

희귀질환 연구와 치료제 개발 동향

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Rare Disease Research and Orphan Drug Development

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희귀질환이란 일반적으로 그 유병율이 인구 일만 명당 5명 이하인 질환을 말한다. 세계에는 약 7,000여종의 희귀질환이 알려져 있고 학술지에 매 주 대략 5종의 새로운 희귀질환이 보고되고 있다. 희귀 의약품(orphan drug)이란 희귀질환치료제 또는 수익성이 없어 개발을 기피하는 일반질환 치료제로서 정부가 지정한 의약품을 말한다. Orphan 의약품의 개발에는 많은 장점이 있다. Orphan 의약품으로 정부의 지정을 받으면 세금감면을 통한 연구비 지원, 임상시험 비용 지원, 신약허가 심사비 면제, 시장독점권 부여 등의 특혜가 주어진다. 희귀질환의 대부분은 단순한 유전적 결함에 의한 경우가 많아 치료제의 표적발견이 비교적 쉬우므로 개발 성공률이 높고, 임상시험기간이 짧으며, 시판 허가를 받을 확률이 높아 연구개발비용이 적게 든다. 그 결과 전세계 orphan 의약품 시장은 최근 매년 6%씩 성장하여 2014년에는 약 1,120억달러의 시장을 형성할 것으로 추정된다. Orphan 의약품 시장은 현재 매년 8.9%씩 성장하고 글로벌 시장의 51%를 점유하는 미국을 중심으로 확장되어 가고 있으며, 총매출액의 64.3%가 유전자재조합의약품에 의한 것으로 알려져 있다. 이러한 의약품시장의 변화와 사회적 요구에 부응하여 한국 또한 희귀질환 치료제 개발의 활성화를 위해 재정적 지원체계를 구축하고, 허가관리를 개선하며, 법률적 제도를 완비하는 과정에 있다. 현재 희귀질환의 치료적 타겟을 찾아 신물질이나 기존의 약물을 발굴하는 과정이 주로 대학이나 연구 중심 병원에서 이루어지고 있다. 제도가 잘 정립되어 있는 미국 시장을 겨냥하여 orphan 의약품 개발을 전략적으로 수행한다면 큰 성공을 거둘 수 있을 것으로 기대된다.

□ Key words - rare disease, orphan drug, orphan designation, orphan drug act, academic institution

INTRODUCTION

A disease is categorized into a rare disease and a common disease based on the prevalence. Although the definition of a rare disease varies slightly in different countries, it is generally accepted as a disease with the prevalence of less than five in 10,000 people.¹⁾ The incidence of a rare disease at birth is less than one in 2,000 people. It represents 6% to 8% of the world population. There are about 7,000 rare diseases already known and about 250 dis-

eases are newly reported in medical journals every year.²⁾ Approximately 80% of rare diseases are from genetic origins. Other causes include infections, allergies, and proliferations. Signs and symptoms of some rare diseases such as lysosomal storage diseases, patent ductus arteriosus, and cystic fibrosis may appear at birth or in childhood. However, more than 50% of rare diseases appear during adulthood. Examples of such diseases include glioma and acute myeloid leukemia.³⁾

Similar to a rare disease, an orphan drug is defined slightly differently in different countries.¹⁾ In general, it is a drug intended to treat either a rare disease or a common disease where pharmaceutical manufacturers cannot expect to make profits from the sales of the drug. Drugs and vaccines for tropical diseases are good examples of

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such orphan drugs. They are not profitable to their manufacturers since the patients suffering from those tropical diseases are too poor to afford the price of such medications.

Orphan drugs differ from essential medicines in many aspects. Concrete policies were established for orphan drugs in 1983 in the United States⁴⁾ and in 2000 in European Union.⁵⁾ Whereas essential medicines focus on the public health, which aims for bringing effective medicines to the maximum number of patients, orphan drugs are primarily for individual patients and even a single patient warrants all possible treatments.¹⁾ Due to their differences, essential medicines are drug-driven, while orphan drugs are disease-driven. Target populations of essential medicines were initially low-income countries but now it is for all countries, while orphan drugs target high-income and developed countries. Economics differ between essential medicines and orphan drugs. Non-orphan drugs are to achieve cost-effectiveness, sustainability, and affordable access, while orphan drugs are relatively expensive and cost-maximization per population is the goal.

