April 14, 2017

Provisional Translation

Ministry of Health, Labor and Welfare

Mr. Yuji Kanda, Director General, Pharmaceutical and Food Safety Bureau

Mr. Yasumasa Fukushima, Director General, Health Service Bureau

Mr. Toshihiko Takeda, Director General, Pharmaceutical Safety and Environmental Health Bureau

Dr. Yasuhiro Suzuki, Director General, Health Insurance Bureau

Dr. Yasuyuki Sahara, Director, Health Sciences Division, Minister's Secretariat

Japan Pharmaceutical Manufacturers Association

Proposal regarding Measures for Research and Development Promotion of Drugs, etc. against Drug Resistance (AMR)

Antimicrobial resistance (AMR), which is attracting worldwide attention as a problem of drug resistance in pathogens other than the so-called three major infections including tuberculosis, malaria, and HIV, was covered as a main health issue in the G7 Ise-Shima Summit and Kobe Health Ministers' Meeting held last year under the strong leadership of Japan. In addition, the G7 expressed a strong commitment to the policy for working on the measures in a more coordinated manner. We understand that this was an extremely important milestone. We also deeply respect and highly appreciate that, in Japan, the "Public-Private Partnership Committee on Measures for Preventing Infections Developing Countries," "National Awareness Committee for Promoting Measures for Drug Resistance (AMR)," and "Subcommittee on Drug Resistance (AMR) of Health Science Council Infectious Disease Working Group" were swiftly established and discussions have been steadily advancing based on the action plan on the measures for AMR that was formulated prior to the G7 Ise-Shima Summit along with the establishment of the priority review framework for AMR drugs.

Japan Pharmaceutical Manufacturers Association member companies consist of research-and-development-driven pharmaceutical companies and are conducting economic activities with the drug discovery, research, and development engine representative of Asia. We recognize that our mission is to contribute to the improvement of health and welfare of people worldwide through the continuous discovery and stable supply of innovative medicines, and we strongly feel that the JPMA member companies need to play a role in measures for AMR, which is a significant international health issue and is assumed it will become an extremely large problem in the future, especially in Asia. However, companies are unable to prioritize research and development as well as commercialization of therapeutic agents (including vaccines and diagnostics) for AMR in their development due to low marketability and

predictability and as a result, research and development activities starting from the discovery of seeds have not been advanced as expected despite the high social needs.

Therefore, we propose, as shown below, the introduction of research and development promotion measures including an incentive system, such as a stockpiling/purchasing system, that can promote (stimulate) the research and development of new AMR drugs, etc. in Japan and improve their profit predictability. These are proposed by JPMA as a whole upon taking into consideration the incentive plans being examined overseas as well. However, the items we present here are only an overview of each, and we understand that various considerations, including priorities and correlations, will arise in order to actually implement them. Therefore, when considering the specific details to make them more effective, we propose that JPMA personnel participate in the discussion.

<Proposals and Requests> The details are as shown in the Attachment.

○ Stockpiling/purchasing system for new AMR drugs, etc.

○ Establishment of AMR-specific fund and research-and-development institute (consortium) by public-private partnership (PPP)

○ Formulation of international common clinical evaluation guidelines to promote clinical development of new AMR drugs, etc.

○ Reward system for marketing approval

○ Drug price preliminary review system based on drug profiles

<Attachment> Proposals and Requests (Overview of 5 proposals>

○ **National stockpiling/purchasing system of new AMR drugs**

<Proposal overview>

This is a system in which the government buys a certain quantity of a new AMR therapeutic agent approved for marketing on the government's responsibility from the standpoint that the government is taking measures for AMR as an important public health issue. The government distributes the agent it bought to core institutions in each prefecture so there is a stockpile of it or asks the company to stock it. In this case, the government buys the agent according to the expiry date, etc. and does not return it to the company. How much will be stockpiled is determined by the government, but the transaction price may be determined between the government and the company as transparently as possible depending on the stockpile. Regarding the handling of the agent in health insurance, the agent is not listed in the NHI drug price list but defined as a "usable drug" that can be used in terms of health insurance. Thus, the drug costs are covered by national/public expenditures, not by health insurance. Moreover, based on "6. International Cooperation" in the "National Action Plan on Antimicrobial Resistance (AMR)," from the standpoint of international contribution, the stockpile should be determined taking into account measures for AMR in developing countries. In addition, when providing drugs, it is necessary to cooperate with WHO and establish a mechanism for the proper distribution of such drugs in developing countries.

○ **Establishment of AMR-specific fund and research-and-development institute (consortium) by public-private partnership (PPP)**

<Proposal overview>

An AMR-specific fund and a research and development institute (consortium) by public-private partnership (PPP) should be established to accelerate the research and development of new AMR therapeutic agents, vaccines, and rapid diagnostic agents. It is preferable that this consortium be constructed mainly by the Japan Agency for Medical Research and Development (AMED) with the participation of appropriate members from industry, government, and academia. The consortium organically links and utilizes drug seeds that pharmaceutical companies possess (including antimicrobial agents, of which research and development was interrupted in the past from the perspectives of profitability and business strategy) as well as those in academia/universities, compound libraries, and research and development know-how with the concept of an open innovation to promote research and development for the practical use of "treatment," "prevention," and "diagnosis" that can be brought to the clinical phase soon. In addition, it also aims to promote global research and development by enabling coordination, such as with the Joint Programming Initiative on AMR (JPIAMR) and CARB-X, which is an advanced PPP on a global level started in 2016, at the exit strategy phase of research seeds in the future.

