Expert Opinion on Orphan Drugs

ISSN: (Print) 2167-8707 (Online) Journal homepage: informahealthcare.com/journals/ieod20

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Peipei Song, Wei Tang & Norihiro Kokudo

To cite this article: Peipei Song, Wei Tang & Norihiro Kokudo (2013) Rare diseases and orphan drugs in Japan: developing multiple strategies of regulation and research, Expert Opinion on Orphan Drugs, 1:9, 681-683, DOI: 10.1517/21678707.2013.832201

To link to this article: https://doi.org/10.1517/21678707.2013.832201

Published online: 26 Aug 2013.

EXPERT OPINION

Rare diseases and orphan drugs in Japan: developing multiple strategies of regulation and research

Peipei Song, Wei Tang† & Norihiro Kokudo
The University of Tokyo, Department of Surgery, Tokyo, Japan

As far back as 1972, measures to combat rare diseases have been part of the Japanese national health system. Thanks to extensive support from the government, measures to combat rare diseases in Japan have made considerable progress over the past 40 years, including specific orphan drug legislation enacted in 1993 to encourage the development of and research on orphan drugs, pricing and reimbursement systems to facilitate access to orphan drugs, specific research programs to promote research on and development of orphan drugs, and a government-supported information centre to promote the understanding of rare diseases. Multiple strategies for regulation of orphan drugs and research on rare diseases have been adopted in Japan. Moreover, a new project to establish a national rare diseases database to collect a wide range of information on patients with rare diseases was launched in 2013 with government support. And in order to ensure quality data, designated doctors specialised in rare diseases will be responsible for directly sending data to the national rare disease database starting in 2015. Quality national data will lead to new opportunities to research and treat rare diseases and also encourage the discovery of orphan drugs in the near future.

Keywords: database, drug discovery, health system, orphan drug legislation

Expert Opinion on Orphan Drugs (2013) 1(9):681-683

1. Introduction

Rare diseases fall under 'intractable diseases (Nanbyo)' in Japan. The 'rarity' of a disease was not specified until 1995, when the Japanese Ministry of Health and Welfare revised the definition of intractable diseases to include 'a disease of unknown aetiology with no effective treatment that presents a major financial and psychological burden and that is rare – affecting fewer than 50,000 total patients' [1]. As far back as 1972, measures to combat rare diseases have been part of the national health system with the implementation of the 'Outline of Measures to Combat Intractable Diseases' issued by the Japanese Government. On January 2013, the 'Revision of Measures to Combat Intractable Diseases' was also approved by the Japanese Ministry of Health, Labor, and Welfare (MHLW) [2]. These revised measures emphasised the three pillars of development of effective strategies to treat rare diseases and improvement of care for those affected, creation of fair and consistent mechanisms to reimburse medical expenses and implementation of measures to enhance public understanding and encourage the social participation of those affected.

Currently, orphan drugs – the medicinal products intended for the diagnosis, prevention or treatment of rare diseases – are a major component of steps to deal with rare diseases, but such drugs do not lead to substantial sales under normal market conditions because of the high costs and risks of drug development, insufficient knowledge of the pathophysiological mechanisms of rare diseases that the drugs

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10.1517/21678707.2013.832201 © 2013 Informa UK, Ltd. e-ISSN 2167-8707

diagnose or treat and difficulties in conducting clinical trials with small patient populations and a small potential market [3]. This fact has been acknowledged by many countries. Accordingly, specific legislation to encourage the development of and research on orphan drugs has been enacted in many countries and regions, including the USA in 1983, Japan in 1993, Australia in 1997, the European Union (EU) in 1999, Taiwan in 2000 and South Korea in 2003. Incentives include financial subsidies, exclusive marketing rights, tax credits, fee waivers, fast-track approval and protocol assistance, resulting in substantial improvements in the treatment of patients with a range of rare diseases.

2. Orphan drug legislation in Japan

In Japan, Revised Orphan Drug Regulations (amendment of the Pharmaceutical Affairs Act and the Act Establishing a Fund for Relief of Adverse Drug Reactions and Promotion of Research) were implemented in 1993. Incentives include financial subsidies for up to 50% of expenses for clinical and non-clinical research during the entire research process, exclusive marketing rights for 10 years (compared with 6 years for other medications), 15% tax credits on research costs excluding financial subsidies and up to a 14% reduction in corporate tax (these pharmaceutical companies are required to pay a 1% sales tax to offset the subsidies they received from the government when their orphan drug annual profits exceed 100 million yen), priority review and fast-track approval, free protocol assistance and user fee waivers [3-5]. As a result of these incentives, 269 drugs were designated as orphan drugs prior to June 2012. Of these, 173 orphan drugs have been approved for marketing, with an approval rate of 64.3%. Due to the strong incentives by the Revised Orphan Drug Regulations, especially with the support of government financial subsidies and 10 years' exclusive marketing rights, the approval rate of orphan drugs in Japan (64.3%) is higher than that in the USA (15.4%, with 403 of 2609 designated orphan drugs being approved for marketing) or in the EU (7.0%, with 70 of 1000 designated orphan drugs being approved for marketing) as of June 2012 [6].