There are many challenges in rare disease research and orphan drug development. Due to the nature of rare diseases not having sufficient information, lack of knowledge and training can be a big challenge. For example, deficient diagnostic systems and lack of effective and safe treatment for these diseases have been problematic. Even for those with available treatment, the cost for the treatment of rare disease is very expensive. Because of the high cost in drug development, the pharmaceutical industry is reluctant to make such risky investment in relatively small markets. These obstacles cause the global debate on deficiencies in supplying orphan drugs. Therefore, rare diseases and orphan drugs will appear more often on the future public health agenda.

Recently, the President of the United States signed the Food and Drug Administration Safety and Innovation Act (FDASIA), the landmark legislation that will encourage the development of new treatments for the 30 million Americans suffering from rare diseases.⁶⁾ Along the FDASIA, the FDA Commissioner signed a commitment letter agreeing to a Rare Disease Initiative, which includes increased

staffing to provide expertise in orphan drug development to the product review divisions, increased efforts to ensure that product reviewers, industry, and patients are working together, and broadening of research and programming in the areas of non-traditional clinical trial design, study endpoints, and statistical analyses associated with orphan drug development.⁷⁾

In Korea, although the majority of orphan drugs have been imported from other countries, some orphan drugs are recently developed domestically. Hunterase[®] for the treatment of Hunter disease and Cupistem[®] for Crohn's fistula were approved in 2012. In the near future, rare disease research and orphan drug development in Korea is expected to be accelerated with emphasis on targeted therapy, genetic recombination, and stem cell therapy under the government's stimulus policy.

Under such circumstances, the authors perceive that it is important to share the knowledge with the scientific community and industry on the regulatory policies in different countries on rare diseases and orphan drugs, the advantages in the development of orphan drugs, and the role of academia in rare disease research and orphan drug development. The authors suggest paying more attention to rare disease research and orphan drug development not just for the profit of pharmaceutical industry but also for the benefit of patients suffering from rare diseases.

DEFINITION OF A RARE DISEASE AND AN ORPHAN DRUG

The definition of a rare disease and an orphan drug are slightly different between different regions in the world. In this article, the authors summarized the definitions in Korea, the United States, the European Union and Japan, and compared them in Table 1.

In Korea, a rare disease is defined as a disease or condition with less than 20,000 patients among Korean population residing in South Korea (Table 1).⁸⁾ An orphan drug is a drug to treat a rare disease or a disease with no available treatment in Korea. If the drug is manufactured in Korea, the total production cost should be less than 5 billion won per year. If it is imported for sale, the total imports of the

Table 1. Definition of Rare Diseases and Orphan Drugs in Each Region of the World.

	Korea	United States	European Union	Japan
Rare Disease	Disease with < 20,000 patients in Korea	Disease or a condition with less than 200,000 patients in the United States	Disease affecting no more than 5 in 10,000 persons (0.05%)	Disease with less than 50,000 patients in Japan (0.04%)
Orphan Drug	Drug for treating a rare disease Drug targeted for treating a disease with no available treatment Drug with annual import less than \$1.5 million Drug with annual production less than 1.5 billion Korean wons for drugs manufactured in Korea	Drug for treating a rare disease Drug that is not profitable within 7 years of approval	Drug for treating a rare disease Drug that is withdrawn from market due to economic or therapeutic reasons Drug that is not developed due to difficulty in patenting or lack of demand	Drug for treating a rare disease Drug that treats a disease where no other treatments are available in Japan or a clinically superior drug compared to drugs already available

drug should be less than 5 million U.S. dollars per year. The orphan drugs are supplied to the patients by pharmaceutical companies or Korea Orphan Drug Center.

In the United States, a rare disease is defined as a disease or condition that affects less than 200,000 people among United States Population (Table 1).⁴⁾ An orphan drug is any drug developed under the federal Orphan Drug Act (ODA) of January 1983. ODA defines an orphan drug as either a drug or a biological product that is used for the prevention, diagnosis or treatment of a rare disease in the United States, or a drug that will not be profitable within 7 years following approval. If the drug at issue is diagnostic, preventive, or is a vaccine, the number of people subjected to the drug in the year of the application must be less than 200,000.

In European Union, a rare disease is defined as a disease affecting less than 5 in 10,000 people (Table 1).⁵⁾ According to European Organization for Rare Diseases, there are 6,000 to 8,000 known rare diseases and 25~30 million people are affected by rare diseases in Europe. An orphan drug is defined as a product intended to treat rare diseases, a product withdrawn from the market for economic or therapeutic reasons, or a product that have not been developed either because they are derived from a research process that cannot be patented or because they concern important markets which are, however, not creditworthy.

