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Matched analysis on orphan drug designations and approvals: cross regional analysis in the United States, the European Union, and Japan

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Orphan drugs have become a key area of focus in drug development for resolving unmet medical needs. The Orphan Drug Act in the USA and similar legislation in Japan, the European Union (EU), and several other countries has been enacted since 1983. This study provides a quantitative review of all orphan drug designations and approvals since the implementation of orphan drug legislation in key three regions. This study also identified and reviewed 'commonly designated' drugs across regions. Out of approximately 5000 designations, approximately 800 designations were common among the USA, EU, and/or Japan. Regional similarities, differences, and trends were identified. It is important to understand these aspects and the crucial role of orphan drug designation in global drug development.

Introduction

Despite the fact that rare diseases are often chronically debilitating, life threatening, and/or life limiting, the relatively small number of patients affected by such diseases reduces the incentive for the pharmaceutical industry to develop drugs to treat them. To date, nearly 7000 rare diseases have been identified, many of which have a genetic basis and affect patients early in childhood. This represents substantial unmet medical and social needs (https://rarediseases.info.nih.gov/Files/GARD_brochure_English.pdf). Technological advances, such as phenotypic assays, target-based approaches, and biologic strategies, have increased the number of orphan drugs, particularly in oncology and metabolic diseases [1–3]. Furthermore, a recent trend to 'repurpose' commercialized products for other rare diseases also encourages the industry to develop orphan drugs [4].

The development of orphan drugs represents a challenge for the pharmaceutical industry, because the limited number of patients with rare diseases necessarily means lower profit margins. In 1983, the US Government implemented the Orphan Drug Act to encourage the pharmaceutical industry to increase and accelerate the development of orphan drugs, with similar mechanisms implemented in Japan in 1993 and the EU in 2000. Although the eligibilities for the orphan drug designation differ slightly depending on the legislation and policies adopted by each region, they are similar in that they mainly focus on the number of patients along with the likelihood that the product will have utility in the disease [5].

Rare diseases represent a key area of focus in drug development, with approval rates in 2014 for orphan new active substances (NASs) in each region as follows: USA, 47%; EU, 43%; and Japan, 37% [6]. Countries in Asia, Oceania, and South America, such as Australia, Mexico, Argentina, Chile, Columbia, Taiwan, and Korea, have implemented, or are planning to implement, orphan drug mechanisms similar to those in the USA, EU, or Japan to promote orphan drug development [7,8]. Several initiatives and programs have also been implemented by non-industry organizations specifically for rare diseases, or for various disorders, including rare

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diseases, such as the Drugs for Neglected Diseases initiative by the nonprofit organization Doctors Without Borders, and Therapeutics for Rare and Neglected Diseases and the Rare Diseases Clinical Research Network by the National Institutes of Health [9–11]. Organizations of all types (governmental, commercial, and academic) are now collaborating in orphan drug development to ensure that more of these medicines reach patients as swiftly as possible.

Several reviews of regulations and accumulated experience in specific regions have been conducted [12–14], and one study conducted a cross-regional comparison of orphan drug designations and approvals [5]. Another analysis used data from commercial databases, although the databases did not cover all regional designations [15]. However, as yet, no quantitative comparative study across regions has conducted a data-matched analysis of orphan drug designations and approvals among the USA, EU, and Japan.

Here, the trends and identified differences in orphan drug designations and marketing approvals among the USA, EU, and Japan following the implementation of legislation are characterized by region. This was accomplished by analyzing the status of orphan drug designations and approvals based on the matched data across the three regions. We consider this approach to serve as the basis for future examination of measures to further optimize orphan drug development.

Two data sets were used for the analysis. The first data set was the entire data set, which included all paired and unpaired data ('all data'). After integrating and after pairing and/or matching designations among the USA, EU, and Japan, as presented in Box 1, we obtained one integrated data set. This second data set included only paired data with matches between either two or all three regions ('matched data').

BOX 1

Data sets

Lists of designated orphan drugs as of February 28, 2015 were obtained from the databases of the websites of the US Food and Drug Administration (FDA), the European Commission, and the National Institute of Biomedical Innovation in Japan (http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm; http://ec.europa.eu/health/documents/community-register/html/orphreg.htm; and http://www.nibio.go.jp/shinko/orphan/kisyoiyaku-hyo1.html).

