provisions are in place for murepavadin, for example, through partnerships.

## PERFORMANCE BY RESEARCH AREA

RESEARCH & DEVELOPMENT	Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	3 projects 3 target priority pathogens
		○	●	●	○	●	●		

**A.2.1-2.2 Novel antibiotics that address cross-resistance.**

Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. Polyphor invested more than USD 5 million in antibiotic drug development in 2016. The company has three projects in its antimicrobial R&D pipeline targeting priority pathogens, focussed on gram-negative bacteria. Polyphor's novel antibiotic murepavadin (POL7080) targeting *P. aeruginosa* is entering Phase III clinical trials. Murepavadin is a synthetic macrocyclic protein that binds to a specific protein in the outer membrane of *P. aeruginosa*, interfering with its proper functioning and ultimately killing the pathogen. The company has more compounds in preclinical stage using the same molecular target class, outer membrane pro-

teins. This makes Polyphor one of the few companies developing innovative antibiotics that address cross-resistance.

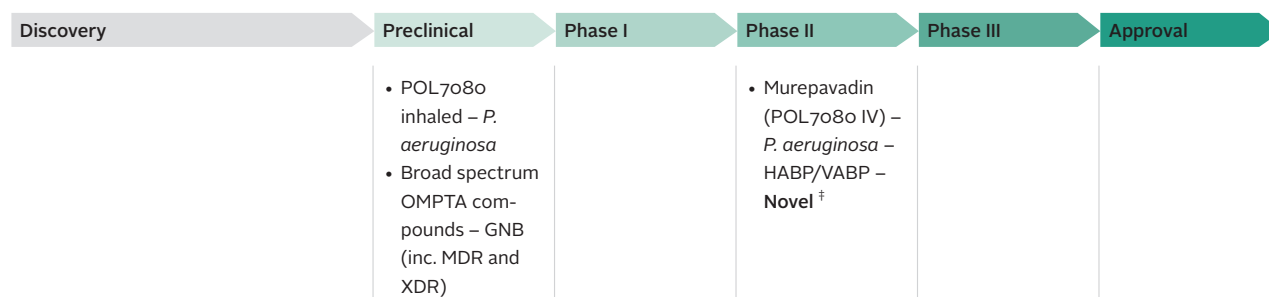
**A.3 At least one R&D project being developed with public partners.\***

Polyphor is developing one R&D project in its priority pathogen pipeline through a public-private partnership\*: this is its preclinical OMPTA platform, developed in collaboration with the University of Zürich and with financial support from the Swiss government (amount not known). In 2017, the development of this broad-spectrum platform targeting gram-negative pathogens also received funding from the Wellcome Trust (CHF 2.3 million). Polyphor is not developing its clinical stage candidate, murepavadin, via public-private partnership. In

2013, the company signed an exclusive worldwide licence agreement with Roche to develop and commercialise murepavadin. In 2015, Roche decided to discontinue its involvement and Polyphor continues the clinical development of the compound.

**A.4 No information on access or stewardship provisions**

Polyphor reports no information on access or stewardship provisions for its antibiotic candidate in late-stage development. It has signed the Davos Declaration, which includes a general commitment to ensuring access to antimicrobial medicines and vaccines, and to support the appropriate and responsible use of these products.

**Pipeline targeting priority pathogens**

GNP = Gram-negative bacteria

HABP/VABP = Hospital-acquired/Ventilator-associated bacterial pneumonia

‡ Phase III clinical trials are expected to commence in the first months of 2018.

**B MANUFACTURING & PRODUCTION**

As a biopharmaceutical company with no products on the market, Polyphor was not eligible for this Research Area.

**C APPROPRIATE ACCESS & STEWARDSHIP**

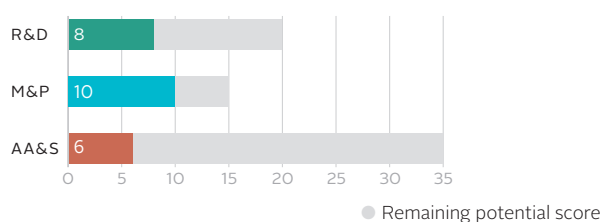
As a biopharmaceutical company with no products on the market, Polyphor was not eligible for this Research Area.

\* After the Benchmark's period of analysis, Polyphor entered into collaboration with the public-private partnership Innovative Medicines Initiative (IMI), as part of the iABC consortium, to co-fund and advance the development of its inhaled formulation of murepavadin.

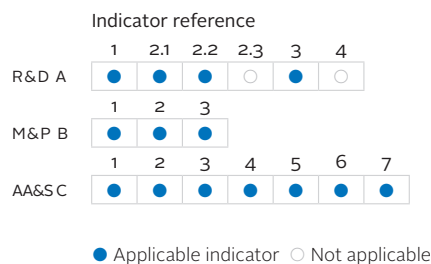
# Roche Holding AG

Stock exchange: XSWX • Ticker: ROG • HQ: Basel, Switzerland • Employees: 94,052 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: Yes

## Performance by Research Area



## How Roche was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Roche has relatively low sales of antibiotics compared to the other large research-based pharmaceutical companies in scope. The company is currently making efforts to re-enter the antibiotics market and performs less well in the Benchmark compared to other large research-based pharmaceutical companies. It performs well in Manufacturing & Production, but falls behind in the areas of Research & Development and Appropriate Access & Stewardship. It has a comparatively small antimicrobial R&D pipeline of eight projects, three of which target priority pathogens, including one novel biological antibiotic. Roche discloses a comprehensive

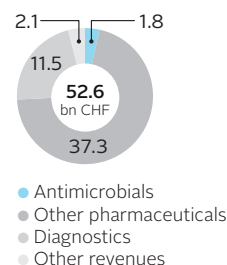
environmental risk-management strategy, which includes discharge limits and reportedly applies to all Roche's third-party suppliers of antibiotic APIs and drug products. Roche, currently actively marketing antibiotics only in China, has filed two of its newest antibiotics in some countries in scope.\* It makes no information available regarding equitable pricing for antimicrobials. Roche reports engaging in some stewardship activities, including *ad hoc* AMR educational activities for healthcare professionals. It provides funding to two surveillance programmes in China.

## SALES AND OPERATIONS

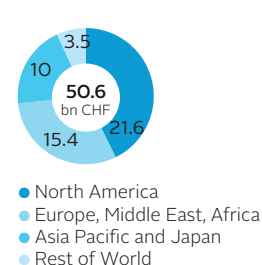
Roche is a large research-based pharmaceutical company with two divisions: pharmaceuticals and diagnostics. Its pharmaceutical business includes therapeutic areas such as oncology, neuroscience, infectious diseases and immunology. Although it is the third-largest company in scope of the Benchmark (based on total revenues), its antibiotic sales are low compared to several other large research-based pharmaceutical companies in scope. The company had reduced its antimicrobial research at the turn of the century but has since sought to rebuild it by collaborating with smaller biopharmaceutical companies. Examples include a licensing agree-

ment with Polyphor (ended in 2015), a company also in scope of the Benchmark, and agreements with two different biotechnology companies, Discuva and Warp Drive Bio, for use of their bioinformatics platforms to search for new classes of antibiotics. Roche also develops and commercialises a wide array of point-of-care diagnostic tests for viruses (e.g. HIV, HBV and HCV) and bacteria (e.g., *M. tuberculosis*, *C. difficile* and methicillin-resistant *S. aureus*).

## Revenues by product<sup>§</sup>



## Revenues by region<sup>||</sup>

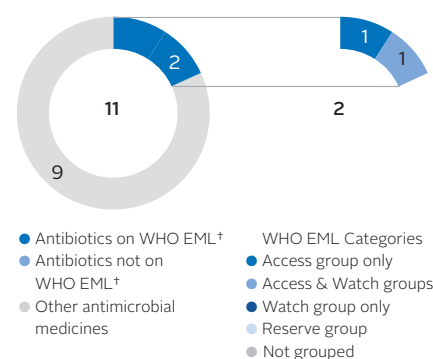


## ANTIMICROBIAL PORTFOLIO

Roche markets at least 11 antimicrobial medicines, seven of which are listed on the WHO EML (Section 6). Two of the company's antimicrobial medicines are antibiotics, both listed on the WHO EML (Section 6): sulfamethoxazole/trimethoprim (Bactrim®), in the EML's Access

group, and ceftriaxone (Rocephin®), in both the Access and Watch groups. The remaining nine medicines are two antiprotazoals and seven antivirals (including one PEGylated and one non-PEGylated interferon for the treatment of viral hepatitis).

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Revenues from external customers, inc. sales, royalties and other operating income; FYE 31 December 2016

<sup>||</sup> Sales; FYE 31 December 2016

## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Roche has two candidates in clinical development, both in Phase I. Roche is encouraged to implement access and stewardship plans for these candidates as they move into Phase II clinical development.

**Ensure access by addressing affordability for antimicrobial medicines.** Roche has reported that it has low-priced generic antibiotics available on the market, and that the price of its originators has also decreased. Roche can improve the affordability of its antimicrobial medicines by developing an equitable pricing strategy that takes socio-economic factors into account.

**Engage in antimicrobial stewardship.** Roche currently supports some education and surveillance programmes. It can engage more actively in stewardship activities, e.g., through strengthening its role in more surveillance activities, educational activities for healthcare professionals on AMR (while mitigating conflicts of interest) and engage in appropriate promotion practices.

**Improve transparency regarding environmental risk management.** Roche can share more information on how it manages environmental risk, e.g., disclose the levels of antibiotic discharge and publish the identities of third parties who manufacture antibiotic APIs and drug products

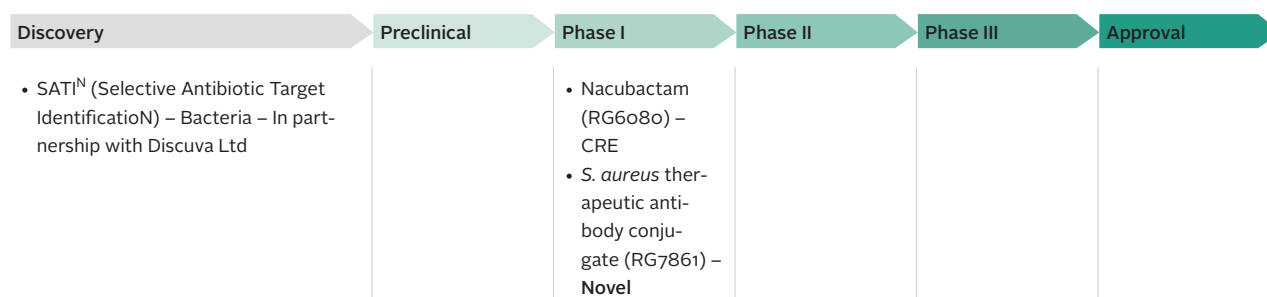
on its behalf. Roche currently discloses several policies on environmental risk management.

**Expand environmental risk-management strategy.** Roche has set discharge limits for its own and third party manufacturing sites as part of its environmental risk-management strategy. Roche can ensure these discharge limits are applied to its external waste treatment plants.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT		Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	8 projects 3 target priority pathogens
<b>A.1 No information on antimicrobial R&amp;D investments.</b>		Roche reports no information on its antimicrobial R&D investments.								
<b>A.2.1-2.2 One novel biological agent in the clinical pipeline.</b>		Roche has eight** antimicrobial R&D projects in its pipeline, seven of which are in clinical stage development. Three of the company's projects target priority pathogens, the lowest number of projects targeting priority pathogens among large research-based pharmaceutical companies. However, all three of these projects are focussed on bacteria. Roche also focusses its R&D activities on influenza and hepatitis B. The company has at least one project in preclinical stage.*** Roche is developing an antibody-drug conjugate, a novel antibody bound to a rifamycin analogue, against <i>S. aureus</i> . It is a highly specific and innovative biological agent. Additionally,								
<b>A.3 One R&amp;D project being developed with public partners.</b>		Roche is developing one R&D project in its priority pathogen pipeline through public-private partnership. The company received funding from BARDA (potentially up to USD 150 mn) to further develop its $\beta$ -lactamase inhibitor nacubactam and accelerate the development of tests for detecting specific viral and bacterial infections. Roche also conducts R&D with private-sector partners.†								
<b>A.4 No R&amp;D candidate in late-stage development.</b>		Roche is not eligible for this indicator as it does not have any R&D candidates in late-stage development.								

### Pipeline targeting priority pathogens



\*\* After the Benchmark's period of analysis, Roche reported termination of one of these projects (MHAA4549A).

\*\*\* After the Benchmark's period of analysis, Roche entered into collaboration with Warp Drive Bio around the Genome Mining™ Platform, which provides access to over one hundred novel classes of natural antibiotics.

† After the Benchmark's period of analysis, Roche reported having 13 active research collaborations with academic groups globally to support novel antibiotic discovery focussing on multidrug-resistant gram-negative bacteria.

**B MANUFACTURING & PRODUCTION**Indicators  
scored on 1 2 3**B.1 Comprehensive environmental risk-management strategy.**

Roche undertakes almost all environmental risk-management activities that the Benchmark examines. Namely, it applies an environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge. It includes auditing and limits on antibiotic discharge, both for its own manufacturing sites and those of third-party manufacturers of antibiotic APIs and drug products. Roche states that its strategy applies to external waste-treatment plants, yet it also reports that it does not set discharge limits for these plants nor audits implementation of the strategy.

**B.2 Limited transparency regarding environmental risk management.**

Roche publishes elements of its environmental risk-management strategy on its website. It does not disclose audit results, or the discharge levels of antibiotics. The company also does not share the identities of its third-party suppliers of antibiotic APIs and drug products or external waste-treatment plants.

**B.3 Commits to following GMP, including at 3rd-party sites.**

Roche reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. Roche requires its third-party suppliers of drug products to apply the same quality standards to their production facilities.

**C APPROPRIATE ACCESS & STEWARDSHIP**Indicators  
scored on 1 2 3 4 5 6 7**C.1 Filed two newest antibiotics in some countries in scope.**

Roche has provided filing information on two of its newest antibiotics: ceftriaxone (Rocephin®) was introduced in 1984 and has now been filed for registration in 49 countries in scope.\* Sulfamethoxazole/trimethoprim (Bactrim®) was introduced in 1969 and has now been filed for registration in 34 countries in scope,\* mainly in Latin America and sub-Saharan Africa.

**C.2 No equitable pricing approach.**

Roche does not disclose an equitable pricing approach for its highest-volume antibiotics and/or antimicrobial medicines. It does report that it views competition from generic medicines as the main mechanism triggering price reductions.

**C.3 No insight into steps addressing supply chain efficiency.**

Roche does not disclose how it works with stakeholders (e.g., governments, procurers) to align supply and demand for antimicrobial medicines, specifically to prevent or minimise stock-outs in countries in scope\*. The company also does not report on whether it has processes in place to respond to stock-outs in countries

in scope.\* After the period of analysis, Roche reported to the Benchmark that it does have a global expert group to allocate available supply to prevent stock-outs from happening.

**C.4 Some involvement in AMR-related education.**

Roche has provided information for its China headquarters, the only country where it actively markets antibiotics. The company reported that its China headquarters provides on-demand educational materials for rational use of antibiotics for self-learning purposes, but stated that due to limited resources, it does not initiate educational programmes independently.

**C.5 No involvement in appropriate promotion practices.**

The Benchmark measures how companies address stewardship through appropriate promotion. The company does not report taking action in this regard either through reflecting AMR trends in its marketing materials or decoupling its sales force's incentives from volume of antibiotic sales. Roche has only provided information for the antibiotic ceftriaxone (Rocephin®), which is used in community-ac-

quired infections. The company reports that it only actively markets and promotes this antibiotic in China.

**C.6 No information regarding brochure and/or packaging adaptations.**

Roche does not provide sufficient information on linguistic, cultural or literacy adaptations made to its brochures or packaging to facilitate appropriate use of antibiotics by patients.

**C.7 Supports academic surveillance programmes financially.**

Roche has only provided information for surveillance activities taking place in China, the only country where it actively markets antibiotics. The company supports two surveillance programmes focussed on AMR trends in China. It provides funding for these two programmes, which focus on community-acquired *E. coli* and pneumonia infections in secondary and tertiary care hospitals in China. The sharing of the results from these studies is the sole responsibility of the researchers; however, the leading researchers have stated plans to publish the results in peer-reviewed journals.

**ANIMAL HEALTH & DIAGNOSTICS**

*Activities in this area are not scored by the Benchmark. This information is provided given the importance of animal health and diagnostics on the topic of AMR.*

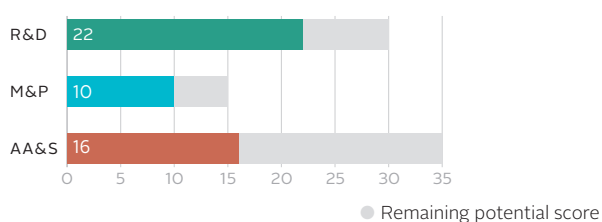
Roche develops and commercialises a wide array of diagnostic tests for viruses (e.g., HIV, HBV and HCV) and bacteria (e.g., *M. tuberculosis*, *C. difficile* and methicillin-resistant *S. aureus*). For example, the cobas® Liat® system is an *in vitro* diagnostic platform where results can be made available in less than 30 minutes for viruses (e.g., influenza A/B) and bacteria (e.g., *C. difficile*).

Additionally, since 2014, Roche has partnered with UNAIDS and the Clinton Health Access Initiative (CHAI), among others, to help diagnose and combat HIV infections in children and adults in 82 developing countries with a high burden of disease.

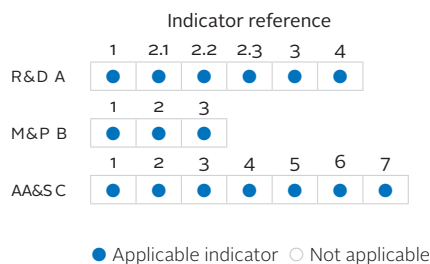
# Sanofi

Stock exchange: XPAR • Ticker: SAN • HQ: Paris, France • Employees: 106,859 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: Yes

## Performance by Research Area



## How Sanofi was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Sanofi is among the top performing large research-based pharmaceutical companies in scope, following close behind the leaders. This is driven by strong performance in Research & Development with average performance in Manufacturing & Production and Appropriate Access & Stewardship. The company's R&D pipeline consists of 32<sup>†</sup> antimicrobial projects, of which 18<sup>†</sup> target priority pathogens, including one novel antimalarial candidate and six new vaccine candidates. It has access provisions in place for three out of five of its vaccines in late-stage development. Sanofi discloses a comprehensive environmental risk-management strategy, which

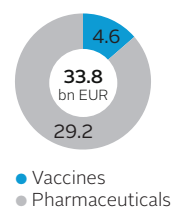
reportedly applies to all the company's third-party suppliers of antibiotic APIs and drug products, as well as mechanisms to assure quality of antibiotic manufacturing is maintained. Sanofi reports that it has filed its five newest antibiotics in some countries in scope.\* The company engages in equitable pricing strategies on non-antibiotic antimicrobials only. Sanofi reports having mechanisms in place for responding efficiently to stock-outs in countries in scope.\* The company engages in a number of AMR educational activities, as well as surveillance programmes.

## SALES AND OPERATIONS

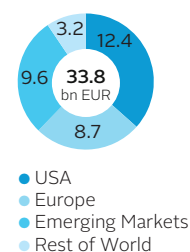
Sanofi is a large research-based pharmaceutical company organised into five business units: general medicines and emerging markets; diabetes and cardiovascular; consumer healthcare; specialty care; and vaccines. Its specialty care business unit develops treatments for rare diseases, multiple sclerosis, oncology and immunology. The company sells antimicrobial medicines and vaccines in 140 countries globally, including 72 low- and middle-income countries.\* Sanofi's vaccine business is run via subsidiary

Sanofi Pasteur. In 2016, the company sold more than 1 billion doses of vaccines globally. At the end of 2016, Sanofi Pasteur and Merck & Co., Inc. ended their vaccines joint venture in Europe (Sanofi Pasteur MSD, established 1994) to independently manage their product portfolios. At the same time, the company completed the acquisition of Boehringer Ingelheim's consumer healthcare business, in exchange for its animal health business (Merial).

## Revenues by product<sup>§</sup>



## Revenues by region<sup>§</sup>

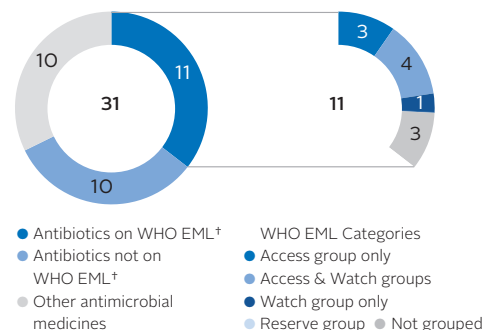


## ANTIMICROBIAL PORTFOLIO

Sanofi markets at least 31\*\* antimicrobial medicines, 18 of which are listed on the WHO EML (Section 6). Twenty-one of the company's antimicrobial medicines are antibiotics, with 11 listed on the WHO EML (Section 6), including five in the EML's Watch group. The remainder (ten) of the company's portfolio consists of antiprotozoal medicines, including seven indi-

cated for the treatment of malaria. Its vaccines portfolio is one of the largest of the companies assessed by the Benchmark and covers a wide range of indications, including pneumococcal disease (Pneumo™ 23), meningococcal disease (e.g., Menomune®) and infections caused by *Haemophilus influenzae* type B (ActHib®).

## Antimicrobial portfolio breakdown



## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Sanofi discloses no information regarding access and stewardship provisions for its antimicrobial medicines in late-stage clinical development. For its vaccine candidates, it plans to,

e.g., apply for WHO prequalification. Sanofi can implement further access and stewardship plans for all its candidates in late-stage clinical development.

## Increase engagement in stewardship activities.

Sanofi engages in some stewardship activities. Sanofi can take steps to ensure that its current AMR educational activities for healthcare professionals include processes to mitigate conflicts

\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Net sales not inc. the held-for-exchange Animal Health segment; FYE 31 December 2016

\*\* Sanofi provided only a sample (approx. 50%) of its global antimicrobial portfolio.

of interest. It can also expand its current surveillance activities to more countries, collaborating with public health authorities and ensuring that the data is made publicly available via an open database. Sanofi can also engage in appropriate promotion practices.

**Ensure access by addressing affordability for antimicrobial medicines.** Sanofi currently states a commitment to applying product-specific inter-country equitable pricing to two of its anti-

microbial medicines. Sanofi can seek to improve access for more antimicrobial medicines (specifically antibiotics) by expanding its affordability strategy to more products and more countries in need.

**Improve transparency regarding environmental risk management.** Sanofi can share more information on how it manages environmental risk, e.g., disclose the levels of antibiotic discharge, and publish the identity of third party manu-

facturers of antibiotic APIs and drug products. Sanofi currently discloses several policies on environmental risk management.

