

“Rational Medicine” Initiative

—serving the best overall interests of the patient through an all-inclusive approach to medicine that is thoroughly based on the latest science and most advanced technology in all relevant areas—

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Introduction

Throughout my experience in clinical practice, I have continued to believe that medical care must always be administered on the basis of the most rational judgments possible.

“Rational Medicine” is the idea that a patient-centric system should be created—a system under which optimal medical care from the patient’s point of view, which is based on the latest scientific knowledge, is provided—from the perinatal to the final stages of life. I strongly feel that this idea should always be borne in mind by healthcare professionals, companies, government authorities, and all other parties concerned.

The Pharmaceuticals and Medical Devices Agency (PMDA) is, of course, proud to be a key player among these parties. As given in the Mission Statement I made public upon assuming the post of Chief Executive, PMDA has striven to conduct its review, safety and relief service operations based on its mission “to protect public health and the lives of our citizens”, to “develop its human resources so that they possess the latest expertise and wisdom in their areas of expertise”, and to combine their strengths so as to “make thoroughly appropriate, science-based judgments on the efficacy and safety of medical products”.

In seeking to make a holistic approach to medicine—an approach that takes the whole spectrum of considerations to account in order to serve the best overall interests of the patient, not just the specialist’s view in a defined area of expertise—the norm, PMDA is pursuing two more specific aims. The

first is to provide better insight into the risk/benefit balance of drugs, medical devices, and regenerative medical products by furthering regulatory science. The second is to create a medical environment where the care provided is strictly evidence-based. To achieve these ends, in 2017 PMDA will continue its initiatives in the following four areas. As a result I hope to bring forward the date when the public can begin to enjoy the benefits of the “Rational Medicine” approach. Under this approach the patient will receive optimal medical treatment, including in cases where that treatment is based on innovative new technologies and has only just become available:

- (1) Innovation through product approval reviews of enhanced rigor and rationality
- (2) Further promotion of regulatory science
- (3) Increased sophistication of safety measures through the use of real-world data
- (4) Enhanced international partnerships

1. Innovation through product approval reviews of enhanced rigor and rationality

In 2014, PMDA recorded the world’s shortest median review time with regard to new drug product applications, i.e. shorter than that of the European and US regulatory authorities. This level was further reduced the following year. In addition, “device lag” concerning “brand-new” medical device products has now been virtually eliminated.

Looking to the future, I believe that in addition to the emphasis on speed it is crucial to enhance the rigor and rationality with which reviews are conducted. In October 2016, PMDA began to accept clinical data supporting new drug applications in electronic form, and started to utilize it in individual product reviews in anticipation of future use for the formulation of disease-specific guidelines and other purposes. As for medical devices, PMDA aims to further enhance the speed, rigor, and rationality of product reviews in accordance with the “Cooperation Plan to Accelerate Reviews of Medical

Devices” (2014), and to advance discussions with the Ministry of Health, Labour, and Welfare (MHLW) concerning the modalities of early approval.

Consultations between industry and regulatory authority prior to product review application are important for the sake of enhancing the rigor of reviews and the pace of reviews of innovative products. This is particularly the case at the early stages of product development. PMDA plans to further enhance its Pharmaceutical Affairs Consultations on R&D Strategy and other consultation services. In addition, it will strive to further shorten review times in 2017 through active use of the SAKIGAKE (Global Front Runner) Designation System for product reviews.

Furthermore, in October 2016 PMDA set up a “Preparatory Support Office for the Practical Application of Innovation Gains” (*Inobeishon Jitsuyouka Shien Junbishitsu*), which will be expanded and begin work in earnest in April 2017. This was done in response to the proposal to “establish an ‘MHLW-wide’ venture firm support structure” contained in the July 2016 report by the “Advisory Panel on Venture Companies Supporting Innovation in Medicine” (*Iryou no Inobeishon wo Ninau Benchaa Kigyou no Shinkou ni kansuru Kondankai*), a group convened by the MHLW Minister.

2. Further promotion of regulatory science

PMDA has advanced a variety of innovative policies based on regulatory science, such as the introduction of Pharmaceutical Affairs Consultations on R&D Strategy, the formation of a Science Board, implementing the SAKIGAKE Designation System, Comprehensive Collaboration Agreements (with overseas counterpart agencies), a collaboration agreement with the Japan Agency for Medical Research and Development (AMED), and cross-sectional standards development. It will continue in this vein *inter alia* through the establishment a “Regulatory Science Center” in 2018.

This Center will actively promote “Rational Medicine” in collaboration with medical practitioners and academia, working on the basis of regulatory science. Its goals will include the formulation of guidelines to encourage the optimal use of novel medical products with innovative mechanisms of action.

