# Special feature: Why has SHIONOGI joined the fight against infectious diseases?

## Access to Medicine

## Takuko Sawada
**Director and Vice Chairperson of the Board, SHIONOGI**

and

## Manica Balasegaram
**Executive Director, GARDP**

## Dialogue

### Takuko Sawada

Was appointed Director of the Company in 2015 and Vice President in 2018. Since fiscal year 2020, has supervised the Integrated Disease Care Division, Corporate Strategy Division, Pharmaceutical Commercial Division and DX Promotion Division to achieve the Medium-Term Business Plan "Shionogi Transformation Strategy 2030 (STS2030)" and its revised version, "STS2030 Revision." Became Vice Chairperson of the Board in July 2022.

### Manica Balasegaram

Has led GARDP since its creation in 2016. With over 20 years of experience working in global health, Dr. Balasegaram is a global health leader and medical professional specializing in infectious diseases and clinical development. He has worked as a doctor and researcher in countries across sub-Saharan Africa and Southern Asia, focusing on humanitarian emergencies.

The silent pandemic of increasing antimicrobial resistance (AMR) is said to be a problem worldwide, and within this, it is particularly concerning that it will become serious in low- and middle-income countries (LMICs). SHIONOGI, through the conclusion of a licensing agreement including technology transfer with GARDP, and a tripartite partnership agreement adding CHAI, aims to improve access to antibiotics in LMICs. Manica Balasegaram, Executive Director of GARDP and Takuko Sawada, Director and Vice Chairperson of the Board of SHIONOGI, discuss how their partnership on the cefiderocol access project will contribute to tackling this urgent issue.

## The necessity to improve access

**Q Access to the right drugs is regarded as critical in the fight against AMR. Can you say a few words on the topic?**

Balasegaram We can define access as bringing products or services to the world. In the private sector, it is simply called marketing, but from a public health perspective, we typically look at what healthcare systems need, what tools can have a significant impact and how we can ensure equity in this equation. Antibiotics have a particular status in that regard, since they are an integrated component of healthcare delivery. They play an essential role in treating patients, from surgery to oncology to critical care. So we cannot talk about healthcare without including antibiotics. We need both innovation, to create the right tools, and sustainable access.

**Q Dr. Balasegaram mentioned innovation, as there is no access without innovation. What challenges do you encounter at SHIONOGI with respect to innovation?**

Sawada As you mentioned, innovation and access are key components of the fight against AMR. Speaking of innovation, the challenge is that the number of researchers in this field is decreasing worldwide. We must promote the health of the market and provide an attractive environment so that many young researchers will enter this field. And the problem of access may become serious even in developed countries. For example, there are some AMR therapeutic drugs that are approved in the U.S. but cannot be sold in places like the EU because they cannot secure a price that matches the cost. On the other hand, antibiotics classified as "Reserve" are effective against infections that respond to normal antibiotics, but they must be used for appropriate patients such as those with carbapenem-resistant bacterial infections, and should not be used widely or carelessly. Even when supplying to low- and middle-income countries, it is necessary to establish a system that can comply with stewardship in each country's medical system, and ensure continuous surveillance and monitoring of proper use. This is because doing this will also make it possible to distribute our products. Such establishment of medical systems and education need to be carried out extensively and cannot be done by a single company. Governments, NGOs, and industries need to broadly share information and collaborate.

Balasegaram We are definitely seeing a cascading effect, with the broken market leading to a significant slowdown in innovation and a lack of brain power which further impedes innovation. To reverse that trend, we have to recognize that government and policy play an important role in creating favorable conditions and, when it comes to AMR, no one country can do it alone. If innovation is not supported by a nurturing environment, the pipeline dries up and the portfolio of antibiotics becomes redundant. And if we don't talk about access, it is hard to convince countries that they must support innovation if they won't see any of the benefits. So focusing on one or the other exclusively is a misguided way of thinking about the issue.

**Q How does One Health fit into the issue of AMR?**

Balasegaram One Health can be a tricky concept for policymakers to understand. It refers to a global approach encompassing human health, animal health and agriculture. Since we use antibiotics across the board, AMR definitely qualifies as a One Health issue. For us, it could mean asking how to use what we know about the effect of antibiotics on human health to improve animal health, for example.