In Japan, a rare disease is defined as a disease with fewer than 50,000 prevalent cases on the Japanese territory, which corresponds to a maximal incidence of four per 10,000

people (Table 1).⁹⁾ An orphan drug is defined as a drug that treats a rare disease or condition for which there are no other treatments available in Japan or the proposed drug is clinically superior to drugs already available on the Japanese pharmaceutical market.

POLICIES ON ORPHAN DRUG DEVELOPMENT

Government's stimulatory policies and legislations have been pivotal in facilitating rare disease research and orphan drug development. In the United States, prior to ODA, only about one drug was independently developed by pharmaceutical industry per year. During the process to pass ODA, the U.S. Congress recognized that the drugs for rare disease treatment were inadequately researched and developed due to economic reasons. Financial incentives were needed to improve the development of products for rare diseases. Protection of unpatented drugs, tax credits for qualified clinical study expenses and grants for orphan drug development were suggested. Not only financial supports, but also was protocol assistance proposed for pharmaceutical companies that develop an orphan drug product.¹⁰⁾ As the result of ODA enactment, approximately 400 orphan drugs were approved over the last three decades in the United States.¹¹⁾

Orphan Drug Designation

In Korea, regulatory policies on orphan drug designa-

tion have been implemented since 1998.⁸⁾ Initially, the purpose of the designation was to promptly supply imported orphan drugs to the patients suffering from rare diseases that had no currently available effective therapy. Recently, the policy was extended to the orphan drugs to be developed domestically.¹²⁾

In the United States, the policies and procedures for orphan designation are well established based on the ODA. To obtain an orphan drug designation, the applicant should request for designation to the Office of Orphan Products Development (OOPD) in FDA prior to submitting a New Drug Application (NDA) or a biologics license application (BLA).¹³⁾ Once the application for orphan drug designation is accepted, the drug is said to be under "orphan status." It differs from new drug approval; therefore, it must still undergo the review for drug approval by submitting either NDA or BLA. Since orphan status designation is a separate process from NDA process, the orphan status does not directly affect the NDA review process. In order to get approved with a new orphan drug, the applicant still needs to design and conduct adequate and well-controlled clinical trials to prove its safety and efficacy.

An applicant may request orphan drug designation with a previously unapproved drug, or a new orphan indication for an already marketed drug.¹³⁾ In addition, an applicant of a drug that is otherwise the same drug as an already approved orphan drug may seek and obtain orphan drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug. Furthermore, more than one sponsor may receive orphan drug designation for the same drug for the same rare disease or condition, but each sponsor seeking an orphan drug designation must file a complete request for designation.

To request an orphan drug designation, the applicant must provide the evidence that the product will be promising in the treatment, prevention or diagnosis of a rare disease or condition. The application is a straightforward process and designation request may be submitted any time during the drug development steps before NDA or BLA submission. A prior IND submission is not necessary

to apply for an orphan product designation. For an orphan drug designation request, the following information has to be submitted to the FDA.¹³⁾

- A description of the rare disease or condition for which the drug is being or will be investigated, the proposed indication or indications for use of the drug, and the reasons why such therapy is needed.

- A description of the drug and a discussion of the scientific rationale for the use of the drug for the rare disease or condition, including all data from nonclinical laboratory studies, clinical investigations, and other relevant data that are available to the applicant, whether positive, negative, or inconclusive.

- Where the applicant of a drug that is otherwise the same drug as an already approved orphan drug seeks orphan drug designation for the subsequent drug for the same rare disease or condition, an explanation of why the proposed variation may be clinically superior to the first drug.

- Where a drug is under development for only a subset of patients with a particular disease or condition, a demonstration that the subset is medically plausible.

- Documentation to demonstrate that; (1) The disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the individuals to whom the drug will be administered in the United States are fewer than 200,000 per year, or (2) For a drug intended for diseases or conditions affecting 200,000 or more people, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug.

Scientific rationale submitted for orphan drug designation must provide evidence that the drug holds promise for being effective in treating, preventing, or diagnosing the disease.¹³⁾ Scientific data include clinical data, case studies/reports, animal models, or even in vitro data where no animal model exists with proposed mechanism of action and pathogenesis of the disease. If there is a standard of care or other treatment options available, clinical superiority should be demonstrated.