**Expand environmental risk-management strategy.** Sanofi has set discharge limits for its own manufacturing sites as part of its environmental risk-management strategy. It can ensure these discharge limits are applied to third parties who manufacture APIs on its behalf, as well as to external waste-treatment sites.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT		Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	32 projects 18 target priority pathogens
<b>A.1 Comparatively high vaccine R&amp;D investments.</b>										
Sanofi reports that it invested more than USD 500 million in the development of vaccines in 2016, which is high compared to other large research-based pharmaceutical companies in the Benchmark. The company reports no information on investments made for the development of antimicrobial medicines.		cene-containing compound active against both chloroquine-susceptible and chloroquine-resistant <i>P. falciparum</i> , while artefenomel displays important chemical dissimilarities to other artemisinins, making it likely to remain effective against artemisinin-resistant strains. Six out of 12 of Sanofi's innovative vaccines in development target priority pathogens. Four of these are clinical-stage projects, including an HIV vaccine candidate (for which no vaccines currently exist).								organisation, on the development of its tuberculosis vaccine, currently in Phase II clinical development. The remaining three R&D projects (two preclinical, one clinical) involve public research institutes.
<b>A.2.1-2.3 Eighteen R&amp;D projects in priority pathogen pipeline, with broad focus.</b>		<b>A.3 Eleven R&amp;D projects being developed with public partners, including seven PDPs.</b>								<b>A.4 Access provisions in place for most vaccines in late-stage development.</b>
Sanofi has 32 <sup>†</sup> antimicrobial R&D projects in its pipeline, 19 <sup>‡</sup> of which are in clinical stage development. Eighteen <sup>‡</sup> of the company's projects target priority pathogens. Its pipeline size is above average when comparing it to other large research-based pharmaceutical companies assessed by the Benchmark. Its pipeline covers a broad range of priority pathogens, including both gram-negative and gram-positive bacteria, HIV, <i>P. falciparum</i> (malaria) and <i>M. tuberculosis</i> . Looking only at R&D for multidrug-resistant bacteria, the company has seven discovery-stage projects, one vaccine in preclinical stage and three vaccines in clinical development, including one that targets <i>M. tuberculosis</i> . The company has one novel antimalarial medicine in clinical development (artefenomel/ferroquine), in collaboration with the Medicines for Malaria Venture (MMV). Ferroquine is a promising ferro-		Sanofi is developing 11 R&D projects in its priority pathogen pipeline through public-private partnerships (including non-profit organisations).*** Eight of these R&D projects are in development through a PDP or open research consortium. Seven projects are in development through a PDP, five are in preclinical stage and two are in clinical stage. For the development of its Phase II HIV vaccine, Sanofi partners with the Pox-Protein Public Private Partnership (P5), a project that includes the US National Institute of Allergy and Infectious Diseases (NIAID), the Bill & Melinda Gates Foundation, the South African Medical Research Council, the HIV Vaccine Trials Network (HVTN), the US Military HIV Research Program and GSK. The company also collaborates with Aeras, a non-profit biotechnology								Sanofi reports that it has access provisions in place for three out of five of its vaccines in late-stage development. It reports that it has an access commitment in place for its antimalarial candidate in late-stage development, but does not report information on access provisions. For its three vaccines in late-stage development, Sanofi plans to file for WHO prequalification and/or for the European Medicines Agency (EMA) article 58 (a scientific assessment of a medicine for use outside the EU). For the antimalarial candidate in late-stage development (artefenomel/ferroquine), the company commits to ensuring sufficient supply, but does not provide a clear strategy for achieving this goal. For this indicator, countries in scope are 106 low- and middle-income countries where access to medicine is likely limited. Regarding stewardship provisions, Sanofi signed the Davos Declaration, which includes a general commitment to support the appropriate and responsible use of antimicrobial medicines and vaccines.

### Pipeline targeting priority pathogens

Discovery	Preclinical	Phase I	Phase II	Phase III	Approval
<ul style="list-style-type: none"> <li>Novel natural product discovery – GNB</li> <li>Influx enhancement – GNB – In partnership with GSK</li> <li>Phenotypic Screening – GNB</li> <li>Staphylococcus project – <i>S. aureus</i></li> <li>Tuberculosis growth inhibitors (macrolides) – <i>M. tuberculosis</i></li> <li>Tuberculosis growth inhibitors (Griselimycin) – <i>M. tuberculosis</i></li> <li>Tuberculosis growth Inhibitors (Persisters) – <i>M. tuberculosis</i></li> <li>Malaria project – <i>P. falciparum</i></li> <li>▶ Malaria vaccine – <i>P. falciparum</i></li> </ul>	<ul style="list-style-type: none"> <li>▶ <i>S. pneumoniae</i> vaccine</li> <li>• Malaria blood stage inhibitor – <i>P. falciparum</i></li> </ul>	<ul style="list-style-type: none"> <li>▶ <i>S. pneumoniae</i> paediatric vaccine (PPrV)</li> </ul>	<ul style="list-style-type: none"> <li>▶ DTP-HepB-Polio-Hib hexavalent paediatric vaccine (Shan6, PR5I) – Adaptation</li> <li>▶ <i>M. tuberculosis</i> bivalent vaccine (H4:IC31®)</li> <li>▶ HIV Vaccine – In partnership with GSK</li> <li>• Artefenomel/Ferroquine – <i>P. falciparum</i> – Novel</li> </ul>	<ul style="list-style-type: none"> <li>▶ <i>C. difficile</i> toxoid bivalent vaccine<sup>‡</sup></li> <li>▶ DTP-Polio-Hib paediatric pentavalent vaccine (Pentaxim®) – Adaptation (new target demographic: Japan)</li> </ul>	

▶ Vaccine

GNB = Gram-negative bacteria

‡ *C. difficile* vaccine has been terminated after the period of analysis.

\*\*\* Sanofi is involved in the COMBACTE-CDI network, a recently launched project within the IMI COMBACTE research consortium.

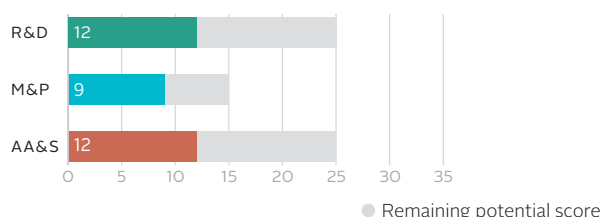
B MANUFACTURING & PRODUCTION		Indicators scored on	1	2	3
<b>B.1 Comprehensive environmental risk-management strategy.</b> Sanofi undertakes almost all of the environmental risk-management activities that the Benchmark examines. Namely, it applies an environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge. It includes auditing for its own manufacturing sites and those of third-party manufacturers of antibiotic APIs and drug products, and for external waste-treatment plants. Sanofi has also set antibiotic discharge limits for its own manufacturing sites.			●	●	●
<b>B.2 Limited transparency regarding environmental risk management.</b> Sanofi publishes elements of its environmental risk-management strategy on its website. It does not disclose audit results, or the discharge levels of antibiotics. The company also does not share the identities of its third-party suppliers of antibiotic APIs and drug products or external waste-treatment plants.					
<b>B.3 Commits to following GMP, including at 3rd-party sites.</b> Sanofi reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. Sanofi requires its third-party suppliers of drug products to apply the same quality standards to their production facilities.					

C APPROPRIATE ACCESS & STEWARDSHIP		Indicators scored on	1	2	3	4	5	6	7
<b>C.1 Filed five newest antibiotics in some countries in scope.</b> Sanofi reports that it has filed its five newest antibiotics, introduced between 1989 and 1997, for registration in some countries in scope* (between 20-45 countries). Two of these antibiotics are on the WHO EML (Section 6): cefixime (Oroken®), which is registered in 20 countries mainly in sub-Saharan Africa; and levofloxacin (Tavanic®), which is registered in 45 countries across multiple regions.			●	●	●	●	●	●	●
<b>C.2 Inter-country equitable pricing for antimicrobials.</b> Sanofi discloses inter-country equitable pricing approaches for two of its highest-volume antimicrobial medicines in some countries in scope.* The two approaches cover: (1) meglumine (Glucantime®) indicated for Leishmaniasis, mainly in Latin American countries; and (2) amodiaquine/artesunate (ASAQ Winthrop®) indicated for malaria, mainly in Africa. For amodiaquine/artesunate, the pricing approach is being implemented in cooperation with partners such as the Global Fund, WHO and MSF.									
<b>C.3 Global mechanisms in place for responding to stock-outs.</b> Sanofi reports that it has global mechanisms in place for responding efficiently to stock-outs of									

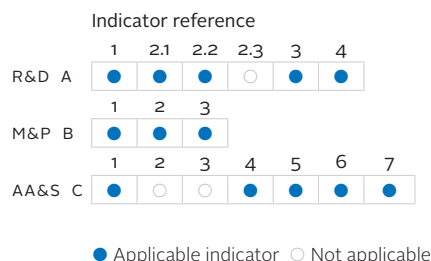
# Shionogi & Co., Ltd.

Stock exchange: XTKS • Ticker: 4507 • HQ: Osaka, Japan • Number of employees: 5,896 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: Yes

## Performance by Research Area



## How Shionogi was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Shionogi is the smallest research-based pharmaceutical company in scope, with sales mostly in Japan. The company's performance is lower compared to large research-based pharmaceutical companies in scope in Research & Development, Manufacturing & Production and Appropriate Access & Stewardship. The company's R&D pipeline consists of 25 antimicrobial projects, of which 15 target priority pathogens. Shionogi discloses an environmental risk-management strategy, which is not applied to the company's third-party suppliers of antibiotic APIs and drug products. The company provides no evidence of activities related to facilitating access. Shionogi's commitment to stewardship is driven by engagement in a number of stewardship educational activities, as well as surveillance programmes in partnership with academic institutions in Japan. It does not remunerate sales staff based on sales volume of antibiotics.

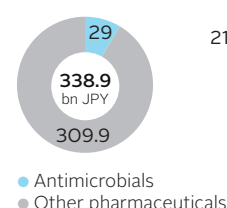
ers of antibiotic APIs and drug products. The company provides no evidence of activities related to facilitating access. Shionogi's commitment to stewardship is driven by engagement in a number of stewardship educational activities, as well as surveillance programmes in partnership with academic institutions in Japan. It does not remunerate sales staff based on sales volume of antibiotics.

## SALES AND OPERATIONS

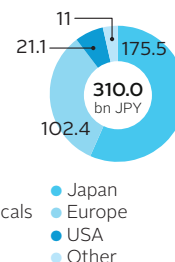
Shionogi is a large research-based pharmaceutical company headquartered in Japan. Its core therapeutic areas are infectious diseases and pain/central nervous system disorders, though its portfolio also covers additional areas, such as cardiovascular health and paediatrics. Within the infectious diseases area, the company is especially focused on three areas of research: severe bacterial and fungal infections, HIV/AIDS and viral respiratory infections and emerging/re-emerging infections. The company markets

eight antimicrobial medicines in Japan, Taiwan and the US. During the fiscal year 2016, it sold approximately 15 million doses of antimicrobial medicines. In 2012, following a long-term collaboration on the development of several novel integrase inhibitors for the treatment of HIV/AIDS, Shionogi joined ViiV Healthcare, a joint venture originally established by GSK and Pfizer, solely focused on the development of HIV/AIDS medicines. Equity positions in ViiV Healthcare are GSK: 76.5%, Pfizer: 13.5% and Shionogi: 10%.

## Revenues by product<sup>§</sup>



## Revenues by region<sup>||</sup>

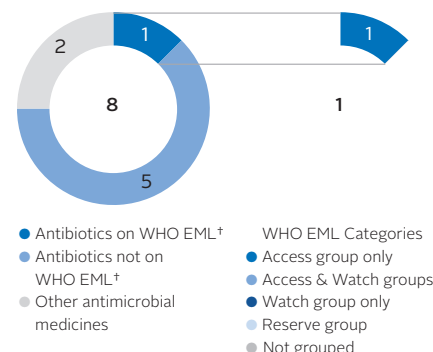


## ANTIMICROBIAL PORTFOLIO

Shionogi markets eight antimicrobial medicines, two of which are listed on the WHO EML (Section 6). Six of the company's antimicrobial medicines are antibiotics, including the combination sulfamethoxazole/trimethoprim (Baktar®), listed on the EML's Access group. The remaining two medicines are antivirals: one indicated for influenza A/B infections and the other, dolutegravir (Tivicay®), indicated, in combination with

other antiretroviral agents, for the treatment of HIV/AIDS. Dolutegravir was developed in collaboration with ViiV Healthcare and is listed on the WHO EML (Section 6).

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Net sales; FYE 31 March 2017

<sup>||</sup> Net sales; FYE 31 March 2016

## OPPORTUNITIES

### Improve access to antimicrobial medicines.

Shionogi can develop an access strategy for countries in scope,\* that includes the filing of its newest antibiotics (including flomoxef (Flumarin®)), for registration. Currently, Shionogi has not filed its antibiotics for registration in countries in scope.\*

### Plan ahead for access and stewardship during R&D.

Shionogi is developing one antibiotic candidate (cefiderocol) in late-stage clinical development. It is currently seeking partners to plan for its commercialisation, through licensing. Shionogi can ensure that these partnership agreements include access and stewardship provisions.

### Ensure transparency on its approach to environmental risk management.

Shionogi has stated a commitment to disclose its environmental risk-management strategy, the identities of its third-party suppliers and its external waste-treatment sites.

### Expand environmental risk-management strategy.

Shionogi can ensure its environmental risk-management strategy is applied to third parties who manufacture antibiotic APIs on its behalf, as well as to external waste-treatment sites. It currently has an environmental risk-management strategy that includes discharge limits, which are applied to its own manufacturing sites.

### Continue developing early-stage projects.

Shionogi has a large early-stage pipeline of R&D projects targeting priority pathogens. It can ensure that these early-stage projects move along the pipeline into clinical development.

### Increase engagement in stewardship activities.

Shionogi has engaged with academic institutes for several short-term surveillance programmes. It can ensure the development of long-term AMR surveillance programmes, and ensure that data is made publically available through open databases and collaboration with public health authorities.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT		Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	25 projects 15 target priority pathogens
<b>A.1 Comparatively high antimicrobial R&amp;D investments.</b>	Shionogi reports that it invested more than USD 200 million in antimicrobial R&D in 2016, which is relatively high compared to other large research-based pharmaceutical companies in the Benchmark. The company's antimicrobial R&D investments are almost as high as its revenues earned from antimicrobial medicines. These investments cover antimicrobial medicines only, as Shionogi is not involved in vaccine development.	including bacteria, fungi, HIV and <i>M. tuberculosis</i> . Cefiderocol, a new cephalosporin, is its most advanced compound which is currently in Phase III clinical development. Shionogi is also developing an antibody against <i>P. aeruginosa</i> .	●	●	●	○	●	●		
	<b>A.2.1-2.2 Fifteen R&amp;D projects in priority pathogen pipeline, one in clinical stage.</b>	Shionogi is developing four preclinical projects in its priority pathogen pipeline through public-private partnerships. Three of these projects involve collaboration with universities, which are focused on the discovery of novel medicines that target HIV and multidrug-resistant gram-positive bacteria. The remaining project involves the screening of Shionogi's compound libraries for candidates with activity against <i>M. tuberculosis</i> through the PDP with TB Alliance.								
	Shionogi has 25 antimicrobial R&D projects in its pipeline, two of which are in clinical stage development. Fifteen of the company's projects target priority pathogens. It has an average-sized pipeline when comparing it to other large research-based pharmaceutical companies assessed by the Benchmark. Shionogi is the only company engaged in antifungal drug development. Its preclinical activities have a broad focus									
<b>A.3 Some preclinical R&amp;D projects being developed with public partners.</b>										
<b>A.4 Stewardship commitment in place, but no information regarding access.</b>		Shionogi reports that it has a stewardship commitment in place for its antibiotic candidate in late-stage development, but reports no informa-								

### Pipeline targeting priority pathogens

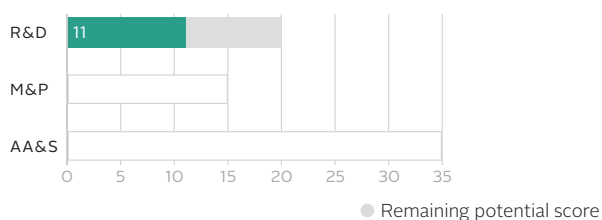
Discovery	Preclinical	Phase I	Phase II	Phase III	Approval
<ul style="list-style-type: none"> <li>Antibacterial programme 1 – GNB</li> <li>Antibacterial programme 2 – GNB</li> <li>Antibacterial programme 3 – GPB</li> <li>Anti-tuberculosis programme – <i>M. tuberculosis</i></li> <li>Anti-tuberculosis programme 2 – <i>M. tuberculosis</i></li> <li>Anti-HIV programme 1 – HIV</li> <li>Anti-HIV programme 2 – HIV</li> <li>Anti-HIV programme 3 – HIV</li> <li>Anti-HIV programme 4 – HIV</li> <li>Anti-HIV programme 5 – HIV</li> <li>Antifungal programme 1 – <i>Candida</i></li> <li>Antifungal programme 2 – <i>Candida</i></li> </ul>	<ul style="list-style-type: none"> <li>Antibody – <i>P. aeruginosa</i></li> <li>YF-49-92 – <i>M. tuberculosis</i></li> </ul>			<ul style="list-style-type: none"> <li>Cefiderocol (S649266) – CRE, ESBL, <i>P. aeruginosa</i>, <i>A. baumannii</i> – BSI, cUTI, HAPB/VABP, Sepsis</li> </ul>	
BSI = Bloodstream infections cUTI = Complicated urinary tract infection GNB = Gram-negative bacteria GPB = Gram-positive bacteria HAPB/VABP = Hospital-acquired/Ventilator-associated bacterial pneumonia					

B MANUFACTURING & PRODUCTION		Indicators scored on	1	2	3				
			●	●	●				
<b>B.1 Environmental risk-management strategy for own sites.</b>									
Shionogi has an environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge that includes auditing and discharge limits. The strategy currently applies to Shionogi's own sites. Shionogi has committed to extending it, within a year, to its third-party manufacturers of antibiotic APIs and drug products. The company has made no statement about extending the strategy to external waste-treatment plants.									
<b>B.2 Commitment to increase transparency regarding environmental risk management.</b>									
Shionogi does not currently disclose its strategy to minimise the impact of manufacturing discharge of antibiotics. Notably, however, it has made a commitment to publish this strategy as well as the identities of its third-party manufacturers. It currently does not publish any elements looked for by the Benchmark, namely: antibiotic discharge levels, audit results, and the identities of its third-party manufacturers of antibiotic APIs and drug products, or of its external waste-treatment plants.									
<b>B.3 Commits to following GMP, including at 3rd-party sites.</b>									
Shionogi reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. Shionogi requires its third-party suppliers of drug products to apply the same quality standards to their production facilities.									
C APPROPRIATE ACCESS & STEWARDSHIP		Indicators scored on	1	2	3	4	5	6	7
			●	○	○	●	●	●	●
<b>C.1 Newest marketed antibiotics not filed for registration.</b>									
Shionogi reports that it has not filed its newest marketed antibiotics for registration in countries in scope.*									
<b>C.2-C.3 No marketed products in countries in scope.</b>									
Shionogi reports that it is not marketing any antimicrobials in any countries in scope.* Hence, in these countries, Shionogi does not report having equitable pricing approaches or processes in place to improve supply chain efficiency and prevent and/or respond to stock-outs.									
<b>C.4 Some involvement in AMR-related education.</b>									
Shionogi reports that it is involved in educational programmes for HCPs that include AMR stewardship, with conflict of interest (COI) mitigation measures in place. It has strategies in place for independent content development. Half of the programmes disclosed were delivered through courses, while the remaining programmes are delivered via web pages and leaflets.									
<b>C.5 Adopts appropriate promotion practices.</b>									
The Benchmark measures how companies address stewardship through appropriate promotion practices. Shionogi reports that it takes action in this regard: it reflects AMR trends in its marketing materials and does not remunerate its sales teams based on antibiotic sales volume.									
<b>C.6 No information regarding brochure and/or packaging adaptations.</b>									
Shionogi does not provide sufficient information on any language, cultural or literacy adaptations made to its brochures or packaging that would promote appropriate use.									
<b>C.7 Surveillance programmes focused on Japan.</b>									
Shionogi has engaged with academic institutes for several short-term surveillance programmes. These programmes are aimed at measuring the current AMR landscape in different regions across Japan. All Shionogi's studies will be published in peer-reviewed journals. After the period of analysis, the company reported engagement in further surveillance programmes in more countries, details of which are not available.									

# Summit Therapeutics plc

Stock exchanges: XLON; XNAS • Tickers: SUMM; SMMT • HQ: Abingdon, UK • Employees: 40 • Signatory to Davos Decl.: No • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Summit was evaluated: applicable indicators

		Indicator reference						
		1	2.1	2.2	2.3	3	4	
R&D	A	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	
		1	2	3				
M&P	B	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>				
		1	2	3	4	5	6	7
AA&S	C	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Summit is a biopharmaceutical company, selected for having a pipeline that targets priority pathogens. It was evaluated in the area of Research & Development only. It invested USD 5 million in antibiotic drug development in 2016. The company performs well compared to other biopharmaceutical companies in scope. It has one project in its antimicrobial R&D pipeline targeting priority pathogens. Summit engages in pub-

lic-private partnerships to develop its antibiotic candidates. The company reports that it has an access commitment in place for its antibiotic candidate in late-stage development, but reports no information on stewardship provisions.

## OPERATIONS

Summit is a biopharmaceutical company focusing on the development of novel medicines for indications for which current therapies are lacking or inadequate. The company was founded in 2003 as a spin-off from the University of Oxford and is currently conducting two clinical programmes: one on the genetic disease Duchenne muscular dystrophy and the other on *C. difficile* infections (CDI). Its only antimicrobial drug candidate is ridinilazole, currently in Phase II development. The compound is designed to selec-

tively target *C. difficile* bacteria without disrupting the gut flora, thereby reducing CDI recurrence rates—a common clinical issue in this disease. The company plans to start Phase III trials for ridinilazole in the first half of 2018. Summit has no products on the market. In September 2017, the company was awarded a contract from BARDA of up to USD 62 million for the development of ridinilazole for the treatment of CDI. In December 2017, Summit acquired UK-based Discuva Ltd, a biotechnol-

ogy company with a proprietary genetics-based platform facilitating the discovery and development of differentiated antibiotics. Summit was listed on the AIM market of the London stock exchange in 2004, after raising GBP 15 million from investors. In 2015, it was listed on the NASDAQ stock exchange, where it raised USD 34 million.

## ANTIMICROBIAL PORTFOLIO

Summit does not have any products on the market.

