SHIONOGI

SHIONOGI & CO LTD

ANTIMICROBIAL RESISTANCE (AMR) POSITION PAPER

OCTOBER 2020

SUMMARY

Antimicrobial resistance (AMR) is a global threat with potentially devastating consequences to those infected with resistant pathogens and high direct and indirect cost to society. In the future, lack of effective antibiotics could make routine medical interventions extremely dangerous, make other more complex interventions and procedures impossible, and reduce our ability to respond to outbreaks of new infectious diseases. For these reasons, AMR must be regarded as a global, regional, and national priority for health organizations and governments.

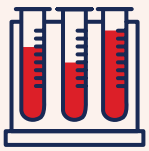
Shionogi is a cosignatory of the January 2016 Davos Declaration. This document, signed by > 100 companies and trade associations, called for collective action to create a sustainable and predictable market for antibiotics, vaccines, and diagnostics whilst emphasizing the need for conservation of new and existing treatments. Together with 12 other leading companies, Shionogi has gone further, signing an Industry Roadmap that includes action plans for antibiotic research and science, appropriate use, access, and manufacturing and environmental actions to achieve this goal. In addition, Shionogi is a founding member of the AMR Industry Alliance, which brings together generic drug manufacturers, biotech companies, and diagnostic manufacturers, as well as leading research and development (R&D) pharmaceutical companies in a united effort to address AMR.

Successfully addressing AMR requires coordinated action by all stakeholders, including governments and international organizations, prescribers, and users of antibiotic products.

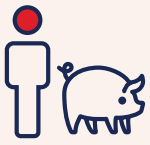
Shionogi believes that the following actions are required:

Create a predictable and sustainable market for AMR products through economic incentives, such as pull incentives and new value assessments for reimbursement

Harmonize global regulations for development and approval of new antibiotics



Establish clinical trial networks to help execute clinical studies more efficiently



Ensure appropriate use of antibiotics through regulation of animal use, stewardship, and timely surveillance of resistance epidemiology

Make effective medicines available for patients in need directly or via alliance partners

Reduce environmental impact from manufacture of antibiotics

We are proud of our ongoing commitment to the research and development of new antimicrobial therapies, and we are working hard to ensure that both individual patients and society as a whole will continue to benefit from effective AMR drugs. We call on all stakeholders to join the fight against AMR.

BACKGROUND

A significant unmet need:
'Time is running out'

Antimicrobial resistance is a real and immediate global threat. The damaging effects caused by resistant pathogens are already responsible for an estimated 700,000 deaths every year globally,[1] with 33,110 lives lost per year in Europe,[2] more than 35,000 lives lost per year in the United States (US),[3] and about 8,000 lives lost per year in Japan.[4] The impact in other areas of the world is estimated to be even more profound.[1] Future projections of the impact of unresolved AMR have been as high as 10 million additional deaths per year by 2050, a figure that surpasses the projected number of deaths caused by cancer (8.2 million).[1] The European Commission reports that combined direct and indirect costs due to AMR amount to €1.5 billion each year in the European Union (EU).[5] In the United States, some estimates have ranged as high as $20 billion in excess direct healthcare costs, with additional costs to society for lost productivity as high as $35 billion a year.[3] By 2050, the world is at risk of losing up to 3.8% of its annual gross domestic product (GDP), with an annual shortfall of up to $3.4 trillion by 2030, a figure on par with the losses provoked by the 2008 global financial crisis.[6] The cumulative cost to the global economy could be as high as US$100 trillion.[1] Moreover, as life-threatening infections can arise after many medical procedures, such as surgery or cancer treatment,[7] the rise of AMR threatens to make routine medical interventions extremely dangerous or even impossible in the future.[1] For these reasons, AMR is a global, regional, and national priority for many organizations and governments. There have been calls for collaborative, multisectoral, and transdisciplinary "One Health" approaches to combat AMR, with the goal of achieving optimal health outcomes and recognizing the interconnection between people, animals, and plants and their shared environment.[8]

