Otsuka Pharmaceutical Co, Ltd

Large R&D-based pharmaceutical company
Stock exchange: TSE • Ticker: 4578 (Otsuka Holdings Co, Ltd) • HQ: Tokyo, Japan • Employees: 5,700

PERFORMANCE

Otsuka is middle-performing in its evaluated Research Areas when compared to other large R&D-based pharmaceutical companies in scope. R&D: Middle-performing. Pipeline consists of four projects for medicines for priority pathogens. Reports commitments to access planning for one of its late-stage R&D projects and is active in intellectual capital sharing. Responsible Manufacturing: Performs less well. Reports a general environmental risk-management strategy for own sites without stating a specific aim to limit AMR.

Appropriate Access: Middle-performing. Filed delamanid (Deltyba®) for registration in access countries. Reports using long-term demand forecasting to ensure continuous supply.

Stewardship: Middle-performing. It has opted to not deploy sales agents to promote delamanid. It is not involved in AMR surveillance. It translates brochures for delamanid, but makes no further adaptations.

SALES AND OPERATIONS

Therapeutic areas: Cardiovascular diseases; Kidney diseases; Infectious diseases; Neurology; Oncology; Ophthalmology
Business segments: Pharmaceuticals; Nutraceuticals
Product categories: Innovative medicines; Nutraceuticals
Manufacturing & supply: Otsuka reports having two manufacturing sites that produce antibacterial APIs and/or drug products. Its antibacterial medicine delamanid is available in 84 countries, 50 of which are low- and middle-income countries.
M&A since 2018: In August 2018, Otsuka completed the acquisition of Visterra for USD 430 million cash. From the Visterra pipeline Otsuka acquired, among the various projects, a preclinical stage candidate for severe P. aeruginosa infection.

Pipeline size: 4 projects for priority pathogens* (*4 antibacterial medicines)

Development stages: 2 clinical projects, including OPS-2071, a Phase II clinical candidate for the treatment of enteritis caused by C. difficile, and 1 preclinical project
Novelty: 1 novel project, OPC-167832, a Phase II clinical candidate for the treatment of tuberculosis (TB) that meets all four criteria set by WHO for innovativeness
Regulatory approvals: 0 approvals for priority pathogens
Access plans: 1 of 2 late-stage R&D projects with project-specific access plans, with a commitment to ensure availability and access to OPC-167832 through a partnership with the Bill & Melinda Gates Foundation.
Stewardship plans: Neither of its 2 late-stage R&D medicine projects have project-specific stewardship plans.

PORTFOLIO for diseases in scope

Comparatively small portfolio: At least 1 product (1 antibacterial medicine)
Essential medicines: 1 product is on the 2019 WHO EML
AWaRe medicines**: None
Anti-TB medicines**: 1 product (1 antibacterial medicine)

Pipeline for priority pathogens

Products on the market

The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Otsuka’s entire portfolio.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

** Listed on the 2019 WHO EML (Section 6).
OPPORTUNITIES FOR OTSUKA

Develop an AMR-specific environmental risk-management strategy. Otsuka can tailor its environmental risk-management strategy to AMR and implement the Common Antibiotic Manufacturing Framework and PNEC limits, as published by the Industry Alliance, of which it is a member. Otsuka can also work with stakeholders to develop a practical mechanism to publicly disclose (1) a list of its suppliers and waste-treatment plants and (2) the results of environmental audits and the levels of antibacterial discharge from its own sites and the sites of its suppliers.

Improve availability and affordability of delamanid (Deltyba®). Otsuka can expand the availability of delamanid by ensuring that a file for registration is submitted (by Otsuka or delamanid’s licenscees) in more access countries, in particular the 30 countries with a high burden of TB. Otsuka can also improve affordability and supply to more access countries through licences with more manufacturers other than Mylan, assess where the price of other new TB medicines is lower and take into consideration the overall price of new TB regimens including multiple products.

Engage in TB surveillance activities. Otsuka can engage in a multinational, long-term surveillance programme focusing on resistance of delamanid in the countries where it markets the product. Otsuka can also encourage delamanid’s licenscees to engage in similar programmes in the countries where they are marketing the product.

PERFORMANCE BY RESEARCH AREA

RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Above average investments in relevant R&D, as proportion of pharmaceutical revenues
Otsuka reports that it invested USD 51 million in R&D for anti-tuberculosis medicines in 2017 and 2018. As a proportion of its revenues from pharmaceuticals, these investments are above average compared to investments in such R&D made by other large research-based pharmaceutical companies evaluated in the Benchmark. Otsuka does not invest in vaccines R&D. Otsuka’s investment in R&D for TB medicines in 2017 is the largest reported by a Benchmark company. In addition to its own investments, Otsuka received USD 10 million for TB R&D from the Bill & Melinda Gates Foundation.

A.2.1 Pipeline size small compared to peers
Among the large research-based pharmaceutical companies evaluated, this pipeline is small in size. Otsuka reports four projects targeting priority pathogens, all of which target bacteria, including two medicine projects targeting M. tuberculosis, one targeting C. difficile and another targeting P. aeruginosa. Three projects are in clinical development and one in pre-clinical development.

A.2.2 One clinical-stage novel project
Otsuka’s clinical-stage medicine pipeline for priority pathogens consists of both new and adapted R&D projects. Otsuka has one late-stage antibacterial medicine project that is considered novel: OPC-167832, for pulmonary TB, which meets all four criteria set by WHO for innovativeness.

A.2.3 Vaccines in the pipeline
Otsuka is not eligible for this indicator as it is not active in vaccine development targeting priority pathogens.

