June 12, 2019

Health Minister Takumi Nemoto

Japan Pharmaceutical Manufacturers Association
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Proposal from the pharmaceutical industry about the introduction of pull-type incentives for promoting research and development of AMR drugs

Greetings.

Efforts for promoting research and development of new drugs for antimicrobial-resistant infection (ARI) in Japan have been implemented, such as the establishment of the acceleration scheme for unapproved drugs for ARI, the start of supports by Japan Agency for Medical Research and Development (AMED) Cyclic Innovation for Clinical Empowerment (CiCLE), and the revision of "Guidelines for Clinical Evaluation Methods of Antimicrobial Drugs" under the National Action Plan on Antimicrobial Resistance (AMR) determined at the Cabinet Meeting on Measures on Emerging Infectious Diseases in April 2016. These efforts connect to the contents of "Proposal on Measures for Promoting Research and Development of AMR Drugs" that we submitted in April 2017, and we sincerely thank and highly appreciate them.

However, despite some progress in so-called "push-type" incentives for supporting research and development as described above, "pull-type" incentives to enable a sustainable return on investment in the development of novel antibiotics that meet an unmet medical need have achieved no progress. Without these pull-type incentives to increase the feasibility (profitability) of antimicrobial drug development, both large companies and biotechs will continue to struggle financially and exit the space. This means that antibiotics currently in pipeline may not be developed or reach patients who need them. Further, the various policies newly introduced by the government as “push-type” incentives will end up in vain.

Our member companies, which are research-and-development-oriented pharmaceutical companies, recognize that their mission is to contribute to health and welfare of people worldwide by continuous creation and stable supply of innovative drugs and strongly feel that they need to play the role surely in the measures against AMR, which is an international health challenge. In fact, as measures against AMR, we created posters and videos for the public to promote infection prevention such as the compliance of antibiotics and hand-washing and are now working to raise awareness about them with the cooperation of organizations such as Japan Medical Association and Japan Pharmaceutical Association and academia including infection-related societies. In addition, we consider that the promotion of proper drug use is one of the issues on which we should focus, as we mentioned in Japan Pharmaceutical Manufacturers Association Policy Recommendation 2019 published in January, and we will work to promote proper use of expensive drugs as well as working on necessary investigations and enlightenment not only about measures against AMR but also about polypharmacy and so-called leftover drugs from the perspectives of health maintenance of the public and the optimization of drug costs. Meanwhile, in terms of new drug development, the current AMR

drug area has low marketability and profit predictability, and continuous investments into this area are extremely difficult for companies. Moreover, antibiotic discovery and development present specific scientific, regulatory and economic challenges. For companies to address these challenges and continuously develop antimicrobial drugs, a suite of incentives is needed to establish an economic environment that will incentivize them. Adoption of a suite of incentives that is suitable for a social security system of each country by respective governments would create a business model that enables a predictable and sustainable return on investment for successful innovation to combat AMR. “Predictable” means the predictability of development costs and incomes after product launch, and to achieve that, we believe that establishing both push-type and pull-type incentive systems are essential.

Thus, Japan Pharmaceutical Manufacturers Association proposes a system described in the attached document for the introduction of pull-type incentives in Japan, in addition to the already introduced push-type incentives. Recognizing that each country has different health care financing and delivery systems, similar pull-type incentives are under consideration in other countries or regions, like the US and EU. If this system is implemented in Japan ahead of any other country, pull-type incentives in Japan would accelerate the introduction of these incentives that are being considered in other countries and regions, and Japan would demonstrate leadership in global efforts to address AMR. However, we know that various considerations will arise, including the priority and interrelationship of policies, to actually operate the system described in the attachment. Therefore, we also suggest that the discussion for the embodiment of pull-type incentives including the system we propose should immediately be started, and we join the discussion at such meetings.

<Attachment>

Pull-type incentives in Japan (Proposals)

1. Reward for marketing approval of new AMR drugs addressing high public health need (Market Entry Rewards)

Overview:

- This is a mechanism in which, when a new AMR drug, 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 an additional payment (compensations) from the government or an appropriate public institution so that it can ensure appropriate return on investment
- This system should also be applicable when the existing drugs, etc. obtain an additional indication, etc. for a new AMR pathogen or specific patients such as children.
- As this system is not compensation for medical care, its financial resources should also be considered from the standpoint of rewarding the contribution to the development of new antimicrobials within measures for AMR.
- The company receiving the reward needs to agree with the conditions concerning stewardship and proper promotion, which are required for approval, and provide stable supplies and appropriate sales activities.
- The eligibility and amounts of rewards and payment methods (lump sum payment, installment payment, etc.) need to be established transparently.