Development of resistance to antibiotics is an evolutionary process driven by natural selection and occurring either through spontaneous mutations within the bacterial genome or by the acquisition of exogenous genetic material from other pathogens in the wider environment. The proliferation of resistance genes has in part been driven by overall antibiotic consumption; over the past decades, this problem has been accelerated by inappropriate prescribing, poor infection control practices, incomplete surveillance, and nonhuman use of antibiotics. More recent antibiotic stewardship initiatives that aim to rationalize the use of antibiotics and slow the rate of resistance development have focused on restricting the use of new antibiotics and targeting their use to instances in which treatment options are limited. While it is rational to take steps to ensure the appropriate use of new antibiotics, they have the unintended consequence of making the commercial viability of developing new antibiotics highly uncertain. The uncertainty around market size, combined with the increasingly challenging task of discovering and developing novel antibiotics, has led many large manufacturers to exit, deprioritize, and scale back their antibiotic development programs[9] to focus development activities on more predictable therapeutic areas. Of equal concern, a number of smaller companies with commercialized antibiotics have had to file for bankruptcy or seek acquisition, negatively impacting career opportunities for skilled researchers, as well as commercial diversification. In April 2019, Achaogen filed for bankruptcy after launching plazomicin, and all assets were sold for $16 million; in December 2019, Melinta Therapeutics filed for Chapter 11 bankruptcy protection and was subsequently acquired by Deerfield Management Company. Despite signing a merger agreement to acquire Tetraphase Pharmaceuticals in June 2020, Melinta were outbid by La Jolla Pharmaceutical Company who acquired Tetraphase in July 2020.[10]

Carbapenem-resistant Gram-negative pathogens: New antibiotics are urgently needed

Carbapenems have been the workhorse for treating difficult Gram-negative infections, but resistance to carbapenems is increasing at an alarming rate. Gram-negative bacteria resistant to carbapenems, a class of ß-lactam antibiotics with a broad spectrum of activity, frequently carry multiple resistance mechanisms, limiting their susceptibility to treatment with many different antimicrobial classes. As a result, they have been classified as the highest "critical" priority in the World Health Organization (WHO) global-priority pathogens list. Specifically, these pathogens include carbapenem resistant strains of *Acinetobacter baumannii* (CRAB), *Pseudomonas aeruginosa* (CRPA), and *Enterobacteriaceae* (CRE).[11] These pathogens have been described as "nightmare" bacteria[12] and are considered "urgent or serious" threats by the US Centers for Disease Control and Prevention (CDC).[13]

Infections caused by carbapenem-resistant Gram-negative bacteria are associated with higher mortality rates compared with those involving susceptible strains. However, this varies depending on the pathogen species and infection site. For example, mortality rates for CRE have been reported to be about 30% for nonbacteraemia patients, but can reach up to 70% for bacteraemia or liver transplant patients.[14] Furthermore, the current treatment options available for these patients may address only a subset of resistance mechanisms and/or may be associated with severe adverse events; the polymyxin antibiotic colistin, which was until recently considered a "last-resort" drug used in this context, is associated with reports of nephrotoxicity in up to 60% of patients[15] and was reintroduced to address these resistance issues after withdrawal from use due to safety concerns.[16] More concerning is the fact that even the utility of colistin is under threat because of the recent emergence and worldwide spread of a colistin-resistance genes, such as mcr-1.[17,18]

In terms of economic burden to patients and society, carbapenem-resistant infections are associated with long hospital stays (up to 63 days, depending on pathogen and infection site).[19] In the US, the increases in direct costs per carbapenem-resistant infection have been estimated to range between $22,678 and $65,815 and between $2,599 and $48,106 for indirect costs.[20] Therefore, there exists a significant unmet need in improving the efficacy, safety, and resource use for carbapenem-resistant infections from both clinical and societal perspectives.