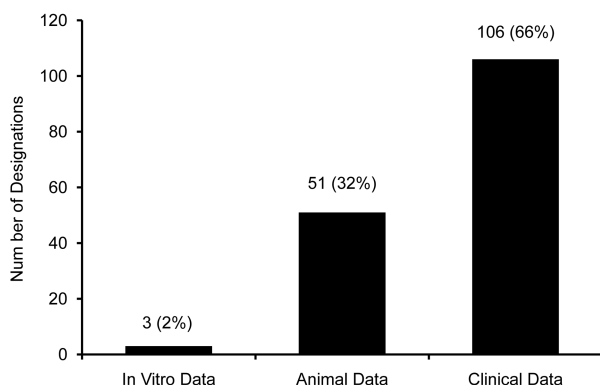


Fig. 1. Types of Supporting Scientific Data for 160 Orphan Designations in 2009¹⁴.

Scientific rationale presented by the applicants of orphan product designation in 2009 was examined.¹⁴ There were 160 orphan designations granted in the year. Even with options of submitting animal study data (51 designations) or in vitro study data (3 designations), the majority of the applicants submitted clinical experience (106 designations) reporting drug's efficacy in various phases of trial as the scientific rationale support (Fig. 1). Among 106 clinical experience data as scientific rationale (Fig. 2), Phase 2 data were predominant (47 designations), followed by Phase 3 (21 designations) and Phase 1 (19 designations). The timing of obtaining orphan product designation differs depending on the applicants' strategies. For some applicants, ODA-stipulated tax credit incentive encourage them to submit the request earlier in the developmental process. However, most applicants apply only after gathering data from clinical experience. At the time of obtaining orphan designation, approximately half (56 out of 106 designations) had an active IND.

The review of designation request begins with determining the distinct disease or condition which would be treated, diagnosed or prevented by the proposed drug/biologic.¹⁵ For example, lymphoma is categorized to non-Hodgkins and Hodgkins' lymphoma. Then non-Hodgkins lymphoma is further classified into 3 different types, B-cell, T-cell, and null-cell lymphoma according to WHO classification.¹⁶ Each subtype of lymphoma is treated as a distinct disease and treatment strategy may be different for each specific condition so that each is subject to being designated sepa-

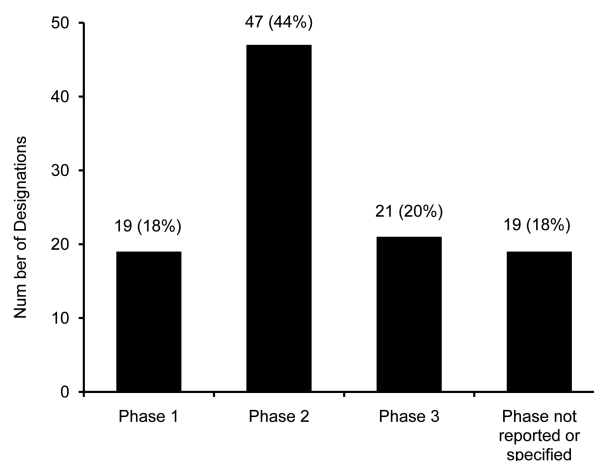


Fig. 2. Types of Supporting Clinical Data for 106 Orphan Designations in 2009¹⁴.

rately.

Whether a disease is rare or not is determined by prevalence of the disease in the United States, except acute illnesses such as malaria, in which the incidence is used instead of the prevalence.³ Applicants must demonstrate a specific number of patients affected by the disease at the time of request. Stating that the disease occurs in less than 200,000 people is not sufficient to be accepted for orphan designation. For preventive drugs, everyone who is at risk of the disease is counted as the number of patients affected. In case of prevention of ischemic reperfusion injury associated with solid organ transplantation, the number of patients to be undergone organ transplantation would be the potential population considered for an orphan designation. There are various sources of data to demonstrate prevalence: published literature, registries, and opinions of three experts if the supporting data are not publically available. If a range exists for the prevalence, the highest estimate is applied. If the disease is common with more than 200,000 patients, orphan designation may be granted for use in a medically plausible subset. Medically plausible subset is subset of all individuals with the disease or condition who would only be expected to receive benefit from the drug. While preeclampsia is a very common condition, for example, it can be narrowed down to a medically plausible subset such as severe preeclampsia due to toxicity of a drug.

