

Provisional Translation*

Report on Clinical Evaluation of Antimicrobial Agents for AMR

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Subcommittee on AMR of the Science Board

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1. Background

The focus of drug development has shifted towards drugs that are expected to be used for a long period of time, such as those for lifestyle-related diseases and anticancer drugs. Many pharmaceutical companies have already withdrawn from antimicrobial development. However, there are still many antimicrobial resistant (AMR) infections for which no effective antimicrobials are available. A publication estimates that AMR infections would lead to 10 million deaths globally every year by 2050 exceeding the number of deaths from cancer. Drug resistant infections must be tackled on a global scale.¹

To address these issues, actions to combat AMR were placed on the agenda of Group of Seven Summit (G7 Summit), etc. At the G7 Summit in Elmau in 2015, One Health Approach was proposed which encompasses medicines, farming and agriculture to emphasize the importance of international cooperation in the development of new antimicrobials, vaccines, etc.² At the G7 Ise-Shima Summit in 2016, promotion of appropriate antimicrobials use and development was also stressed.³

In Japan, a ministerial group to address global infections threats has published a National Action Plan on Antimicrobial Resistance (AMR) in 2016. This action plan encourages new antimicrobial development. In line with it, the Pharmaceuticals and Medical Devices Agency (PMDA) announced the commencement of discussions with the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for convergence of requirements in clinical trials for antimicrobials development.⁴ These three regulatory agencies recognize that it may be appropriate to accept a greater degree of uncertainty regarding the benefit-risk balance when developing new antimicrobials that can be used to treat patients with limited treatment options. Currently, discussions on this view seem to be underway.

To contribute to the above discussion, the expert committee investigated methods to evaluate antimicrobials for AMR infections. This investigation was focused on AMR infections whose incidences are extremely low for reliable efficacy evaluation in controlled clinical trials, but not those common enough for controlled clinical trials, such as methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

2. Development Phase

In Japan, where effective infection control measures, including those against hospital acquired infection, are in place, AMR infections are currently very occasionally reported. This makes it very limited to recruit participants for clinical trials in a conventional way, i.e., enrolling patients with infections by each infection site (organ). Trial contracts with medical institutions can also be an obstacle for the conduct of a clinical trial in patients with AMR infections. It is common for pharmaceutical companies to make a trial contract with a single department of each medical institution. This may result in no enrollment of patients with AMR infections at clinical trial sites. Patients with emergent severe infections must be first given life-saving treatments, which almost always involve premedication with antimicrobials. These factors must be taken into consideration in designing a clinical trial.

Conventionally, multiple phase III trials are conducted as controlled trials for registration. Recruitment of patients with AMR infectious diseases for clinical trials may be limited when, for example, their incidence rates are very low. If this is the case, the use of a compact clinical data package consisting of supplemental nonclinical data, Pharmacokinetics/Pharmacodynamics (PK/PD) data, and data from small-scale clinical trials are proposed.⁵ To improve profitability of antimicrobial developers, the necessity of an overhaul of the present business model on a global scale has also been suggested.⁶ On the basis of these suggestions, several measures were presented at the Summit on Financial Markets and the World Economy in 2016 (G20). One of which is incentives to overcome challenges in antimicrobial development.⁷ Information gathering throughout the Product Life Cycle from development phase to post-marketing phase is also considered useful.⁸

Below are a summary of discussions on necessary actions to be taken in the development phase.

2.1 Challenges in Global Clinical Trials and Proposals for facilitation

A list of pathogens that require new antimicrobials has been published by the World Health Organization (WHO). Pathogens classified as “Critical” in this list includes antimicrobial resistant (AMR) bacteria, represented by Carbapenem-resistant *Acinetobacter baumannii* (CRAB), Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and Carbapenem-resistant Enterobacteriaceae (CRE). Infections caused by AMR bacteria are generally very rare across the world, although the frequency of their isolation and the incidence of AMR infections vary among countries. Given this, the clinical development of effective antimicrobials for AMR infections requires global clinical trials with international cooperation, but not single-region/country trials.

To conduct global clinical trials in patients with AMR infections, primary efficacy endpoints, timing of evaluation, etc. need to be standardized among participating countries for each target infections. At present, however, even primary endpoints of clinical trials in general infections caused by bacteria

susceptible or not susceptible to study drug depend on the country where the trial is conducted. In the development of drugs for AMR infections, convergence of entry criteria and efficacy endpoints is needed across countries. Some proposals for harmonization are presented in Appendix.

Patients with AMR infections tend to have a greater variety of baseline characteristics and would result in a unfavorable outcome due to treatment failure, etc. Despite these differences between general and AMR infections, similar efficacy endpoints and evaluation timing could be generally used in clinical trials for AMR and general infections.

