Commentary

Accelerating Regulatory Science Initiatives for the Development of Drugs for Alzheimer's Disease in Japan

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ABSTRACT

Purpose: The Ministry of Health, Labour and Welfare (MHLW) of Japan launched a regulatory science research project in which the aim is to promote the establishment of guidelines for the development of innovative drugs thorough interactions between academia and Japan's regulatory agency, the Pharmaceuticals and Medical Devices Agency (PMDA). In this project, a research system with the aim of developing a guideline for the clinical evaluation of drugs intended for the treatment of Alzheimer's disease (AD) was established.

Methods: Two research groups were set up: (1) the Biomarker and Clinical Evaluation Group to establish biomarker-based criteria for the clinical evaluation of drugs for AD, and (2) the Modeling and Simulation (M&S) Group to create a disease model of AD using M&S techniques based on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Furthermore, a human resource exchange between the University of Tokyo Hospital and the PMDA is conducted to establish a guideline that is suitable for regulatory use.

Findings: As an interim report of this project, issues that require consideration for the clinical evaluation and development were summarized, including topics such as the use of biomarkers in the inclusion criteria, the efficacy endpoint, and the clinical data package required for application in Japan.

Implications: As the result of collaboration between the University of Tokyo Hospital and PMDA, this document is the first to summarize perspectives on the development of drugs for AD in Japan. (*Clin Ther*. 2015;37:1622–1626) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: Alzheimer's disease, regulatory science, biomarker, clinical evaluation.

INTRODUCTION

Alzheimer's disease (AD) is the most common disease of dementia and is characterized by a gradual progression of cognitive impairment that interferes with the patient's independent activities of daily living. AD has severe effects not only on patients but also on their caregivers. Japan is now an aging society, and AD is one of the most worrisome and urgent matters of concern from a socioeconomic point of view. In 1999, donepezil was the first drug approved for the treatment of AD in Japan. In 2011, 2 cholinesterase inhibitors (galantamine and rivastigmine) and an *N*-methyl-D-aspartate receptor inhibitor (memantine) were approved as symptomatic drugs, and the prescription of 3 drugs to patients with AD thus became clinically possible, thereby overcoming the "drug lag for AD" issue.[1]

The Japan Health Sciences Foundation has surveyed, on a periodic basis since 1994, the satisfaction of physicians with treatment outcomes and the degree to which individual drugs contribute to treatments. According to their reports, AD has received the lowest ranking in terms of both treatment satisfaction and relevant drug contribution.[1] Thus, medications that can inhibit the progression of clinical symptoms are urgently

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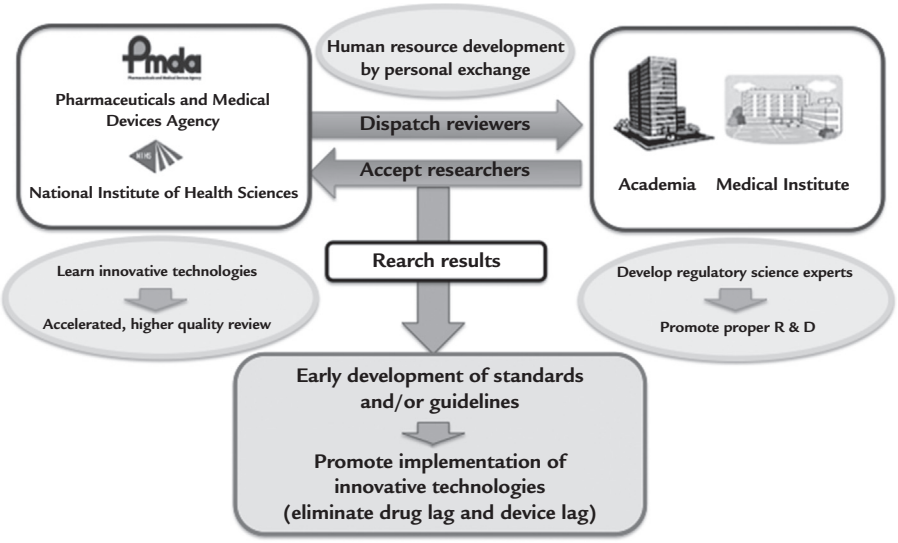

Figure 1. Accelerating regulatory science initiatives in Japan. R & D = Research & Development.

needed. Although disease-modifying drugs have undergone extensive development over the last decade, their clinical efficacy has not yet been successfully demonstrated.[2] Under these circumstances, University of Tokyo Hospital and the Pharmaceuticals and Medical Devices Agency (PMDA) started a novel regulatory science research project for the development of drugs for AD. The objective was to describe the current status of this regulatory science research for the development of drugs for Alzheimer's disease in Japan.

ACCELERATING REGULATORY SCIENCE INITIATIVES IN JAPAN

In 2012, the Ministry of Health, Labour, and Welfare of Japan launched a novel project entitled "Accelerating Regulatory Science Initiatives" to facilitate the development of innovative drugs and medical devices, as well as to facilitate its approval review (Figure 1). One of the aims of this project was to develop a guideline for innovative drugs and medical devices. The other aim was to promote the exchange of human resources between the PMDA (or else the National Institute of Health Sciences [NIHS]) and academic research institutions. In this project, PMDA (or NIHS) members, mainly reviewers or pharmacists, work at academic research institutions (eg, universities) and study the latest advances in science and technology, thereby enabling the introduction of accelerated, higher quality reviews for innovative drugs and medical devices. Academic researchers, mainly physicians, may also work at the PMDA (or NIHS), where they learn about regulatory issues and thus are able to address such issues when working to translate their product into practical use. This exchange will enable the development of regulatory experts and will promote proper research and development at academic research institutions.

These interactions in human resources are expected to lead to the early development of standards and/or guidelines and to promote the implementation of innovative technologies. In 2012, 70 research institutions applied for the program, and 21 institutes (8 related to pharmaceuticals, 7 related to medical devices, and 6 related to regenerative medicine) were selected. Then 18 researchers were accepted as specially appointed experts in PMDA (or NIHS), while 30 reviewers were dispatched to research institutions. From 8 institutions of application, 3 more institutions (2 for the field of pharmaceuticals and 1 for the field of regenerative medicine) joined in 2013. For projects concerning AD, University of Tokyo Hospital was selected to study clinical issues and Kyoto University Graduate School of Medicine was selected to study preclinical issues.

NOVEL REGULATORY RESEARCH FOR THE DEVELOPMENT OF DRUGS FOR AD IN JAPAN

The University of Tokyo Hospital, in cooperation with the PMDA, performed a novel regulatory science research project to establish a guideline for the clinical