Objectives:

- Promote continuous research and development of new AMR drugs in Japan by improving profit predictability and profitability for developers

Process of providing incentives:

- Establish list of high-priority unmet medical needs (list of drug-resistant bacteria in Japan, etc.) and determine eligibility criteria for Market Entry Reward (including amounts of rewards).

  The amount of reward may vary depending on the product value and unmet medical need. The assessments of the product value and unmet medical need are preferably discussed between the public and private sectors in reference to published research and development costs* per product, etc.
- Late clinical study phase:
  - Drug sponsors seek designation of “eligible antimicrobial drug” from relevant government or adequate public institution (Health Science Council, National Institute of Infectious Diseases (NIID), National Institutes of Biomedical Innovation, Health and Nutrition, etc.) based on review of documents submitted by a company against established eligibility criteria. If drug candidate meets eligibility criteria, it receives a designation as “eligible antimicrobial drug”.
- Marketing approval:

- If any “eligible antimicrobial drug” receives marketing approval from the MHLW, the MHLW would pay reward.
- After drug price is set; company starts offering drug.

➢ Post-marketing phase:
- Post-marketing surveillances and reviews are implemented in the same way as the regular new drugs.

*Tackling Drug-Resistant Infections Globally: Final Report and Recommendations
The Review on Antimicrobial Resistance Chaired by Jim O’Neill May 2016

Others:

➢ A system in which, when a new AMR drug obtains approval (including when an existing drug, etc. obtains an additional indication, etc. for a new AMR pathogen), the government or appropriate public institution guarantees the purchase of the drug in a form without spot transaction and the company receives appropriate compensation based on the product value and unmet medical need as discussed above can be considered as another form of reward.

2. Extension of market exclusivity period transferable to another pharmaceutical product (Transferable Exclusivity Extensions)

Overview:

➢ This is a system for granting a company the right to extend the market exclusivity period (put off generic entry) for a drug of its choice when it receives manufacturing and marketing approval of a new AMR drug or vaccine.
➢ Marketability of AMR drugs or vaccines are limited and extending exclusivity for the drugs does not offer incentive for a company. Therefore, a company can execute the right with another drug of its choice (including a drug of another company).
➢ The period can be extended up to 12 months.
➢ Market exclusivity period for an AMR drug will be within the regular re-evaluation period.
➢ The company obtaining the right will agree to be bound by the terms and conditions regarding stewardship and adequate promotion, which are required for approval, and provide stable supplies and appropriate sales activities.
➢ To avoid hindering generic entry, a company will announce the execution of the right. The announcement should be made by a certain period (depending on generic development status) prior to the end of the initial exclusivity period of a drug for which exclusivity would be extended.
➢ If the company does not have a product to which the exclusivity extension is applied in its portfolio, it is desirable that the company sells the exclusivity to make it applicable to a product of another company.

Objectives:

➢ Promote continuous research and development of new AMR drugs in Japan by improving profit

predictability and profitability for developers

Process of providing incentives:

- Establish list of high-priority unmet medical needs (list of drug-resistant bacteria in Japan, etc.) and determine eligibility criteria for Transferable Exclusivity Extensions.
- Late clinical study phase:
  - Drug sponsors seek designation of “eligible antimicrobial drug” from relevant government or adequate public institution (Health Science Council, National Institute of Infectious Diseases (NIID), National Institutes of Biomedical Innovation, Health and Nutrition, etc.) based on review of documents submitted by a company against established eligibility criteria. If drug candidate meets eligibility criteria, it receives a designation as “eligible antimicrobial drug”.
- Marketing approval:
  - If any “eligible antimicrobial drug” receives marketing approval from the MHLW, the MHLW issues a voucher to the manufacturer of the drug to extend the market exclusivity period.
  - After drug price is set; company starts offering drug.
- Post-marketing phase:
  - Post-marketing surveillances and reviews are implemented in the same way as the regular new drugs.
  - If the company applies the voucher to a product in its portfolio, it informs the government of the product. If it sells the voucher to another company, the company that purchases the voucher informs the government of the name of the product to which the voucher is applied.
  - The MHLW extends the market exclusivity period of the designated product.

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