In Europe and the US, the following guidelines have been issued regarding the clinical evaluation of antimicrobials for bacterial infections with unmet medical needs, such as those for which no treatment option is available. In Japan, the Guidelines for the Clinical Evaluation of Anti-Microbials (Notification No. 1023-3 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour, and Welfare dated October 23, 2017) includes a brief description of AMR infections. The guidelines, however, unfortunately do not focus on clinical evaluation of patients with AMR infections

- FDA : Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases (August 2017)
- FDA : Limited Population Pathway for Antibacterial and Antifungal Drugs (DRAFT GUIDANCE, June 2018)
- EMA : Guideline on the evaluation of medicinal products indicated for the treatment of antibacterial agents, addendum (October 2013)

Developing new antimicrobials for AMR infections in Japan with reference to the clinical guidelines/guidance in Europe and the US would be a feasible option to obtain regulatory approval. This option requires discussion to figure out the antimicrobial development that suits the circumstances and situations of each country. In each country, the procedures for clinical trials and views on indications/applicable pathogens differ among the regional regulatory authorities.

If a Japanese pharmaceutical company decides to participate in a global clinical trial, the company should preferably hold a clinical trial consultation with PMDA at the same time of consultations with European/US regulatory authorities in principle to avoid a situation that Japan alone is not left behind. To facilitate clinical trials of antimicrobials for AMR infections, the following infrastructures need to be developed.

- Even if the target number of Japanese patients would not be achieved in a global clinical trial, it may be acceptable as long as the target sample size of the entire trial is met.
- Convergence of data required for regulatory approval of drugs for AMR infections between FDA/EMA and PMDA needs to be promoted. For the efficient development of individual antimicrobials for AMR infections, information exchange among the three regulatory authorities and other measures are also required. Information should be gathered and shared worldwide from the development phase to the post-marketing phase to

enhance evidence on efficacy and safety, which will be inevitably limited at the time of approval.

- In the case of drugs for AMR infections already registered in European/US countries, it may also be reasonable to approve them in Japan based on data (e.g., clinical, nonclinical, PK/PD data) from these countries. This will minimize clinical evidence for approval needed to be collected in Japan (e.g., only safety data).

2.2 Possible Alternative Development Methods

The number of patients with AMR infections dealt with in this report is too small for statistical verification of data in controlled clinical trials. Below are proposals to supplement insufficient data from clinical trials.

1) Modelling & Simulation

The recent drug development process not only explores the relationship between pharmacokinetics (PK) and pharmacodynamics (PD) using a PK/PD model but also focuses on model analysis in relation to outcomes, such as efficacy, safety, survival rate, and bacterial resistance rate. These approaches are evolving particularly in Europe and the US. At each stage of clinical drug development, data are analyzed using quantitative models. Modelling & Simulation (M&S) using Monte Carlo simulation (MCS) enables the estimation of the success rate of clinical trials. This model-based approach is used for decision-making in drug development.⁹

M&S approaches are roughly classified into a top-down approach which builds models based on observed data from clinical trials and a bottom-up approach which analyzes data while building models using human physiological information, along with biochemistry and biochemistry information such as *in vitro* study data. Both approaches are used to predict blood concentrations, clinical endpoints, etc. In Europe and the US, efforts to formulate guidelines for these approaches are intensifying.

The M&S or model-based drug development (MBDD) approaches are used in various drug development processes. Modelling is an essential tool for drug development. The key for successful drug development is preparing a model with high predictability for a target patient population. Originally, the drug development method using modelling was called MBDD in Europe and the US. The White Paper compiled by the European Federation of Pharmaceutical Industries and Associations (EFPIA) extends this concept to model-informed drug discovery and development (MID3). To ensure consistency in implementation of MID3 across the pharmaceutical industry, this document i) informs how integration of MID3 can benefit pharmaceutical companies in decision making during drug development; ii) provides MID3 analysts with materials to enhance the planning and consistency of the application of MID3; and iii) provides regulatory authorities with materials to develop MID3-related guidelines.¹⁰

On the other hand, M&S using Physiologically Based Pharmacokinetics (PBPK) helps companies to predict possible drug interactions and obtain information on the feasibility of clinical trials or study design at each drug

development stage. This M&S approach can also be used for antimicrobial development in special populations, such as pediatric and elderly patients. An M&S-based analysis requires full understanding of the nature of the model and simulation to be used according to their purposes of use. The reliability of obtained results also needs to be ensured. When applications for regulatory approval are based on simulation results, it is necessary to provide the hypotheses used to create the model and the information regarding the process of model building. It is also required to explain the validity of the model and simulation results from statistical aspects and physiological, medical, and pharmaceutical viewpoints.¹¹ In fact, in line with growing expectations for M&S, pharmaceutical companies have already developed excellent drugs using M&S approaches, contributing to improved public benefits.¹² The use of M&S is essential in the development of drugs for AMR infections, which has been stagnating.