The proposed orphan product should ideally have a bet-

ter safety and efficacy profile than existing treatment option.¹³⁾ Wilate[®], which was FDA designated as an orphan drug in 2007, was determined to be superior in safety profile to Humate-P[®].¹⁷⁾ Two dedicated viral inactivation steps of von Willebrand/Factor VII complex for Wilate[®] was clinically safer than a single step for Humate-P[®]. In addition, interferon beta-1a product, Rebif[®] indicated for relapsing-remitting multiple sclerosis was shown to be more effective than Avonex[®].¹⁸⁾ Not only clinical superiority, but also are factors contributing to patient care considered in the review process. One of the major concerns in patient care is compliance. Human growth hormone for growth hormone deficiency is similar in clinical profile, however once a month intramuscular administration is preferred over once a day subcutaneous administration.¹⁹⁾

Success of the orphan drug designation program is growing and more than 3660 designation requests were received until 2011 since the enactment of ODA in 1983.²⁰⁾ Out of 3660 requests, 2550 drugs (approximately 70%) received orphan drug designations and 395 drugs were brought to the orphan drug market. Therefore, potential opportunities for new orphan drug development are limitless for more than 4400 new orphan diseases. Orphan drug approvals were obtained for 395 orphan designated products by the end of year 2010. Drugs for rare diseases represented for all FDA approved NMEs and new biologics comprise 31% of the drug market in 2008, 37% in 2009, and 24% in 2010.¹⁴⁾

To qualify for an orphan drug designation in European Union, a drug must meet a number of criteria.⁵⁾ The drug must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating. No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the drug must be of significant benefit to those affected by the condition. Applications for orphan designation are examined by the European Medicines Agency's Committee for Orphan Medicinal Products, using the network of experts that the Committee has built up. The evaluation process takes a maximum of 90 days from application.

In Japan, a drug must meet the following conditions in

order to be considered for orphan drug designation.⁹⁾ Any disease with fewer than 50,000 prevalent cases (0.4%) is Japanese definition of rare. The drug treats a disease or condition for which there are no other treatments available or the proposed drug is clinically superior to drugs already available in Japan. The applicant should have a clear product development plan and scientific rationale to support the necessity of the drug in Japan. Once clinical trials are completed, an NDA can be submitted. It is important that while Japan has orphan drug legislation, this legislation has room for interpretation. The Ministry of Health, Labor and Welfare (MHLW) makes orphan drug designation and approval decisions on a case-by-case basis. This is especially true when determining the number of Japanese clinical trials required for the approval.¹⁾

Stimulus for Orphan Drug Development

Almost all countries having well-established pharmaceutical market implement policies and provide incentives that stimulate orphan drug development. Table 2 shows a summary of incentives that the applicant can take from the development of a drug product after receiving orphan drug designation. In Korea, the stimulus package for orphan drug development is under revision.²¹⁾ Currently, the incentives for the drug product with orphan designation include a fast track regulatory review for marketing approval, a user fee reduction by 50% when the clinical trials were conducted in Korea, an exemption from reevaluation after marketing approval. In addition, the applicant that develops an orphan drug can take an advantage of receiving a preliminary regulatory review for orphan designation. Once the orphan designation is granted, Korean FDA assigns a project manager who delivers consults in the development of the designated product from a regulatory standpoint and provides a comprehensive support to reduce the time length of clinical development and marketing application review.

In the United States, once FDA designates the candidate product as an orphan drug, the applicant receives various incentives (Table 2).²²⁾ First, the applicant is granted with seven-year marketing exclusivity. Because this marketing exclusivity is given not just for the orphan drug itself but for the rare disease to treat, financial profit expected

is greater than with other types of marketing exclusivity. Secondly, tax credit equals to 50% of clinical research expenses is provided. The applicant can also receive a waiver of user fee for NDA or BLA review request, which is approximately \$2,000,000 at this time.

In addition, throughout the clinical development of an orphan designated product, the applicant can receive clinical research funding from Orphan Products Grant Program administered by OOPD in FDA.²²⁾ FDA informs the available funds through the Federal Register each year. Applications are reviewed by outside experts and funded according to their priority score. Clinical trials may be awarded to cover both direct and indirect costs. For Phase 1 studies, up to \$200,000 may be awarded per year for up to three years. For Phase 2 and 3 studies, up to \$400,000 may be awarded per year for up to four years. Until now, approximately \$14 million has been distributed to 60 to 85 projects every year.²²⁾ It is known that OODP allocates research funding for 10 to 15 new projects every fiscal year.

