

**Overall Performance**

2020	2021
63%	58%▼

# Shionogi & Co, Ltd

Large R&D-based pharmaceutical company

Stock exchange: TSE • Ticker: 4507 • HQ: Osaka, Japan • Employees: 5,233

## PERFORMANCE

Shionogi performs average overall in its evaluated Research Areas compared to the other large research-based pharmaceutical companies in scope.

**R&D:** Shionogi performs well in R&D. Eight of its 11 projects target critical and/or urgent pathogens. For the first time Shionogi has a vaccine in their pipeline. Shionogi is working on improving access and stewardship of its antibacterial cefiderocol.

**Responsible Manufacturing:** Shionogi leads. Reports comprehensive environmental risk-management strategy for own sites and suppliers; co-leads in compliance with limits at own sites; leads in public disclosure of strategy and compliance

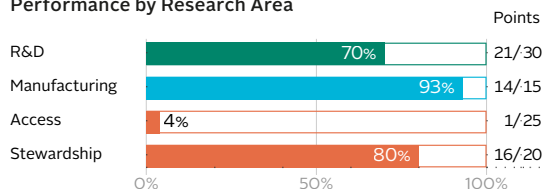
**Appropriate Access:** Performs low. Its relevant on- and off-patent products are not available in access countries.

**Stewardship:** Performs well. It fully decouples incentives for sales agents from sales volumes. It publicly shares aggregated results of its surveillance programmes. It reports comprehensive conflict of interest mitigation for its educational programmes. It adapts brochures for patients.

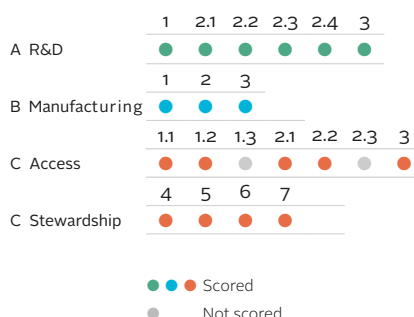
### Performance in the Benchmark



### Performance by Research Area



### How Shionogi was evaluated



## OPPORTUNITIES FOR SHIONOGI

**Expand breadth of R&D pipeline and depth of R&D access and stewardship plans.** Shionogi has one of the most diverse pipelines across all large research-based companies in the AMR Benchmark. It can expand the focus of its pipeline to target resistant pathogens for which R&D is limited, such as *Campylobacter* spp. and *H. pylori*. For its recently approved cefiderocol (Fetroja®/ Fetroja®), Shionogi engages with generic medicines manufacturers and access-related organizations such as GARDP and the Clinton Health Access Initiative to increase affordability and availability. Shionogi can intensify these engagements to reach more patients and countries. Shionogi can continue to build towards a comprehensive surveillance programme to ensure cefiderocol is not used excessively.

**Expand registration to cefiderocol (Fetroja®/ Fetroja®) in access countries.** Shionogi can file cefiderocol (Fetroja®/ Fetroja®) for registration in access countries. Further, to accelerate the availability of cefiderocol in access countries Shionogi can consider voluntary non-exclusive licensing, compassionate use programs and public/private partnerships.

**Expand adaptations to brochures and packaging to consider more patient needs.** Shionogi adapts brochures to take account of paediatric use to support the appropriate use of cefcapene pivoxil (Flomox®) by patients. It can further adapt its brochures and packaging of all antibacterial and anti-fungal medicines to consider local languages, literacy levels, environmental conditions and patient adherence to treatment.

**Publicly share raw data from surveillance programmes.** Shionogi runs the multinational SIDERO-WT programme, which is focused on resistance against antibacterials targeting Gram-negative bacteria. It can publicly share raw data from this surveillance programme, following through on commitments to share this with the AMR Register in 2021. Additionally, either Shionogi or the managing partners should publicly share raw data from the other surveillance programmes it is involved in.

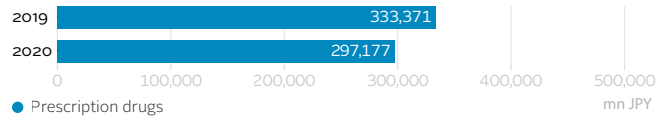
## CHANGES SINCE 2020

- In response to an opportunity from the 2020 AMR Benchmark, in July 2021, Shionogi entered into a collaboration with the Global Antibiotic Research and Development Partnership (GARDP) and the Clinton Health Access Initiative (CHAI) to accelerate access, including in LMICs, to the antibiotic cefiderocol.
- In October 2020, Shionogi expanded investments into vaccine development through a licensing partnership agreement with HanaVax for research, development, manufacturing, distribution and commercialisation of their *S. pneumoniae* nasal vaccine candidate.
- In its 2020 Environmental Report, Shionogi discloses compliance with limits of its own and suppliers' sites, some details of audit results and some names and/or locations of its suppliers and sole waste contractor.
- In 2020, Shionogi started to support the SENTRY programme for the surveillance of cefiderocol. The results are shared publicly via open-access journal articles and the SENTRY website.

