Provisional Translation (as of March 2025) *

Points to Consider for Clinical Development of Drugs Intended for Treatment of Antimicrobial-resistant Gram-negative Bacterial Infections (Early Consideration)

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Pharmaceuticals and Medical Devices Agency
Office of New Drug IV

1. Background

The spread of drug resistance in pathogens such as bacteria is considered a major issue of global public health. The World Health Organization (WHO) has identified carbapenem-resistant gram-negative bacteria (i.e., *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter* species) as antimicrobial-resistant bacteria for which the development of new antimicrobial drugs is needed [1)]. For infections caused by gram-negative bacteria resistant to existing antimicrobial drugs (hereinafter referred to as "antimicrobial-resistant GNBI"), treatment options are limited. Therefore, the development of new effective antimicrobial drugs is expected.

The known mechanisms of antimicrobial resistance in gram-negative bacteria include the production of β-lactamase, decrease or deletion of porins, and/or the overexpression of efflux pumps [2)]. If the antibacterial-resistant pathogen or the mechanism of resistance is extremely rare, or the types of resistance (e.g., types of β-lactamase) are different in Japan and overseas, it may be difficult to plan and conduct a clinical study with sufficient sample size and design to clearly demonstrate the efficacy of an investigational drug (i.e., a randomized controlled study with high statistical power to confirm the non-inferiority or superiority of an investigational drug over a control drug).

The basic concepts for clinical studies of antimicrobial drugs, that are conducted for the purpose of the regulatory applications for marketing approval (hereinafter referred to as "application for approval") are described in "Guideline for Clinical Evaluation of Antibacterial Drugs" [3)]. However, descriptions of the development of drugs indicated for treatment of antimicrobial-resistant GNBI are limited. On the other hand, the Subcommittee on AMR of the Science Board, which has been established for regulatory science operations of the Pharmaceuticals and Medical Devices Agency (PMDA) published the "Report on Clinical Evaluation of Antimicrobial Agents for AMR" [4)] in which its views on the method of clinical evaluation of antimicrobial drugs against antimicrobial resistant bacterial infections were presented.

Against such background, we have prepared this document to specifically present PMDA's views on the clinical development of drugs intended for treatment of antimicrobial-resistant GNBI, taking into account recent clinical trial consultations, approval review cases, etc.

* The English translation is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

It should be noted that the views presented in this document have been prepared based on current scientific knowledge and international trends, and may be subject to revision in the future depending on changes in such knowledge and trends. It is recommended that developers contact PMDA for consultation in cases where they wish to discuss individual clinical study plans and the clinical data package for the regulatory application of investigational drugs.

2. Development Strategy for Drugs Intended for Treatment of Antimicrobial-resistant GNBI

Drugs indicated for the treatment of antimicrobial-resistant GNBI should be developed on the premise that a clinical study in patients with antimicrobial-resistant GNBI is conducted in accordance with the points to consider described in Section 3 below to confirm a favorable benefit-risk balance of investigational drugs. Other points to consider are stated in Sections 2.1 and 2.2 according to types of characteristics of the investigational drugs.

If the number of patients is limited both in Japan and overseas, and if the mechanism of resistance or types of resistance (e.g., types of β-lactamase) differ between Japan and overseas, a multi-regional study including Japan should be planned with the purpose of establishing solid evidence regarding investigational drugs.

As is the case with adults, pediatric drug development is also important. For such development, see "Section 2.5 Pediatric Development Strategy" of aforementioned "Report on Clinical Evaluation of Antimicrobial Agents for AMR" [4], regulatory notifications related to pediatric development such as "Considerations for the Clinical Evaluation of Drugs in Pediatric Patients (10 or 12 Years of Age and Older) Who Can be Evaluated Together with Adults" [5], "Clinical Investigation of Medicinal Products in the Pediatric Population" [6], and "Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population" [7].

2.1 Development of a New Active Pharmaceutical Ingredient Expected to Have Antimicrobial Activity against Antimicrobial-resistant Gram-negative Bacteria

For a new active pharmaceutical ingredient (API) expected to have antimicrobial activity against target pathogens, clinical studies in patients with antimicrobial-resistant GNBI are, in principle, to confirm the efficacy of the API in representative disease areas (i.e., infections at body sites (organs or tissues) from which causative bacteria are frequently isolated.) and to evaluate its safety based on data from a certain number of patients [3]. That is in the same manner as the development of other antimicrobial drugs. However, as described in Section 1, it may be difficult to conduct a clinical study in patients with antimicrobial-resistant GNBI with sufficient sample size and design.