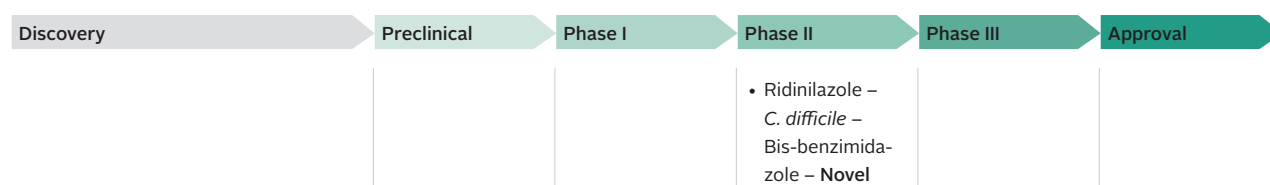
## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Summit has committed to ensure access and stewardship provisions are in place for its antibiotic candidate (ridinilazole), through its agreement with the Wellcome Trust. It can ensure that these plans are applied and implemented accordingly.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT		Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	1 project 1 target priority pathogens
<p><b>A.2.1-2.2 One novel antibiotic in the clinical pipeline.</b></p> <p>Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. Summit invested USD 5 million in antibiotic drug development in 2016. The company has one project in its antimicrobial R&amp;D pipeline targeting a priority pathogen. Summit's antimicrobial pipeline consists of the antibiotic ridinilazole, currently in clinical Phase II development for the treatment of CDI. The drug candidate is a bis-benzimidazole, a new class of antibiotics for which the mode of action is yet unknown.</p>			○	●	●	○	●	●		
<p><b>A.3 One R&amp;D project being developed with public partners.</b></p> <p>Summit is developing one R&amp;D project in its priority pathogen pipeline through public-private partnership (including non-profit organisations). The company has received GBP 6.3 mil-</p>		<p>lion from the Wellcome Trust for the preclinical and clinical development of ridinilazole. Under the agreement, Summit is solely responsible for the preclinical and clinical development of the CDI programme. The Wellcome Trust is eligible to receive a tiered portion of the net revenue made by Summit or its affiliates (of up to a low-to mid-single digit percentage) following signing of a revenue share agreement in 2017. The Wellcome Trust is also eligible to receive a milestone of a specified amount if cumulative net revenues exceed a specified amount. In addition, in September 2017, the company was granted up to USD 62 million by BARDA for advancing the clinical and regulatory development of ridinilazole, including through Phase III clinical trials.</p>								
<p><b>A.4 Access commitment in place, but no information regarding stewardship.</b></p> <p>Summit reports that it has an access commitment in place for its antibiotic candidate in late-</p>										
			<p>stage development, but reports no information on stewardship provisions. The access commitment for its investigational antibiotic (ridinilazole) has been made through an agreement with the Wellcome Trust. If the company or its licensees do not develop, commercialise or exercise their IP rights in underserved markets within a specified timeframe, the Wellcome Trust is permitted to take over exploitation of the IP in those markets. The IP rights were granted to Summit for a number of major territories including the United States, Europe and Japan. No specific strategy has been made for lower- and middle-income countries. For this indicator, countries in scope are 106 low- and middle-income countries where access to medicine is likely limited.</p>							

### Pipeline targeting priority pathogens



## B MANUFACTURING & PRODUCTION

As a biopharmaceutical company with no products on the market, Summit was not eligible for this Research Area.

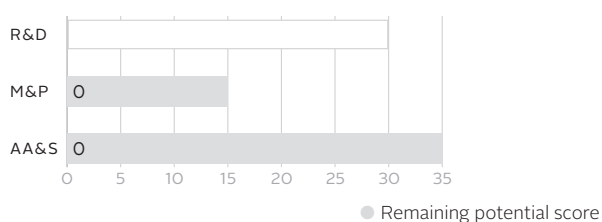
## C APPROPRIATE ACCESS & STEWARDSHIP

As a biopharmaceutical company with no products on the market, Summit was not eligible for this Research Area.

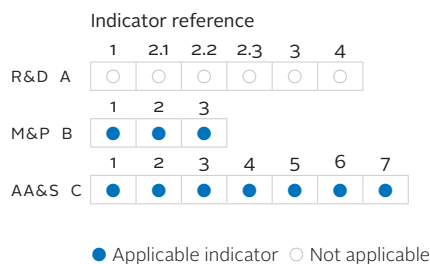
# Sun Pharmaceutical Industries Ltd.

Stock exchange: XNSE • Ticker: SUNPHARMA • HQ: Mumbai, India • Employees: > 30,000 • Signatory to Davos Decl.: No • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Sun Pharma was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Sun Pharma is a prominent producer of antibiotics globally by sales volume. As a generic medicine manufacturer, Sun Pharma was evaluated in Manufacturing & Production and Appropriate Access & Stewardship only. Its performance is low compared to other generic medicine manufacturers in scope. It reported no information to the Benchmark, and

publicly available information is limited, specifically regarding its approach to manufacturing high quality antibiotics, its approach to equitable pricing, where it has filed antibiotics for registration, its actions to ensure efficient supply and its involvement in stewardship activities.

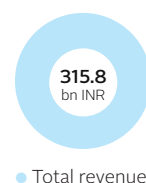
## SALES AND OPERATIONS

Sun Pharma, founded in 1983, is an Indian-based generic medicine manufacturer focussing on the production of generic medicines, specialty products, over-the-counter (OTC) products, antiretrovirals (ARVs) and active pharmaceutical ingredients (APIs). The company's business segmentation is based on a mix of geographical and therapeutic areas. It listed its anti-infectives segment as its fourth-biggest therapeutic segment by revenue, after cardiology, neuropsychiatry and gastroenterology. The company's specialty business focusses on the therapeutic areas of dermatology, ophthalmology, oncology and the

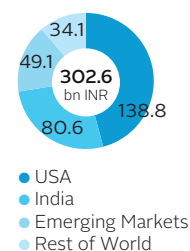
central nervous system (CNS). The company has 42 manufacturing sites spread across six continents and markets its products in more than 150 countries worldwide.

In 2015, Sun Pharma completed the acquisition of Ranbaxy Laboratories Limited, an Indian-based company focussed on generic medicines with international operations, and a member of the Daiichi Sankyo group (at the time of acquisition). The merger combined Sun Pharma's established specialty business with Ranbaxy's global operations in generic medicines.

## Revenues by product<sup>§</sup>



## Revenues by region<sup>||</sup>

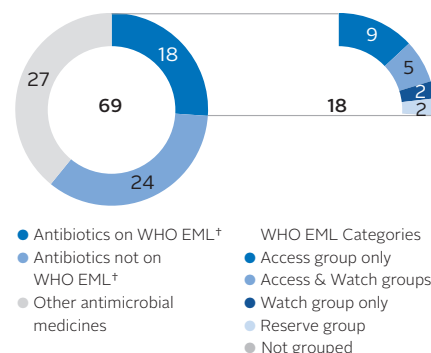


## ANTIMICROBIAL PORTFOLIO

According to publicly available data, Sun Pharma markets at least 69 antimicrobial medicines, 35 of which are listed on the WHO EML (Section 6). Forty-two of the company's antimicrobial medicines are antibiotics, with 18 listed on the WHO EML (Section 6), including two in the EML's Reserve group (colistin and tigecyclin).

The remainder (27) of the company's portfolio is diverse, comprising antifungals, anthelmintics, antiprotazoals and antivirals, 13 of which target HIV.

## Antimicrobial portfolio breakdown



## OPPORTUNITIES

**Engage in antimicrobial stewardship.** Sun Pharma can engage in stewardship activities, e.g., through surveillance activities, educational activities for healthcare professionals on AMR (while mitigating conflicts of interest), and engage in appropriate promotion practices.

**Ensure transparency regarding environmental risk.** Sun Pharma can share information on how it manages environmental risk, e.g., disclose the

levels of antibiotic discharge. Currently, the company does not report having an environmental risk-management strategy.

**Ensure affordability and registration plans for new and existing antimicrobials.** Sun Pharma can seek to improve access in low- and middle-income countries through the registration of new and existing antimicrobials, and ensure that they are priced affordably. Currently, the com-

pany does not disclose such information.

**Engage in R&D innovation.** Sun Pharma can engage in incremental R&D innovation to address resistance, improve adherence and the appropriate use of antimicrobial medicines.

\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Revenue from operations; FYE 31 March 2017

<sup>||</sup> Sales; FYE 31 March 2017

## PERFORMANCE BY RESEARCH AREA

### A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Sun Pharma's main focus is the manufacturing of generic products and, as such, was not in scope for this Research Area.

### B MANUFACTURING & PRODUCTION

Indicators  
scored on

1 2 3  
● ● ●

#### B.1 Reports no environmental risk-management strategy.

Sun Pharma does not report having an environmental risk-management strategy in place to minimise the environmental impact of manufacturing discharge of antibiotics.

#### B.2 No transparency on environmental risk management.

Sun Pharma does not disclose its strategy to minimise the impact of manufacturing discharge of antibiotics. It does not publish any element looked for by the Benchmark, namely: antibiotic discharge levels, audit results, and the identities of its third-party suppliers of antibiotic APIs and drug products, or of its external waste-treatment plants.

#### B.3 No statement on how antibiotic quality is maintained.

Sun Pharma makes no statement regarding how it ensures high-quality antibiotic production following international manufacturing standards accepted by recognised national and international authorities (such as GMP).

### C APPROPRIATE ACCESS & STEWARDSHIP

Indicators  
scored on

1 2 3 4 5 6 7  
● ● ● ● ● ● ●

**C.1 No information on filing for registration.**  
Sun Pharma reports no information on where it has filed its newest antibiotics for registration in countries in scope.\* This information is not otherwise publicly available.

#### C.2 No disclosure on equitable pricing approach.

Sun Pharma does not disclose an equitable pricing approach for its highest-volume antibiotics and/or antimicrobial medicines.

#### C.3 No insight into steps addressing supply chain efficiency.

Sun Pharma does not disclose how it works with stakeholders (e.g., governments, procurers) to align supply and demand for antimicrobial medicines, specifically to prevent or minimise stock-outs in countries in scope.\* The company also does not report on whether it has processes in place to respond to stock-outs in countries in scope.\*

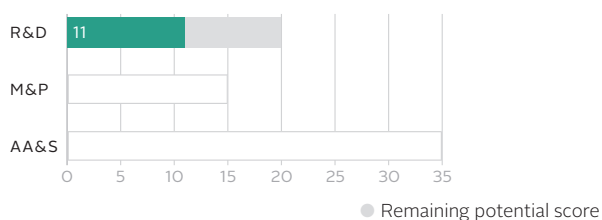
#### C.4-C.7 No apparent involvement in stewardship activities.

Sun Pharma does not report any involvement in stewardship activities (from education to surveillance to appropriate promotion practices) that promote appropriate antibiotic use.

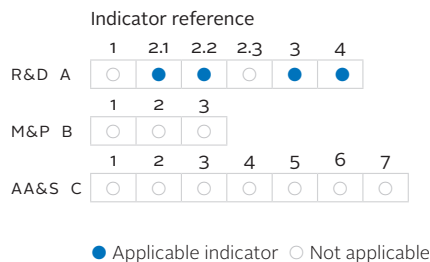
# Tetraphase Pharmaceuticals, Inc.

Stock exchange: XNAS • Ticker: TTPH • HQ: Watertown, MA, USA • Employees: 66 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Tetraphase was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Tetraphase is a biopharmaceutical company, selected for having a pipeline that targets priority pathogens. It was evaluated in the area of Research & Development only. It invested USD 64 million in antibiotic drug development in 2016, which is high compared to other biopharmaceutical companies in the Benchmark. The company performs well compared with other biopharmaceutical companies in scope. It has three pro-

jects in its antimicrobial R&D pipeline, all targeting priority pathogens. Tetraphase engages in public-private partnerships to develop its antibiotic candidates. The company has one antibiotic in late-stage clinical development. Tetraphase is the only biopharmaceutical company identified by the Benchmark to have both an access and stewardship provision in place for an antibiotic in late-stage clinical development.

## OPERATIONS

Tetraphase, founded in 2006, is a biopharmaceutical company focussing on the design and development of fully synthetic tetracycline antibiotics targeting multidrug-resistant bacteria. The company's proprietary chemistry platform has resulted in a library of tetracycline analogues containing more than 2,500 compounds. The company's most advanced drug candidate, eravacycline, is a broad-spectrum antibiotic being developed in both oral and intravenous formulations for the treatment of resistant and multidrug-resistant infections. The compound

is currently undergoing Phase III trials for the treatment of complicated intra-abdominal infections and complicated urinary tract infections. Tetraphase has no products on the market. In recent years, Tetraphase has secured several grants from various partners, including the US National Institute of Allergy and Infectious Diseases (NIAID) and BARDA. The latter currently supports the joint development of eravacycline with the R&D company CUBRC. In 2017, Tetraphase was awarded USD 4 million (over an 18-month period) by CARB-X, to further develop

TP6076, an investigational synthetic fluorocycline antibiotic that targets multidrug-resistant gram-negative bacteria. The company is also exploring the use of its tetracycline candidate compounds in other therapeutic areas, including oncology and inflammatory diseases. In 2013, Tetraphase was listed on the NASDAQ stock exchange, where it raised USD 75 million.

## ANTIMICROBIAL PORTFOLIO

Tetraphase does not have any products on the market.

## OPPORTUNITIES

**Expand stewardship provisions for eravacycline.** Tetraphase is the only company to have access and stewardship provisions (involving a surveillance programme), for an antibiotic in late-stage clinical development. It can ensure that further stewardship provisions are in place, e.g., appropriate promotion practices.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT	Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	3 projects 3 target priority pathogens
		○	●	●	○	●	●		

**A.2.1-2.2 Pipeline focussed on tetracycline antibiotics.**

Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. Tetrphase invested USD 64 million in antimicrobial R&D in 2016. The company has three projects in its antimicrobial R&D pipeline targeting priority pathogens, all of which are broad-spectrum fluorocycline candidates. Its leading candidate is eravacycline, a broad-spectrum antibiotic in development for complicated intra-abdominal infections and complicated urinary tract infections. Its two other tetracycline compounds (TP271 and TP6076) are in Phase I clinical development for the treatment of gram-negative bacterial infections.

**A.3 All R&D projects being developed with public partners.**

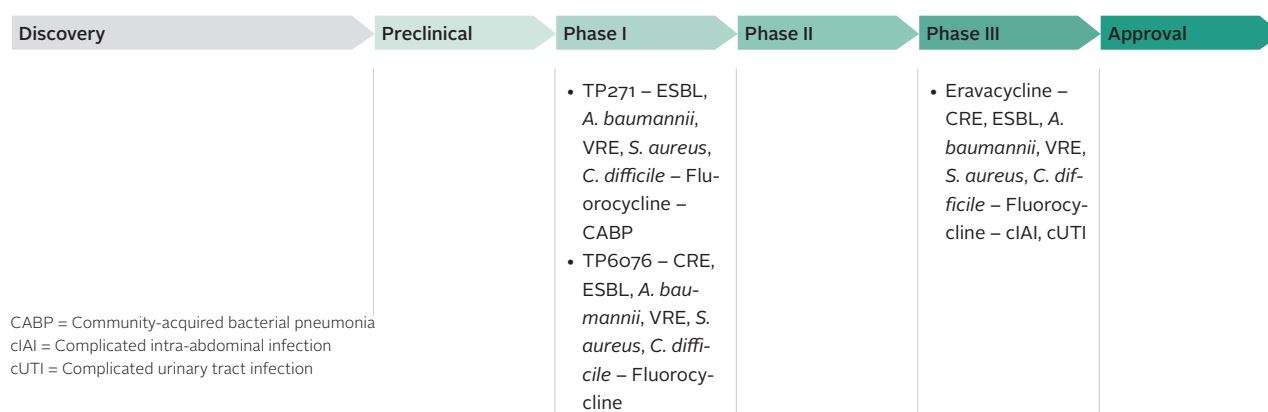
Tetrphase is developing all three R&D projects in its priority pathogen pipeline through public-private partnership (including a non-profit

organisation). Tetrphase has received funding from BARDA for the development of eravacycline, NIAID for TP271 and CARB-X for TP6076. Through CARB-X, Tetrphase also shares IP rights with the Wellcome Trust for TP6076. This enables the Wellcome Trust to commercialise the medicine in underserved markets, if necessary.

**A.4 Only biopharmaceutical company to have both an access and stewardship provision in place.**

Tetrphase reports that it has both an access and stewardship provision in place for its antibiotic in late-stage development. It is the only biopharmaceutical company to have these provisions in place for an investigational antibiotic (eravacycline). Following approval, the company intends to commercialise eravacycline directly in the USA and the EU. The company is actively seeking partners to develop and commercialise eravacycline in regions including Asia-Pacific,

Eastern Europe, India, Middle East, North Africa and South America. For this indicator, countries in scope are 106 low- and middle-income countries where access to medicine is likely limited. Tetrphase has an ongoing global surveillance programme in collaboration with IHMA, Inc., which monitors the susceptibility to eravacycline of gram-negative and gram-positive bacteria and anaerobes in all types of hospitals (government, teaching, community, etc.). 1.5 full-time equivalent employees (FTEs) are dedicated to the surveillance programme and its Antimicrobial Voluntary Evaluation Program (AVEP). AVEP provides strips and disks that enable hospitals to test susceptibility of pathogens to the antibiotic. The annual cost of the global surveillance programme is USD 750,000, and the annual cost of AVEP is USD 350,000 (for US and EU markets).

**Pipeline targeting priority pathogens****B MANUFACTURING & PRODUCTION**

As a biopharmaceutical company with no products on the market, Tetrphase was not eligible for this Research Area.

**C APPROPRIATE ACCESS & STEWARDSHIP**

As a biopharmaceutical company with no products on the market, Tetrphase was not eligible for this Research Area.

**ANIMAL HEALTH & DIAGNOSTICS**

Activities in this area are not scored by the Benchmark. This information is provided given the importance of animal health and diagnostics on the topic of AMR.

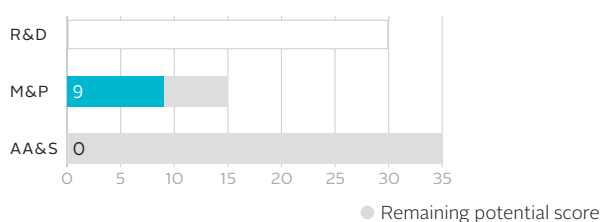
Tetrphase supports the Antimicrobial Voluntary Evaluation Program (AVEP), which provides strips and disks that enable hospitals to test the susceptibility of pathogens to its antibiotic can-

didate eravacycline.

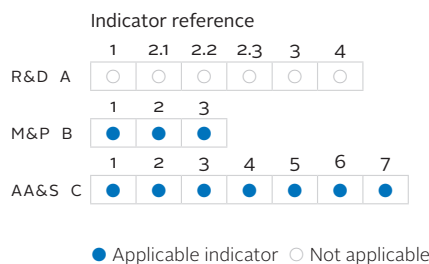
# Teva Pharmaceutical Industries Ltd.

Stock exchanges: XNYS; XTAE • Ticker: TEVA • HQ: Petach Tikva, Israel • Employees: 56,960 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: No

## Performance by Research Area



## How Teva was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Teva is a prominent producer of antibiotics globally by sales volume. As a generic medicine manufacturer, Teva was evaluated in Manufacturing & Production and Appropriate Access & Stewardship only. The company performs well when compared with the other generic medicine manufacturers in scope. It discloses a comprehensive environmental risk-management strategy, which it does not apply to third-party manufacturers of antibiotic APIs and drug products or to exter-

nal waste-treatment plants. The company reports that it has mechanisms for maintaining a high quality of antibiotic production, and requires its third-party suppliers to apply the same quality standards to their production facilities. Teva reported no information on its access strategies regarding antimicrobial medicines in countries in scope\* or its involvement in stewardship activities that promote appropriate antibiotic use.

## SALES AND OPERATIONS

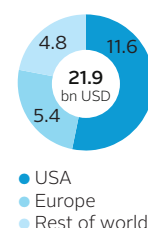
Teva is an Israeli-based generic medicine manufacturer founded in 1901. The company operates in two business segments: generic and specialty medicines. Its specialty medicines segment focusses on delivering medicines, devices and services in the core therapeutic areas of respiratory illness, central nervous system (including pain, migraine, movement and neurodegenerative disorders), oncology and women's health. It engages in R&D activities within both its business segments, focussing on the development of complex technologies and formulations. Teva is active in 80 countries and has 87 manufacturing facilities, manufacturing and supplying active pharmaceutical ingredients on a global scale. It also has a global over-the-counter (OTC) business, including a collaboration with Procter &

Gamble called PGT Healthcare. Teva has the highest revenue among the generic medicine manufacturers included in the Benchmark. The company markets its antimicrobial medicines in 54 countries globally, seven of which are low- or middle-income countries.\* In 2016, Teva acquired Actavis Generics, the global generic pharmaceuticals business from Allergan plc, for approximately USD 33.4 billion cash and 100 million Teva shares. The acquisition required the divestment of certain assets and operations in the USA and Europe to meet anti-trust regulatory requirements. Later in 2016, the company completed the acquisition of Anda Inc., a US-based distributor of generic pharmaceuticals from Allergan for USD 500 million.

## Revenues by product<sup>§</sup>



## Revenues by region<sup>§</sup>

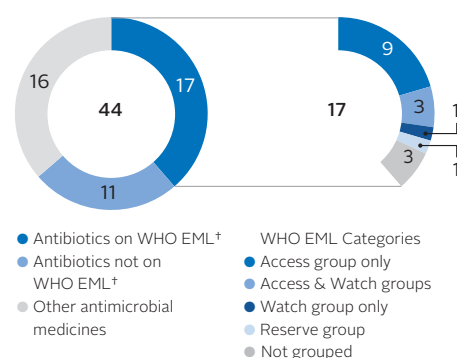


## ANTIMICROBIAL PORTFOLIO

Teva markets at least 44 antimicrobial medicines, 30 of which are listed on the WHO EML (Section 6). Twenty-eight of the company's antimicrobial medicines are antibiotics, with 17 listed on the WHO EML (Section 6), including one on the EML's Reserve group (linezolid). The remain-

ing 16 medicines consist of nine antivirals, four antifungals and three antiprotozoals indicated for treatment of malaria.

## Antimicrobial portfolio breakdown



\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Net revenues; FYE 31 December 2016

## OPPORTUNITIES

**Engage in antimicrobial stewardship.** Teva can engage in stewardship activities, e.g., through surveillance activities, educational activities for healthcare professionals on AMR (while mitigating conflicts of interest), and engage in appropriate promotion practices.

**Ensure affordability and registration plans for new and existing antimicrobials.** Teva can seek to improve access in low- and middle-income countries through the registration of new and existing antimicrobials, and ensure that they are priced affordably. Currently, the company does not disclose such information.

**Improve transparency regarding environmental risk management.** Teva can share more information on how it manages environmental risk, e.g., disclose the levels of antibiotic discharge and publish the identities of third parties who manufacture antibiotic APIs and drug products on its behalf. Teva currently discloses its environmental risk-management principles.

**Expand environmental risk-management strategy.** Teva has an environmental risk-management strategy that includes discharge limits, which are applied to its own manufacturing sites. It can ensure its environmental risk-manage-

ment strategy is applied to external waste treatment plants and can apply its discharge limits and auditing processes to third-party suppliers of antibiotic APIs and drug products.

**Engage in R&D innovation.** Teva can engage in incremental R&D innovation to address resistance, improve adherence and the appropriate use of antimicrobial medicines.

## PERFORMANCE BY RESEARCH AREA

### A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Teva's main focus is the manufacturing of generic products and, as such, was not in scope for this Research Area.

### B MANUFACTURING & PRODUCTION

Indicators scored on 1 2 3

#### B.1 Environmental risk-management strategy for own sites.

Teva applies an environmental risk-management strategy to minimise the impact of antibiotic manufacturing discharge that includes auditing and discharge limits. The strategy applies to Teva's own sites and to its third-party manufacturers of antibiotic APIs and drug products; however, the discharge limits and auditing processes are applicable to its own manufacturing sites only. The strategy does not apply to external waste-treatment plants.