Similar to the United States, European Union also grants various assistance and incentives for orphan drug development (Table 2).¹⁾ Applicants with an orphan designation benefit from incentives by protocol assistance and scientific advice during the product development phase. Once the designated product is approved, the applicant is granted with ten-year marketing exclusivity. Since January 2007, orphan medicinal products are eligible for fee reductions. They include 100% reduction for protocol assistance and follow up, 100% reduction for preauthorization inspections, 50% reduction for new applications for marketing authorization, and 50% reduction for post-authorization activities, including annual maintenance fees in the first year.

In Japan, MHLW provides consultation services to the applicants that are granted for orphan drug designation (Table 2).¹⁾ Applicants may receive financial aid for the collection of supporting clinical data. They receive financial aid for as much as 50% of the cost of the clinical trials, tax exemptions up to 6% of research costs and 10% of corporate tax. Also, application will be placed on a fast-track approval process of ten months instead of twelve months for typical approval process. Once the designated

product is approved, the applicant is granted with ten-year marketing exclusivity. Product renewal for orphan drugs is to be done every ten years instead of six years for non-orphan drugs.

ADVANTAGES IN THE DEVELOPMENT OF ORPHAN DRUGS

There are many technical, regulatory, and economical advantages in orphan drug development as compared with non-orphan drug development. First, it is easier to discover the treatment target because many of the rare diseases are caused by relatively simple genetic defects. Once the drug target is identified the research and development of the drug is more likely to be successful.²³⁾

Second, the time length required for clinical trials of an orphan drug is shorter than that for a non-orphan drug. According to Meeking²⁴⁾, average time period from the beginning of Phase 2 trial to the market approval was 3.9 years for orphan drugs and 5.4 years for non-orphan drugs. It is probably due to the fact that the less number of clinical trials and study subjects were required for the clinical development of orphan drugs. In addition, as mentioned above, the regulatory review time length for the marketing approval of orphan drugs is shortened by the priority review pathway of six months which is faster than the standard review pathway that takes ten months.²⁵⁾

Third, orphan drugs are more likely to receive marketing approval than non-orphan drugs. Recently, the rate of marketing authorization for orphan drugs was 93%, which was greater by 5% than the rate of 88% for non-orphan drugs.²⁴⁾ Higher percentage of approval of orphan drugs reflects rare diseases' unmet medical need where less competition is present.

Lastly, as also mentioned above, research and development of orphan drugs are supported in various ways including fee reduction, tax exemption, and research funding. Such financial assistance greatly helps reducing cost for orphan drug research and development.

Reflecting the advantages of orphan drug development mentioned above, global orphan drug market reached \$84.9 billion in 2009 growing from \$54.5 billion in

Table 2. Comparison of Government's Stimulation Policy on Orphan Drug Development.

	Korea	United States	European Union	Japan
Stimulus Law	Regulation on Orphan Drug Designation. Notification No.1998-23	Orphan Drug Act 1983	Orphan Drug Regulation #141/2000	Orphan Drug Amendment to Pharmaceutical Affairs Law 1993
Market Exclusivity		7 years	10 years	10 years
Regulatory Privileges	Orphan drug designation information provided Exemption from re-examination	Fast track review Protocol assistance/consultation	Protocol assistance, scientific advice during product development phase	Consultation service for all phases of research and development Fast track review (12months → 10 months) Extension of re-examination period from 6 years to 10 years
Tax Benefits		50% federal tax credit for clinical research	Different for each signatories	Exemption of 10% corporate tax Additional tax exemption of 6% of research and development expanses
Incentives	Fast track review 50% reduction of application fee if domestic clinical trial data submitted	Waiver of user fee for NDA or BLA review which is approximately \$2,000,000	Protocol review fee exemption Exemption of preauthorization inspection fee 50% reduction for new applications for marketing authorization 50% reduction for post-authorization activities (annual fees) in the first year	
R&D Funding		Clinical research funding (both direct and indirect costs) Approximately \$14,000,000 has been distributed every year	Different for each signatories	Financial aid for 50% of the clinical trials