2) Estimation of Dosage Regimens Using Pharmacokinetic/Pharmacodynamic Model⁸

Pharmacokinetics (PK) refers to the relationship between dose/mode of administration and the time course of drug behavior (absorption, distribution, metabolism, and excretion) in the body. Pharmacodynamics (PD) indicates the relationship between drug exposure in the body and effects (expected therapeutic effects and adverse effects). The PK/PD model for anti-infective drugs is a tool to enable their appropriate clinical use. By combining and linking PK and PD data, dosage regimens related to their effects can be understood, which helps find the optimal dosage regimens of anti-infective drugs in terms of their efficacy and safety.⁸

In nonclinical and clinical studies conducted for registration of new antimicrobials or their additional indications, it is important to find the optimal mode of administration of antimicrobials that minimizes adverse reactions to them and to maximize their clinical effects. There are some critical issues to be clarified in nonclinical studies. First, PK/PD parameters that correlate with therapeutic effect (e.g., C_{max} or C_{peak}/MIC ,¹ AUC/MIC ,² and $T > MIC$ ³) in a nonclinical PK/PD study(ies) should be determined to calculate the therapeutic thresholds of these parameters. Second, factors that are involved in suppression of AMR need to be identified from the relationship between PK and Mutant Prevention Concentration (MPC). Third, PK parameters that are associated with the occurrence of adverse reactions should be determined to calculate their thresholds that may be associated with adverse reactions. Active conduct of PK/PD analysis based on nonclinical results helps optimize dosage regimens of antimicrobials more effectively in terms of their efficacy and safety, and realize their appropriate clinical use. To predict the occurrence of adverse reactions, nonclinical data alone are not sufficient. Safety assessment, including post-marketing surveillance, is also required.

Since FDA issued the guidance regarding exposure-response (E-R) relationships,¹³ PK/PD analysis in patients has increased the success rate of late-phase clinical trials, which are generally associated with increased

costs of drug development. PK/PD analysis is also expected as an M&S strategy that provides information regarding dose adjustments in routine clinical practice. It has started being used to predict not only the efficacy and safety of antimicrobials, but also bacterial resistance rate.¹⁴

Drug concentration information obtained with specimens other than blood, such as surgically resected specimens, bronchoalveolar lavage fluids (BALFs), and spinal fluids, even from a limited number of subjects, is important because such information clarifies the relationship between the blood concentration and tissue distribution of a drug.⁸ It is advised to include measurement of drug concentrations in specimens (including those from affected sites in which drug concentrations can be relatively easily measured, such as sputum and urine) in the study protocol as far as possible, considering the characteristics of antimicrobials.

The advisory committee of FDA reported that microdialysis was an attractive methodology for drug distribution research of antimicrobials.¹⁵ Microdialysis can be a useful evaluation tool for clinical PK/PD in patients with rare diseases, such as AMR infections.

- *1: Maximum concentration or peak concentration/Minimum Inhibitory Concentration (MIC)
- *2: Area Under the time-concentration Curve/MIC
- *3: Percentage of a 24-h period that the drug concentration exceeds the MIC under steady-state PK conditions (Time above MIC)

3) Monte Carlo Simulation⁸⁾

PK/PD analysis and M&S in clinical trials help increase the success rate of clinical trials. More specifically, the probability of PK/PD target attainment is estimated by MCS using population pharmacokinetic (PPK) parameters in each target patient population and sensitivity distribution (MIC distribution) data of pathogens to find the optimal dosage regimens. In estimation of the target values of PK/PD parameters in clinical trials, PPK analysis and Bayesian estimation, calculation of PK/PD targets, and other methods that consider individual characteristics, such as protein binding rate (unbound drug concentration) and other influential factors (e.g., host factors and bacterial factors), are helpful.

It is preferable to clarify which one of the following factors was randomly generated for MCS according to its purpose:

- Inter-individual variation in population model
- patient's baseline characteristics included in covariates, or
- MIC

4) Determination of Pediatric Dosage Regimens using Results from Adult Clinical Trials⁸⁾

Clinical development using PK/PD analysis is also recommended in the field of pediatric medicine. The details are presented in the section of pediatrics.

5) Hollow-Fiber Simulation

Currently, Hollow-Fiber Infection Model (HFIM) is used in Europe and the US as a nonclinical PK/PD model to estimate the dosage regimens of antimicrobials. FDA and EMA have accepted the use of this model as a tool for antimicrobial development.¹⁶ This tool is also expected to be used in Japan. Conventionally, Chemostat Model is used as a PK/PD model. In this model, bacterial survival is monitored after a medium containing an antimicrobial is pumped into a culture vessel seeded with a test strain. Its use is, however, limited to short-term tests (approximately 24 hours) because bacteria flow out of the culture vessel over time. HFIM uses Hollow Fiber Cartridge (HFC) with Extra Capillary Space (ECS), in which a test strain is seeded. Bacteria cannot pass through the dialysis membrane of the HFC and stay inside the ECS, which enables long-term assessment for approximately 2 weeks to 1 month. During the test, an antimicrobial-containing medium is sent to the drug reservoir by a syringe pump and a tube pump, which mimics the human PK. The drug reservoir forms a circulation pathway with the HFC through a duet pump so that bacteria in the ECS grow or die in an environment that reflects the human PK. Samples are taken from the ECS over time. In general, viable bacteria are counted by the colony count method. Antimicrobial concentrations are measured by high-performance liquid chromatography. To detect resistant bacteria with decreased sensitivity, an agar medium containing a drug at a concentration three times higher than the MIC is often used. In many reported tests, samples were taken from the drug reservoir to obtain antimicrobial concentration data.