Sawada The One Health approach is very important. In addition to use in agriculture, livestock, and fisheries, the pharmaceutical industry also needs to avoid the environmental impact of antibiotics during manufacturing. Because bacteria exist everywhere in the environment surrounding us, such as inside living organisms, in the soil, and in water, antibiotics scattered in the environment cause the production of resistant bacteria. Therefore, as a company involved in pharmaceutical manufacturing, we consider wastewater management during manufacturing to be very important. On the other hand, the manufacture of antibiotics is very complex, and when manufacturing β-lactam (penicillin and cephem) antibiotics, there is the difficulty that antibiotics other than β-lactam antibiotics cannot be manufactured at that manufacturing site, and it must be a dedicated factory. In other words, there are also the challenges that investment is difficult unless a stable required quantity can be foreseen, and that it is difficult to respond to sudden increases in demand.

Balasegaram You bring up a very important point which is the issue of manufacturing. The One Health components that are particularly important here are the environment and quality-assured manufacturing, which I see as a basic prerequisite. Manufacturing is to us a central piece of our collaboration. The development phase, including manufacturing, is frequently where it gets complicated, and unfortunately a lot of funders and governments do not recognize that additional investment is necessary. The "D" is often the neglected child of "R&D," and we have to address this issue globally, particularly with antibiotics, as lack of funds could lead to shortages, high cost of goods and, more importantly, a diminished ability to fight environmental contamination and implement One Health.

The cefiderocol access project serves as a very important pathfinder initiative, as we must not only look at access, but also work to create a more sustainable global supply infrastructure in a responsible, cost-effective manner. It requires that we work with companies like Orchid on the manufacturing side. It also required SHIONOGI to take a calculated risk in partnering with us, and we both had to establish risk mitigation plans. There are many factors at play here with cefiderocol, including the setting up of new

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infrastructure with good, sterile conditions. We must also guarantee quality to meet WHO Prequalification.

Addressing all these issues related to access takes years, and picking the right partners is key.

## A closer look at SHIONOGI and GARDP's access initiative: the cefiderocol access project

**Q You've explained the challenges related to access, let's now move towards the solutions. GARDP, CHAI and SHIONOGI have entered a partnership. What were you aiming for and what were you each looking for in a partner?**

Sawada Regardless of the future, currently, the areas that our Group companies can cover are limited, but on the other hand, we strongly recognized the public health importance and need for access to this drug around the time when the approval of cefiderocol came into view. This is because we developed HIV treatment drugs through joint development with ViiV, which are provided to the market by ViiV, but we had been partnering with MPP from the development stage to provide them to LMICs. However, although regulatory procedures are relatively similar, unlike antiviral disease treatments, diagnostic methods for selecting appropriate treatments are not simple for AMR treatments, and the way of dealing with them is very different, including cooperation among doctors, pharmacists, and laboratory technicians. We needed partners who would understand the regulations and medical environment of each country, properly recognize the unique problems of bacterial infections, and be passionate about promoting surveillance, education, system building, and proper use. Before that, we had been talking with GARDP, who had been looking for neonatal sepsis treatment drugs, about other drugs, and when we consulted with them, GARDP was about to launch this program with CHAI, so we were happy to move the conversation forward. We are grateful that they launched this program at a very good time, and we are also pleased that we will be able to deliver cefiderocol to patients who need it in new regions.

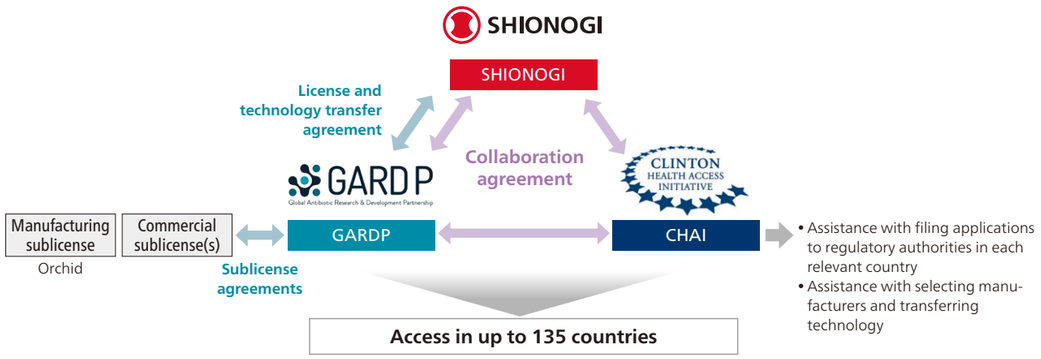
Balasegaram GARDP is a relatively young organization: we were launched as a concept in 2016 and became a legal entity in 2018. We have spent the last few years building a health portfolio, with a mission to accelerate the development and access of antimicrobials with a public health impact in LMICs. We rapidly defined our scope, which includes serious bacterial infections for adults, children and neonates, as well as sexually transmitted infections. We then looked to build portfolio projects to work directly with partners to accelerate development and access.