In such a case, in addition to these clinical studies in patients with antimicrobial-resistant GNBI, developers should examine the efficacy of the new API in an exploratory manner in patients with antimicrobial-susceptible GNBI in any one of the typical disease areas relevant to the indications

sought in the development program in order to obtain supplementary information on the efficacy of the investigational drug. Such clinical studies in patients with antimicrobial-susceptible GNBI should preferably be conducted prior to those in patients with antimicrobial-resistant GNBI. In general, patients with antimicrobial-resistant GNBI tend to have more severe disease manifestations [8] due to complicated clinical management pathways that are attributed to the fact that there are limited treatment options for those patients in contrast to patients with antimicrobial-susceptible GNBI. That is to say, by conducting those clinical studies in patients with antimicrobial-susceptible GNBI first, the efficacy and safety of investigational drugs can be examined to a certain extent before they are administered to patients who are likely to have more severe disease manifestations.

2.2 Development of a New Active Pharmaceutical Ingredient *Not* Expected to Have Direct Antimicrobial Activity against Antimicrobial-resistant Gram-negative Bacteria

In cases where a new API itself has little or no direct antimicrobial activity ***and*** where other antimicrobial drugs that have been approved for indications related to the target disease area and target microorganisms are to be concomitantly used with the API or combined with it in a single dosage form (e.g., a new β-lactamase inhibitor developed for use in combination with approved antimicrobial drugs for co-administration or as co-formulated products), it is usually considered less necessary to conduct a clinical study in patients with antimicrobial-susceptible GNBI mentioned in Section 2.1.

However, if sufficient safety data for investigational drugs cannot be obtained from clinical studies in patients with antimicrobial-resistant GNBI, the results of clinical studies in patients with antimicrobial-susceptible GNBI may be useful.

It should also be noted that if the dose of the approved antimicrobial drugs to be co-administered or co-formulated with the API exceeds the maximum dose approved in Japan, it is necessary to justify that the safety in such a dose level would be acceptable.

2.3 Proposed Indications at the Time of Application for Approval

Target microorganisms

Essentially, microorganisms identified as causative bacteria in patients with antimicrobial-resistant GNBI in clinical studies are candidates for target microorganisms to be listed in proposed indications.

Target diseases

In principle, target diseases described as the proposed indications of drugs intended for treatment of antimicrobial-resistant GNBI shall be the disease area for which reasonable efficacy and safety of the drugs are confirmed based on the results of clinical studies [3]. That is in common with other antimicrobial drugs.

However, it may be appropriate to propose *various infections* as target diseases in the proposed

indication without limiting to specific disease areas, if all of the following conditions apply:

- It is a drug that would be regarded as the last resort in the treatment algorithm at the time of development (e.g., drugs for carbapenem-resistant GNBI).
- The drug is expected to show a certain level of efficacy in disease areas other than those which have been studied in clinical studies based on its pharmacokinetic characteristics including tissue distribution and the results of clinical studies in representative disease areas.

3. Design of Clinical Studies in Patients with Antimicrobial-resistant GNBI

3.1 Efficacy and Safety Evaluation

If it is difficult to plan and conduct clinical studies with sufficient sample size and design (see Section 1) for each disease area in patients with antimicrobial-resistant GNBI because of the limited number of patients both in Japan and overseas, it may be acceptable to enroll patients with infections in different types of representative disease areas caused by target microorganisms together in the same clinical study to evaluate the efficacy (e.g., in the case of carbapenem-resistant GNBI due to *Enterobacterales*, *Pseudomonas aeruginosa* and/or *Acinetobacter* species, possible combinations of disease areas may be complicated urinary tract infection/pyelonephritis, hospital-acquired pneumonia/ventilator-associated pneumonia, and/or complicated intra-abdominal infection). However, the key inclusion/exclusion criteria and efficacy endpoints should be defined individually for each of the disease areas that will be included in the study.

It is anticipated that the results of the efficacy evaluation on merged multiple disease areas based on common efficacy criteria across disease areas would be difficult to interpret due to different inclusion/exclusion criteria and varied efficacy endpoints for individual disease areas. For instance, if the magnitude of efficacy is different among the disease areas, developers have to be careful in interpreting the pooled efficacy results of the overall population in which the clinical efficacy results (i.e., responder or non-responder) in the individual disease areas are pooled. In such a case, the efficacy of study drugs will be comprehensively evaluated based on efficacy results in each of the disease areas as well as the merged efficacy results.

In addition, in the clinical study in patients with antimicrobial-resistant GNBI, it is necessary to clarify the safety profile of the study drugs in those patients and to evaluate whether their safety is acceptable considering the expected benefits, including the viewpoint of comparisons with drugs in the control group (e.g., standard treatment).

3.2 Enrollment of Patients Suspected of Having Antimicrobial-resistant GNBI

In some indications, it is anticipated that the drug will be administered to patients suspected of having antimicrobial-resistant GNBI without waiting for the results of the drug susceptibility test in

actual clinical practice [9]. For investigational drugs that are anticipated to be used in this way, it is appropriate that patients suspected of having antimicrobial-resistant GNBI are enrolled in a clinical study and that administration of investigational drugs is started without waiting for the results of the drug susceptibility test. However, the primary efficacy analysis should be performed in the population who have been confirmed to have antimicrobial-resistant GNBI.