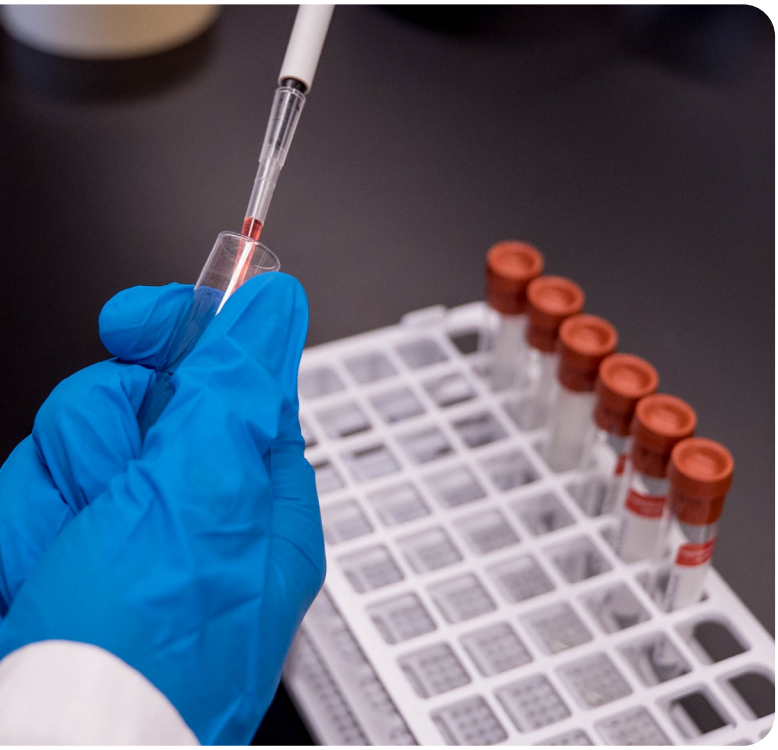
Delay in appropriate therapy: The importance of early diagnosis

Appropriate therapy can be defined as the timely prescription of an antibiotic to which the pathogen is susceptible. Any prolonged delay in receiving appropriate therapy can therefore have a detrimental impact on the patient's clinical outcome.[21] This is particularly true of fragile or severely ill patients, such as those with sepsis, in whom delays in effective therapy have been associated with higher mortality rates, increased resource usage, and increased length of hospital stay[22]. Currently, there is often a delay in the accurate diagnosis of infections, especially when

infections are caused by resistant organisms, and hence a delay in time to effective therapy.[23] Therefore, to improve patient outcomes, there is a clear need to encourage and facilitate rapid identification of a resistant pathogen and its resistance mechanism to ensure that appropriate antibiotic therapy is initiated as early as possible.

Shionogi's long-term commitment to improving research and development to provide treatments for infectious disease[24]

Shionogi is a global pharmaceutical company established more than 140 years ago in Osaka, Japan. Shionogi has been developing antimicrobial therapies for more than 50 years, both by itself and through innovative alliances. In a recent Antimicrobial Resistance Benchmark 2020 survey,[24] Shionogi was found to invest a greater proportion of revenue in antimicrobial R&D than all other companies evaluated. The development of antibiotics is expensive, at about US $1 billion[25] per new antibiotic, and additional postmarketing expenses, for example to address new indications and pediatric use, are likely.[26] According to a Pew Charitable Trust report, only approximately 1 in 4 antibiotics belong to a completely new class or have a novel mechanism of action, and only 1 in 5 of the infectious disease drugs in Phase 1 clinical testing will ultimately be commercialized.[27] We are committed to putting patients first and recognize the importance of investing in infectious disease research despite the uncertainties surrounding returns on investment.



Milestones in Shionogi's antibiotic development history include the following:[28]

- 1959: *sulfamethoxazole*, the first sulfonamide antibiotic drug discovered and developed by Shionogi
- 1982: *moxalactam*, the world's first oxacephem antibiotic
- 1988: *flomoxef*, the world's second oxacephem antibiotic
- 1992 and 1997: *ceftibuten* and *cefcapene*, new oral cephem antibiotics
- 2005: *doripenem*, a new carbapenem antibiotic
- 2019: *cefiderocol*, the world's first approved siderophore cephalosporin antibiotic

Cefiderocol, recently approved by both the FDA[29] and the EMA,[30] is the first of a new class of siderophore-cephalosporin antibiotics with activity against multidrug-resistant (MDR) Gram-negative bacteria potentiated by its novel mechanism of cell entry.[31] Building on our legacy, Shionogi is currently developing several other infectious disease drug candidates discovered in our in-house R&D programme.