In antimicrobial evaluation, the antimicrobial is added to a HFIM seeded with a specific bacterial strain at various doses and dosing frequencies to select PK/PD parameters that can be used as efficacy indicators. Then, various types of bacterial species/strains are exposed to the antimicrobial to determine PK/PD targets that are expected to ensure efficacy. PK/PD targets possibly associated with the containment of drug-resistant bacteria also need to be determined. These 3 steps will provide the optimal clinical antimicrobial dosage regimen.

Currently, HFIM simulates 1-compartment PK for not only antimicrobial monotherapy but also combination therapy with antimicrobials having different half-lives. The theory behind it is described in Blaser's report.¹⁷ This model cannot mimic 2-compartment PK, and may underestimate or overestimate target PK/PD values. Currently, however, all PK analyses are performed using 1-compartment models. This situation needs to be changed.

The ECS (particularly capillary) is susceptible to biofilm formation. However, not many assays have been conducted on biofilm-associated infections.¹⁸ A biofilm that has formed in the ECS prior to an assay can be observed only after it is collected. Biofilms need to be collected in an appropriate way.

The methods for creation and use of HFIM have not been standardized yet. Overseas, HFIM is used to support the application for antimicrobials. To assure the reliability of the model, HFIM needs to be standardized.

6) Scope and Challenge of Modelling and Simulation

M&S is a useful tool that helps improve the quality of product development, reduce development costs, and shorten development time. On the other hand, this approach does not replace clinical trials in terms of fitting of parameters of adverse reactions and special pathological conditions, etc. It is important to fully understand the limits of M&S when it is used. The following issues must also be kept in mind in using M&S for the development of drugs for AMR infections:

- The PK in patients with sepsis, etc. changes in a short period of time as the pathology changes.
- The protein binding rate is extrapolated to an M&S model assuming that it generally does not change. In the case of high protein-bound drugs, however, the correlation between effect and unbound or total drug concentration changes as the protein binding rate changes within a patient.
- What needs to be verified, including validation of M&S, to help design a clinical trial should be clarified.

M&S is considered useful in predicting efficacy. To assure safety, accumulation of actual use experience is essential. All-case surveillance as a post-marketing surveillance may be accepted as a condition for approval. Utilization of M&S requires various knowledge and skills. Fostering pharmacometricians is also urgent.

2.3 Clinical Trial Networks

In Japan, the clinical trial system has been created by establishing “Early/exploratory clinical trial centers” and “Clinical research core hospitals,” and implementing “Five Year Activation Plan for Clinical Study/Trial 2012” to promote R&D in the medical field.¹⁹ However, R&D in the infections field has not necessarily led to the development of new medical products or applications in other medical fields.

In Japan, surveillance systems and quarantine systems that investigate and control the occurrence of infections have been established, including the National Epidemiological Surveillance of Infections (NESID), the Japan Nosocomial Infections Surveillance (JANIS), the AMR Clinical Reference Center, the National Center for Global Health and Medicine (hereinafter, the AMR Clinical Reference Center), and the Three Academic Societies Joint Antimicrobial Susceptibility Surveillance.²⁰ These systems have reinforced detection and public awareness in the event of an outbreak of afferent infections, and supported special medical care available at medical institutions. In accordance with the JANIS report, medical institutions participating in this program account for 16.9% of all medical institutions in Japan; 45% of hospitals with 200 or more beds or 77% of hospitals with 500

or more beds.^{21,22,23} These surveillance systems, however, have a time lag between the occurrence and reporting of infection. Unfortunately, they do not function in the role of finding participants for clinical trials of aggressive infections.

Overseas, there are medical cooperative programs in the global health field, such as the Japan International Cooperation Agency (JICA) and the National Center for Global Health and Medicine (NCGM), and international joint research projects, such as the Science and Technology Research Partnership for Sustainable Development (SATREPS). All recognize that infections are a primary issue. AMR infections are a focus for future threats. Globalization, high-speed transport systems, and high population density all together make it easy even for rare infections to enter and spread in Japan. There are always potential threats of an outbreak of AMR infections or emerging infections for which no appropriate treatment is available.²⁴

Patients need to be enrolled in a clinical trial almost immediately because such infections progress rapidly in most cases. Patients cannot be moved from one hospital to another. The primary hospital that diagnoses a patient as having an AMR infection will inevitably need to serve as a clinical trial site. However, not all medical institutions where AMR infections occur are sufficiently equipped to conduct a clinical trial. This hinders efficient enrollment of eligible patients in clinical trials. On the other hand, many medical institutions with plenty of experience with clinical trials have already installed high-quality infection control measures. At these institutions, AMR infections are more likely to be well contained. For these reasons, creating networks that involve only advanced medical institutions that are leading clinical trials in each country does not necessarily accumulate AMR infection cases.