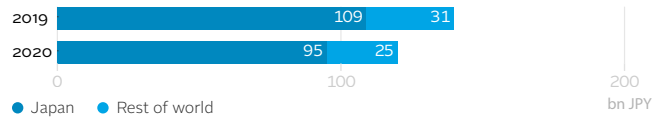
**SALES AND OPERATIONS**

**Therapeutic areas:** Infectious diseases, Psycho-neurological diseases  
**Business segments:** Prescription drugs  
**Product categories:** Generic medicines, Innovative medicines, Vaccines  
**M&A since 2020:** In July 2020, Shionogi entered into agreement with Ping An Life Insurance of China, Ltd. to establish of a joint venture called Ping An Shionogi Company Ltd

**Revenue by business segment**



**Revenue by region**



**PIPELINE for pathogens in scope**

**Pipeline size:** 11 projects targeting pathogens in scope\* (8 antibacterial medicines; 1 antibacterial vaccine; 2 antifungal medicines).  
**Development stages:** 5 discovery programmes for antifungals, antituberculosis and antibacterial candidates; 2 preclinical projects including an antibody against *P. aeruginosa* and a vaccine for *S. pneumoniae*; and 1 Phase II adaptive project.  
**Novelty:** 0 novel clinical-stage medicine projects.  
**'Critical' and/or 'urgent' pathogens:** 8 projects, cefiderocol (Fetroja®/Fetrocra®) and its adaptations target CRAB, CRE and CRPA. Furthermore, Shionogi has discovery/preclinical projects targeting *C. auris* and *P. aeruginosa*.  
**Regulatory approvals:** 3 approvals. In November 2019, cefiderocol (Fetroja®/Fetrocra®) was approved by the FDA for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis. In September 2020, the FDA approved the supplemental indication for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP). In April 2020 the EMA approved cefiderocol (Fetroja®/Fetrocra®) for the treatment of gram-negative bacterial infections.

**PORTFOLIO for pathogens in scope**

**Comparatively small portfolio:** At least 8 products: 8 antibacterial medicines  
**On-patent medicine:** 1 (cefiderocol)  
**Off-patent/generic medicines:** 7 of which 2 were selected for analysis\* (cefcape [W], flomoxef [W])  
**AWaRe medicines\*\*:** 2 Access group; 5 Watch group

**Pipeline for priority pathogens**



**Products on the market**



**PERFORMANCE BY RESEARCH AREA**

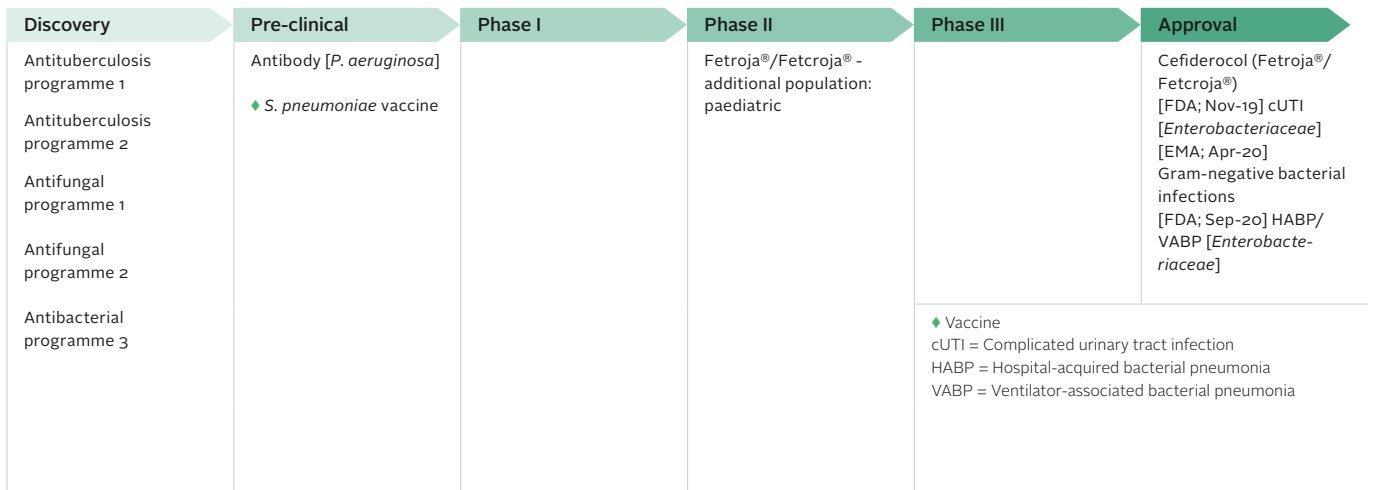
**A RESEARCH & DEVELOPMENT** Evaluated: medicine & vaccine pipelines for priority\* bacteria & fungi