A.2.4 Two candidates targeting critical and/or urgent priorities
Otsuka’s pipeline includes a clinical antibacterial medicine candidate in Phase II (OPS-2071) that targets C. difficile and a pre-clinical candidate (VIS705) that targets P. aeruginosa, including multi-drug resistant strains. These pathogens have been identified by WHO and/or the US Centers for Disease Control and Prevention (CDC) as an urgent R&D target for limiting AMR.

A.3 One intellectual capital sharing initiative
Otsuka commits to the stipulations set out by the Bill & Melinda Gates Foundation under the terms of its grants: namely, to provide unrestricted access, including re-use, to all peer-reviewed published research funded by the Foundation, including any underlying data sets.

A.4 Access plans for 1 of 2 projects
Otsuka has two late-stage R&D projects targeting priority pathogens, both medicines. For its project OPC-167832, Otsuka has committed itself contractually to the access plans stipulated by the Bill & Melinda Gates Foundation, which is co-developing the project. This includes commitments to make the product available and accessible at an affordable price to people most in need within developing countries. Otsuka does not report stewardship plans for either project.

PipeLine targeting priority pathogens: 4*** As at 16 October 2019

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIS705 antibody - P. aeruginosa (including MDR strains)</td>
<td></td>
<td></td>
<td>OPC-167832 - M. tuberculosis - Novel</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OPS-2071 - C. difficile - Bacterial enteritis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHANGES SINCE 2018

This section lists notable changes in companies’ activities since the 2018 Benchmark. Since Otsuka was not in scope for evaluation in 2018, no changes are reported.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.
B RESPONSIBLE MANUFACTURING

Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 General environmental risk-management strategy for own sites

Otsuka’s general environmental strategy includes a commitment to manufacture its products in an environmentally responsible manner. However, this does not include any actions specific to delamanid (Deltyba®), the only antibacterial product produced at its manufacturing sites, in both its API and drug product forms. Further, Otsuka does not report making any requirements in this regard to the third-party drug product manufacturer contracted for an intermediate step in the delamanid production. There is limited information on the requirements the company makes of external private waste-treatment plants in terms of environmental strategy, audits and antibacterial discharge limits.

B.2 Publicly discloses some information on environmental risk management

Otsuka publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Otsuka does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers’ sites; no requests for official corrective action

Otsuka reports having a system to maintain high-quality antibacterial production, consistent with international standards. This includes periodic internal audits and tracking of corrective actions. The company reports requiring suppliers to abide by regulatory and company quality standards, as specified in GMP agreements. It reports auditing its suppliers and tracking implementation of corrective actions. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Otsuka’s own sites or any subsidiaries.

C APPROPRIATE ACCESS & STEWARDSHIP — ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries

C.1 Filed to register its one on-patent antibacterial medicine in 9 access countries

Otsuka is a middle-performing company when it comes to filing relevant on-patent products for registration in access countries. It has one product that qualifies for this analysis – delamanid (Deltyba®), used for TB – which it has filed for registration in 9 access countries.

C.2 Pricing strategies for off-patent products

Otsuka was not eligible for this indicator, as it does not report having relevant off-patent antibacterial or antifungal medicines or vaccines.

C.3 Some strategies to ensure the continuous supply of relevant products

Otsuka performs less well than other large research-based pharmaceutical companies evaluated when it comes to taking steps to ensure the continuous supply of its relevant products to access countries. It discloses some strategies for achieving this aim. It uses long-term demand forecasting and organises regular meetings to align with its supply chain team and other third parties, such as production sites. Otsuka’s antibacterial delamanid (Deltyba®) is only produced in Japan, but since 2016, the company has partnered with the Global Drug Facility to supply this antibacterial to more than 100 countries, including access countries. To increase access and help ensure a secure supply of ingredients, Otsuka is currently conducting a technology transfer to Mylan. To mitigate against falsified medicines reaching the supply chain, Otsuka meets EU requirements for product serialisation and closely monitors products on markets outside the EU.

C.4 Educational stewardship activities

Otsuka is not eligible for this indicator as it reports no involvement in AMR-related educational programmes aimed at healthcare professionals (HCPs).

C.5 Does not promote its antibacterial medicine

Otsuka engages in practices that aim to address the appropriate use of antibacterial and/or antifungal medicines. It is one of the two companies evaluated to report that it does not deploy any sales agents nor develop any marketing materials to promote such products, namely for Otsuka the antibacterial delamanid (Deltyba®), because treatment is only available in specialised centres under tightly controlled conditions.

C.6 Translates brochures to facilitate appropriate use

Otsuka adapts brochures to facilitate the appropriate use by patients of relevant products: namely its antibacterial delamanid (Deltyba®). These adaptations only take account of language needs. Otsuka has translated its Educational Risk Minimisation Materials into English, French, Spanish and Russian. These are distributed through the Global Drug Facility by MSF.

C.7 No involvement in AMR surveillance programmes but shares some consumption data

Otsuka does not report any involvement in AMR surveillance programmes. Otsuka currently shares some consumption data, about delamanid (Deltyba®) (e.g., from its compassionate use programme), with national authorities and WHO.

† Including only wholly-owned direct subsidiaries of the company. More information in Appendix I.
‡ 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.
§ See Appendix VII.

Access to Medicine Foundation
Activities in this area are not scored by the Benchmark. This information is provided given the importance of diagnostics, animal health and agriculture on the topic of AMR.

Otsuka has its own diagnostics business and develops diagnostic devices and products. It is developing a treatment monitoring tool to determine the severity of pulmonary TB by measuring lipoarabinomannan (LAM), a major component of M. tuberculosis' cell wall. Currently, the treatment monitoring tool is only available for use in clinical research, but Otsuka is working with a third party to make the platform commercially available. The tool has received CE-marking, which is required for all in vitro diagnostic devices sold in the EU.