Cefiderocol is the first treatment ready to go into the access phase. The project was different than others that we were pursuing because the drug was already available to patients in many countries, but still a new technology. When we approached SHIONOGI, you told us that there were not many options for difficult-to-treat Gram-negative infections but this one looked interesting. That was the primary point of interest for us: the clinical utility of the drug.

Next, we tried to identify the areas where we could contribute the most. We set up innovative licensing agreements, looked at alternatives for quality-assured supply, searched for partners who could really commercialize this drug in LMICs, and then prioritized the target markets for introduction. Since we do not have extensive financial resources, we have to work smartly and sustainably, and that's where public-private partnerships are key. We have various governments and funders among our partners, as well as companies like SHIONOGI and Orchid. The collaboration with SHIONOGI is very important for GARDP, because it will set a template and leave behind lessons for future projects.

Sawada We indeed see as it our responsibility at SHIONOGI to work on introducing this highly useful reserve antibiotic in countries with weaker healthcare systems, and are truly grateful for the opportunity to engage in this partnership.

Partnership on the cefiderocol access project




**Q What have you achieved in the last couple of years and what upcoming milestones should we look forward to?**

Balasegaram First, we signed a license agreement between GARDP and SHIONOGI, and then a collaboration agreement between CHAI, GARDP and SHIONOGI. We were then able to move to the next crucial phase: identifying a partner. We deliberately took our time to properly select this partner and, in the third quarter of 2023, we signed a sub-licensing and manufacturing agreement with Orchid. We are now in the technology transfer process between SHIONOGI and Orchid, and Orchid is currently setting up new facilities. Going forward, we will need to validate manufacturing processes, test batches, submit to the relevant regulatory authorities and look at the World Health Organization for an expression of interest. With your support, we will also start to identify relevant partners for commercial agreements.

We view this collaboration as a long-term partnership. The pathway to patients, with all the steps I have previously described, will probably take us to 2027, and then we will focus on effective roll-out. So this will be a continuous process and we will learn many different lessons along the way.

**Q You've probably been asked when cefiderocol would be finally available in the target markets?**

Sawada I am concerned that you might think that we can respond quickly in this case as well because, regarding COVID-19 vaccines, we were able to build a system to supply hundreds of millions of people in a short period of time and provide products. This time, we have gained a wonderful partner in Orchid, but new equipment is also needed, and it will take at least 2-3 years to complete the technology transfer, obtain approval as a manufacturing site, and for Orchid to actually provide products. During that time, I hope we can proceed with environmental improvements to enable proper use in accordance with stewardship.

Balasegaram I believe expectations should be tempered, because we are dealing with a broken market and introducing a product in countries with limited resources, among other challenges. The ambition of both SHIONOGI and GARDP is to go as fast as we can but we have to be careful, avoid cutting corners and remain aware of the mismatch between resources and need.

**Q Would you like to speak about the role the Japanese government can play?**

Sawada The Japanese government can have an impact through the G7 and G20. Funding is important, but it is also important to lead the world in terms of policy, and since Japan is also a country that has been successful in suppressing the occurrence of multidrug-resistant Gram-negative bacterial infections, I think educational support from that perspective would also be effective.

Balasegaram The Japanese government has been a critical partner for us and came on board quite early. It continues to play a very strong role in universal health coverage, which to me is key to strengthening healthcare systems and ensuring more sustainable funding. It has been a key supporter of global health initiatives, including GARDP. It is important that the people of Japan understand what remarkable progress and achievements have been done by both the public and the private sector. I also want to give my personal thanks to SHIONOGI. We at GARDP are not a company, we have a partnership model, so leveraging the power of our partners is how we will achieve our mission.