PMDA's Science Board, which entered its third term of activity in 2016, began discussions on the following three areas for the purpose of reinforcing the foundations of regulatory science. In 2017 it will deepen deliberations on these topics so as to achieve results that contribute to the introduction of innovative medical technologies:

(1) Suitable methodologies for clinical assessment of rare diseases

Within wider orphan drug product areas (drugs serving patient populations of 50,000 or lower), rare cancers are an important example of diseases with particularly small patient populations, a characteristic which severely limits the possibility to evaluate the efficacy of drugs through comparative studies.

In order to support future clinical development activities in such rare disease areas, the Board will review the current status of clinical assessments and clarify possible methods of assessment.

(2) Issues in new drug development (by academia in particular)

In order to benefit future product reviews and consultation activities, the Board will review the current situation of bottlenecks in drug development and suggest approaches to overcome them. The latter includes the application of new nonclinical methodologies pertaining to such tasks as efficacy and safety assessments that use disease model cells (e.g. iPS cells).

(3) Medical applications of artificial intelligence (AI)

Expectations have risen in recent years on the practical use of medical devices and related software which function with AI. As the application of AI-related technologies to medicine could take various forms, the Science Board will: (a) review and analyze the current status of R&D of such technologies as well as the limitations faced; and (b) discuss from a scientific perspective the challenges in promoting the practical application of these technologies to medicine.

3. Increased sophistication of safety measures through the use of real-world data

PMDA continues to advance its MIHARI (Vigilance) Project, which consists *inter alia* of the quantitative assessment of adverse event risk

through pharmacoepidemiological methods. Data that is electronically generated and stored by medical institutions is utilized.

Since 2011, PMDA has been developing its Medical Information Database Network (MID-NET) as one of the databases to be used in this project. The network is composed of 23 hospitals in 10 sentinel sites throughout Japan. Each sentinel site will establish a database of ordering data, laboratory data, claim data, Diagnosis Procedure Combination (DPC) system data, and other data types, to be integrated by PMDA into an analytical system that can extract and parse data in a tailored manner to meet specific purposes and then compile and analyze the results. Data analysis testing has begun in preparation for full-scale operations from 2018. In 2017 the testing will be conducted at more advanced levels and further work will be done to establish a system for utilizing real-world data for safety measures.

After the start of full-scale operations, PMDA plans to make MID-NET accessible to drug companies and other third parties to use for example for their post-marketing surveillance activities. The rules concerning data handling and the modalities of cost allocation are currently under discussion by an advisory committee formed by MHLW.

4. Enhanced international partnerships

Based on the “PMDA International Strategic Plan 2015” launched in June 2015, PMDA continues to promote information sharing/public communication and international cooperation while sustaining its contributions to regulatory harmonization activities between different nations and regions. In this context, PMDA opened an Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) in April 2016. The PMDA-ATC has offered seven training programs to date, including a seminar on good manufacturing practice (GMP) concerning drug products held at PMDA’s Hokuriku Branch, and seminars in Thailand and Taiwan on topics such as drug product review. In 2017 PMDA will vigorously continue such training programs both in Japan and abroad,

starting with PMDA-ATC seminars on multiregional clinical trials and regulatory oversight of medical products.

PMDA is actively engaged with international regulatory coordination activities at the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the International Medical Device Regulators Forum (IMDRF), and other fora. In particular, Japan will host the 12th Summit of Heads of Medicines Regulatory Agencies in autumn 2017. PMDA will take this opportunity to reinforce its international cooperation activities and attempt to exercise leadership on the issues of international regulation of medical products.

Approving new drug and medical device products in the world's shortest review times and making them accessible is a crucial aspect of providing patients with cutting-edge, innovative medical care. I am deeply proud of PMDA's contribution to this effort.

In parallel to swift approvals of products that utilize innovative new medical technologies, ensuring that these technologies are used in the optimal manner from the patient's point of view from the day they become available is of the essence. This is precisely to make "Rational Medicine" the prevalent norm. Cutting-edge, innovative medical care by definition lacks a record of real-world administration in any country or region. We must work harder than ever to pool our collective wisdom regarding new technologies in order to identify the most rational methods of product evaluation, relying on the latest regulatory science. We must then promote the most rational uses of these technologies (in terms of designated indications, regimen, and method of use) so that they bring optimal treatment benefits to the patient.

At the same time, we must also ensure that rational methods are used to monitor whether medical care is being administered optimally in the real world and that the results are fed back as appropriate.

I am confident that Japan's efforts to promote "Rational Medicine" through PMDA's International Strategic Plan will transcend borders and benefit patients around the world.

As outlined, in 2017 PMDA will continue its utmost so that "Rational Medicine" becomes the prevalent norm.