Other anti-infectives that Shionogi has developed include baloxavir marboxil (Xofluza®) for influenza A/B infections and dolutegravir (Tivicay®) for the treatment of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).[31]

SHIONOGI'S POSITIONS AND STRATEGIES

Davos Declaration/AMR industry roadmap and Shionogi AMR positions

Shionogi is a leader in anti-infective development within the pharmaceutical industry and supports various global and regional initiatives and recommendations, such as the declaration on addressing antibiotic resistance by the G7[32] and G20[33] countries in the United Nations,[34] the Global Action Plan by WHO,[35] and the AMR Review on Antimicrobial Resistance (also known as the O'Neill Report).[1] We also strongly believe in the importance of continuing to address the AMR issue and support pragmatic action at the country level to address immediate needs while global frameworks are established.

Shionogi is a cosignatory of the Davos Declaration (January 2016),[36] together with more than 100 companies and trade associations. The declaration called for collective action to create a sustainable and predictable market for antibiotics, vaccines, and diagnostics, simultaneously emphasizing the need for conservation of new and existing treatments. Based on this declaration, Shionogi, together with 12 leading companies, has signed an Industry Roadmap outlining action plans to achieve this goal.37 We believe in consolidated action and have joined with other industry stakeholders to progress initiatives through the AMR Industry Alliance, an initiative sponsored by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) that includes generic drug manufacturers, biotech companies, and diagnostic manufacturers, as well as leading R&D pharmaceutical companies.[38]

To address the complex, global AMR issue, we believe that a combination of actions is required:

1. Create a predictable and sustainable market for AMR products through economic incentives, such as pull incentives and new value assessments for reimbursement

2. Harmonize global regulations for development and approval of new antibiotics

3. Establish clinical trial networks to help execute clinical studies more efficiently

4. Ensure appropriate use of antibiotics through regulation of animal use, stewardship, and timely surveillance of resistance epidemiology

5. Make effective medicines available for patients in need directly or via alliance partners

6. Reduce environmental impact from manufacture of antibiotics

1. Create a predictable and sustainable market for AMR products through economic incentives, such as pull incentives and new value assessments for reimbursement

Economic incentives

As pathogens continually evolve their response to antibiotic therapies, there is a need for R&D to develop new molecules to outpace the development of resistance. Shionogi strongly supports the introduction of new incentives, funding, and reimbursement models to restore a viable commercial market and maintain R&D, innovation, and excitement in this critical field.

Measures to support the widespread implementation of antibiotic stewardship are of vital importance in combating AMR and prolonging the utility of antibiotics. Shionogi therefore supports the delinking of sales volume from revenue reward; this will support more appropriate use over the long term, leading to better outcomes for patients and improved antibiotic sustainability. Addressing the economic model for antibiotic development and commercialization is critical. We advocate for a mix of "push" (eg, subsidies for R&D) and "pull" (eg, financial incentives for commercialization) options, as well as other regulatory or government incentives designed to stimulate continued development and commercialization of novel antimicrobial agents.[39]

Shionogi is excited to see the visible progress with respect to "push" incentives, for example, the Biomedical Advanced Research and Development Authority (BARDA) [40] Broad Spectrum Antimicrobials Program, the Combating Antibiotic-Resistant Bacteria (CARB-X) partnership,[41] the Global Antibiotic Research and Development Partnership (GARDP),[42] the Innovative Medicines Initiative (IMI),[43] New Drugs 4 Bad Bugs (ND4BB)[44] program, and the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR).[45] We have been working with partners across various parts of the health sector to find workable solutions to the numerous unmet needs in infectious disease. Since its inception in 2013, Shionogi has participated in the Global Health Initiative Technology (GHIT) Fund, Japan's first public-private partnership fund[46] created to advance the research and development of innovative medicines for the treatment of infectious diseases in the developing world.

While "push" funding is important, "pull" incentives are critical to ensure that new antibiotics are made available to consumers. To date, there has been much discussion but little tangible action in terms of pull incentives. We recognize that pull incentives have to fit country and regional situations, and therefore support implementation of a suite of pull incentives, such as partially delinked or fully delinked market-entry rewards, subscription payment schemes,[47] and government purchases, in addition to

innovative, anti-infective-specific, value-based pricing and reimbursement initiatives, such as Diagnosis-Related Group (DRG)-linked reimbursement reform. Shionogi appreciates the ongoing discussion of pull incentives by governments and other organizations and strongly advocates for quickly moving from discussion to implementation.