To address these situations, it is necessary to install local base networks between advanced medical institutions who are experienced in clinical trials and hospitals in areas vulnerable to AMR infections. In addition, a 24-hour-a-day system needs to be created to enroll patients in a clinical trial immediately in the event of an AMR infection which occurs at a medical institution with little clinical trial experience.

For more efficient recruitment of patients with AMR infections, core medical institution networks that cover the whole nation and work with overseas clinical trial networks are also required as well as local networks.

Good examples of clinical trial networks are the Southwest Oncology Group (SWOG) and the Japan clinical oncology group (JCOG), which have contributed to the optimization of multidisciplinary treatment which combines multiple therapies, such as drug therapy and radiotherapy. This has been going on for more than 30 years. In Europe, the European Clinical Research Infrastructure Network (ECRIN), which links clinical research networks across Europe, have contributed to medical advancements through efficient conduct of global clinical trials (e.g., efficient recruitment of patients with rare and refractory diseases).^{25,26,27}

Although existing advanced medical institutions do not necessarily have many patients with AMR infections, they have sufficient clinical trial support

functions. These institutions also exchange knowledge and experience through constant cooperation. Through these, advanced medical institutions have gained experience in planning and strategizing resolutions for global issues, improving operational efficiency and quality control, risk management, etc. Successful cooperation between medical institutions that participate in infection surveillances and advanced medical institutions that have clinical trial support infrastructures in constructing clinical trial networks will be more likely to facilitate antimicrobial development.

Adding information necessary for clinical trials to the Real World Data (RWD) collected by surveillance systems in Japan will help make plans and strategies, serve as historical control, and be used in registry studies or new types of clinical trials, such as Virtual Randomized Controlled Trial (Virtual RCT).^{28,29}

Global clinical trials involve various tasks (other than academic and regulatory related activities); selection of study sites and the principle investigator (PI) in each country; gathering information regarding the doctor group organization; transfer of specimens; standardization of test precision; addressing differences in standard treatment, equipment, procedures, and an infection control system; creation of procedures and formats for various contracts; and establishing a compensation/indemnification system. A comprehensive support organization is necessary that covers not only expertise in a clinical trial but also its administrative aspects, such as protection of intellectual property, contracts, logistics, compensation/indemnification, and legal affairs.

With this in mind and with reference to documents on clinical trial networks for antimicrobial development created by the Wellcome Trust, the following was considered necessary:³⁰

- Extensive clinical trial networks that are centered on medical institutions that are experienced in clinical trials,
- Support by core institutions for less experienced medical institutions that are participating in the clinical trial networks to conduct smooth clinical trials,
- A real-time surveillance system to immediately report patients who have an acute course.

In addition, the following network will improve the efficiency of clinical trials and reduce their costs:

- A network among fine medical institutions that can be shared by sponsors from all over the world to test their investigational products in a timely manner.

Investigator-initiated clinical trials using a network that links industry-academia-government stakeholders will reduce costs for companies. Government support given to activities of public interest such as investigator-initiated clinical trials within a network will also promote antimicrobial development.^{31,32}

Since formulation of the General Principles for Planning and Design of Multi-Regional Clinical Trials (ICH E17), an increasing number of global clinical trials has been conducted in developing countries and emerging countries. Japan is also expanding cooperation to more countries in the area of infections.^{33,34,35} To contribute to health and medicine in each country, and consequently to Sustainable Development Goals (SDGs), it is necessary to promote clinical trials and development of new drugs for AMR infections in Japan and overseas. To achieve this, domestic and overseas clinical trial networks, and other systems need to be established.^{36,37,38}

2.4 Antimicrobial Development Strategies Including the Use of New Methods

In many cases, AMR infections occur sporadically. Since the number of patients with each AMR infection is limited, finding medical institutions prior to its occurrence is almost impossible. Conventional clinical trials, which are conducted after contracts are concluded with study sites, are therefore not suitable for antimicrobials for AMR infections. Instead, more practical clinical trial systems and development strategies are required. It is preferable to have more flexible study contracts between study sites and sponsors. For example, a study contract that encompasses multiple relevant departments, rather than a single department, at a single study site. A study contract between a single medical institution and a single sponsor is not ideal either. Ideally, study contracts should allow each medical institution which detects an AMR infection within the network in each area of Japan to enroll patients in a clinical trial immediately. For this purpose, institutional aspects of the GCP and administrative aspects of clinical trials, including a supply system for study products, will need to be discussed in the future to clarify responsibility in clinical trials.

In designing clinical trials, active consideration should be given to the use of new methods. For example, a design called Single Master Protocol or Continuous Master Protocol that allows multiple clinical trials to share a control group, a platform design that uses historical data as a control if possible, and a design that uses information in the AMR registry database as a virtual control group.

Obtained data - even if limited - should be fully utilized. At the same time, how to supplement insufficient data needs to be discussed. Since the number of patients with AMR infections is limited, the feasibility of clinical trials should be taken into consideration. In some cases, antimicrobial efficacy may have to be verified in a small-scale randomized study or an uncontrolled study that is large enough for exploratory evaluation of efficacy, instead of a statistical verification study.