All regional data were then entered into a spreadsheet and coded by drug type, applicant type, and therapeutic classification. Drug type was coded as small molecule, biologic, nucleic acid/vector/cell/tissue, vaccine, or others. Chemicals, amino acids, and small peptides (<100 amino acids in length) were coded as small molecules. Antibodies, fusion proteins, and high-molecular-weight enzymes (>10 kDa) were coded as biologics. Plasmids and vectors were coded as vectors, cells as cells, and tissue products as tissues. Vaccines for infectious disease prophylaxis, such as influenza vaccine, were coded as vaccines. Applicant type was categorized based on the SCRIP 100 total revenue ranking in 2013 as in the top 1–10, 11–30, 31–50, 51–100, or 101+ companies in the pharmaceutical industry (http://www.scrip100.com/scrip100.html). If an applicant was not from a pharmaceutical company but rather from an academic or research institution, they were categorized as academia/institution. Therapeutic classifications were assigned based on ATC codes, referencing existing medications and WHO guidelines (http://www.whocc.no/filearchive/publications/2015_guidelines.pdf). First designation dates and approval dates were integrated into the spreadsheet if multiple dates were available for a single product, for reasons such as a change in applicant in Japanese orphan designations.

After spreadsheet entry, data were matched by pairing drugs in each region with drugs in other regions as follows: integrated data were sorted by drug name, then, pairings were performed repeatedly based on the brand name, applicant name, and proposed indication to provide the best match. Databases such as Orphanet were also referenced to identify drug pairs (http://www.orpha.net).

Individual data were duplicated in the spreadsheet when the granularity for a specific indication differed among regions. For example, for a recombinant human factor VIIa, the proposed indication in the USA was 'hemophilia'. By contrast, the indications were more granular in the EU, which were 'hemophilia A' and 'hemophilia B'. In this case, the original USA item was duplicated to make two complete pairs with the EU items in the data set.

We ultimately obtained two data sets from the integrated spreadsheet: the first data set included all paired and unpaired data ('all data'), whereas the second included only paired data with matches between USA and EU and between USA and Japan ('matched data'). Descriptive statistics on drug type, applicant type, and therapeutic classification were calculated for 'all data', while the time difference for orphan drug designations and marketing approvals were compared using 'matched data'. Data in the USA were used as references, and comparisons were made between the EU and the USA, and between Japan and the USA.

Overall characteristics of orphan drug designations and marketing approvals

Overview

From the implementation of legislations up to February 28, 2015, the following number of orphan designations were identified in each region: 3345 in the USA, 1146 in the EU, and 359 in Japan (Table 1). Of these designations, marketing approval was given to 496 products in the USA, 87 in the EU, and 236 in Japan.

The USA continues to have the most designations and the most approvals, with 290 orphan drug designations and 40 approvals in 2014 alone. The EU ranked second for orphan drug designations, whereas Japan ranked second for approvals. Orphan drug designations and their marketing approvals in 2014 were 184 and 14, respectively, in the EU, and 38 and 14, respectively, in Japan. Given that the EU had adopted the legislation most recently (in 2000), it has been rapidly and intensively focusing its attention on orphan drug designations.

The percentage of successful marketing approvals to orphan drug designations was identified in each region: 14.6% in the USA, 7.6% in the EU, and 64.8% in Japan. Matching each drug yielded the following orphan drug designations: 3390 in the USA, 1146 in the EU, and 364 in Japan (Table 1). Annual designations since the implementation of orphan drug legislation for each region are shown in Fig. 1.

Number of orphan drug designations

The number of orphan drug designations has steadily increased across all three regions since the introduction of relevant legislation. The number of designations increased over time, with the following numbers of products in each region designated as orphan drugs in 2014: 290 in the USA, 184 in the EU, and 36 in Japan.

This continuously increasing number of orphan drug designations suggests that orphan drug legislation remains a critical part of the drug development process. Each regulatory body has implemented, or is planning to implement, expedited mechanisms to deliver new drugs to patients as quickly as possible, and the scope is not limited to orphan drugs but includes any drugs that meet their criteria. In the USA, the breakthrough designation mechanism was implemented to support existing expedited pathways, such as accelerated approvals and fast track. In the EU, existing guidelines on accelerated assessment and conditional marketing