New value assessment of antibiotics for reimbursement and health technology assessment (HTA)

In relation to implementing economic incentives, there is an urgent need for new approaches to assessment and payment for new antibiotics, including the use of nonclinical pharmacokinetic/pharmacodynamic data and in vitro microbiological data to predict response for MDR pathogens and recognition of societal value, such as avoidance of the spread of infection to the wider population.[48]

Measures designed to assess wider public benefits, such as diversity value (benefits of having a range of treatments); transmission value (benefits of avoiding the spread of infection in the population); enablement value (benefits of enabling surgical and medical procedures to take place); spectrum value (benefits of replacing broad spectrum with narrow spectrum antimicrobials that target specific pathogens); and, potentially, insurance value (benefits of having treatments available in case of sudden, or major, increase in prevalence of infections) of new antibiotics should be included, as recommended in reports by the Policy research Unit in Economic Methods of Evaluation in Health & Social Care Intervention,[49] Driving Reinvestment in R&D for Antibiotics and Advocating Their Responsible Use (DRIVE-AB),[50] the Duke Margolis Center for Health Policy,[47] and the Office of Health Economics.[51] In addition, budget constraints resulting from imposed bundle payment systems, such as the Diagnosis-Related Group-based (DRG) hospital reimbursement system, should be addressed where they create hurdles for use of the most appropriate antibiotic.[50] For example, some have suggested that the reimbursement value of the antibiotic should be removed from the DRG, a so-called "DRG carve-out", which would enable antibiotics to be reimbursed independently, potentially removing any economic disincentive for use.[50]

In the short to medium term, while a global framework is maturing, Shionogi is exploring new valuation and reimbursement models with the European Network for Health Technology Assessment agencies (EUnetHTA)[52] and national healthcare systems.

Risk-sharing scheme in manufacturing

Shionogi has made a significant investment in manufacturing facilities, in part because some antibiotics require dedicated manufacturing equipment, and plant capacity must be prepared in advance of need. Adoption of appropriate use policies make it likely that many new antibiotics targeting AMR bacteria will be manufactured in low volume. Further, planning for future demand is complicated by our inability to predict future resistance patterns. Together, these issues drive up the cost of goods and thereby exacerbate access issues. Shionogi supports implementation of measures that address manufacturing issues as part of the overall development and commercialization need.

2.1 Harmonize global regulations for development and approval of new antibiotics

The introduction of clearer and more streamlined regulatory approaches and guidelines by the European Medicines

Agency (EMA; Priority Medicines [PRIME],[53] Adaptive Pathways,[54] and US Food and Drug Administration (FDA; Generating Antibiotic Incentives Now [GAIN],[55] Limited Population Pathway for Antibacterial and Antifungal Drugs [LPAD][56] in the 21st Century Cures Act), which may allow faster development, expedited review processes, and eventually earlier access for patients, have been well received. We believe that further harmonization of the clinical trial requirements across regions, beginning with parallel tripartite meetings among the EMA, FDA, and Pharmaceuticals and Medical Devices Agency,[57] would further support faster access to new antibiotics globally. Further, we see opportunities for additional regulatory incentives for antibiotics, such as those that exist for orphan drugs or for drugs that target neglected tropical diseases.

3. Establish clinical trial networks to help execute clinical studies more efficiently

One of the biggest challenges for developing new antibiotics addressing resistant bacterial infections is the generation of comparative data from target patients with resistant infections. Usually, clinical trials for resistant infections are conducted in a nonresistant patient population using a noninferiority study design,[50] since it would be unethical to study patients with resistant infections with a comparator agent that is already known to be ineffective against resistant pathogens. If patients with resistant infections are studied with a comparator drug or best available therapy, underlying complexities, such as heterogeneity in the epidemiology, underlying conditions, and causal pathogens, make not only a superiority design, but also statistical powering of the study, challenging. Shionogi believes that creation of a clinical network focused on antibiotic studies would allow for more efficient and cost-effective study execution. Shionogi has collaborated with Combatting Bacterial Resistance in Europe–Networks (COMBACTE-NET), a part of the EU ND4BB program, for microbiology support for the cefiderocol development program and will look for opportunities to participate in more extensive network opportunities.