#### B.2 Limited transparency regarding environmental risk management.

Teva publishes its environmental risk-management strategy in its CSR report. It does not disclose audit results, or the discharge levels of antibiotics. The company also does not share the identities of its third-party suppliers of antibiotic APIs and drug products or external waste-treatment plants.

#### B.3 Commits to following GMP, including at 3rd-party sites.

Teva reports that it has mechanisms for maintaining a high quality of antibiotic production — namely following GMP standards. This commitment applies to its own manufacturing sites. Teva requires its third-party suppliers to apply the same quality standards to their production facilities.

### C APPROPRIATE ACCESS & STEWARDSHIP

Indicators scored on 1 2 3 4 5 6 7

#### C.1 No information on filing for registration.

Teva reports no information on where it has filed its newest antibiotics for registration in countries in scope.\* This information is not otherwise publicly available.

#### C.2 No disclosure on equitable pricing approach.

Teva does not disclose an equitable pricing approach for its highest-volume antibiotics and/or antimicrobial medicines.

#### C.3 No insight into steps addressing supply chain efficiency.

Teva does not disclose how it works with stakeholders (e.g., governments, procurers) to align supply and demand for antimicrobial medicines, specifically to prevent or minimise stock-outs in countries in scope.\* The company also does not report on whether it has processes in place to respond to stock-outs in countries in scope.\*

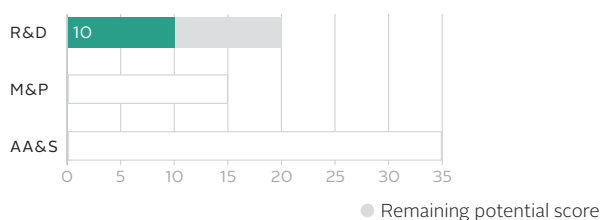
#### C.4-C.7 No apparent involvement in stewardship activities.

Teva does not report any involvement in stewardship activities (from education to surveillance to appropriate promotion practices) that promote appropriate antibiotic use.

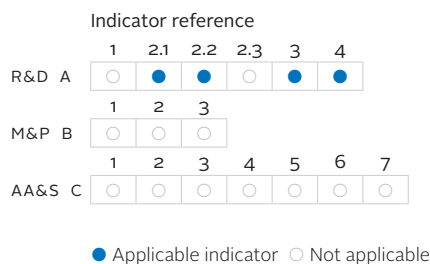
# The Medicines Company

Stock exchange: XNAS • Ticker: MDCO • HQ: Parsippany, NJ, USA • Employees: 410 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: No

## Performance by Research Area



## How The Medicines Company was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

The Medicines Company\* is a biopharmaceutical company, selected for having a pipeline that targets priority pathogens. At the end of 2017, the company announced that it would divest its infectious disease business to Melinta, another biopharmaceutical company in scope of the Benchmark. The divestment was completed in January 2018. The Medicines Company was evaluated in the area of Research & Development only, although it has a number of antibiotics on the market. It performs well compared to other biopharmaceutical companies in scope. The Medicines Company

received FDA approval for its meropenem/vaborbactam combination in August 2017. The company engages in public-private partnerships to develop its antibiotic candidates. The company reports no information on access or stewardship provisions for its recently FDA-approved antibiotic. The Medicines Company was not evaluated in the Manufacturing & Production area; however, it is the only company in scope to disclose identities of third-party manufacturers of its antibiotics.

## SALES AND OPERATIONS

The Medicines Company is a US-based biopharmaceutical company with core therapeutic areas in infectious disease care, cardiovascular care, surgery and perioperative care. The company's revenues in the past three years have come primarily from the US sales of its cardiovascular medicine bivalirudin (Angiox® or Angiomax®), a direct thrombin inhibitor. These revenues include approximately USD 71.2 million in royalties derived from the authorised sale of the generic version of bivalirudin (Angiomax®) by Sandoz. In August 2017, the company received FDA approval to commercialise its intravenous formulation of meropenem/vaborbactam (Vabomere™), which is active against multidrug-resistant gram-negative bacteria, for the treatment of complicated urinary tract infec-

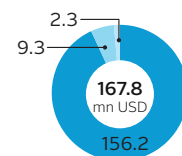
tions. The compound was developed with funding from BARDA, first under a contract of USD 90 million and, starting in 2016, under a new five-year contract of up to USD 132 million. At the end of 2017, The Medicines Company announced that it would divest its infectious disease business to Melinta, another biopharmaceutical company in scope of the Benchmark. The divestment was completed in January 2018 and included three marketed antimicrobial medicines: meropenem/vaborbactam (Vabomere™), minocycline (Minocin®) and oritavancin (Orbactiv®). The company's two other marketed antimicrobial medicines (azithromycin and clindamycin) are generic medicines commercialised via a licensing and supply agreement with APP Pharmaceuticals, LLC.

## Revenues by product<sup>§</sup>



● Total revenue

## Revenues by region<sup>§</sup>



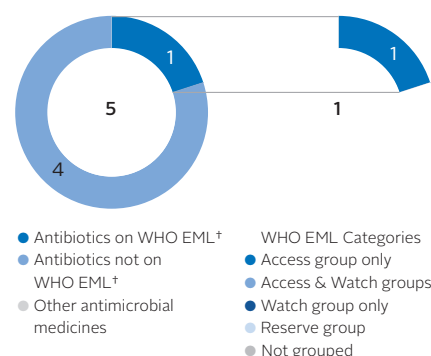
● USA  
● Europe  
● Rest of World

## ANTIMICROBIAL PORTFOLIO

According to publicly available data, The Medicines Company's portfolio of antimicrobial medicines consists of five antibiotics. One of these antibiotics, clindamycin, is listed on the WHO EML (Section 6), in the Access group. The remaining four medicines are the recently approved meropenem/vaborbactam (Vabomere™), azithromycin (for intravenous administration) and powder-for-injection formu-

lations of two other antibiotics: the broad-spectrum agent minocycline (Minocin®), approved to treat *Acinetobacter* species infections, and the antibiotic oritavancin (Orbactiv®), active against gram-positive pathogens and indicated for the treatment of acute bacterial skin and skin structure infections in adults, including those due to methicillin-resistant *S. aureus* (MRSA).

## Antimicrobial portfolio breakdown



<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Net revenues; FYE 31 December 2016

\* In January 2018, The Medicines Company completed the divestment of its infectious disease business to Melinta Therapeutics, Inc.

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT	Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	1 projects 1 target priority pathogens
		○	●	●	○	●	●		

**A.2.1-2.2 One antibiotic recently approved.** Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. The Medicines Company received FDA approval for its meropenem/vaborbactam (Vabomere™, formerly Carbavance™) in August 2017. Vaborbactam is a β-lactamase inhibitor (BLI) with a novel chemical structure. Meropenem is an existing carbapenem β-lactam. Vaborbactam restores susceptibility to meropenem in carbapenem-resistant *Enterobacteriaceae* (CRE).

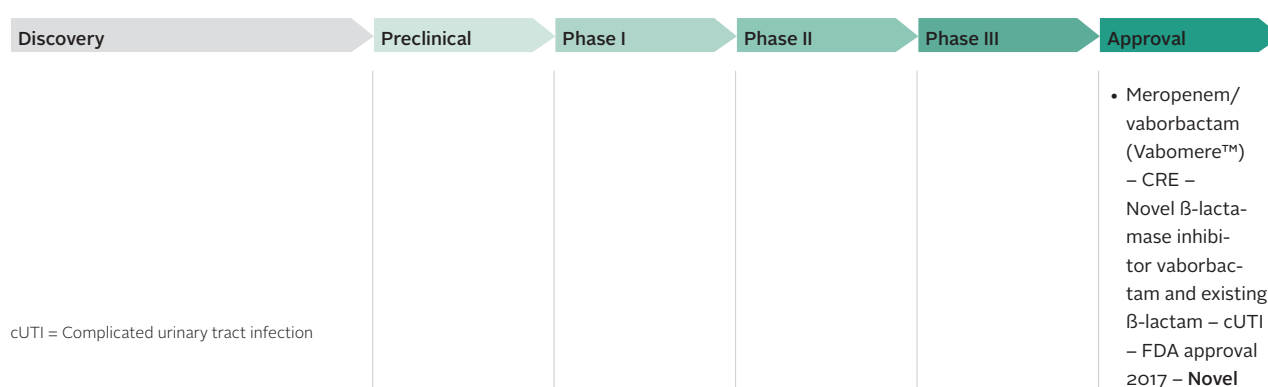
**A.3 One R&D project being developed with public partners.**

The Medicines Company developed meropenem/vaborbactam (Vabomere™) in partnership with BARDA, which began with a five-year contract in 2014, followed by a new five-year contract in 2016 (≤ USD 132 million).

**A.4 No information on access or stewardship provisions.**

The Medicines Company reports no information on access or stewardship provisions for its recently FDA-approved antibiotic. It has signed the Davos Declaration, which includes a general commitment to ensuring access to antimicrobial medicines and vaccines, and to support the appropriate and responsible use of these products.

## Pipeline targeting priority pathogens



## B MANUFACTURING &amp; PRODUCTION

The Medicines Company is a biopharmaceutical company that did not meet the criteria for evaluation in this Research Area. It does, however, have products on the market, and notable practices relevant to this area are mentioned.

**B.2 Only company to disclose identities of third-party suppliers.**

On reviewing publicly available information, the Benchmark found that The Medicines Company has disclosed the identities of third-party manufacturers of its antibiotics, per product, in its annual report. It is the only company to publish this information.

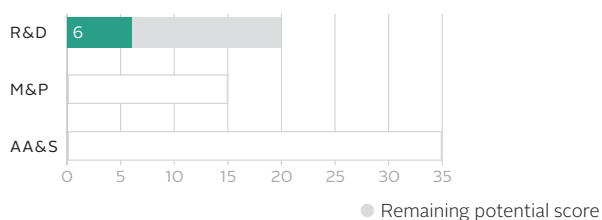
## C APPROPRIATE ACCESS &amp; STEWARDSHIP

The Medicines Company is a biopharmaceutical company that did not meet the criteria for evaluation in this Research Area. It does, however, have products on the market.

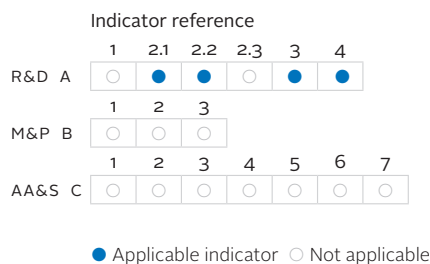
# Wockhardt Limited

Stock exchange: XNSE • Ticker: WOCKPHARMA • HQ: Mumbai, India • Employees: 6,768 • Signatory to Davos Decl.: Yes • Signatory to Industry Roadmap: Yes

## Performance by Research Area



## How Wockhardt was evaluated: applicable indicators



Due to the variation between companies in scope, not all indicators are applicable to every company. See Appendix for full overview.

## PERFORMANCE

Wockhardt is a biopharmaceutical company, selected for having a pipeline that targets priority pathogens. It was evaluated in the area of Research & Development only, although it has a number of antimicrobials on the market. Although its performance in the Benchmark is lower compared to other biopharmaceutical companies in scope, all five of its R&D projects target priority pathogens. Wockhardt does not engage in public-private partnerships; however, it conducts R&D

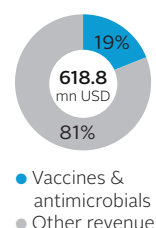
in-house and/or with private-sector partners to develop its antibiotic candidates. The company reports no information on access or stewardship provisions for its five antibiotic candidates in late-stage development. Wockhardt was not evaluated in the Appropriate Access & Stewardship area. However, it engages in patient and community educational programmes in India and also coordinates an AMR surveillance programme to monitor resistance trends in India.

## SALES AND OPERATIONS

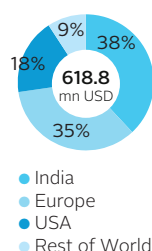
Wockhardt is an Indian-based biopharmaceutical company with a focus on R&D. Besides pharmaceutical research, the company's research programme includes areas such as genomics, biotechnology and novel drug delivery systems. Wockhardt is currently developing a new drug discovery programme focussing on unmet needs in bacterial infections (both gram-negative and gram-positive). The company is also involved in the development of diagnostics for antibiotic

susceptibility testing (AST) relevant to its novel antibacterial drugs under development. Wockhardt sells antimicrobial medicines in the USA, the UK, Ireland, Puerto Rico, Russia, Norway, India and Vietnam. The latter two are considered low- or middle-income countries.\* Its vaccines are sold exclusively in India. In the fiscal year 2016, Wockhardt sold 142 million Standard Units (SUs) of antimicrobial medicines and 1.1 million SUs of vaccines.

## Revenues by product<sup>§</sup>



## Revenues by region<sup>§</sup>

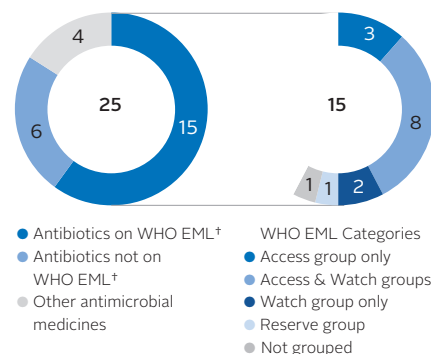


## ANTIMICROBIAL PORTFOLIO

Wockhardt markets at least 25 antimicrobial medicines, 19 of which are listed on the WHO EML (Section 6). Twenty-one of the company's antimicrobial medicines are antibiotics, with 15 listed on the WHO EML (Section 6), including one in the EML's Reserve group (colistin, Wockstin®). The remainder (four) of the company's portfolio consists of two antifungals, the antimalarial quinine and the antiviral aciclovir, all

listed on the WHO EML (Section 6). The company's vaccines target hepatitis A (Biovac A®) and chickenpox (Biovac V®).

## Antimicrobial portfolio breakdown



## OPPORTUNITIES

**Plan ahead for access and stewardship during R&D.** Wockhardt is developing five antibiotic candidates in late-stage clinical development. Wockhardt can ensure access and stewardship provisions are in place for these candidates, for example, through partnerships.

\* Countries in scope are 106 low- and middle-income countries where access to medicine is likely limited

<sup>†</sup> EML Section 6: Anti-Infective Medicines

<sup>§</sup> Revenue from operations; FYE 31 March 2017

## PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT	Indicators scored on	1	2.1	2.2	2.3	3	4	Antimicrobial pipeline	5 projects 5 target priority pathogens
		○	●	●	○	●	●		

### A.2.1-2.2 Five broad-spectrum antibiotics targeting priority pathogens.

Biopharmaceutical companies in scope were selected based on their pipelines that target priority bacteria. Wockhardt has five antibiotics that target priority pathogens, one of which is a combination of two existing agents. All five medicines are in Phase III clinical stage development. The company's pipeline includes a new  $\beta$ -lactam enhancer (zidebactam), developed in combination with  $\beta$ -lactam cefepime for the treatment of multidrug-resistant gram-negative bacterial infections. In 2017, the FDA agreed to an abridged Phase III clinical trial for this anti-

biotic. The other four medicines in the company's pipeline are: one macrolide (nafithromycin); two broad-spectrum antibiotic fluoroquinolones (alalevonadifloxacin and levonadifloxacin), which are being developed specifically for gram-positive bacterial infections (including MRSA infections and community-acquired bacterial pneumonia); and a new high-dose combination of cefepime/tazobactam, which is active against multidrug-resistant *Enterobacteriaceae*, including ESBL-, KPC- and OXA-181-expressing strains.

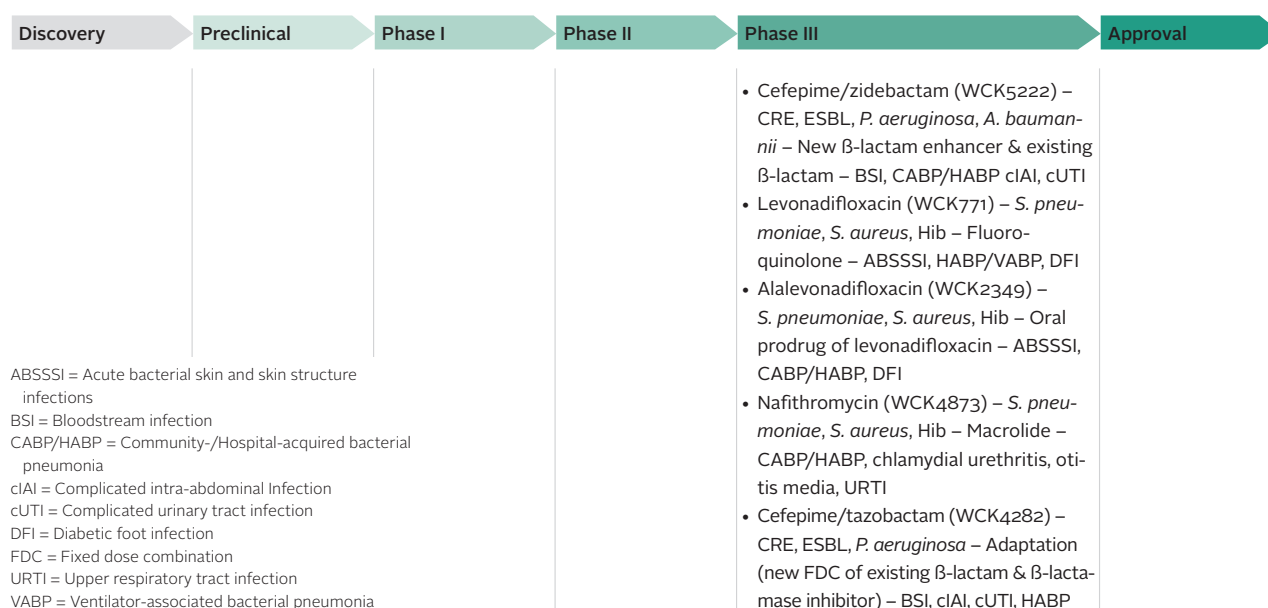
**A.3 No public-private partnerships reported.** Wockhardt conducts R&D in-house and/or with

private-sector partners. It does not participate in public-private partnerships, or in partnerships with non-profit organisations, for antimicrobial R&D.

### A.4 No information on access or stewardship provisions.

Wockhardt reports no information on access or stewardship provisions for its five antibiotic candidates in late-stage development. It has signed the Davos Declaration, which includes a general commitment to ensuring access to antimicrobial medicines and vaccines, and to support the appropriate and responsible use of these products.

### Pipeline targeting priority pathogens



## B MANUFACTURING & PRODUCTION

Wockhardt is a biopharmaceutical company that did not meet the criteria for evaluation in this

Research Area. It does, however, have products on the market.

## C APPROPRIATE ACCESS & STEWARDSHIP

Wockhardt is a biopharmaceutical company that did not meet the criteria for evaluation in this Research Area. It does, however, have products on the market, and notable practices relevant to this area are mentioned.

### C.4 No apparent involvement in AMR-related education for HCPs.

Wockhardt was not eligible for this indicator, and does not provide any information in AMR-related education for HCPs. Notably, however, the company engages in patient education with its Mobile 1000 programme in India through the Wockhardt Foundation. This programme includes Water, Sanitation and Hygiene (WASH) education and other health promotion activities.

### C.7 Only biopharmaceutical company to report running a surveillance programme.

Wockhardt was not eligible for this indicator. Notably, however, the company coordinates a surveillance programme in India, which works with hospitals and laboratories to monitor resistance trends. This programme is completely funded by Wockhardt.

## ANIMAL HEALTH & DIAGNOSTICS

Activities in this area are not scored by the Benchmark. This information is provided given the importance of animal health and diagnostics on the topic of AMR.

Wockhardt is involved in the development of diagnostics for antibiotic susceptibility testing (AST) relevant to its novel antibacterial drugs under development.



# Appendices

I - Methodology scopes	160
II - Priority pathogens for R&D	163
III - Products for access	164
IV - Countries for access	169
V - Analysis, scoring and review	170
VI - Limitations	173
VII - Scoring guidelines	174
VIII - Guide to report cards	179
IX - List of figures	180
X - Definitions	181
XI - Acronyms	183

## APPENDIX I

## Methodology scopes

The Antimicrobial Resistance Benchmark assesses pharmaceutical company behaviour regarding specific diseases and product types and in a specific geographic scope, depending on the Research Area in question. The following pages set out the rationale for these analytical scopes and how they have been defined.

### COMPANY SCOPE

The Benchmark covers pharmaceutical companies with antimicrobial medicines and/or R&D projects and the ability and a commitment to address AMR. Thirty companies are in scope, selected based on a combination of factors, including R&D focus and experience, antibiotic market share and public commitment to address AMR.

The landscape of pharmaceutical companies with antimicrobials for human health can be divided into three broad and overlapping groups: large research-based pharmaceutical companies; generic medicine manufacturers; and biopharmaceutical companies. There are key differences in the expertise and capacities of each type, notably in the size and nature of their product portfolios and their R&D focus and expertise. As a result, each group can address AMR in different ways.

With this in mind, the Foundation used these broad categorisations to structure its analytical framework. The 30 companies in scope have been grouped according to their key defin-

ing characteristic. The Foundation acknowledges that several companies in scope could be placed in more than one group. Where possible and appropriate, in the Benchmark report, such nuances are used to inform the analysis of company performance. Each company is evaluated in those areas where it has relevant products and/or activities.

#### Criteria for inclusion

The companies in scope have been selected based on a combination of factors. Companies with an antibiotics focus have been prioritised in this first iteration of the Benchmark. Bacteria represent the greatest number of resistant pathogens, the widest geographic scope of resistance, and the bulk of the interventions at the government, manufacturer, healthcare provider and patient levels. The final selection of companies was based on several size and opportunity criteria, including: (1) relevance of marketed portfolio, (2) relevance of antimicrobial pipeline, and (3) commitment to addressing AMR. A small number of companies were selected following clear stakeholder recommendations and based

on their readiness to engage with the data-collection process.

Large research-based pharmaceutical companies were selected based on their antibiotic business volume and revenue, their antimicrobial pipelines and portfolios and/or public commitments to tackling AMR (i.e., they had signed, per September 2016, the Davos Declaration and Industry Roadmap on AMR).<sup>1,2,3</sup> Generic medicine manufacturers were selected if they ranked within the global top ten by antibiotics sales volume and/or if they are signatories to the Industry Roadmap on AMR.<sup>2,4</sup> Biopharmaceutical companies were identified as having at least one drug in clinical development targeting a priority pathogen as overviewed by The Pew Charitable Trusts' report<sup>5</sup> on antibiotics registered at clinicaltrials.org. All of the companies selected from this list for inclusion have signed the Davos Declaration, except one (Summit Therapeutics). Industry associations representing these and other companies have signed the Davos Declaration.