**A.1 Highest relative investment in R&D**  
 Shionogi discloses to the Benchmark its R&D investments during 2019 and 2020 in antibacterial and antifungal medicines and/or vaccines for pathogens in scope. Shionogi reports that it

invested USD 74.22 mn in R&D for antibacterial and antifungal medicines and vaccines in 2019 and 2020. Shionogi invests the highest proportion of its revenues in R&D in this area and the third highest absolute amount compared to the

other companies who reported investments to the Benchmark.. Shionogi has pledged USD 20 mn to the AMR Action Fund over the next ten years.

Pipeline targeting priority pathogens: 11 As at 24 September 2021



\* See Appendix V for information about eligibility for R&D projects and Appendix VII for eligibility criteria of products.  
 \*\* Listed on the 2019 WHO EML.

**A.2.1 Medium-sized diverse pipeline**

The company reports 11 projects targeting pathogens in scope: ten medicines and one vaccine, nine targeting bacterial pathogens and two targeting fungal pathogens. Out of the 11 projects, five are in discovery stage, two are in preclinical development, one is in clinical development and three received marketing approval during the period of analysis.

**A.2.2 No clinical-stage novel projects**

Shionogi's clinical-stage medicine pipeline consists of one innovative R&D medicine, cefiderocol, a siderophore cephalosporin antibacterial for the treatment of multi-drug resistant infections. Cefiderocol (Fetroja®/Fetroja®) obtained marketing approval for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, from the FDA in November 2019, and for HABP/VABP in September 2020. In April 2020, it received approval from the EMA for the indication of gram-negative bacterial infections. Cefiderocol is in Phase II trials for

the extension of its indication to treat children. Cefiderocol does not meet any of WHO's innovativeness criteria.

**A.2.3 Newly active in vaccine development**

Shionogi reports one innovative vaccine project in its pipeline. It consists of a preclinical vaccine candidate against *S. pneumoniae* developed in collaboration with HanaVax Inc.

**A.2.4 Investing in early stage programmes targeting critical and/or urgent priorities**

Shionogi has eight projects targeting pathogens defined as 'critical' by WHO's list of priority pathogens and/or characterised as 'urgent' threats by the US Centers for Disease Control and Prevention (CDC). Cefiderocol, which accounts for four of these projects, targets several MDR gram-negative pathogens such as *A. baumannii* and Carbapenem-resistant/ESBL-resistant *Enterobacteriaceae*. Shionogi is carrying out several discovery and preclinical programmes targeting *P. aeruginosa* and *C. auris*.

**A.3 Plans to improve access and stewardship for cefiderocol**

Shionogi has four projects in its late-stage pipeline, all related to different indications of the same compound, cefiderocol, first marketed in December 2019.

Shionogi reports having an ongoing Global Compassionate Use programme for cefiderocol. It is discussing a potential technology transfer agreement with generic medicine manufacturers to extend access to cefiderocol to other territories. It is also building partnerships with not-for-profit organisations to build a system to support stewardship of cefiderocol. Shionogi reports plans to conduct surveillance of cefiderocol. Shionogi applied for the inclusion of cefiderocol in the WHO's EML and suggested including it in the Reserve (AWARE) category.

**B RESPONSIBLE MANUFACTURING** Evaluated: antibacterials manufacturing (APIs and drug products)**B.1 Comprehensive environmental risk-management for own sites and suppliers; tracks compliance with limits at own sites and suppliers**

Shionogi reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits every five years. It reports setting discharge limits in the receiving environment for all antibacterials manufactured at its site, based on PNECs to limit AMR, as recommended by the AMR Industry Alliance, or the EMA. It also reports quantifying discharge levels at its site using a mass balance approach, verified by chemical analysis if applicable. Its sole manufacturing site in scope is reported to be fully compliant with discharge limits.

Shionogi requires third-party suppliers of antibacterials to follow the same standards, including limits based on PNECs. It reports conducting on-site audits every five years. It requests and reviews the discharge levels of its suppliers. It also reports five out of nine supplier sites have quantified discharge levels and three, or 33%, of those are compliant with discharge

limits.

Shionogi expects its only external private waste-treatment plant to comply with its general environmental standards. It audits this plant every year which includes the suitability of technologies used for processing waste and protocols for preventing contamination. All solid waste and wastewater sent to this plant is set to be incinerated.