4. Ensure appropriate use of antibiotics through regulation of animal use, stewardship, and timely surveillance of resistance epidemiology

The use and misuse of antibiotics accelerates the emergence of drug-resistant strains.[58] To maintain the efficacy of currently available antibiotics, inappropriate antibiotic use should be minimized. Antibiotic use in animals exceeds use in humans (eg, 72.5% animal versus 27.5% human in the US).[1] Therefore, addressing AMR requires a significant emphasis on appropriate use in agriculture. Shionogi welcomes the changes introduced in some countries to ban last-resort antibiotic use in animals (eg, the colistin ban in China)[59] and welcomes retail and food chain efforts to reduce antibiotic use in food production (eg, Marks & Spencer, McDonald's).[60,61]

For human use, as a first step, Shionogi believes that the regulatory label for anti-infective products should reflect patient need and guide physicians appropriately. This points to the need for pathogen-focused labels with a focus on ensuring efficacy against the specific bacterial infection rather than traditional labels based only on sites of infection. Regulatory agencies have already made progress with respect to harmonizing both clinical development requirements and product labels, and we encourage further progress.

Treatment should be appropriate for the bacteria causing the infection, using the correct dosage for the correct length of time. We support the implementation of financial stewardship incentives, such as financial penalties/rewards along the healthcare value chain. We participate in educational programs for healthcare professionals to raise awareness of issues around AMR stewardship, and we do not remunerate sales staff based on sales volume of antibiotics.[24] In addition, we fully support efforts to promote rapid microbiological diagnosis and antimicrobial susceptibility testing, as quick initiation of appropriate therapy is critical both to patient outcomes and to ensuring the appropriate use of antibiotics. Incentives for the use of rapid diagnosis could limit the empirical use of anti-infectives, support the transition to targeted antibiotic therapy, and improve patient outcomes.

Along with aligning incentives for appropriate antibiotic use, we also support global and national action plans to conduct more timely and coordinated surveillance for resistant infections. Timely and well-coordinated surveillance activities to understand the epidemiology and emergence of resistant bacteria are critical, for both front line physicians and healthcare stakeholders setting strategies to address AMR. For clinicians, this provides supportive information, enabling them to choose the most appropriate therapy when susceptibility information is limited. For healthcare stakeholders, the timely understanding of the issue is fundamental to target the most critical priorities. Shionogi has been conducting global surveillance of Gram-negative infections to support the cefiderocol development program and would be willing to participate in initiatives designed to share surveillance data.

5. Make effective medicines available for patients in need directly or through alliance partners

Infectious diseases resulting from acute viral infections such as influenza or COVID-19 can result in large numbers of patients with secondary bacterial infections, often with difficult-to-treat nosocomial pathogens.[62] A bioterrorism event could also result in mass exposure to a bacterial strain with bioengineered resistance. Shionogi is committed to supporting society and patients in need directly, through government agencies, or via alliance partners.

To improve global access to medicines, exploring and establishing new business models with other stakeholders is essential. Shionogi has been working to improve access to our innovative medicines through alliances and licensing partnerships with other global companies. For example, we have established collaborations for novel drugs originated by Shionogi that treat HIV/AIDS and influenza. Contributing to our core business model of commercialization of R&D innovation through alliances and licensing, we recognize the importance of considering access provisions in possible future partnership agreements related to AMR.

6. Reduce environmental impact from manufacture of antibiotics

It is crucial for antibiotics manufacturers to implement measures to reduce the environmental impact from production. Shionogi has been engaged in the development, manufacture, and sale of antimicrobials for many years and has always strictly controlled the release of antimicrobials into the environment. We have committed to environmental impact control strategies[63] and will work together with other pharmaceutical companies on environmental risk management through the Pharmaceutical Supply Chain Initiative (PSCI) and implementation of Industry Roadmap commitments.

CONCLUSION

Shionogi recognizes that establishing pull incentives, introducing new value assessments/reimbursement systems, and implementing other initiatives to address AMR will take time, stakeholder engagement, and political goodwill at national and global levels. Even if effective appropriate use measures are deployed globally, the emergence of microbial resistance can only be slowed. Given the long timeframe required to develop new medicines, society now needs a strategy to incentivize development and commercialization of new antibiotics. While many pharmaceutical companies have moved away from infectious disease R&D, we are proud to be committed to ensure that both individual patients and society as a whole will benefit from new antibiotics and will take a leadership role in ensuring access and appropriate use.

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