### 2018 Antimicrobial Resistance Benchmark – companies in scope

#### LARGE RESEARCH-BASED PHARMACEUTICAL COMPANIES

	Country	Ticker	Stock exchange	Revenue (bn USD) <sup>1</sup>	Global antibiotic sales Kgs <sup>2</sup>	Signatory to the	
						Davos Decl. <sup>3</sup>	Industry Roadmap <sup>4</sup>
GlaxoSmithKline plc	GBR	GSK	XLON	34.4	28,810.0	●	●
Johnson & Johnson	USA	JNJ	XNYS	71.9	2,053.6	●	●
Merck & Co., Inc.	USA	MRK	XNYS	39.8	12,273.1	●	●
Novartis AG	CHE	NOVN	XSWX	47.6	3,000.0	●	●
Pfizer Inc.	USA	PFE	XNYS	52.8	9,028.9	●	●
Roche Holding AG	CHE	ROG	XSWX	49.6	349.5	●	●
Sanofi	FRA	SAN	XPAR	35.6	unknown	●	●
Shionogi & Co., Ltd.	JPN	4507	XTKS	3.0	unknown	●	●

## GENERIC MEDICINE MANUFACTURERS

	Country	Ticker	Stock exchange	Revenue (bn USD) <sup>1</sup>	Global antibiotic sales International Units <sup>5</sup>	Signatory to the Davos Decl. <sup>3</sup>	Industry Roadmap <sup>4</sup>
Aspen Pharmacare Holdings Limited	ZAF	APN	XJSE	2.4	3.2		
Aurobindo Pharma Limited	IND	AUROPHARMA	XNSE	2.3	unknown		
Cipla Limited	IND	CIPLA	XNSE	2.3	unknown	●	●
Dr. Reddy's Laboratories Ltd.	IND	DRREDDY; RDY	XNSE; XNYS	2.2	2.1		
Fresenius Kabi AG	DEU	FRE	XFRA	6.3	8.3	●**	
Lupin Limited	IND	LUPIN	XNSE	2.6	2.7	●**	
Macleods Pharmaceuticals Ltd.*	IND	n/a	n/a	unknown	unknown		
Mylan NV	USA	MYL	XNAS	11.0	11.5	●	
Sun Pharmaceutical Industries Ltd.	IND	SUNPHARMA	XNSE	4.7	5.5		
Teva Pharmaceutical Industries Ltd.	ISR	TEVA	XNYS; XTAE	21.9	13.3	●	

## BIOPHARMACEUTICAL COMPANIES

	Country	Ticker	Stock exchange	Revenue (mn USD) <sup>1</sup>	Priority R&D projects <sup>6</sup>	Signatory to the Davos Decl. <sup>3</sup>	Industry Roadmap <sup>4</sup>
Achaogen Inc.	USA	AKAO	XNAS	41.8	1	●	
Cempra Inc.	USA	CEMP	XNAS	18.0	2	●	
Entasis Therapeutics Inc.	USA	n/a	n/a	unknown	2	●	
Melinta Therapeutics Inc.	USA	MLNT	XNAS	unknown	1	●	
MGB Biopharma	GBR	n/a	n/a	unknown	1	●	
Motif Bio plc	GBR	MTFB	XLON; XNAS	0.0	1	●	
Nabriva Therapeutics plc	IRL	NBRV	XNAS	6.5	1	●	
Polyphor Ltd.	CHE	n/a	n/a	unknown	1	●	
Summit Therapeutics*	GBR	SUMM; SMMT	XLON; XNAS	3.0	1		
Tetraphase Pharmaceuticals Inc.	USA	TTPH	XNAS	5.1	3	●	
The Medicines Company	USA	MDCO	XNAS	167.8	1	●	
Wockhardt Ltd.	IND	WOCKPHARMA	XNSE	619.0	4	●	●

\* Company included on basis of stakeholder recommendations and willingness to participate.

\*\* via Medicines for Europe (MFE)

<sup>1</sup> Revenue = fiscal year 2016/17 (Exchange rates from www.x-rates.com, the exchange rate of the last day of the fiscal year was used)

<sup>2</sup> Mordor Intelligence. (2016). Global Antibiotics Market Leaders – Top 10 by value, volume and company profiles.

<sup>3</sup> Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance. Signatories as at January, 2017.

<sup>4</sup> Industry Roadmap for Progress on Combating Antimicrobial Resistance. September 2016.

<sup>5</sup> Mordor intelligence (2016). Top 10 Generic Antibiotic Manufacturers by Volume – Custom Study.

<sup>6</sup> The PEW Charitable Trusts. (March, 2016). Antibiotics Currently in Clinical Development.

## DISEASE SCOPE

The disease scope is deliberately broad. This is to ensure the Benchmark can capture the full range of companies' AMR-related policies and practices. All infectious diseases are in scope for analysis. Certain pathogens have been deemed by stakeholders to be a priority for efforts to

curb AMR, particularly for R&D. Priority pathogens identified by the Benchmark are listed in Appendix II. These are drug-resistant pathogens as defined by WHO's R&D Priority List and by CDC's Biggest Threat List. The Benchmark applies a wide definition of

infectious disease: as occurring when microbial pathogens invade a host and harm tissues, and can be transmitted to other individuals. It encapsulates diseases caused by the five main groups of infectious microorganisms relevant to AMR: bacteria, viruses, fungi, helminths, and protozoa.

## PRODUCT SCOPE

The product scope covers antimicrobial medicines on the market and in development, and vaccines in development. Vaccines are undoubtedly critical for limiting AMR. See the 2017 Access to Vaccines Index for an assessment of vaccine companies' practices for improving vaccination coverage. Each of the Benchmark's three Research Areas has a tailored product scope:

**Research & Development:** antimicrobial medicines and vaccines in discovery, preclinical and clinical phases I-III, or approved (or awaiting approval) in 2016–17.

**Manufacturing & Production:** marketed antibiotics; the potential impact of companies' manufacturing processes on AMR mainly relate to antibiotic discharge into the environment and parameters that promote antibacterial resistance.

## Access &amp; Stewardship:

• **For Access indicators (C.1 – C.3):** antibiotics for indicator C.1; antimicrobial medicines on the WHO Model List of Essential Medicines 2017 (EML), Section 6, for indicators C.2, C.3 (see Appendix III). These medicines are deemed essential to the basic functioning of

any health system. Access to these medicines, particularly in low- and middle-income countries, is a continued priority that must be considered alongside efforts to curb AMR.

• **For Stewardship indicators (C.4 – C.8):** marketed antibiotics. Stewardship practices to prevent overuse can limit the emergence and spread of resistance.

**How products are assessed per Research Area**

The table shows which products are relevant to each Research Area.

Whether a particular product group is relevant has been determined through stakeholder consultation.

Products	AMR Benchmark Research Areas			
	Research & Development	Manufacturing & Production	Appropriate Access & Stewardship	
			Access	Stewardship
Innovative and adaptive antimicrobial medicines and vaccines in development	●			
Antimicrobial medicines on WHO Model List of Essential Medicines 2017			●	
Antibiotics		●	●	●

**GEOGRAPHIC SCOPE**

The geographic scope is global. Access indicators have an exclusive focus on low- and middle-income countries.

Antimicrobial resistance is emerging across the globe. The need for new antimicrobials and sustainable antibiotic production are global priorities. The rational use of antibiotics in particular is needed wherever antibiotics are available.

**Access metrics focus on low- and middle-income countries**

The challenges of sufficient access and affordability are significantly higher in poorer countries.<sup>6</sup> A group of indicators (A.4, C.1, C.2, C.3) measure how companies either plan for or already address access to prioritised antimicrobial medicines in 106 low- and middle-income countries. This group of countries has

been defined using three criteria: (1) countries' level of income (gross national income [GNI] per capita); (2) their levels of development; and (3) the scope and scale of inequality in each country. These assessments are based on data from the World Bank, the United Nations Development Programme (UNDP), and the United Nations Economic and Social Council (ECOSOC).<sup>7,8,9</sup>

## APPENDIX II

## Priority pathogens for R&D

In the Research & Development Research Area, the Benchmark assessed companies' R&D projects that target priority pathogens. The pathogens deemed priority by the Benchmark are listed here and comprise (emerging) drug-resistant pathogens as defined by WHO's R&D Priority List and by the Centers for Disease Control's US Biggest Threat List.

Pathogen	Stakeholder prioritisation	
	WHO Priority List <sup>1</sup>	CDC Biggest Threats <sup>2</sup>
<b>BACTERIA</b>		
Carbapenem-resistant <i>Enterobacteriaceae</i> (CRE)	Critical	Urgent
Extended-spectrum $\beta$ -lactamase <i>Enterobacteriaceae</i> (ESBL)	Critical	Serious
Multidrug-resistant <i>Acinetobacter</i> spp. (including <i>A. baumannii</i> )	Critical	Serious
Multidrug-resistant <i>Pseudomonas aeruginosa</i>	Critical	Serious
<i>Neisseria gonorrhoeae</i>	High	Urgent
Drug-resistant <i>Campylobacter</i> spp.	High	Serious
Vancomycin-resistant <i>Enterococcus</i> (VRE) ( <i>E. faecalis</i> & <i>E. faecium</i> )	High	Serious
Drug-resistant <i>Salmonella</i> spp. (including non-typhoidella <i>Salmonella enterica</i> & <i>Salmonella enterica</i> sero-type Typhimurium)	High	Serious
Drug-resistant <i>Staphylococcus aureus</i> (methicillin-resistant <i>S. aureus</i> & vancomycin-resistant <i>S. aureus</i> )	High	Serious / Concerning
Clarithromycin-resistant <i>Helicobacter pylori</i>	High	
Drug-resistant <i>Shigella</i> spp.	Medium	Serious
Drug-resistant <i>Streptococcus pneumoniae</i>	Medium	Serious
Ampicillin-resistant <i>Haemophilus influenzae</i> type b (Hib)	Medium	
Drug-resistant <i>Mycobacterium tuberculosis</i>	WHO AMR priority area	Serious
<i>Clostridium difficile</i>		Urgent
Erythromycin-resistant group A <i>Streptococcus</i>		Concerning
Clindamycin-resistant group B <i>Streptococcus</i>		Concerning
<b>VIRUSES</b>		
Human immunodeficiency virus (HIV)	WHO AMR priority area	
<b>PROTOZOA</b>		
Multidrug-resistant <i>Plasmodium falciparum</i>	WHO AMR priority area	
<b>FUNGI</b>		
Fluconazole-resistant <i>Candida</i> spp.		Serious

1. WHO. (2017). Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Retrieved from [http://www.who.int/medicines/areas/rational\\_use/antibacterial\\_agents\\_clinical\\_development/en/](http://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/)

2. U.S. Centers for Disease Control and Prevention (CDC). (April, 2013). Antibiotic resistance threats in the United States, 2013. Retrieved from <http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf>

## APPENDIX III

## Products for access

Only anti-infective medicines on the WHO Model List of Essential Medicines 2017 (EML), Section 6, are in scope for indicators C.2 and C.3. They are deemed essential by WHO to the basic functioning of any health system. Access to these medicines, particularly in low- and middle-income countries, must be considered alongside to curb AMR.

## WHO MODEL LIST OF ESSENTIAL MEDICINES (MARCH 2017). SECTION 6. ANTI-INFECTIVE MEDICINES.

## 6.1 ANTHELMINTHICS

albendazole	Tablet: (chewable): 400 mg
ivermectin	Tablet: (scored): 3 mg
levamisole	Tablet: 50 mg; 150 mg (as hydrochloride)
mebendazole	Tablet (chewable): 100 mg; 500 mg
niclosamide	Tablet (chewable): 500 mg
praziquantel	Tablet: 150 mg; 600 mg
pyrantel	Oral liquid: 50 mg (as embonate or pamoate)/mL Tablet (chewable): 250 mg (as embonate or pamoate)
diethylcarbamazine	Tablet: 50 mg; 100 mg (dihydrogen citrate)
triclabendazole	Tablet: 250 mg
oxamniquine	Capsule: 250 mg Oral liquid: 250 mg/5 mL

## 6.2 ANTIBACTERIAL MEDICINES

amikacin	Injection: 250 mg (as sulfate)/mL in 2-mL vial Powder for injection: 100 mg; 500 mg; 1 g (as sulfate) in vial
amoxicillin	Powder for oral liquid: 125 mg (as trihydrate)/5 mL; 250 mg (as trihydrate)/5 mL Solid oral dosage form: 250 mg; 500 mg (as trihydrate) Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial
amoxicillin + clavulanic acid	Oral liquid: 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL; 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt) Powder for injection: 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial
ampicillin	Powder for injection: 500 mg; 1 g (as sodium salt) in vial
azithromycin	Capsule: 250 mg; 500 mg (anhydrous) Oral liquid: 200 mg/5 mL
aztreonam	Powder for injection: 1 g; 2 g in vial
bedaquiline	Tablet: 100 mg
benzathine benzylpenicillin	Powder for injection: 900 mg benzylpenicillin (= 1.2 million IU) in 5-mL vial; 1.44 g benzylpenicillin (= 2.4 million IU) in 5-mL vial
benzylpenicillin	Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial
capreomycin	Powder for injection: 1 g (as sulfate) in vial
cefalexin	Powder for reconstitution with water: 125 mg/5 mL; 250 mg/5 mL (anhydrous) Solid oral dosage form: 250 mg (as monohydrate)
cefazolin	Powder for injection: 1 g (as sodium salt) in vial
cefixime	Capsule or tablet: 200 mg; 400 mg (as trihydrate) Powder for oral liquid: 100 mg/5 mL
cefotaxime	Powder for injection: 250 mg per vial (as sodium salt)
ceftazidime	Powder for injection: 250 mg or 1 g (as pentahydrate) in vial
ceftriaxone	Powder for injection: 250 mg; 1 g (as sodium salt) in vial
chloramphenicol	Capsule: 250 mg Oily suspension for injection: 0.5 g (as sodium succinate)/mL in 2-mL ampoule Oral liquid: 150 mg (as palmitate)/5 mL Powder for injection: 1 g (sodium succinate) in vial

<b>ciprofloxacin</b>	Oral liquid: 250 mg/5 mL (anhydrous) Solution for IV infusion: 2 mg/mL (as hyclate) Tablet: 250 mg (as hydrochloride)
<b>clarithromycin</b>	Solid oral dosage form: 500 mg Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL Powder for injection: 500 mg in vial
<b>clindamycin</b>	Capsule: 150 mg (as hydrochloride) Injection: 150 mg (as phosphate)/mL Oral liquid: 75 mg/5 mL (as palmitate)
<b>clofazimine</b>	Capsule: 50 mg; 100 mg.
<b>cloxacillin</b> □	Capsule: 500 mg; 1 g (as sodium salt) Powder for injection: 500 mg (as sodium salt) in vial Powder for oral liquid: 125 mg (as sodium salt)/5 mL
<b>cycloserine</b>	Solid oral dosage form: 250 mg
<b>dapsone</b>	Tablet: 25 mg; 50 mg; 100 mg
<b>daptomycin</b>	Powder for injection: 350 mg; 500 mg in vial
<b>delamanid</b>	Tablet: 50 mg
<b>doxycycline</b>	Oral liquid: 25 mg/5 mL; 50 mg/5 mL (anhydrous) Solid oral dosage form: 50 mg; 100 mg (as hyclate) Powder for injection: 100 mg in vial Tablet (dispersible): 100 mg (as monohydrate)
<b>ethambutol</b>	Oral liquid: 25 mg/mL Tablet: 100 mg to 400 mg (hydrochloride)
<b>ethambutol + isoniazid</b>	Tablet: 400 mg + 150 mg
<b>ethambutol + isoniazid + pyrazinamide + rifampicin</b>	Tablet: 275 mg + 75 mg + 400 mg + 150 mg
<b>ethambutol + isoniazid + rifampicin</b>	Tablet: 275 mg + 75 mg + 150 mg
<b>ethionamide</b>	Tablet: 125 mg; 250 mg
<b>fifth-generation cephalosporins</b> (with or without beta-lactamase inhibitor) e.g., ceftaroline	Powder for injection: 400 mg; 600 mg (as fosamil) in vial
<b>fosfomycin</b>	Powder for injection: 2 g; 4 g (as sodium) in vial
<b>fourth-generation cephalosporins</b> (with or without beta-lactamase inhibitor) e.g., cefepime	Powder for injection: 500 mg; 1g; 2g (as hydrochloride) in vial
<b>gentamicin</b>	Injection: 10 mg; 40 mg (as sulfate)/ mL in 2-mL vial
<b>isoniazid</b>	Oral liquid: 50 mg/5 mL Tablet: 100 mg to 300 mg Tablet (scored): 50 mg
<b>isoniazid + pyrazinamide + rifampicin</b>	Tablet: 75 mg + 400 mg + 150 mg; 150 mg + 500 mg + 150 mg Tablet (dispersible): 50 mg + 150 mg + 75 mg
<b>isoniazid + rifampicin</b>	Tablet: 75 mg + 150 mg; 150 mg + 300 mg; 60 mg + 60 mg; 150 mg + 150 mg Tablet (dispersible): 50 mg + 75 mg
<b>kanamycin</b>	Powder for injection: 1 g (as sulfate) in vial
<b>levofloxacin</b>	Tablet: 250mg; 500 mg; 750 mg
<b>linezolid</b>	Injection for intravenous administration: 2 mg/mL in 300 mL bag Powder for oral liquid: 100 mg/5 mL Tablet: 400 mg; 600 mg
<b>meropenem</b>	Powder for injection: 500 mg (as trihydrate); 1 g (as trihydrate) in vial
<b>metronidazole</b>	Injection: 500 mg in 100-mL vial Oral liquid: 200 mg (as benzoate)/5 mL Suppository: 500 mg; 1 g Tablet: 200 mg to 500 mg
<b>moxifloxacin</b>	Tablet: 400 mg
<b>nitrofurantoin</b>	Oral liquid: 25 mg/5 mL Tablet: 100 mg
<b>oxazolidinones</b> e.g., linezolid	Injection for intravenous administration: 2 mg/mL in 300 mL bag Powder for oral liquid: 100 mg/5 mL Tablet: 400 mg; 600 mg
<b>p-aminosalicylic acid</b>	Granules: 4 g in sachet Tablet: 500 mg
<b>phenoxymethylpenicillin</b>	Powder for oral liquid: 250 mg (as potassium salt)/5 mL Tablet: 250 mg (as potassium salt)
<b>piperacillin + tazobactam</b>	Powder for injection: 2 g (as sodium salt) + 250 mg (as sodium salt); 4 g (as sodium salt) + 500 mg (as sodium salt) in vial
<b>polymyxins</b> e.g., colistin	Powder for injection: 1 million IU (as colistimethate sodium) in vial
<b>procaine benzylpenicillin</b>	Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial

□ Primarily intended to indicate similar clinical performance within a pharmacological class.

<b>pyrazinamide</b>	Oral liquid: 30 mg/mL Tablet: 400 mg Tablet (dispersible): 150 mg Tablet (scored): 150 mg
<b>rifabutin</b>	Capsule: 150 mg
<b>rifampicin</b>	Solid oral dosage form: 150 mg; 300 mg Oral liquid: 20 mg/mL
<b>rifapentine</b>	Tablet: 150 mg
<b>spectinomycin</b>	Powder for injection: 2 g (as hydrochloride) in vial
<b>streptomycin</b>	Powder for injection: 1 g (as sulfate) in vial
<b>sulfamethoxazole + trimethoprim</b>	Injection: 80 mg + 16 mg/mL in 5-mL ampoule; 80 mg + 16 mg/mL in 10-mL ampoule Oral liquid: 200 mg + 40 mg/5 mL Tablet: 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg
<b>tigecycline</b>	Powder for injection: 50 mg in vial
<b>vancomycin</b>	Capsule: 125 mg; 250 mg (as hydrochloride) Powder for injection: 250 mg (as hydrochloride) in vial

### 6.3 ANTIFUNGAL MEDICINES

<b>amphotericin B</b>	Powder for injection: 50 mg in vial (as sodium deoxycholate or liposomal complex)
<b>clotrimazole</b>	Vaginal cream: 1%; 10% Vaginal tablet: 100 mg; 500 mg
<b>fluconazole</b>	Capsule: 50 mg Injection: 2 mg/mL in vial Oral liquid: 50 mg/5 mL
<b>flucytosine</b>	Capsule: 250 mg Infusion: 2.5 g in 250 mL
<b>griseofulvin</b>	Oral liquid: 125 mg/5 mL Solid oral dosage form: 125 mg; 250 mg
<b>itraconazole</b>	Capsule: 100 mg Oral liquid: 10 mg/mL
<b>nystatin</b>	Lozenge: 100,000 IU Oral liquid: 50 mg/5 mL; 100,000 IU/mL Pessary: 100,000 IU Tablet: 100,000 IU; 500,000 IU
<b>potassium iodide</b>	Saturated solution
<b>voriconazole</b>	Tablet: 50 mg; 200 mg Powder for injection: 200 mg in vial Powder for oral liquid: 40 mg/mL

### 6.4 ANTIVIRAL MEDICINES

<b>abacavir</b>	Tablet: 300 mg (as sulfate) Tablet (dispersible, scored): 60 mg (as sulfate)
<b>abacavir + lamivudine</b>	Tablet (dispersible, scored): 600 mg (as sulfate) + 300 mg*; 60 mg (as sulfate) + 30 mg; 120 mg (as sulfate) + 60 mg
<b>aciclovir</b> □	Oral liquid: 200 mg/5 mL Powder for injection: 250 mg (as sodium salt) in vial Tablet: 200 mg
<b>atazanavir</b>	Solid oral dosage form: 100 mg; 300 mg (as sulfate)
<b>atazanavir + ritonavir</b>	Tablet (heat stable): 300 mg (as sulfate) + 100 mg
<b>daclatasvir</b>	Tablet: 30 mg; 60 mg (as hydrochloride)
<b>darunavir</b>	Tablet: 75 mg; 400 mg; 600 mg; 800 mg
<b>dasabuvir</b>	Tablet: 250 mg
<b>dolutegravir</b>	Tablet: 50 mg
<b>efavirenz</b>	Tablet: 200 mg (scored); 600 mg
<b>efavirenz + emtricitabine + tenofovir</b>	Tablet: 600 mg + 200 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil)
<b>efavirenz + lamivudine + tenofovir</b>	Tablet: 400 mg + 300 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil)
<b>emtricitabine + tenofovir</b>	Tablet: 200 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil)
<b>entecavir</b>	Oral liquid: 0.05 mg/mL Tablet: 0.5 mg; 1 mg

□ Primarily intended to indicate similar clinical performance within a pharmacological class.

\* Corrected based on page 153 of 'Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access Recommendations for a public health approach' 2010 revision and page 15 of 'The Selection and Use of Essential Medicines' Report of the WHO Expert Committee, 2013.