**B.2 Publicly discloses information on environmental risk management; aggregated audit results and compliance with limits**

Shionogi leads in public disclosure of its environmental risk-management strategy. It publishes some information on audit results, based on its ERM strategy, and covers wastewater management, solid waste management and discharge limits. It is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. It publicly discloses that all 5 antibacterials manufactured at its own site are compliant with discharge limits. In addition, it is publicly disclosed that five out of nine supplier sites have quantified discharge levels and three, or 33%, of those, which supply

flomoxef (Flumarin®), doripenem (Doribax®) and sulfamethoxazole/trimethoprim (Bakuta®), are compliant with discharge limits. It also publishes a table listing its antibacterials in scope, their connection to own sites and suppliers, and which are compliant with discharge limits. Further, it publishes where five of its suppliers in scope are located (Japan and India) and the respective products supplied by each. The name of its only external private waste-treatment plant in scope is also disclosed.

**B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action**

Shionogi reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. Shionogi also requires its suppliers to audit their own suppliers. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Shionogi's own sites or any subsidiaries that manufacture antibacterials.

**C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS**

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

Shionogi is not eligible for indicators: C.1.3 and C.2.3. For more information, see Appendix VII.

**C.1.1 No filings for relevant on-patent medicines**

Shionogi's performance is low as it has not yet filed its relevant on-patent medicine in access countries. Its relevant on-patent medicine is the antibiotic cefiderocol (Fetroja®/Fetroja®), used to treat infections caused by aerobic Gram-

negative bacteria when there are few treatment options available. It was approved by the FDA in 2019. Cefiderocol is newly included in the WHO 22nd EML (2021) as a 'Reserve' group antibiotic effective against multi-drug resistant bacteria.

**C.1.2 Limited filings for relevant off-patent medicines**

Shionogi's performance is low. It filed its off-patent antibiotics flomoxef and cefcapene, used to

treat several bacterial infections, in one access country (China).

\*\*\* 102 low- and middle-income countries where better access to medicine is most needed.

**C.2.1 No access strategy for relevant on-patent medicine**

Shionogi's performance is low as it does not report strategies to expand access to its relevant on-patent medicine in access countries during the period of analysis. However, in July 2021, Shionogi, GARDP and CHAI announced a MOU to accelerate access to cefiderocol in low- and middle-income countries.

**C.2.2 Expanding access to off-patent/generic medicines**

Shionogi's performance is low as it does not provide access to its two relevant off-patent/generic antibacterial medicines, flomoxef and cefcapene, in access countries. These two medicines did not meet all regulatory requirements because their respective clinical trials were conducted prior to the ICH guidelines. Shionogi does not actively promote these medicines. However,

in July 2021, GARDP identified flomoxef as a potential treatment option for neonatal sepsis.

**C.3 No supply in access countries**

Shionogi's performance is low as it does not yet make its relevant products available in access countries.

**C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP**

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

**C.4 Comprehensive COI mitigation strategies in place for its educational programmes**

Shionogi performs strongly in conflict of interest (COI) mitigation for the five AMR-related educational programmes for HCPs assessed by the Benchmark. To mitigate COI for one programme, it provides financial resources to an independent third party (Radio Nikkei) to develop the programme. The remaining four programmes have all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a pledge not to provide financial or material incentives to participants; and (3) it does not use branded materials.

**C.5 Fully decouples incentives for sales agents from sales volumes, and engages in marketing practices to address appropriate use**

Shionogi performs strongly in sales practices. It reports that it fully decouples incentives for sales agents from sales volumes of its antibacterial and/or antifungal medicines.

Shionogi engages in marketing practices that aim to address the appropriate use of its

antibacterial and/or antifungal medicines. Its marketing materials reflect emerging resistance trends and/or include treatment guidelines for healthcare professionals: for cefiderocol (Fetroja®/Fetcroja®), doripenem (Finibax®) and flomoxef (Flumarin®).

**C.6 Makes one type of brochure and/or packaging adaptation to facilitate appropriate use by patients**

Shionogi adapts brochures to facilitate the appropriate use of cefcapene pivoxil (Flomox®) by patients. Shionogi is middle-performing in this measure, taking account of paediatric use. It has created a brochure that is easy to understand using simple illustrations, which is tailored to the treatment of children to improve paediatric use.

**C.7 Active in multiple AMR surveillance programmes; openly publishes aggregated results**

Shionogi is active in multiple AMR surveillance programmes. It runs the multinational SIDERO-WT programme, which is focused on resistance against Gram-negative bacteria in 13 countries and has been running since 2014. Shionogi only shares the aggregated results through peer-reviewed open-access journal articles, however, within 2021, it is planning to share the raw data on the AMR Register, an open-access data platform. For the remaining programmes, the aggregated results are shared through peer-reviewed open-access journal articles, as well as on an open-access data platform for the SENTRY programme (a programme managed by JMI laboratories).