<Overseas cases>

Measures for AMR in the United States and Europe are systematically developed by ND4BB, a consortium model by the partnership of IMI and EFPIA (a total of €700MM) and CARB-X, a PPP model centered on the United States ($350MM planned for 5 years), and the timeline is focused on continuity from a mid-term view. GARDP, which was established by the partnership of WHO and DND*i*, started operation as an NPO. ND4BB and CARB-X set AMR gram-negative bacteria, which are global threats, as a focused research topic and include the embodiment of the measures either from the perspective of "treatment," "prevention," or

"diagnosis" in the scope. "Prevention," which refers to the approach by means of vaccines, is important because it leads to the proper regulation of antimicrobial usage and enables the suppression of bacterial virulence factors.

○ Formulation of international common clinical evaluation guidelines to promote clinical development of new AMR drugs, etc.

<Promotional measures at the development approval review level>

<Proposal overview>

As measures for promoting the clinical development of AMR therapeutic agents in Japan, the "formulation of international common clinical evaluation guidelines" and "establishment of a priority review system for therapeutic agents for antimicrobial-resistant infection (ARI)" were mentioned in the AMR Action Plan formulated last April and have already been discussed mainly with academic societies and PMDA. We will propose more specific details here.

- Formulation of international common clinical evaluation guidelines
  - As the number of patients with ARI is extremely limited, drugs should be reviewed based on the minimal efficacy/safety data packages (data packages such as TierB and TierC*[1] that are advocated overseas), rather than conventionally requiring comparative studies with control drugs such as non-inferiority studies from the viewpoint of feasibility and early development. Evaluations not limited to organ-specific ones should also be considered.
  - Minimal criteria common in Japan, the United States, and Europe should be clarified to enable the use of common efficacy/safety data in each country/region.
  - Japan should play a leading role in the application of the international common clinical evaluation guideline in neighboring Asian countries.
  - While collecting post-marketing efficacy/safety information is important for drugs approved with minimal data, collecting a sufficient number of ARI cases is extremely difficult. Instead of the conventional method of post-marketing surveillance based on a contract between a company and individual institutions, a registry system should be organized under the initiative of the government and academic societies to ensure that the precious data of each patient are covered from the development phase to post-marketing phase and accumulated.
  - An appropriate system should be created; for example, when clinically important resistant bacteria are detected in Japan, they are stored in an appropriate public institution, such as the "Three Academic Societies Joint Antimicrobial Susceptibility Surveillance Program," and may be licensed for use by researchers (including companies) involved in new drug development.
- Establishment of the priority review system for therapeutic agents for antimicrobial-resistant infection (ARI)
  - "Antimicrobial-Resistant Infection (ARI) Unapproved Drugs Rapid Practical Use Scheme (Draft)" was submitted at the "Evaluation Committee on Unapproved or Off-Label Drugs with High Medical Needs" held last August, but drugs that are already under development in the United States, Europe, or Japan should also be within the scope of this priority review. The development of rapid diagnostics and vaccines for AMR should similarly be promoted by priority consultations, priority reviews, early insurance coverage, etc.

*[1]: John H Rex et al. A comprehensive regulatory framework to address the unmet need for new antibacterial treatments. Lancet Infect Dis 2013;13:269-75

○ **Reward system for marketing approval of new AMR therapeutic drugs**

<Proposal overview>

This is a system in which, when a new AMR therapeutic agent, vaccine, diagnostic, or the like for a pathogen with high priority finally obtains marketing approval after research and development, the company in question can receive appropriate rewards (compensations) from the government or an appropriate public institution so that it can ensure appropriate profit. This system should also be applicable when the existing drugs, etc. obtain an additional indication for a new AMR infection or specific patients such as children. In exchange for receiving the rewards, the company in question needs to agree with the conditions, such as concerning stewardship and proper promotion, and conduct appropriate sales activities. As this system is not compensation for medical care, from the standpoint of rewarding the contribution to the development of new antimicrobials within measures for AMR, its financial resources should be operated separately from the usual medical service fee system. Moreover, the amounts of rewards and payment methods (lump sum payment, installment payment, etc.) need to be determined transparently between the government and the company in question.

○ **Drug price preliminary review system based on drug profiles**

<Proposal overview>

This is a system in which the development company can file and agree on the drug price in advance based on the target product profile (TPP) of the covered developed product before the start of a human clinical trial or before the conduct of a phase 3 study. The drug price agreed upon in advance does not go lower unless a change is made in the TPP or medical technology environment in the course of development or in the details of the approval. In the context of the long-term history of development and sales of antimicrobials, the risk of drug price setting with the existing drugs with lowered drug prices that are considered as related drugs has lowered the profit predictability even though the drug has new indications that cover resistant bacteria. As such, this system should be introduced to improve profit predictability.

End of Document