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	Tablet (scored): 300 mg + 25 mg + 800 mg + 160 mg
lamivudine	Oral liquid: 50 mg/5 mL Tablet: 150 mg
lamivudine + nevirapine + zidovudine	Tablet: 30 mg + 50 mg + 60 mg; 150 mg + 200 mg + 300 mg
lamivudine + zidovudine	Tablet: 30 mg + 60 mg; 150 mg + 300 mg
ledipasvir + sofosbuvir	Tablet: 90 mg + 400 mg
lopinavir + ritonavir	Oral liquid: 400 mg + 100 mg/5 mL Tablet (heat stable): 100 mg + 25 mg; 200 mg + 50 mg Capsule containing oral pellets: 40 mg + 10 mg
nevirapine	Oral liquid: 50 mg/5 mL Tablet: 50 mg (dispersible); 200 mg
ombitasvir + paritaprevir + ritonavir	Tablet: 12.5 mg + 75 mg + 50 mg
oseltamivir	Capsule: 30 mg; 45 mg; 75 mg (as phosphate) Oral powder: 12 mg/mL
pegylated interferon alfa (2a or 2b)	Vial or prefilled syringe: 180 micrograms (peginterferon alfa-2a); 80 microgram, 100 microgram (peginterferon alfa-2b)
raltegravir	Tablet (chewable): 25 mg; 100 mg Tablet: 400 mg
ribavirin	Injection for intravenous administration: 800 mg and 1 g in 10-mL phosphate buffer solution Solid oral dosage form: 200 mg; 400 mg; 600 mg
ritonavir	Oral liquid: 400 mg/5 mL Tablet (heat stable): 25 mg; 100 mg
simeprevir	Capsule: 150 mg
sofosbuvir	Tablet: 400 mg
sofosbuvir + velpatasvir	Tablet: 400 mg + 100 mg
tenofovir disoproxil fumarate	Tablet: 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)
valganciclovir	Tablet: 450 mg Powder for oral solution: 50 mg/mL
zidovudine	Capsule: 250 mg Oral liquid: 50 mg/5 mL Solution for IV infusion injection: 10 mg/mL in 20-mL vial Tablet: 300 mg Tablet (dispersible, scored): 60 mg (as sulfate)

## 6.5 ANTIPROTOZOAL MEDICINES

amodiaquine	Tablet: 153 mg or 200 mg (as hydrochloride)
amphotericin B	Powder for injection: 50 mg in vial (as sodium deoxycholate or liposomal complex)
artemether	Oily injection: 80 mg/mL in 1-mL ampoule
artemether + lumefantrine	Tablet: 20 mg + 120 mg Tablet (dispersible): 20 mg + 120 mg
artesunate	Injection: ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria Rectal dosage form: 50 mg; 100 mg; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care) Tablet: 50 mg
artesunate + amodiaquine	Tablet: 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg
artesunate + mefloquine	Tablet: 25 mg + 55 mg; 100 mg + 220 mg
artesunate + pyronaridine tetraphosphate	Tablet: 60 mg + 180 mg Granules: 20 mg + 60 mg
benznidazole	Tablet: 12.5 mg; 100 mg Tablet (scored): 50 mg
chloroquine	Oral liquid: 50 mg (as phosphate or sulfate)/5 mL Tablet: 100 mg; 150 mg (as phosphate or sulfate)
dihydroartemisinin + piperaquine phosphate	Tablet: 20 mg + 160 mg; 40 mg + 320 mg
diloxanide	Tablet: 500 mg (furoate)
doxycycline	Capsule: 100 mg (as hydrochloride or hyclate) Tablet (dispersible): 100 mg (as monohydrate)
eflornithine	Injection: 200 mg (hydrochloride)/ mL in 100-mL bottle
mefloquine	Tablet: 250 mg (as hydrochloride)
melarsoprol	Injection: 3.6% solution, 5-mL ampoule (180 mg of active compound)

□ Primarily intended to indicate similar clinical performance within a pharmacological class.

metronidazole □	Injection: 500 mg in 100-mL vial Oral liquid: 200 mg (as benzoate)/5 mL Tablet: 200 mg to 500 mg
miltefosine	Solid oral dosage form: 10 mg; 50 mg
nifurtimox	Tablet: 30 mg; 120 mg; 250 mg
paromomycin	Solution for intramuscular injection: 750 mg of paromomycin base (as the sulfate)
pentamidine	Tablet: 200 mg; 300 mg (as isethionate) Powder for injection: 200 mg (as isethionate) in vial
primaquine	Tablet: 7.5 mg; 15 mg (as diphosphate)
proguanil	Tablet: 100 mg (as hydrochloride)
pyrimethamine	Tablet: 25 mg
quinine	Injection: 300 mg quinine hydrochloride/mL in 2-mL ampoule Tablet: 300 mg (quinine sulfate) or 300 mg (quinine bisulfate)
sodium stibogluconate or meglumine antimoniate	Injection: 100 mg/mL, 1 vial = 30 mL or 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5-mL ampoule
sulfadiazine	Tablet: 500 mg
sulfadoxine + pyrimethamine	Tablet: 500 mg + 25 mg
sulfamethoxazole + trimethoprim	Injection: 80 mg + 16 mg/mL in 5-mL ampoule; 80 mg + 16 mg/mL in 10-mL ampoule Oral liquid: 200 mg + 40 mg/5 mL Tablet: 100 mg + 20 mg; 400 mg + 80 mg
suramin sodium	Powder for injection: 1 g in vial

## MEDICINES IN SCOPE, IN ADDITION TO 2017 WHO MODEL LIST OF ESSENTIAL MEDICINES <sup>1,2</sup>

I. The WHO Model List of Essential Medicines incorporates 'fourth generation cephalosporins (with or without beta-lactamase inhibitor)' and 'fifth generation cephalosporins (with or without beta-lactamase inhibitor)'. Based on the examples listed on the 2017 Model List of Essential Medicines, ceftaroline and cefepime, and using the Anatomical Therapeutic Chemical (ATC) Classification system by WHO the following cephalosporins were evaluated as if on the WHO Model List of Essential Medicines:

Product	ATC class
ceftaroline	J01DI
ceftobiprole	J01DI
ceftolozane + tazobactam	J01DI
cefepime	J01DE
cefpime	J01DE
cefpirome	J01DE
cefazopran	J01DE

II. The WHO Model List of Essential Medicines incorporates square box symbols (□) to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. Based on the examples listed on the Model List of Essential Medicines and using the Anatomical Therapeutic Chemical (ATC) Classification system by WHO, the following antimicrobial medicines, that are not specifically mentioned on the Model List of Essential Medicines, were evaluated as if on the WHO Model List of Essential Medicines.

Product	ATC class	Corresponding product with □
idoxuridine	J05AB	aciclovir
vidarabine	J05AB	aciclovir
ganciclovir	J05AB	aciclovir
famciclovir	J05AB	aciclovir
valaciclovir	J05AB	aciclovir
cidofovir	J05AB	aciclovir
penciclovir	J05AB	aciclovir
brivudine	J05AB	aciclovir
dicloxacillin	J01CF	cloxacillin
meticillin	J01CF	cloxacillin
oxacillin	J01CF	cloxacillin
flucloxacillin	J01CF	cloxacillin
nafticillin	J01CF	cloxacillin
tinidazole	P01AB	metronidazole
ornidazole	P01AB	metronidazole
azanidazole	P01AB	metronidazole
propenidazole	P01AB	metronidazole
nimorazole	P01AB	metronidazole
secnidazole	P01AB	metronidazole

1 WHO. (March, 2017). WHO Model List of Essential Medicines, 20th List. Retrieved from <http://www.who.int/medicines/publications/essentialmedicines/en/>

2 WHO. (March, 2017). WHO Model List of Essential Medicines for Children, 6th List. Retrieved from <http://www.who.int/medicines/publications/essentialmedicines/en/>

## APPENDIX IV

## Countries for access

The challenges of sufficient access and affordability are significantly higher in poorer countries. Access indicators (A.4, C.1, C.2, C.3) measure how companies address access in 106 low- and middle-income countries. This group has been

defined using three criteria: (1) countries' level of income (GNI per capita); (2) their levels of development; and (3) the scope and scale of inequality in each country. These assessments are based on data from the World Bank, the United

Nations Development Programme (UNDP), and the United Nations Economic and Social Council (ECOSOC).<sup>1,2,3</sup> This is the same geographic scope as used by the 2018 Access to Medicine Index.

**EAST ASIA & PACIFIC**

Cambodia	LMIC
China	HiHDI
Indonesia	LMIC
Kiribati	LMIC
Korea, Dem. Rep.	LIC
Lao PDR	LMIC
Micronesia, Fed. Sts.	LMIC
Mongolia	LMIC
Myanmar	LMIC
Papua New Guinea	LMIC
Philippines	LMIC
Samoa	LMIC
Solomon Islands	LMIC
Thailand	HiHDI
Timor-Leste	LMIC
Tonga	LMIC
Tuvalu	LDC
Vanuatu	LMIC
Vietnam	LMIC

**EUROPE & CENTRAL ASIA**

Armenia	LMIC
Kosovo	LMIC
Kyrgyz Rep.	LMIC
Moldova	LMIC
Tajikistan	LMIC
Turkmenistan	MHDC
Ukraine	LMIC
Uzbekistan	LMIC

**LATIN AMERICA & CARIBBEAN**

Belize	HiHDI
Bolivia	LMIC
Brazil	HiHDI
Colombia	HiHDI
Dominican Rep.	HiHDI
Ecuador	HiHDI
El Salvador	LMIC

Guatemala	LMIC
Guyana	MHDC
Haiti	LIC
Honduras	LMIC
Mexico	HiHDI
Nicaragua	LMIC
Paraguay	MHDC
Peru	HiHDI
Suriname	HiHDI

**MIDDLE EAST & NORTH AFRICA**

Djibouti	LMIC
Egypt, Arab Rep.	LMIC
Iran, Islamic Rep.	HiHDI
Iraq	MHDC
Morocco	LMIC
Palestine, State	LMIC
Syrian Arab Rep.	LMIC
Tunisia	LMIC
Yemen, Rep.	LMIC

**SOUTH ASIA**

Afghanistan	LIC
Bangladesh	LMIC
Bhutan	LMIC
India	LMIC
Maldives	HiHDI
Nepal	LIC
Pakistan	LMIC
Sri Lanka	LMIC

**SUB-SAHARAN AFRICA**

Angola	LHDC
Benin	LIC
Botswana	MHDC
Burkina Faso	LIC
Burundi	LIC
Cameroon	LMIC
Cape Verde	LMIC

Central African Rep.	LIC
Chad	LIC
Comoros	LIC
Congo, Dem. Rep.	LIC
Congo, Rep.	LMIC
Côte d'Ivoire	LMIC
Equatorial Guinea	MHDC
Eritrea	LIC
Ethiopia	LIC
Gabon	MHDC
Gambia, The	LIC
Ghana	LMIC
Guinea	LIC
Guinea-Bissau	LIC
Kenya	LMIC
Lesotho	LMIC
Liberia	LIC
Madagascar	LIC
Malawi	LIC
Mali	LIC
Mauritania	LMIC
Mozambique	LIC
Namibia	MHDC
Niger	LIC
Nigeria	LMIC
Rwanda	LIC
São Tomé and Príncipe	LMIC
Senegal	LIC
Sierra Leone	LIC
Somalia	LIC
South Africa	MHDC
South Sudan	LIC
Sudan	LMIC
Swaziland	LMIC
Tanzania	LIC
Togo	LIC
Uganda	LIC
Zambia	LMIC
Zimbabwe	LIC

**Table legend**

LIC: Low-income country (*World Bank income classifications*)

LMIC: Lower middle-income country (*World Bank income classifications*)

LDC: Least Developed Country (*UN Human Development Index*)

LHDC: Low Human Development Country (*UN Human Development Index*)

MHDC: Medium Human Development (Country *UN Human Development Index*)

HiHDI: High Human Development Country with high inequality (*UN Inequality-adjusted Human Development Index*)

1 World Bank Country and Lending Groups [Online].

Retrieved 15 June 2017 from <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519>

2 United Nations Development Programme. (2016). Global Human Development Report 2016. New York, NY.

3 United Nations Committee for Development Policy. (June, 2017). List of Least Developed Countries (as of June 2017). Retrieved from [https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/publication/ldc\\_list.pdf](https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/publication/ldc_list.pdf)

## APPENDIX V

# Analysis, scoring and review process

## PROCESS FOR ANTIMICROBIAL PORTFOLIO ANALYSIS

The Benchmark requested companies to provide data on their antimicrobial portfolio for analysis. Companies were required to list each of their antimicrobial products' International Non-proprietary Name (INN), brand name(s), primary indication(s), formulation(s), dose(s) and route(s) of administration. They were also asked to indicate whether or not the product was listed on Section 6 of the WHO Model List of Essential Medicines (EML).

This request to companies was accompanied by a pre-populated database of marketed antimicrobial medicines which the research team collected from one or more publicly available, company-specific sources. The company was asked to verify the database and include additional necessary information.

All products on the market as of 8 September 2017 (when the data collection period ended) were eligible for inclusion in the descriptive analysis of the antimicrobial portfolio. The research team verified whether R&D projects included for analysis in the R&D Research Area were approved between the date of submission and the end of data collection. If so, the product was included in the company's portfolio. However, R&D projects with market approval dates between 8 September 2017 and 31 October 2017 (the time period during which the status of R&D projects was monitored by the Benchmark) were not added to the company's portfolio.

In some cases, companies did not submit their entire antimicrobial portfolio during the data collection period. Products not submitted may include products with different INNs as well as products with the same INN but marketed under different brand names (e.g. in different countries/regions). For companies that did not participate in the Benchmark's survey, the initially pre-populated database was used for all descriptive portfolio analyses.

To ensure products were within scope and eligible for analysis – i.e. antimicrobial medicines for human use, both systemic and topical, but not vaccines – and that there were no duplicate products within a company's submission, the research team reviewed and validated companies' submitted portfolios. For analyses at the individual company level, product data was aggregated at the INN level, since these were used to showcase the different active antimicrobial ingredients that the company marketed (formulations, doses, routes of administration or brand names were not differentiated). INN-level aggregation was performed both in the case of products with a single INN and fixed-

dose combinations (FDCs) composed of two or more single-INN elements – therefore, two FDCs containing, e.g., the same single-INN components but with different doses in one or more of the components, were considered equivalent and aggregated. The Benchmark also considered that different salts of the same single-INN product or FDC component (e.g. tenofovir disoproxil and tenofovir disoproxil fumarate, or chloramphenicol palmitate and chloramphenicol as sodium succinate) were considered equivalent and aggregated. On the other hand, product modifications that resulted in significantly different chemical/pharmaceutical properties were considered non-equivalent to the original product (examples include benzathine benzylpenicillin, benzathine phenoxymethylpenicillin and tenofovir disoproxil alafenamide, relative to benzylpenicillin, to phenoxymethylpenicillin and to tenofovir disoproxil fumarate, respectively). The Benchmark also considered that combination products differing only in components that are not antimicrobials (e.g. oxytetracycline and the combination hydrocortisone/oxytetracycline) were equivalent and hence aggregated. Lastly, co-packaging of two products already marketed by a company (single-INN or FDC) did not count as an additional product. For the analysis combining companies' portfolios (in the Portfolio Analysis section of this report) no further data aggregation took place, meaning a product with a given INN, marketed by more than one company, was counted as many times as the number of companies that market it. The purpose of this was to provide an overview of the antimicrobial medicines market.

Information regarding whether or not the product was listed on WHO EML (Section 6) was also verified by the research team. Antimicrobial medicines were determined as being on the WHO EML (Section 6) if they fulfilled any of the following four criteria: (a) appeared directly on the list; (b) were part of a pharmacological class appearing directly on the list (e.g. fourth-generation cephalosporins or oxazolidinones); (c) were in the same pharmacological class as a medicine listed on the WHO EML (Section 6) with a square box (i.e. the antibacterial cloxacillin, the antiviral aciclovir and the antiprotozoal metronidazole); (d) were listed on the WHO EML (Section 6) as an alternative to another directly listed medicine (e.g. imipenem/cilastatin as alternative to meropenem). The dose, formulation and route of administration of the medicine was taken into consideration for points (a) and (b) only.

Antimicrobial medicines were further classified into five antimicrobial categories: anthelmintic; antibacterial; antifungal; antiprotozoal and antiviral. These are the categories used to

group anti-infective medicines in the WHO EML (Section 6). For products already listed on the WHO EML (Section 6), the classification was exclusively based on this list, whereas for products not on the WHO EML (Section 6) the classification was based on the product's pharmacological properties and clinical indications. Products that fell into more than one of the five categories above were counted in all relevant categories. Within the five categories, products were further classified into subcategories. Products that fell into more than one subcategory were counted in a separate 'multiple categories' subcategory.

The research team also analysed whether antibacterial medicines (antibiotics) listed on the WHO EML (Section 6) were part of the EML Access, Watch or Reserve groups. The Watch and Reserve groups include antibiotics and antibiotic classes that should be priority targets of local, national and global stewardship activities. These groups also include antibiotics that are not part of the WHO EML, for example, norfloxacin (a fluoroquinolone) or teicoplanin (a glycopeptide). Only antibiotics listed on the WHO EML (Section 6) were assigned to these groups.

## SUMMARY OF THE SCORING PROCESS

Companies were assessed and scored by the Benchmark in three Research Areas: Research and Development, Manufacturing and Production and Appropriate Access and Stewardship, with each area composed of several indicators. Due to the variation between companies in scope, not all indicators were applicable to every company, as shown in the Indicators and Scoring Eligibility table in this Appendix.

The Benchmark included ongoing/active projects up until 8 September 2017 (when the data collection period ended), with two exceptions: (1) for R&D indicators, the status of R&D projects included for analysis was monitored between 8 September 2017 and 31 October 2017 (for termination or changes in clinical phase); all R&D projects had to be ongoing, approved or awaiting approval on 31 October 2017; however, no additional R&D projects were included for analysis after 8 September 2017; (2) for stewardship indicators, such as C.4 and C.7, programmes active at some point during the period of analysis were included, regardless of their ending date. Financial data from fiscal year 2016 was used for analysis (the exact date marking the fiscal year end varies among companies).

### Data review

Companies were asked to verify the accuracy of publicly sourced data and to provide additional necessary information. Prior to analysis, the Benchmark team reviewed companies' submissions for each of the Research Areas:

**Research & Development:** R&D projects consisting of antimicrobial medicines and vaccines were included for the overall pipeline. R&D projects eligible for scoring had to target at least one of the pre-defined priority pathogens (see Appendix II). R&D projects were classified as new or adaptive. Adaptive R&D projects do not involve a new chemical or biological entity (NCE or NBE); new R&D projects involve either an NCE or NBE. New medicines in clinical development were further classified as novel when they fulfilled one or more of the following criteria, defined by WHO in its 2017 analysis of the antibacterial clinical development pipeline<sup>1</sup>: (a) it represents a new chemical class; (b) it aims at a new target; (c) it has a new mode of action; (d) it displays no cross-resistance from existing antimicrobials. After final submission and any necessary clarifications with the companies, all R&D projects were evaluated according to this standardised procedure.

**Manufacturing & Production:** the Benchmark requested companies to share their policies on the manufacturing of antibiotics. For transparency indicator B.2, the research team reviewed companies' public information on, e.g., corporate websites, annual reports and corporate social responsibility reports.

**Appropriate Access & Stewardship:** the Benchmark requested companies to share their access and stewardship policies for antibiotics. For indicators on access to medicine, companies were requested to disclose their five newest antibiotics, and their five highest-volume antibiotics and non-antibiotic antimicrobial medicines listed on the WHO EML (Section 6) (see Appendix III). Companies' policies and strategies for these medicines were then analysed in the various access-related indicators. For stewardship-related indicators, companies were asked to disclose: (a) product-specific strategies regarding appropriate promotion practices and brochure and packaging adaptations related to their five top-selling antibiotics; (b) non-product specific strategies regarding educational and surveillance activities and over-the-counter sales control.

### Scoring

All indicators were scored from zero to five and weighted equally. When scoring a company on a quantitative indicator, such as financial investments or R&D pipeline size, the corresponding number was first scaled across all companies in scope for relative scoring. This number was then used to determine scoring tiers from zero to five (with possibly non-uniform intervals).

When a given indicator was not applicable to a company, the company's maximum attainable score in the corresponding Research Area was decreased by an amount equal to the number of maximum points attainable in that indicator.

Scoring was carried out based on data from a wide range of information sources including companies themselves, independent reports and databases or documents from the WHO, other multilateral organizations and Non-Governmental Organisations. For analysis and scoring of R&D projects, the Benchmark also reached out, where necessary, to external experts and, in the case of projects developed in collaboration with other partners, to the latter. For currency conversion to USD, exchange rates on the website x-rates.com were used.

Final scoring of the companies was the result of a multi-tiered analysis and quality assurance process. The quality assurance process included both systematic verification of scoring consistency and spot-checking. For each indicator, preliminary scoring results were used to make adjustments in scoring guidelines to ensure maximum variability of final results. These preliminary results also led to the identification of a widespread lack of data in companies' submissions for indicator C.8 in the AA&S Research Area – this indicator was subsequently removed from analysis.

### Review process

Following clarification and cross-check of company scores, the research team wrote the various sections of the Benchmark report. Each Research Area was reviewed by two externally appointed expert advisors. In addition to this, an external editorial review of the Benchmark report was performed.

### METHODOLOGY DEVELOPMENT

To develop the methodology for the 2018 Antimicrobial Resistance Benchmark, the Foundation applied its proven process for building consensus on the role of pharmaceutical companies in tackling global health priorities. Strategic guidance was provided by an Expert Committee for the Benchmark, an independent body of experts, from top-level academic centres, donor governments, local governments in low- and middle-income countries, investors and companies. The Expert Committee met in June 2017 to review proposals for the scope, structure and analytical approach of the Benchmark. Their recommendations helped identify ways forward where disagreement or uncertainty existed regarding areas of research.

The Expert Committee members:

Hans Hogerzeil (Chair)	University of Groningen
Greg Frank	Biotechnology Innovation Organization
Nina Grundmann	IFPMA
Magdalena Kettis	Nordea
Joakim Larsson	University of Gothenburg
Marc Mendelson	University of Cape Town
Katarina Nedog	Medicines for Europe
Evelina Tacconelli	University of Tübingen
Evelyn Wesangula	Ministry of Health, Kenya

### Stakeholders by group

Discussions were held with representatives of a wide range of organisations, a list of which can be found in the methodology report for the 2018 Antimicrobial Resistance Benchmark, available for download at [www.amrbenchmark.org](http://www.amrbenchmark.org).

1. WHO. (2017). Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Retrieved from [http://www.who.int/medicines/areas/rational\\_use/antibacterial\\_agents\\_clinical\\_development/en/](http://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/)

## INDICATORS AND SCORING ELIGIBILITY

Company	IN SCOPE FOR R&D						IN SCOPE FOR M&P			IN SCOPE FOR AA&S						
	A.1	A2.1	A2.2	A2.3	A.3	A.4	B.1	B.2	B.3	C.1	C.2	C.3	C.4	C.5	C.6	C.7
GSK	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Johnson & Johnson	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Merck & Co., Inc.	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Novartis	●	●	●	o*	●	●	●	●	●	●	●	●	●	●	●	●
Pfizer	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Roche	●	●	●	o*	●	o**	●	●	●	●	●	●	●	●	●	●
Sanofi	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Shionogi	●	●	●	o*	●	●	●	●	●	●	o***	o***	●	●	●	●
Aspen							●	●	●	●	●	●	●	●	●	●
Aurobindo							●	●	●	●	●	●	●	●	●	●
Cipla							●	●	●	●	●	●	●	●	●	●
Dr. Reddy's							●	●	●	●	●	●	●	●	●	●
Fresenius Kabi							●	●	●	●	●	●	●	●	o†	●
Lupin							●	●	●	●	●	●	●	●	●	●
Macleods							●	●	●	●	●	●	●	●	●	●
Mylan							●	●	●	●	●	●	●	●	●	●
Sun Pharma							●	●	●	●	●	●	●	●	●	●
Teva							●	●	●	●	●	●	●	●	●	●
Achaogen		●	●		●	●										
Cempra		●	●		●	●										
Entasis		●	●		●	●										
Melinta		●	●		●	●										
MGB Biopharma		●	●		●	o**										
Motif Bio		●	●		●	●										
Nabriva		●	●		●	●										
Polyphor		●	●		●	●										
Summit		●	●		●	●										
Tetraphase		●	●		●	●										
The Medicines Company		●	●		●	●										
Wockhardt		●	●		●	●										

Large research-based pharmaceutical companies were eligible for scoring in every research area, with a few exceptions. Generic medicine manufacturers were eligible for scoring in the M&P and AA&S research areas but not in R&D, as their main focus is the manufacturing of generic products. Biopharmaceutical companies were eligible for scoring in the R&D

research area, with the exception of two sub-indicators: A.1, assessing financial investments, and A.2.3, assessing vaccines in the R&D pipeline. The latter was omitted because none of the biopharmaceutical companies assessed by the Benchmark were active in vaccine R&D, and the former because financial investments into antimicrobial R&D are not reflective of their efforts

in this area. Biopharmaceutical companies were not eligible for scoring in M&P and AA&S because they either did not have products on the market or had small sales volumes and were thus excluded in this iteration of the Benchmark. Any evaluation of access and stewardship plans for R&D projects was done in indicator A.4.