It is also important to introduce and fully utilize a system that improves patient's access. In Japan, the Conditional Early Approval System³⁹ and an unapproved drugs rapid commercialization scheme for antimicrobial resistant infections (ARIs) have been released as measures to improve patient's access. AMR infections are life-threatening serious diseases. It is recommended to use these systems and to make antimicrobial development plans to prepare an environment for early introduction of antimicrobials for AMR infections to clinical settings.

The limited sample size of AMR infections makes it limited to enroll patients with infections for all relevant infection sites (organs) in a registration clinical trial. If tissue distribution data of an antimicrobial show a sufficient drug transfer to organs that efficacy of the antimicrobial agent are expected for, it may be recommended to approve the indication of various infections on a bacterial species basis but not on an organ system basis (like drugs approved for VRE infections). If this is the case, collection of efficacy and safety information should be continued in the post-marketing settings.

2.5 Pediatric Development Strategy

In developing antimicrobials in the pediatric field, pediatric development plans need to be discussed taking medical needs into consideration in parallel to designing development programs for adults. Depending on the nature of the target disease and the characteristics of the investigational product, inclusion of older children in adult clinical trials should be considered.

In particular, the development of drugs for pediatric AMR infections, which are very rare, requires the full use of available methods, such as extrapolation of results of adult clinical studies and M&S. Estimation of efficacy by MCS, etc. using pediatric PK and sensitivity distribution of pathogens of pediatric infectious diseases estimated from the results of an adult phase I study is one option. The antimicrobial safety in pediatric patients can be evaluated based on the results of toxicity studies in juvenile animals and adult clinical trials, as well as safety information on drugs of the same class.^{40,41} If pediatric PK/PD analysis data, even if limited, are collected together with efficacy and safety data in pediatric clinical trials, adult efficacy data may be able to be extrapolated to pediatric patients. In the case of drugs for infections whose pathology in children is similar to that in adults, the efficacy outcome confirmed in adults can be extrapolated to children according to the PK/PD theory. It might be possible to verify the safety in post-marketing settings.

When an adult clinical trial is conducted prior to a pediatric clinical trial, the dosage regimen for the follow-on pediatric trial can be determined by the following methods.⁸

- The data shown below will help understanding of pediatric PK (particularly, developmental changes in distribution volume, renal function related to excretion, metabolic enzymes, etc.), which will help when making decisions on the necessity of dose adjustments according to body weight or surface area.
 - ✧ PK results in juvenile animals and mature animals
 - ✧ Metabolic data from *in vitro* studies, etc. using adult and pediatric tissues or cells
 - ✧ Adult PK data
- For a drug product whose pediatric dosage form is different from that for adults, the similarity of PK between the dosage forms should be examined.
- With these assessments/discussions, the pediatric PK parameters under various exposure scenarios can be estimated from adult PK parameters.
- The sensitivity (MIC) distribution of pathogens of pediatric infections should also be determined considering the frequency of their isolation.
- MCS with the assumed distribution appropriate for estimated pediatric PK parameters and estimated MIC distribution is performed to calculate the probabilities of attainment of PK/PD targets determined in nonclinical studies or adult patients under various exposure scenarios.
- On the basis of the probabilities of PK/PD target attainment, the optimal pediatric dosage regimen that is expected to be effective can be selected.

If there is no adult clinical trial conducted prior to a pediatric clinical trial, a pediatric dosage regimen may be determined based on PK/PD parameters and their target values which are selected from nonclinical study data. To conduct pediatric clinical trials, the following issues should be kept in mind.⁸

- Challenges in PK/PD analysis in pediatric clinical trials⁸
 - ✓ High-sensitivity assays to determine drug concentrations need to be developed because of the restriction on the amount of blood sampling from pediatric patients.
 - ✓ The use of PPK or other optimal sampling theories helps minimize the frequency of blood sampling. Blood sampling through a catheter placed in the body, etc. will minimize pain.⁴⁰
 - ✓ The development of transporters, metabolic enzymes, etc. involved in drug metabolism such as absorption and excretion, and age-related changes in serum protein binding have not been fully understood. The results of *in vitro* study results, etc. using samples collected from children are useful in predicting these factors.

➤ Other issues⁸

It is also essential to adjust (modify) clinically proposed pediatric dosage regimens as necessary according to efficacy, safety, and PK data from pediatric clinical trials especially when these dosage regimens are determined based on adult PK/PD targets. When no adult clinical trial has been conducted prior to a pediatric clinical trial, a certain number of pediatric patients needs to be accumulated for safety evaluation because the correlation between PK and the occurrence of adverse reactions is not necessarily clarified.

In the past, antimicrobial development for neonates was pursued in parallel to the development for older children and adults. Neonates, which are different from older children in PK and many other physiological aspects, are a difficult age group to include in antimicrobial development. Recently, organization such as the International Neonatal Consortium (INC)⁴² has been established and is working internationally to accelerate neonatal drug development. The INC has announced that the clinical evaluation of neonatal sepsis is underway. Active participation of Japanese pharmaceutical companies in such activities will promote neonatal drug development. When PK/PD analysis using clinical trial results in older children and adults can predict the efficacy in neonates, determination of a neonatal dosage regimen based on these results should be considered.