3. Pricing and reimbursement

In addition to special legislation to encourage research and discovery and development of orphan drugs, pricing and reimbursement are two major aspects that affect access to orphan drugs for patients with rare diseases. In the USA, drug manufacturers negotiate with governmental programs such as Medicaid and the Veterans Health Administration and Pharmacy Benefits but remain free to set their own introductory prices, and there is little regulation of competition among manufacturers in comparison with imposed price restrictions [7]. In the EU, orphan designation and marketing authorisation for orphan drugs are decisions made at the European level according to Regulation (EC) No 141/2000, but pricing and reimbursement decisions are a member state responsibility [8]. In contrast to these strategies, the Japanese National Health Insurance (NHI) system negotiates prices with pharmaceutical companies once a drug is approved for use, allowing a selling price of cost plus 10% for orphan drugs; nearly half of the orphan drugs on the Japanese market originated from the EU or the USA. Moreover, 56 of 130 designated diseases in Japan are eligible for reimbursement of medical expenses, with 30% of expenses paid by insurance companies and the rest paid by national and prefectural governments [9].

4. Specific research programs

In accordance with orphan drug legislation in Japan, governments are compelled to allocate funds to promote research on and development of orphan drugs. In Japan, the 'Specified Disease Treatment Research Program' was established in 1972 with the support of the Japanese Ministry of Health and Welfare. One hundred and thirty diseases have been targeted by special research programs and research grants from the government; these funds increased to 11.3 billion yen in 2013 [10]. Recently, 214 diseases were targeted by a second round of special research programs. Moreover, a project establishing 'Bases for Early and Exploratory Clinical Trials in Specific Research Areas' began in 2011 in order to promote the development of innovative orphan drugs and medical devices from Japan. This project has the financial support of and institutional guarantees from the government. Under the project, five institutions were selected as the national bases for early and exploratory clinical trials in specific research areas including cancer, cerebral and cardiovascular diseases, neuropsychiatric disorders and immunological intractable diseases. Two of the bases – the School of Medicine in Keio University, the University of Tokyo Hospital – have formulated specific plans to develop new drugs to combat rare diseases. These steps should lead to new opportunities to develop drugs to treat intractable immunological and neuropsychiatric diseases, thereby facilitating the translation of orphan drugs from basic studies to clinical use [11]. Furthermore, a project entitled the 'Enhanced International Information Exchange' was launched in 2013 under a 'Grant-in-Aid for Publication of Scientific Research Results'; the project enjoys the support of the Japan Society for the Promotion of Science (JSPS), which falls under the auspices of the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) [12]. One of the project's planks is support for a journal of 'Intractable and Rare Diseases Research' thus establishing a system to publicise the results of limited research on rare diseases and orphan drugs to a broader international audience.

5. Information centre and database

In addition to the difficulties in researching rare diseases and orphan drugs, the delay in diagnosis and treatment is also daunting. A survey of 18,000 individuals found that 25% of patients waited for 5 – 30 years before being correctly

diagnosed and 40% of patients were diagnosed incorrectly before being correctly diagnosed [13]. Furthermore, clinical studies on orphan drugs also face challenges due to the small size of the trial population and the fact that patients are often geographically dispersed. In Japan, the Japan Intractable Disease Information Center was established through cooperation of the MHLW and the Japan Intractable Diseases Research Foundation for the purpose of publicising information about rare disease primarily in Japan. The Center's website currently has over 15 million hits per year, and therefore this website is key to understanding the present state of diagnosis and treatment of 130 rare diseases in Japan. Moreover, a new project to establish a national rare diseases database to collect wide range of information on patients with rare diseases was launched with government support in 2013. In order to ensure quality data, designated doctors specialised in rare diseases will be responsible for directly sending data to the national rare disease database starting in 2015. Quality national data will lead to new opportunities to research and treat rare diseases and also encourage the discovery of orphan drugs in the near future.

6. Conclusion

Evidence has shown that incentives offered by orphan drug legislation are necessary and can facilitate the development of orphan drugs to benefit patients with rare diseases. In Japan, the number of approved orphan drugs has increased since specific orphan drug legislation was enacted in 1993. Orphan drugs are approved for marketing at a higher rate than in the USA or the EU. Multiple strategies for regulation of orphan drugs and research on rare diseases have also been adopted with extensive support from the Japanese Government as part of the national health system. These moves include pricing and reimbursement systems to facilitate access to orphan drugs, specific research programs to promote research on and development of orphan drugs and a government-supported information centre to promote the understanding of rare diseases. Moreover, a new project to establish a national rare diseases database to collect a wide range of information on patients with rare diseases was launched in 2013 with government support. Quality national data will lead to new opportunities to research and treat rare diseases and also encourage the discovery of orphan drugs in the near future.

Declaration of interest

The authors have no conflict of interest to disclose and have received no payment for the preparation of this manuscript.

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Affiliation

Peipei Song, Wei Tang† & Norihiro Kokudo
†Author for correspondence
The University of Tokyo,
Department of Surgery,
7-3-1 Hongo, Bunkyo-ku,
Tokyo 113-8655, Japan
E-mail: tang-sur@h.u-tokyo.ac.jp