2005.¹⁾ The market is expected to grow at a compound annual growth rate (CAGR) of nearly 6% to reach \$112.1 billion by 2014. It is more prominent in the United States in taking the advantages of orphan drug development. The orphan drug market in the United States accounted for approximately 51% of the global orphan drug market in 2009 and is expected to grow at a CAGR of 8.9% to reach \$65.9 billion by 2014. Regarding the product category, biological orphan drug products account for a major share (64.3%) of the orphan drug market with sales of \$54.6 billion in 2009 as compared to \$30.2 billion in 2005. The size of the biological orphan drug market is projected to grow at a 6.9% CAGR to reach \$76.2 billion by 2014. This remarkable economic performance is due to a number of orphan drugs that achieved outstanding success. For example, Roche's Rituxan that treats both

chronic lymphocytic leukemia and non-Hodgkin's lymphoma has a lifetime revenue potential of \$154 billion, the second one only to Pfizer's cholesterol blockbuster Lipitor with \$197 billion.²⁶⁾

In addition to the economic success, the advantages in orphan drug development changed the pattern of new drug development. There have been numerous precedents of new molecular entity (NME) drugs approved for the treatment of rare diseases by FDA for marketing. Nowadays, all NME drug approvals in the United States comprise approximately 30% of orphan NME drug approvals.²⁷⁾

Korea will likely be a major beneficiary if the country makes an effort on the domestic development of orphan drug products. Currently, orphan drug market in Korea is growing continually at the 13.8% of overall annual growth rate with the 26.5% of biologics annual growth

rate.²⁸⁾ There are a total of 252 orphan drugs in Korean pharmaceutical market in 2011, of which 232 products are imported and 20 products manufactured domestically. Among those, 47 drugs are biological products, while 205 drugs are non-biological drug products. The total size of Korean orphan drug market is about 99 billion Korean won: biologics and non-biologics represent 63 billion (63.6%) and 36 billion Korean won (36.4%), respectively. Although biologics represent only 18.7% of orphan drug products in the number of products, biologics contributed tremendously to the total orphan drug sales by 63.6%. Considering that only 6 out of 47 biologic products are manufactured domestically, the revenue generating potential for biologics in Korean orphan drug market appears to be high if manufactured domestically.

POINTS TO CONSIDER IN ORPHAN DRUG DEVELOPMENT

Major concerns with rare disease research and orphan drug development include small study patient population. Rare diseases are poorly or incompletely understood and highly heterogeneous. Often high phenotypic diversity within individual disorder makes it difficult to define and understand the disease. Adequate clinical trial endpoints and outcome measures are usually lacking and it requires more considerate study planning. Solid scientific basis and careful attention to scientific study design is required to build an overall development program. Thus, strategic approaches are required for a successful development of an orphan drug product as suggested by FDA staff (personal communication).

The ultimate goal of orphan drug development is to supply a safe and effective drug to the patients with rare diseases. The first step toward this goal is to figure out the factors that the regulatory agency uses to determine the safety and effectiveness of a proposed orphan drug product. Nowadays, most regulatory agencies have policies and scientists to advise the industry in the development of a safe and effective orphan drug product. The industry should take the advantage of such resources. In the United States, FDA established in 2010 the Rare Disease Program (RDP) within

the Office of New Drugs under the Center for Drug Evaluation and Research. RDP supports, facilitates, accelerates and assists with rare disease drug development and approvals. RDP has recommended to the industry the components for successful orphan drug development.²⁹⁾

For a successful initiation of orphan drug development, it would be essential to make an extensive plan. The plan should include mapping out overall development plan early and revisiting as new information becomes available, recruiting necessary stakeholders in the process beginning early and continuing throughout development, and meeting with the regulatory agency early and often in all opportunities for interactions and communications.

It would be helpful to use the concept in basic principles of research design.³⁰⁾ First, the goal and topic of research should be defined. Once they are defined, extensive literature search should be performed to explore what has been done previously on the same topic. From the data retrieved, researchers should be able to identify the existence of drugable target if there is any. Then, study population or subject of interest needs to be determined. After that, reliable diagnostic and prognostic measures to be used should be selected. It is important to evaluate whether the measures selected are the best for the purpose or not. If they are not the best, the researcher needs to explore alternative quantifiable endpoints. Predictors of interest should be identified and the number of subjects included should also be determined.

A key factor in successful orphan drug development is to understand the disease itself. Ideally, a natural history study should be conducted to understand the progression of the disease. Prospective longitudinal study is preferred; however, due to limited time and expense, alternatives are often acceptable. The primary purpose of the natural history study is to collect information in designing a prospective clinical trial. With sufficient knowledge on the disease, understanding the target and expected outcome of intervention is also pivotal in designing the clinical trial. Identifying the target and its outcome as a result of intervention is important for effective clinical trial design in the major development step.