3. Collection of Post-marketing Information

Only a very limited number of cases for AMR infections that are covered in this report can be collected in the clinical development phase. There are high expectations placed on information collected in the post-marketing phase. Predicting when and where AMR infections will occur is, however, even more limited in the post-marketing settings. Efficient collection of post-marketing information and continuous evaluation of risk and benefit balance are essential. To achieve these, marketing authorization holders and all concerned parties must cooperate in information collection.

When a quinolone antimicrobial was approved for the additional indication of Legionnaires' disease, the Ministry of Health, Labour, and Welfare requested the Japanese Society of Chemotherapy to help the marketing authorization holder to collect information in the post-marketing surveillance. This was needed because when and where the disease might occur could not be predicted. This is an example of cooperative information collection by a pharmaceutical company and a relevant academic society. AMR infections are similar to Legionnaires' disease in that their occurrence cannot be predicted. However, having a significantly smaller number of patients with AMR infections than those with Legionnaires' disease necessitates further measures to be taken. For instance, an all-case AMR registry database may serve as a useful reference for post-marketing surveillance, which will be designated as a condition for regulatory approval. Although the details of the AMR registry database need to be decided, it would be a good idea that all medical institutions are officially required to enroll all patients with AMR infections and that the AMR clinical reference center establishes and manages the AMR registry database.

4. Possible Cooperation with Overseas Academic Societies

The prevalence of AMR bacteria is a serious global problem. Few drugs are available for infections with multidrug-resistant *Pseudomonas aeruginosa* (MDRP), carbapenem-resistant *enterobacteriaceae* (CRE), and multidrug-resistant *Acinetobacter* species. Their treatment is often very limited. Increased globalization and borderlessness are associated with concerns that highly resistant bacteria from overseas will spread to Japan. To prevent epidemics, information exchange with overseas researchers is important. The Japanese Association for Infections has established a partnership with the Infections Society of America (IDSA) and the European Society of Clinical Microbiology and Infections (ESCMID). Each organization has agreed to invite researchers from its partner organizations to lectures and symposiums at academic conferences.

Pharmaceutical companies are struggling to build a business model for antimicrobials. Many pharmaceutical companies have already withdrawn from new antimicrobial development. For reliable evaluation of safety and efficacy in clinical trials in AMR infections, whose patient population is very small, conducting more global clinical trials should be encouraged. Traditionally, Japanese academic societies have tried to use the same evaluation criteria for investigational antimicrobials under development to those in Europe and the US (especially the US). However, the Japanese and overseas organizations do not

necessarily align with each other. For example, Japanese organizations revised the criteria to meet the European/US criteria, and afterwards the European/US organizations revised their criteria.

Establishment of universal evaluation criteria for investigational antimicrobials is essential to further promote the conduct of global clinical trials. In addition, more medical institutions need to be accredited by “ISO15189: Laboratory accreditation, quality management system.” Obtaining ISO15189 accreditation has the following advantages for developers: 1. Test results are accepted globally through international mutual recognition; 2. Accreditation by external assessment, such as ISO 15189, is recommended to ensure test precision in clinical trials; and 3. The revision of medical service fees in 2016 sets “New reimbursement fee for medical laboratory management with International Standard.” Japan has 154 ISO15189-accredited institutions as of November 2018, but more are required.

As described in “3. Collection of Post-marketing Information,” collection of information about drugs for AMR infections in the post-marketing settings is essential, but there are many issues that need to be solved. Many drugs for AMR infections are expected to be developed through global clinical trials. Post-marketing information about such antimicrobials should also be collected globally. In this effort, cooperation with overseas academic societies, research networks, etc. should be considered with reference to the Pediatric Rheumatology International Trials Organization (PRINTO) and the registry of large-scale international registry research “REACH.” Extensive information gathering will not be accomplished by pharmaceutical companies alone. Public support is expected. Financial costs of having discussions on the conduct of clinical trials with foreign academic societies also need to be clarified.

PMDA is expected not only to cooperate with Japanese academic societies but also to participate in the American Society For Microbiology (ASM Microbe) and the European Congress of Clinical Microbiology & Infections (ECCMID) to provide necessary information.

5. Importance of Surveillance Activities

Surveillance data of antimicrobials are important in both the development and post-marketing phases.

In the development phase, existing information will give insight to the distribution of pathogens for a target disease and also the drug sensitivity distribution of these pathogens. Some surveillance programs use stored clinical isolates. A stock clinical isolate can be used to obtain the results of *in vitro* drug sensitivity studies for an investigational product under development.

In the post-marketing settings, surveillance is a useful tool to monitor the total dose of an antimicrobial and the time profile of sensitivity from initial use. This will help to promote antimicrobial stewardship.