\* No marketed vaccines

\*\* No late-stage clinical projects (Phase II onwards, inc.) targeting priority pathogens

\*\*\* No marketed products in countries in scope

† The company's antimicrobial medicines are all administered in hospitals, not directly dispensed to patients.

## APPENDIX VI

# Limitations

In this section we cover the main limitations faced in the Benchmark. All limitations, methodological, process or otherwise will be reviewed by the Foundation when undertaking future Benchmarks.

## GENERAL METHODOLOGICAL LIMITATIONS

As in any survey, main limitations relate to coverage, sampling, non-responder and measurement biases. To the extent possible, the Benchmark research team strove to minimise the impact of these biases in the final results. On coverage and representativeness, we attempted to ensure that coverage of our survey represented as much as possible the wider antimicrobial industry players with relevant activities across the three Research Areas. The criteria used to select companies for the Benchmark is outlined in detail in our Methodology 2017. On responsiveness, we strove to minimise non-response rates by making at least three attempts to contact companies included in the Benchmark. Whenever necessary, the Benchmark offered companies personalised calls and/or on-site visits in order to improve understanding and usability of the questionnaire, reduce misinterpretation of questions and improve accuracy of reporting by companies.

## APPLICABILITY OF FINDINGS

### Disease and product scopes

The outputs analysed in this study and the findings generated from it relate only to the disease, and product scopes as outlined in the Antimicrobial Resistance Benchmark Methodology 2017. For this first iteration of the Benchmark, a broad infectious disease scope was chosen with specific focus on company activities for a list of priority pathogens as determined by the WHO and CDC for the R&D research area. For the Manufacturing and Production and Stewardship research areas, the focus through stakeholder and expert review committee consensus was to focus on company's initiatives and activities around antibiotics. The Access research area assessed more broadly antimicrobial activities of included companies.

### Company comparability

The results and findings of this Benchmark relate to a subset of companies especially in the generic and biotechnology industry. Within the biotechnology companies, our findings represent a specific subset of companies involved namely in the clinical development of medicines and vaccines targeting bacterial pathogens in an attempt to align our company selection with other international agencies active in this space

such as the Pew Charitable Trust findings<sup>1</sup>, our findings in this category of companies should therefore not be taken to be representative of all biotechnology companies involved in antimicrobial product development given the sheer volume of such small and medium sized companies coming onto the market in the development of infectious disease medicines and vaccines. Due to resource limitations, the Benchmark analysis could only focus on biotechnology companies targeting bacterial pathogens. Future iterations of the Benchmark may include a broader spectrum of pathogens.

Among the large research-based pharmaceutical companies and generic medicine manufacturers, companies were selected based on their antibiotics business volume, signatories to the Industry Roadmap on AMR or based on stakeholder recommendation and willingness to participate. The Benchmark findings on this category of companies should therefore be taken in this context.

Depending on the research area being analysed, different company types might be included in the analysis. For instance, within the R&D research area, indicators on the pipeline are applicable to both large research-based pharmaceutical companies and smaller biopharmaceutical companies. These are clearly very different company types with vastly different business models. In the Benchmark analysis, we corrected for these variations between company types, company size and company portfolio whenever relevant and possible. Further, the Benchmark provides key information about companies' antimicrobial business in several sections of the report, which readers should take into account as important context when interpreting the Benchmark findings.

Different factors may affect companies' capacity for reporting information. Some companies have submitted only a selection of their antimicrobial business to the Benchmark. Hence, the data presented in the "Portfolio Analysis" section of this report and on individual company report cards may not necessarily represent their entire portfolio. Different companies also use different nomenclature and have different ways of categorising information. For example, when calculating the value of antimicrobial R&D investments or revenue from antimicrobials sales, such disaggregated data might not be readily available. In an effort to minimise variability in interpretation and ensure data consistency, a glossary of definitions was published in the Benchmark Methodology 2017.

### Data Availability

The Foundation includes for the first time, two different categories of companies in its report-

ing: biopharmaceutical companies and generic medicine manufacturers. These companies were therefore not as familiar to the Foundation as the large research-based pharmaceutical companies with whom the Foundation has built a relationship over the last ten years. This may have affected these companies' extent of participation in this first round of the Benchmark, particularly in the case of generic medicine manufacturers, whose participation was relatively poor in comparison to other company types.

As in all survey and questionnaire methodologies, the data of the Benchmark is dependent on company submissions as the source data. In order to mitigate any reporting bias, every effort was made to triangulate company-submitted data by verifying it against public sources such as company annual reports, WHO reports and clinical trial websites. The comprehensiveness and level of detail available in public sources was thus a limiting factor in the analyses. In so far as possible, when triangulation was not possible, data was excluded from scoring. For example, in the R&D research area, only clinical stage products could be verified with publicly available data and then scored. Though not scored, preclinical and discovery stage projects were still included on the overall reporting in the Benchmark. Furthermore, some information was submitted by companies on the basis of confidentiality, thus making the Benchmark's ability to analyse and report conclusions across several indicators challenging.

<sup>1</sup>The PEW Charitable Trusts. (March, 2016). Antibiotics Currently in Clinical Development.

## APPENDIX VII

## Scoring guidelines

## A RESEARCH &amp; DEVELOPMENT

## A.1 R&amp;D INVESTMENTS

[New indicator text]

R&D investments (financial and in-kind) dedicated to the development of antimicrobial medicines and vaccines in the fiscal year 2016.

[Original indicator text]

Financial R&D investments dedicated to the development of antimicrobial medicines and vaccines. The denominator is a company's (i.e. research-based or generic) total revenue from its pharmaceutical and vaccine products. For biopharmaceutical companies, this is an absolute measurement.

[Explanation for change]

For this indicator, only large research-based pharmaceutical companies were scored. Investments were scored as absolute numbers, as this was sufficient to accurately capture a company's commitment to antimicrobial R&D.

- 5 The company reports investments of over USD 1 billion in the development of antimicrobial medicines and vaccines.
- 4 The company reports investments of USD 200 million to USD 1 billion in the development of antimicrobial medicines and vaccines.
- 1 The company has an antimicrobial R&D pipeline, but did not report on its investments.
- 0 There is no information that the company invests in the development of antimicrobial medicines and vaccines.

## A.2 R&amp;D PROJECTS

[Original indicator text]

Size of pipeline and public health value of its investigational antimicrobials and vaccines under development. Public health value is evaluated based on criteria such as targeting a priority pathogen and/or new mode of action.

[Explanation for change]

Following a review of the data, indicator A.2 (R&D projects) was divided into three sub-indicators to enable a more fine-grained comparison of companies' pipelines. The three sub-indicators focus on: pipeline size (A2.1), number of novel candidates in clinical development (A2.2) and number of vaccines in the pipeline (A2.3).

## A.2.1 Pipeline size

The size of a company's R&D pipeline targeting priority pathogens, including medicines, vaccines and adaptations (developed in-house or through collaborations).

- 5-1 The number of medicines and vaccines in development by a company that target priority pathogens. This number is scaled across all companies in the same company group and scored. Preclinical projects are awarded half the points of a clinical project.
- 0 The company has no relevant R&D activity within the scope of this indicator.

## A.2.2 Novelty of pipeline

The novelty of investigational clinical antimicrobial medicines targeting priority pathogens that the company is developing (in-house or through collaborations). A compound is considered novel when it meets at least one of the four criteria (as defined by WHO): a new chemical class; a new target; a new mode of action; and/or an absence of cross-resistance to existing antimicrobials.

- 5-1 The number of novel medicines in clinical development by a company that target priority pathogens. This number is scaled across all companies in the same company group and scored.
- 0 The company has new investigational antimicrobial medicines targeting priority pathogens in its pipeline, none of which are novel.

## A2.3 Vaccines in pipeline

The number of new vaccines that the company is developing for priority pathogens in scope (in-house or through collaborations).

- 5-1 The number of new vaccines in development by a company that target priority pathogens. This number is scaled across all companies in the same company group and scored. Preclinical projects are awarded half the points of a clinical project.
- 0 The company is engaged in vaccine development, but does not report on having new vaccines in development that target priority pathogens.
- NA The company is not engaged in vaccine development and has no relevant R&D activity within the scope of this indicator.

### A.3 R&D COLLABORATIONS

[New indicator text]

The company engages in open collaborations and public-private partnerships (PPP), such as Product Development Partnerships (PDPs), to overcome the scientific challenges of creating new antimicrobial medicines and vaccines targeting priority pathogens.

[Original indicator text]

The company engages in open collaborations to overcome the scientific challenges of creating new antimicrobial medicines and vaccines targeting priority pathogens.

[Explanation for change]

Following data collection, the completeness and quality of all data was reviewed and certain indicators refined. For this indicator, the scope of partnerships was broadened to public-private partnership.

- 5 The company engages in open collaborations and/or PDPs for the development of most of its projects (≥50%) in scope.
- 4 The company engages in open collaborations and/or PDPs for the development of 1-50% of its projects in scope.
- 3 The company does not engage in open collaborations and/or PDPs, but partners with NGOs and governments for the development of some of its projects in scope.
- 2 The company does not engage in open collaborations and/or PDPs, but partners with universities and/or public institutes for the development of some of its projects in scope.
- 0 The company does not engage in open collaborations or PPPs.

### A.4 ACCESS PROVISIONS

The proportion of late-stage antimicrobial R&D projects that target priority pathogens for which the company provides information on having 1) access provisions for the countries in scope, and 2) global stewardship provisions in place. Late-stage R&D includes projects from Phase II clinical development onwards (developed in-house or through collaborations). Access & stewardship provisions refer to plans for ensuring the future availability and affordability of new products in countries in scope, while also ensuring the future appropriate use of these products.

- 5 The company reports having access strategies in place for all its late-stage medicines and vaccines AND stewardship plans in place for all its late-stage medicines.
- 4 The company reports having access strategies in place for all its late-stage medicines and vaccines OR stewardship strategies in place for all its late-stage medicines.
- 3 The company reports having access strategies in place for some of its late-stage medicines and vaccines AND/OR stewardship strategies for some of its late-stage medicines.
- 2 The company reports having general commitments on access AND/OR stewardship in place for some of its late-stage medicines or vaccines.
- 1 The company reports having neither access nor stewardship provisions in place for any of its late-stage medicines or vaccines, but reports a commitment to it by having signed the Davos Declaration.
- 0 The company reports having neither access nor stewardship provisions in place for any of its late-stage medicines or vaccines.

## B MANUFACTURING & PRODUCTION

### B.1 ENVIRONMENTAL RISK MANAGEMENT STRATEGY

The company has an environmental risk-management strategy to minimise environmental impact of manufacturing discharge of antibiotics. This strategy: 1) applies to its own facilities, to third-party manufacturers of antibiotic API and drug products and to external waste-treatment plants; 2) includes auditing; and 3) includes discharge limits.

\*The 9 elements include: 1. Environmental risk-management strategy applicable to 1.1) own manufacturing sites, 1.2) third-party manufacturers of API and drug products, 1.3) external waste-treatment plants; 2. Audits performed on the implementation of its strategy at 2.1) own manufacturing sites, 2.2) third-party manufacturers of API and drug products, 2.3) external waste-treatment plants; 3. Antibiotic discharge limits set and applied to 3.1) own manufacturing sites, 3.2) third-party manufacturers of API and drug products, 3.3) external waste-treatment plants.

- 5 The company demonstrates an environmental risk-management strategy to minimise environmental impact of manufacturing discharge of antibiotics that meets 9 out of the 9 elements\* identified by the Benchmark.
- 4 The company demonstrates an environmental risk-management strategy to minimise environmental impact of manufacturing discharge of antibiotics that meets 6-8 of the 9 elements identified by the Benchmark.
- 3 The company demonstrates an environmental risk-management strategy to minimise environmental impact of manufacturing discharge of antibiotics that meets 3-5 of the 9 elements identified by the Benchmark.
- 2 The company demonstrates an environmental risk-management strategy to minimise environmental impact of manufacturing discharge of antibiotics that meets 2 of the 9 elements identified by the Benchmark.
- 1 The company demonstrates an environmental risk-management strategy to minimise environmental impact of manufacturing discharge of antibiotics that meets 1 of the 9 elements identified by the Benchmark.
- 0 The company demonstrates no information on an environmental risk-management strategy to minimise environmental impact of manufacturing discharge of antibiotics.

### B.2 DISCLOSURE ON ENVIRONMENTAL RISK MANAGEMENT

The company publicly discloses: 1) its environmental risk-management strategy to minimise environmental impact of manufacturing discharge of antibiotics; 2) results of audits on this strategy of the company's manufacturing sites; 3) results of audits on this strategy of third parties' manufacturing sites of antibiotic API and drug products and of wastewater treatment plants; 4) the identities of its third parties manufacturing antibiotic API and drug products, and antibiotic waste treatment plants; 5) the levels of antibiotic discharge.

- 5-1 The company publicly discloses: 1. its environmental risk-management strategy to minimise environmental impact of manufacturing discharge of antibiotics; 2. results of audits on this strategy of the company's manufacturing sites; 3. results of audits on this strategy of third parties' manufacturing sites of antibiotic API and drug products and of wastewater treatment plants; 4. the identities of its third parties manufacturing antibiotic API and drug products, and antibiotic waste treatment plants; 5. the levels of antibiotic discharge. The score is based on the number of these elements that are publicly disclosed.

- o The company demonstrates no information on public disclosure of any of the defined 5 criteria.

### B.3 MANUFACTURING HIGH-QUALITY ANTIBIOTICS

The company makes commitments to ensure that its own and third-party production facilities manufacturing antibiotic drug products maintain high quality of antibiotic production consistent with international standards developed and accepted by recognized national and international authorities.

- 5 The company reports a commitment to maintain high quality of antibiotic production consistent with international standards such as the FDA, EU and/or WHO Good Manufacturing Practice that apply to all company's manufacturing sites AND to third-party manufacturers of antibiotic drug products.
- 2,5 The company reports a commitment to maintain high quality of antibiotic production consistent with international standards such as the FDA, EU and/or WHO Good Manufacturing Practice (GMP) that apply to all company's manufacturing sites, but not to third-party manufacturers of antibiotic drug products.
- o The company demonstrates no information on commitments to maintain high quality of antibiotic production consistent with international standards such as the FDA, EU and/or WHO Good Manufacturing Practices.

## C ACCESS & STEWARDSHIP

### C.1 REGISTRATION OF ANTIBIOTICS

The company files to register its newest antibiotics in the highest number of countries in scope.

- 5 The company provides information on filing to register all five of its newest antibiotics in countries in scope. Each antibiotic is reported as filed for registration in >40% of countries in scope.
- 4 The company provides information on filing to register all five of its newest antibiotics in, on average, >40% of the countries in scope.
- 3 The company provides information on filing to register some of its newest antibiotics in, on average, 20-40% of the countries in scope.
- 2 The company provides information on filing to register all its newest antibiotics in, on average, 1-20% of the countries in scope.
- 1 The company provides information on filing to register some of its newest antibiotics in, on average, 1-20% of the countries in scope.
- o The company demonstrates no information on filing to register any of its newest in any countries in scope.

### C.2 PRICING OF ANTIMICROBIALS

The company commits to implement an appropriate access strategy that includes affordability considerations of its highest-volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope.

- 5 The company makes a general commitment that includes inter- and intra-country equitable pricing on appropriate access for its highest-volume antibiotics and non-antibiotic antimicrobial medicines that is applied in >50% of the countries in scope as well as a product-specific commitment for more than one of its products.
- 4,5 The company makes a general commitment that includes inter- and intra-country equitable pricing on appropriate access for its highest-volume antibiotics and non-antibiotic antimicrobial medicines that is applied in >50% of the countries in scope OR has a product-specific commitment for more than one product.
- 4 The company makes a general commitment that includes inter- and intra-country equitable pricing on appropriate access for its highest-volume antibiotics and non-antibiotic antimicrobial medicines that is applied in ≤50% of countries in scope.
- 3 The company makes a general commitment that includes inter-country equitable pricing on appropriate access for its highest-volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope.
- 1 The company makes a general commitment on appropriate access for its highest-volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope.
- o The company makes no commitment on appropriate access for its highest-volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope.

### C.3 ENSURING CONTINUOUS SUPPLY

The company has mechanisms\* in place to improve supply chain efficiency aimed at preventing stock-outs and improving demand forecasting of its highest-volume antibiotics and non-antibiotic antimicrobial medicines so as to ensure sustainable delivery to countries in scope.

- 5 The company engages with relevant stakeholders to align its supply and demand forecasting for (>50%) of its highest-volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope AND has mechanism(s) in place to respond efficiently in the event of stock-outs for (>50%) of its highest-volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope.

\*Mechanisms include: 1) engagement with relevant stakeholders (e.g., governments, PAHO, UNICEF) to align supply and demand forecasting so as to prevent or minimise stock-outs in countries in scope (i.e. LMIC); and 2) ability to respond efficiently in the event of stock-outs, e.g., faster, more precise and cheaper manufacturing approaches, rationalising the manufacture process so that number of product packs and packaging can be standardised to simplify manufacture and distribution to poor access areas.

- 3 The company engages with relevant stakeholders to align its supply and demand forecasting for ( $\leq 50\%$ ) of its highest-volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope AND has mechanism(s) in place to respond efficiently in the event of stock-outs for ( $\leq 50\%$ ) of its highest-volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope.
- 2 The company engages with relevant stakeholders to align its supply and demand forecasting for ( $> 50\%$ ) of its highest-volume antibiotics and antimicrobial medicines for countries in scope OR has mechanism(s) in place for ( $> 50\%$ ) of its highest-volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope in order to respond efficiently in the event of stock-outs in countries in scope.
- 1 The company engages with relevant stakeholders to align its supply and demand forecasting for ( $\leq 50\%$ ) of its highest-volume antibiotics and antimicrobial medicines for countries in scope OR has mechanism(s) in place for ( $\leq 50\%$ ) of its highest-volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope in order to respond efficiently in the event of stock-outs in countries in scope.
- o The company does not engage with relevant stakeholders to align its supply and demand forecasting for its antibiotics and non-antibiotic antimicrobial medicines for countries in scope and has no mechanism(s) in place to respond efficiently in the event of stock-outs in countries in scope.

#### C.4 SUPPORTING EDUCATIONAL STEWARDSHIP ACTIVITIES

[New indicator text]

The company engages and/or supports educational activities to educate healthcare professionals on antibiotic stewardship, with a clear conflict of interest mitigation strategy\* for its educational materials.

[Original indicator text]

The company engages and/or supports educational activities that are non-product specific to educate healthcare professionals (HCP) about antibiotic stewardship.

\*An educational activity has a conflict of interest mitigation strategy when it does not involve branding materials, product-specific contents or commercial teams, amongst others.

- 5 The company engages in educational activities, most with a clear conflict of interest mitigation strategy and content development independence, focussed on a combination of: AMR specific topics; stewardship topics; and the rational use of antibiotics, all delivered through active learning methods.
- 4 The company engages in educational activities, most with a clear conflict of interest mitigation strategy and content development independence, focussed on a combination of: AMR specific topics; stewardship topics; and the rational use of antibiotics, delivered through passive learning methods.
- 3 The company engages in educational activities, most with a clear conflict of interest mitigation strategy and content development independence, focussed on AMR specific topics or the rational use of antibiotics.
- 2 The company engages in educational activities, and provides for some of its projects, evidence of an independent review of the development of its contents as a conflict of interest mitigation strategy.
- 1 The company engages in educational activities and reported commitment to conflict of interest mitigation, but provided no information on independent content development of its materials.
- o The company does not provide evidence of engaging in any activity to educate healthcare professionals on antibiotic stewardship.

#### C.5 APPROPRIATE PROMOTIONAL ACTIVITIES

[New indicator text]

The company adopts appropriate promotion practices that advance appropriate use of antibiotics in its promotional activities and has mechanisms in place to incentivise appropriate promotion practices for its antimicrobial portfolio.

[Original indicator text]

The company adopts ethical marketing practices that advance appropriate use of antibiotics in its promotional activities, and has mechanisms in place to incentivise ethical marketing practices by its in-house and/or third-party sales representatives.

[Explanation for change]

Following data collection, the completeness and quality of all data was reviewed and certain indicators refined. For this indicator, the aspect focussing on third-party sales representatives was not scored due to the absence of adequate data.

- 5 The company reports taking into account AMR trends and guidelines in its marketing materials AND has formal processes in place to incentivise appropriate promotion practices focussed on antibiotic stewardship, OR deploys no sales agents to promote all of its antibiotics.
- 4 The company reports taking into account AMR trends and guidelines in its marketing materials AND commits to develop strategies to incentivise appropriate promotion practices focussed on antibiotic stewardship, OR deploys no sales agents to promote some of its antibiotics.
- 2 The company reports taking into account AMR trends and guidelines in its marketing materials, but does not implement appropriate promotion practices to its sales agents.
- o The company does not report about engaging in appropriate promotion practices that advance appropriate use of its antibiotics.

**C.6 BROCHURE AND PACKAGING**

[New indicator text]

The company implements brochure and packaging adaptation to facilitate appropriate use of antibiotics by patients, for its highest-volume antibiotics. The company considers local needs, such as literacy and language, when adapting brochure and packaging.

[Original indicator text]

The company implements brochure and packaging adaptation to facilitate appropriate use of antibiotics by patients, beyond local regulatory requirements, for its highest-volume antibiotics. The company considers local needs – literacy, language, cultural, demographic and environmental considerations – when adapting brochure and packaging.

[Explanation for change] Following data collection, the completeness and quality of all data was reviewed and certain indicators refined. For this indicator, the aspect on adaptation beyond regulatory requirements was not scored due to the absence of adequate data.