3.3 Statistical Analysis and Sample Size Setting

Clinical studies in patients with antimicrobial-resistant GNBI mainly include patients in regions with an epidemic at the time of the study. In some cases, multiple disease areas may be investigated together in the same clinical study (see Section 3.1). Therefore, it is assumed that there will be extremely limited external comparable information that is obtained from a patient population with similar backgrounds to those enrolled in the above-mentioned studies (e.g., disease area, causative bacteria, severity, concomitant drugs/concomitant therapies) and that can be used as comparable evidence in the assessment of efficacy and safety of investigational drugs. Thus, if the study was conducted as an uncontrolled study, it would be highly likely that the interpretation of the study results would be difficult. Therefore, clinical studies in patients with antimicrobial-resistant GNBI should be conducted as a randomized controlled study with an appropriate control (e.g., standard treatment) chosen in light of the intended clinical positioning of the investigational drugs.

Furthermore, the confirmation of non-inferiority or superiority of the investigational drugs over drugs in control group, based on statistical tests as the primary analysis on the primary endpoint, may be the most convincing information to demonstrate the efficacy of the investigational drugs [10].

The below shows the points to consider in setting the target sample size:

- Considering the principles in defining target microorganisms in a proposed indication (see Section 2.3), study sites should be selected and target sample size for the entire study should be determined in light of epidemiological information of the regions where an epidemic of each target microorganism occurs so that clinical efficacy against a wide variety of species among the target microorganisms can be studied in the clinical study.
- The target sample size should be set for each disease area so that developers can obtain sufficient data to support the expected efficacy and safety in each disease area under study.
- If there are any potential adverse events expected based on the characteristics of study drugs or other information obtained to date, it is important to make sure that a sufficient number of patients are enrolled in the clinical study in consideration of the frequency of these events in order to appropriately evaluate the safety of investigational drugs in patients with antimicrobial-resistant GNBI (see Section 3.1).

When a clinical study with sufficient sample size and design (see Section 1) is not feasible thus the

clinical study under planning is not intended to confirm either non-inferiority or superiority, the following points should be noted:

- It is necessary to investigate possible sample size based on epidemiological information and other scientific considerations, and appropriately explain that a confirmatory study is infeasible. It is also important to clearly show the clinical significance, validity, and limitations of the efficacy evaluation method specified for the clinical study under planning.
- Even if a confirmatory study is infeasible and the feasibility-based sample size is justified, the developers should still address the fact that it is expected to be difficult to draw a definitive conclusion on the efficacy and safety of the investigational drugs from the results of the study in which extremely few patients would be enrolled. In this regard, the number of participating trial sites and the study period should be thoroughly examined.
- When alternative statistical decision-making methods (e.g., Bayesian method borrowing external data) are used, operating characteristics (e.g., type I error rate, power) under the target sample size should be provided and the validity of those values should be considered.

[1)] WHO Bacterial Priority Pathogens List, 2024: Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance; WHO 2024

[2)] "Position Paper for Control of Multidrug-resistant Gram-negative Bacterial Infection Version 2", Multidrug-resistant Bacterial Infection Control Committee of Japanese Society for Infection Prevention and Control (published on July 25, 2017, Japanese Journal of Infection Prevention and Control 2017; 32: Suppl. III)

[3)] "Guideline for Clinical Evaluation of Antibacterial Drugs" PSEHB/PED Notification No. 1023-3 dated October 23, 2017

[4)] "Report on Clinical Evaluation of Antimicrobial Agents for AMR" dated October 4, 2019 issued by Subcommittee on AMR of the Science Board

[5)] "Considerations for the Clinical Evaluation of Drugs in Pediatric Patients (10 or 12 Years of Age and Older) Who Can be Evaluated Together with Adults" Administrative Notice dated June 30, 2020 by PSEHB/PED

[6)] "Clinical Investigation of Medicinal Products in the Pediatric Population" PMSB/ELD Notification No. 1334 dated December 15, 2000

[7)] "Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population" PSEHB/PED Notification No. 1227-5 dated December 27, 2017

[8)] WHO Fact sheets "Antimicrobial resistance"(https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance [last confirmed on March 24, 2025])

[9)] "Guidance for Implementing an Antimicrobial Stewardship Program in Japan" Joint 8-academic committee for the promotion of the appropriate use of antimicrobials (Japanese Journal of Chemotherapy 2017; 65(5): 650-87, etc.)

[10)] "Statistical Principles for Clinical Trials" PMSB/ELD Notification No. 1047 dated November 30, 1998

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List of abbreviations and definitions of terms

AMR	antimicrobial resistance
API	active pharmaceutical ingredient
GNBI	gram-negative bacterial infections
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
WHO	World Health Organization
PMDA	Pharmaceuticals and Medical Devices Agency
PMSB/ELD	Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health Labour and Welfare
PSEHB/PED	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health Labour and Welfare