The Japan Nosocomial Infections Surveillance (JANIS) is a national surveillance program which provides information on AMR bacteria. The JANIS is a surveillance program regulated by the Statistics Act. The National Institute of Infections, acting as a management office, aggregates and analyzes data submitted by each hospital. It then publishes on their website information on the

prevalence of clinically significant major AMR bacterial species and their isolation rates.²² The JANIS Clinical Laboratory Division is responsible for surveillance of drug resistance. As of September 2018, 1,988 medical institutions participated in this division and submitted bacterial test data collected in clinical laboratories. This large-scale surveillance is collecting bacterial test data from 5,000,000 specimens a year and provides representative national-level data. Unfortunately, this program collects data from clinical laboratories alone. Without patient's clinical information, the difference between bacterial carriers and patients with infections cannot be distinguished. The relationship between the occurrence of an infection and treatment given prior to its occurrence cannot be analyzed. Participation of hospitals in the program is on a voluntary basis, and therefore not a population-based surveillance.

A nationwide surveillance on the antimicrobial susceptibility of infection isolates by the Japanese Society of Chemotherapy, the Japanese Association for Infections, and the Japanese Society for Clinical Microbiology (Three Academic Societies Joint Antimicrobial Susceptibility Surveillance Program) is ongoing in the fields of respiratory infection, urology infection, surgical site infection (SSI), and otological infection. It is also planned to be conducted in dentistry and pediatric departments. Unlike the JANIS program, this surveillance program deals with isolates from patients with a definitive diagnosis of infectious diseases and sends detected bacteria to the reference center for re-identification and susceptibility tests. Extended spectrum beta-lactamase (ESBL)-producing *E. coli* accounts for 12% of isolates from patients with SSI in 2010, but has increased to 23% in 2014 to 2015. This surveillance has shown the time profile of sensitivity of ESBL-producing *E. coli* to tigecycline and colistin, which are indicated exclusively for AMR bacteria, as well as to general antimicrobials. A sensitivity study using new tazobactam/ceftolozane drug is planned for this year. The isolation rates of an MRSA strain with an MIC to vancomycin of 2 µg/mL tended to decrease, indicating an improved susceptibility of the MRSA strain. Clinical introduction of linezolid or daptomycin has been shown not to compromise the susceptibility. Post-hoc analysis of the susceptibility of isolates causing post-operative intra-abdominal infections has shown the resistance of *Bacteroides* sp. to cephamycin and clindamycin. These findings are important data that support the formulation of Japanese future treatment guidelines for SSI and intra-abdominal infections. Hopefully, public involvement and support will be given to these important surveillance programs to ensure their stable and continuous implementation.

Efficient combination of the large-scale nationwide JANIS surveillance, the Three Academic Societies Joint Antimicrobial Susceptibility Surveillance Program (which is relatively small but involves detailed analyses), and the AMR Registry Database (run by the AMR Clinical Reference Center) is expected to help analysis of nationwide disease burdens.

6. Overview Summary

The development of new antimicrobials requires high costs and long development cycle time. Antimicrobials, unlike drugs for lifestyle-related diseases, are used for a limited duration and are therefore financially less attractive for pharmaceutical companies to develop. Amid concerns over the rise of AMR bacteria, however, there is a high demand for new antibacterials.⁴³

A lot of pharmaceutical companies have been closed their laboratories, causing a decrease in the discovery of new compounds. In addition, the costs of clinical trials are on the rise. Given this, it may also be important to reduce developmental costs by, for example, using compound libraries, patient registries, and other existing data, as well as AI-based drug discovery technologies.

The rarity of AMR bacterial infections may require several hundred trial sites to participate in a late-phase clinical trial of a new antimicrobial for registration. Each site needs to prepare for clinical trials and create a basic infrastructures, which makes late-phase trials even more limited. To address these problems, the Generating Antibiotic Incentives Now Act of 2011 (GAIN Act) was issued to extend the exclusivity period for new prescription drugs by 5 years for qualified antimicrobials for drug-resistant bacteria.⁴⁴ Pharmaceutical companies are often unwilling to invest in the field of infections that have low marketability and high development risk. This expert committee mainly discussed clinical evaluation of antimicrobials. To promote the development of antimicrobials for AMR infections, a global development system and other policies following the ICH Harmonized Tripartite Guidelines are essential. As seen in overseas policies, giving special incentives for developing drugs for AMR infections whose incidence are extremely low (push incentives, e.g., funding for R&D; pull incentives, e.g., market-entry rewards and transferable exclusivity vouchers) was also proven to be effective. We hope that a policy that promises developers a fair return on their investment will also be discussed in Japan.

To address the challenges in promoting the development of antimicrobials for AMR infections, cooperation is needed by reviewing organizations such as PMDA and related governmental organizations, academia, and pharmaceutical companies.

The fight against AMR infections requires vigorous education and enlightenment of doctors and medical institutions about clinical trials for AMR infections.

As described in the Japanese National Action Plan on Antimicrobial Resistance (AMR),⁴⁵ cooperation between government, academia, and industry is essential in developing prevention, diagnosis, and treatment methods.

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