- 5 The company provides information on more than two brochure and packaging adaptations, consisting of at least one general statement on appropriate use of antibiotics, and one literacy and language consideration.
- 4 The company provides information on two brochure and packaging adaptations, consisting of at least one general statement on appropriate use of antibiotics, and one literacy and language consideration.
- 3 The company provides information on two brochure and packaging adaptations, which consist of a general statement on appropriate use of antibiotics.
- 2 The company provides information on one brochure and packaging adaptation, which consists of a general statement on appropriate use of antibiotics.
- o The company does not provide information on packaging and brochure adaptations.

**C.7 ANTIMICROBIAL RESISTANCE SURVEILLANCE**

The company has/supports/contributes to local and/or global antibiotic resistance surveillance programmes.

\*Long term AMR-surveillance programmes include programmes that are periodically repeated at least every two years and/or programmes that are ongoing for at least three years.

- 5 The company engages or participates in at least one long-term\* AMR-surveillance programme that shares the results publicly in open data-sets and collaborates with Public Health authorities.
- 4 The company engages or participates in at least one long-term\* AMR-surveillance programme and provides evidence of sharing the results with Public Health authorities.
- 3 The company engages or participates in at least one AMR-surveillance programme, providing evidence of sharing the results via peer-reviewed journals or congresses.
- 2 The company engages or participates in at least one AMR-surveillance programme, but there is no evidence of a clear data-sharing policy.
- o The company does not provide information on engaging or participating in any AMR-surveillance programmes.

**C.8 OTC SALES CONTROL**

The company has innovative models and mechanisms in place with relevant stakeholders to reduce uncontrolled antibiotic purchase, such as over-the-counter (OTC) and non-prescription sales.

Following data collection, all data was reviewed and certain indicators refined. In this case, the completeness and quality of data did not allow for an evaluation of the indicator.

## APPENDIX VIII

# Guide to Report Cards

This document provides a description of each section of the Report Cards for the 2018 Antimicrobial Resistance Benchmark.

Section	Description	Source
<b>General company information (header)</b>	Company name, Stock exchange(s), Stock exchange ticker(s), Location of headquarters, Number of employees, Signatory to Davos Declaration, Signatory to Industry Roadmap	<ul style="list-style-type: none"> <li>Annual report for the fiscal year ending 31 December 2016 or later (or, equivalently, forms 10-K or 20-F)</li> <li>Company website</li> <li>Industry Roadmap for Progress on Combating Antimicrobial Resistance (September 2016)</li> <li>Davos Declaration signatories list (as of January 2017)</li> </ul>
<b>Performance by Research Area (RA) (figure)</b>	This graph shows the company's scores for each of the RAs in which it was scored.	<ul style="list-style-type: none"> <li>Benchmark analysis</li> </ul>
<b>How company was evaluated: applicable indicators (by RA)</b>	This figure shows the indicators that were applicable to the company.	<ul style="list-style-type: none"> <li>Benchmark methodology</li> </ul>
<b>Performance (text)</b>	<p>This section summarises the company's overall performance in the Benchmark. It covers:</p> <ul style="list-style-type: none"> <li>Drivers behind its scores</li> <li>Main areas where the company scores well or poorly compared to peers</li> </ul>	<ul style="list-style-type: none"> <li>Benchmark analysis</li> </ul>
<b>Sales and Operations (text)</b>	<p>This section provides a general description of the company's global operations, including recent changes in its business (e.g., acquisitions or divestments), focusing on its antimicrobial business.</p> <p><i>For biopharmaceutical companies with no products on the market, this section is called "Operations"</i></p>	<ul style="list-style-type: none"> <li>Company's annual report</li> <li>Company's website</li> <li>Press releases by company or other pharmaceutical news websites</li> <li>Stock exchange communications</li> <li>Methodology 2017</li> <li>Benchmark analysis</li> </ul>
<b>Revenues by product (figure)</b>	<p>Where possible, this figure shows a breakdown of the company's revenues into: vaccines, antimicrobial medicines, other.</p> <p><i>When disaggregated revenue figures were not available, the figure shows the company's total revenue.</i></p>	<ul style="list-style-type: none"> <li>Company's annual report</li> </ul>
<b>Revenues by region (figure)</b>	This figure shows a breakdown of the company's sales or operating revenues by geographic region	<ul style="list-style-type: none"> <li>Company's annual report (terminology is as close to the annual report as possible)</li> </ul>
<b>Antimicrobial Portfolio (text)</b>	This section provides a description of the number and type of antimicrobial medicines the company markets as of September 2017 and the proportion included on the WHO EML (Section 6)	<ul style="list-style-type: none"> <li>Benchmark methodology and analysis</li> <li>Registered products identified from the EMA, FDA, PMDA, and the company's website.</li> <li>WHO EML (Section 6), 20th List, March 2017 (amended August 2017)</li> </ul>
<b>Antimicrobial Portfolio (figure)</b>	<p>This figure shows a breakdown of the number of antimicrobial medicines the company markets as of September 2017 into antibiotics and other antimicrobials, and the number of antibiotics on the WHO EML (Section 6).</p> <p>This includes a breakdown of the proportion of the company's EML antibiotic portfolio that falls into the EML's Access, Watch, and Reserve groups.</p>	<ul style="list-style-type: none"> <li>Benchmark methodology and analysis</li> <li>Registered products identified from the EMA, FDA, PMDA, and the company's website</li> <li>WHO EML (Section 6), 20th List, March 2017 (amended August 2017)</li> </ul>
<b>Opportunities (text)</b>	This section outlines opportunities for the company to do more to address AMR. The opportunities take into account company-specific characteristics as far as possible.	<ul style="list-style-type: none"> <li>Benchmark analysis</li> </ul>
<b>Performance by RA (text)</b>	<p>These three sections summarise company performance for each of the RAs, by indicator. The paragraphs describe the company's performance and highlight (where available) relevant examples of its activities.</p> <p><i>Following a review of the data, indicator A.2 (R&amp;D projects) was divided into three sub-indicators to enable a more fine-grained comparison of companies' pipelines. The three sub-indicators focus on, respectively, pipeline size (A2.1), number of novel medicine candidates (A2.2) and number of vaccines in the pipeline (A2.3). In R&amp;D, access and stewardship provisions are analysed for late-stage projects only. This includes projects in clinical Phase II or III as well as projects awaiting approval or approved by 31 October 2017.</i></p>	<ul style="list-style-type: none"> <li>Benchmark methodology</li> <li>Benchmark analysis</li> </ul>
<b>Antimicrobial Pipeline (figure)</b>	<p>This figure shows the company's pipeline of vaccines and antimicrobial R&amp;D projects targeting priority pathogens.</p> <p>Where applicable, regulatory approvals (including label extensions) are noted, including the regulatory body/location and date of approval.</p> <p>Data omissions due to confidentiality agreements are noted, in addition to changes to the status of projects taking place until 31 October 2017.</p>	<ul style="list-style-type: none"> <li>Projects submitted by the company for scoring and analysis in the Benchmark, including verification/cross-reference with publicly available pipeline information. Approval data is verified using public sources.</li> </ul>

## APPENDIX IX

## List of figures

7	Figure 1. Antimicrobial Resistance Benchmark – Company Performances
10	Figure 2. Antibiotic resistance and increased risk of death
12	Figure 3: Change in the Number of New Antibacterial Drug Approvals in USA 1980-2014.
17	Figure 4. Pharmaceutical companies are active in ten AMR priority areas.
18	Figure 5. 30 companies in scope
19, 20	Figure 6. Comparing scores: large research-based pharmaceutical companies.
19, 20	Figure 7. Comparing potential: large research-based pharmaceutical companies.
19, 21	Figure 8. Comparing scores: generic medicine manufacturers.
19, 21	Figure 9. Comparing potential: generic medicine manufacturers.
19, 22	Figure 10. Comparing scores: biopharmaceutical companies.
19, 22	Figure 11. Comparing potential: biopharmaceutical companies.
24	Figure 12. Few late-stage antibiotics with access and stewardship plans.
25	Figure 13a. Nine out of 19 companies support AMR surveillance.
25	Figure 13b. AMR surveillance programmes are being conducted in 147 countries worldwide.
26	Figure 14. Eight companies set discharge limits. No company publishes discharge levels.
27	Figure 15. Decoupling sales volumes from sales agents' bonuses: four companies are taking action
28	Figure 16. Which antimicrobial medicines are available on the market?
29	Figure 17. Companies in scope have 268 antibiotics on the WHO EML (Section 6).
34	Figure 18. Global coverage of older vaccines exceeds 80% - for newer vaccines coverage remains relatively low
36	Figure 19. More research and development needed on vaccines against priority pathogens.
37	Figure 20. Five companies market and develop vaccines for priority pathogens.
40	Figure 21. Company performance: research & development
42	Figure 22. Companies in scope
45	Figure 23. Antimicrobial pipelines contain 276 R&D projects.
45	Figure 25. Breakdown of the clinical pipeline for priority pathogens.
45	Figure 24. Criteria for WHO and CDC prioritisation of pathogens.
46	Figure 26. GSK is developing the most projects that target priority pathogens.
46	Figure 27. Projects targeting priority pathogens by biopharmaceutical companies.
48	Figure 28. What makes an antibiotic novel?
48	Figure 29. Few novel clinical-stage projects targeting priority bacteria.
50	Figure 30. Half of new R&D projects involve partnerships with public or non-profit partners.
50	Figure 31. Half of the partnering bodies are focussed on antibacterial R&D.
55	Figure 32. Almost half of the companies have at least one access and/or stewardship provision in place for a late-stage clinical candidate.
58	Figure 33. Company performance: Manufacturing & Production
60	Figure 34. Companies in scope
62	Figure 35. Depth and breadth of environmental risk-management strategies vary widely.
64	Figure 36. More than half of companies publicly disclose GMP commitments.
66	Figure 37. Company performance: Access & Stewardship
68	Figure 38. Companies in scope
70	Figure 39. Almost 65% of antibiotics are registered in countries where access is less likely.
70	Figure 40. Four antibiotics have been filed in more than half of the countries in scope.
71	Figure 41. Only three companies have registered new antibiotics in low- and middle-income countries this decade.
74	Figure 42. Companies prefer active learning techniques to educate HCPs.
75	Figure 43. Companies deliver AMR-related content through a mix of activities.
75	Figure 44. Only five of the 29 programmes run educational webcasts.
75	Figure 45. Non-branded educational materials are the most common conflict of interest (COI) mitigation techniques.
77	Figure 46. Nine companies commit to reviewing promotional activities.
79	Figure 47. AMR surveillance: Number, geographical scope and length of surveillance programmes
79	Figure 48. AMR surveillance programmes are being conducted in 147 countries worldwide.

## APPENDIX X

## Definitions

**Access provisions**

*[Working definition, used for analysis]*

Provisions to ensure that within the scope of the Benchmark, public health needs are taken into consideration during R&D. Access provisions can be included in R&D partnerships and/or in in-house R&D. They facilitate availability, accessibility and affordability for patients in countries within the scope of the Benchmark (e.g., equitable pricing strategies, sufficient supply commitments, non-exclusivity in specified territories, waiving for patent rights, royalty-free provisions).

**Active pharmaceutical ingredient**

The active pharmaceutical ingredient (API) is the effective part of any medicine. Some medicines, such as combination therapies, have multiple active ingredients to treat different symptoms or act in different ways.

**Active learning methods**

Method of learning in which attendees are actively participating in the learning process, not only passively listening, such as courses and congresses.

**Adaptive R&D**

*[Working definition, used for analysis]*

R&D adaptations to existing medicines and/or vaccines. This includes new formulations, new fixed dose combinations of existing chemical or biological entities, a new target demography or the repurposing of an existing product for additional indications.

**Affordability**

*[Working definition, used for analysis]*

A measure of the payer's ability to pay for a product (whether or not they are the end user). The Benchmark takes this into account when assessing pricing strategies for relevant products in scope.

**Antibiotic**

*[Working definition, used for analysis]*

Antimicrobial medicine to treat bacterial infections by directly targeting the bacteria that cause the infection (as opposed to targeting the symptoms of the infection or toxins produced by the pathogen). Equivalent to antibacterial medicine.

**Antibiotic resistance**

Resistance that occurs when bacteria change in response to the use of antibiotics used to treat bacterial infections (such as urinary tract infections, pneumonia, bloodstream infections) making them ineffective.

**Antibiotic stewardship**

Antibiotic stewardship is a systematic and comprehensive process that aims to ensure that all aspects of prescription (e.g., drug, dose, duration), dispensing and use of antibiotics follow the evidence available in order to minimise the emergence of resistance.

**AMR surveillance**

*[Working definition, used for analysis]*

Continuous, systematic collection, analysis and interpretation of antimicrobial infection and resistance-trend data needed for the planning, implementation, and evaluation of antimicrobial stewardship activities.

**Antimicrobial medicines**

*[Working definition, used for analysis]*

Medicines used to treat infectious diseases by directly targeting the bacteria, fungi, helminths, protozoa or viruses that cause the infection (as opposed to targeting the symptoms of the infection or toxins produced by the pathogen).

**Antimicrobial resistance**

Resistance in different types of microorganisms; encompasses resistance to antibacterial, antiviral, antiprotozoal, antifungal and anthelmintic medicines. See **Antibiotic resistance**.

**Appropriate promotional practices**

*[Working definition, used for analysis]*

Promotional activities targeting the general public, patients and healthcare professionals in such a way that transparency, integrity, accuracy, clarity and completeness of information can be ensured.

**Appropriate use of antibiotics**

The cost-effective use of antibiotics, which maximises clinical therapeutic effect while minimising both drug-related toxicity and the development of antimicrobial resistance (WHO Global Strategy for Containment of Antimicrobial Resistance).

**Broad-spectrum antibiotics**

Broad-spectrum antibiotics are active against a wider number of bacterial types and, thus, may be used to treat a variety of bacterial infections.

**Conflict of interest**

Situation where the primary interest of protecting and promoting public health conflicts with a secondary interest, such as financial incentives or non-financial incentives.

**Drug product**

A finished dosage form, e.g., tablet, capsule, or solution that contains a drug substance, gener-

ally, but not necessarily, in association with one or more other ingredients. Also referred to as formulations.

**Environmental risk management**

*[Working definition, used for analysis]*

Environmental risk management seeks to determine what environmental risks exist from antibiotic production and determines how to manage those risks in the way best suited to protect human health and the environment, in particular to the emergence of antibiotic resistance.

**Equitable pricing strategy**

*[Working definition, used for analysis]*

A targeted pricing strategy, which aims at improving access to medicines and vaccines for those in need by taking affordability for individuals and healthcare systems into account in a manner that is locally appropriate.

**Falsified medicine**

A medicine which is deliberately and fraudulently mislabelled with respect to identity and/or source. Falsified medicines may contain no active ingredient, the wrong active ingredient or the wrong amount of the correct active ingredient.

**Generic medicine**

A medicine that is comparable to an originator medicine in dosage form, strength, route of administration, quality and performance characteristics, and intended use.

**Good Manufacturing Practices**

Good manufacturing practice (GMP) is a system to ensure that products are consistently produced and controlled according to quality standards. It is designed to minimise the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

**Healthcare Professionals**

Any specialised worker in any branch of healthcare that provides preventive, curative or rehabilitative services to the community.

**Herd immunity**

The resistance to the spread of a contagious disease within a population that results if a sufficiently high proportion of individuals are immune to the disease, especially through vaccination.

**Late-stage drug development**

*[Working definition, used for analysis]*

Medicine and vaccine candidates in Phase II or III clinical development. Products approved (or awaiting approval) in 2016-2017 are also categorised as late-stage.

**Narrow-spectrum antibiotics**

Narrow-spectrum antibiotics are active against a selected group of bacterial types. Examples are colistin, an antibiotic that selectively targets gram-negative bacteria, and vancomycin, an antibiotic that selectively targets gram-positive bacteria.

**Novel drug candidate**

*[Working definition, used for analysis]*

To qualify as novel, a candidate must fulfil one or more of the criteria defined by WHO's report on antibacterial agents in clinical development: it represents a new chemical class; aims at a new target; has a new mode of action; and/or has an absence of cross-resistance from existing antimicrobials. This classification was applied to candidates in clinical stage only and validated by WHO and/or external experts.

**One Health**

Approach to designing and implementing public health programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better outcomes. The areas of work in which a One Health approach is particularly relevant include food safety, the control of zoonosis, and combating antimicrobial resistance.

**Open collaborations**

*[Working definition, used for analysis]*

A multi-stakeholder partnership that focusses on pharmaceutical R&D, such as a Product Development Partnership (PDP) and open research consortia, with an open approach to pooling and sharing resources such as data and expertise between partners.

**Originator medicine**

The medicine that was first authorised worldwide for marketing, normally as a patented product, on the basis of the documentation of its efficacy, safety and quality, according to requirements at the time of authorisation. The originator medicine always has a brand name; this name may, however, vary among countries.

**Over-the-counter medicine**

Purchase of a medicine by ordinary retail without prescription from a healthcare professional.

**Preclinical & clinical drug development stage**

*[Working definition, used for analysis]*

Preclinical stage development includes the discovery and preclinical phase of drug development. The clinical development stage com-

prises Phase I-III clinical development. Products approved (or awaiting approval) in 2016-2017 are also categorised as clinical stage.

**Predicted no-effect concentration**

The predicted no-effect concentration (PNEC) is the concentration of a substance in any environment below which adverse effects will most likely not occur during long-term or short-term exposure.

**Priority pathogen**

*[Working definition, used for analysis]*

Pathogens for which new innovative medicines and vaccines are highly needed. The priority pathogens were identified based on the WHO priority pathogens list as of 25 February 2017 and CDC's US Biggest Threats as of April 2013.

**Product Development Partnership**

*[Working definition, used for analysis]*

Product Development Partnerships (PDPs) take the form of centralised non-profit organisations that facilitate financial risk-sharing across the public and private sectors by pooling and sharing resources, both tangible and intangible, for the development of medicines, vaccines and other health tools.

**Public-private partnership**

*[Working definition, used for analysis]*

A partnership between one or more public organisations and the private sector for providing a public asset or service, in which the private party bears significant risk and management responsibility, and remuneration is linked to performance. The Benchmark also considers a partnership between a non-profit organisation and the private sector as a public-private partnership (PPP).

**Pull incentives**

Pull incentives reward a successful result or research and development of a new antimicrobial medicine and provide known return on investment. Examples of pull incentives are extended exclusivity periods, higher reimbursement or market entry rewards.

**Push incentives**

Push incentives lower the cost of and de-risk research and development of a new antimicrobial drug. Examples of push incentives are grants, partnerships or tax credits.

**Stewardship provisions**

*[Working definition, used for analysis]*

Provisions to ensure that public health needs

are taken into consideration during R&D.

Stewardship provisions can be included in R&D partnerships and/or in in-house R&D. They facilitate the appropriate use of antimicrobial medicines and reduce the emergence of resistance (e.g., appropriate promotion and surveillance).

**Substandard antibiotics**

Authorised medical products, in this case antibiotics, that fail to meet either their quality standards or their specifications, or both. Also called "out of specification".

## APPENDIX XI

## Acronyms

AA&S	Appropriate Access and Stewardship	HiHDI	High Human Development Country with High Inequality
ABSSSI	Acute Bacterial Skin and Skin Structure Infection	HIV	Human Immunodeficiency Virus
ACT	Artemisinin-based combination therapy	HVTN	HIV Vaccine Trials Network
AIDS	Acquired immune deficiency syndrome	IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
AMR	Antimicrobial resistance	IP	Intellectual property
API	Active pharmaceutical ingredient	IPO	Initial Public Offering
ARV	Antiretroviral	IV	Intravenous
AST	Antibiotic susceptibility testing	KOL	Key opinion leader
ATC	Anatomical Therapeutic Chemical classification	LDC	Least Developed Country
BARDA	US Biomedical Advanced Research and Development Authority	LHDC	Low Human Development Country
BSAC	British Society for Antimicrobial Chemotherapy	LIC	Low-Income Country
BEAM Alliance	Biotech companies in Europe combating AntiMicrobial Resistance Alliance	LMIC	Lower-Middle Income Countries
BIO	Biotechnology Innovation Organization	M&P	Manufacturing and Production
ciAI	Complicated intra-abdominal infection	MAA	Marketing authorization application
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator	MEB	Medicines Evaluation Board
CABP	Community-acquired bacterial pneumonia	MGB	Minor Groove Binder
CDC	US Centers for Disease Control and Prevention	MHDC	Medium Human Development Country
CDDEP	Center for Disease Dynamics, Economics and Policy	MOOC	Massive Open Online Courses
CDI	<i>C. difficile</i> infection	MRSA	Methicillin-Resistant <i>Staphylococcus aureus</i>
CHAI	Clinton Health Access Initiative	MSF	Médecins Sans Frontières
CME	Continuing medical education	MMV	Medicines for Malaria Venture
CNS	Central nervous system	ND4BB	New Drugs for Bad Bugs
COI	Conflict of interest	NGO	Non-governmental organisation
CRE	Carbapenem-resistant Enterobacteriaceae	NGS	Next Generation Sequencing
cUTI	Complicated urinary tract infection	NIAID	US National Institute of Allergy and Infectious Diseases
DDD	Defined daily dose	OECD	Organisation for Economic Co-operation and Development
DNA	Deoxyribonucleic acid	OMPTA	Outer Membrane Protein Targeting Antibiotic
DNDi	Drugs for Neglected Disease Initiative	OTC	Over-the-counter
DRIVE-AB	Driving reinvestment in research & development and responsible antibiotic use	PAHO	Pan American Health Organization
EC	Expert Committee of the AMR Benchmark	PEPFAR	President's Emergency Plan for AIDS Relief
ECOSOC	United Nations Economic and Social Council	PDP	Product Development Partnership
EML	WHO Model List of Essential Medicine, March 2017 (amended August 2017)	PMDA	Japan Pharmaceuticals and Medical Devices Agency
EMA	European Medicines Agency	R&D	Research and Development
EU	European Union	RNA	Ribonucleic acid
ESBL	Extended-spectrum $\beta$ -lactamase	SARS	Severe Acute Respiratory Syndrome
FAIRR	Farm Animal Investment Risk and Return	SOP	Standard Operating Procedures
FDA	US Food and Drug Administration	SSA	Sub-Saharan Africa
FDC	Fixed dose combination	SU	Standard Units
FYE	Fiscal year end	TGA	Australia Therapeutic Goods Administration
GARDP	Global Antibiotic Research & Development Partnership	The Benchmark	The Antimicrobial Resistance Benchmark
GBS	Group B Streptococcus	The Foundation	Access to Medicine Foundation
GDP	Gross Domestic Product	The Global Fund	The Global Fund to Fight AIDS, Tuberculosis and Malaria
GLASS	Global Antimicrobial Resistance Surveillance System	UNDP	United Nations Development Programme
GMP	Good Manufacturing Practice	USAID	United States Agency for International Development
GNI	Gross national income	USSSI	Uncomplicated skin and skin structure infection
GUARD	Global Union for Antibiotics Research and Development	VABP	Ventilator-associated bacterial pneumonia
HABP	Hospital-acquired bacterial pneumonia	VRE	Vancomycin-resistant <i>Enterococcus</i>
HBV	Hepatitis B Virus	WHO	World Health Organization
HCP	Healthcare professional	ZLD	Zero Liquid Discharge
HCV	Hepatitis C Virus		

### **Report Design**

Explanation Design (Klaas van der Veen

i.c.w. Geeke Voortman)

Photo Jayashree K. Iyer: Patricia Wolf

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