Next component is developing clinical endpoints and outcome measures to evaluate the success of drug treatment for the disease of interest. Biomarkers, outcome assessment tools such as patient reported outcomes or clinical scales and measurements, and potential clinical endpoints are identified and developed using information from the components described above. Different endpoints may be appropriate at different phases of development. Reliable tools of measurement should be chosen to obtain consistent data. Then, the information to file an IND application should be collected for regulatory process. Not only characteristics and quality of the drug, but also non-clinical toxicology and/or other safety information needed to support clinical trials are required.

The next component is using all data that is available throughout the research. It is important not to overlook the value of early phase trials, animal models, other translational science outcome, and pharmacokinetic-pharmacodynamic information. Exploratory endpoints are collected at early phases of development. Use all the information to design pivotal trials to demonstrate the benefit outweighing the risk of drug treatment.

The last component of successful orphan drug development that FDA staff advises is conducting benefit-risk analysis. Designing and conducting pivotal trials to support marketing applications rely on scientific foundation built in previous steps. For a full approval, substantial evidence of clinical benefit must be demonstrated in comparison to risk. Study design and endpoint selection will be highly context dependent. The conduct of the study should be rigorously controlled.

ROLE OF ACADEMIA IN RARE DISEASE RESEARCH AND ORPHAN DRUG DEVELOPMENT

Academic institutions have been important in drug development process. Recent growth in new drug development was largely contributed by academic researchers and their collaboration with pharmaceutical industry. This trend has been facilitated since the passage of many governmental regulations and policies supporting the research

and development of orphan drugs for rare or neglected diseases affecting public health.

Previously academic researchers and research doctors were mainly involved in early-stage research utilizing their expertise in basic science. Pharmaceutical industry had tendency to avoid involvement of academic institutions because of many challenges in collaboration. Challenges include costs, time-consuming regulatory oversights, and the difficulty of recruiting subjects from the specialized care centers.³¹⁾ Despite such challenges in incorporating academic institutions in new drug development programs, academia is becoming more involved and significant in drug development process nowadays.

Due to poor financial return on investment compared to the cost and time until commercialization discouraged pharmaceutical industry to do research towards new drug discovery. Even with increased assistance and incentives toward research and development, the number of new molecular entities approved by FDA did not drastically increase.³²⁾ Innovation gap caused pharmaceutical industries to modify their strategies to acquiring investigational drugs from smaller companies or academic centers rather than conducting the research themselves. The market size of externally researched and acquired products was increased from less than 20% in the early 90s to about 50% of pharmaceutical sales.³³⁻³⁵⁾

As mentioned above, there are several advantages of developing orphan drugs compared to non-orphan drugs. Recently, due to the merits of orphan drug development, many academic researchers are getting involved in drug discovery to generate new revenue stream. Decreased governmental support led academic institutions to commercialize their drug discoveries on their own. Many underlying driving forces including financial support toward universities, patient advocacy groups, and efforts for commercialization resulted in academic institutions as the essential organization in orphan drug development.

Academic institutions well suited for orphan drug research and discovery in many ways. For example, diazepam rectal gel (Diastat) used for the treatment of acute repetitive seizures was developed by collaboration of two faculty members of the University of Minnesota with a

pharmaceutical manufacturer. It demonstrated significant role played by an academic institution in identifying, developing, and getting approval of a new orphan product.³⁶⁾

Some key strategies are used for orphan drug research in academic institutions. Taking advantage of resources of expertise, academic institutions may focus on finding new chemical entities or biologics. In addition, drug repurposing with regulatory approval is more common in academia. For some cases, drug repurposing may lead to clinical use but without commercialization of the product. This strategy is unique to academic settings. Drug repurposing is favored in academic institutions largely because of relatively less risk and less cost required compared to discovering new entities for a disease target.³⁷⁻³⁹⁾

Many universities have established academic centers for rare disease research and of orphan drug development. Several different models of approaches are employed in academic settings which includes disease-focused, discovery-focused, development-focused, and industry-partnership focused.³¹⁾ In the disease-focused model, the researchers focus on the mechanism and biology of the disease and its natural history of progression. This type of model results in development and characterization of disease models and identification of new drug targets. Discovery-focused model deals more with finding out new drug than the characterization of a disease. Once certain target is identified, the center seeks for partnership with pharmaceutical industry for further development. In contrast, development-focused model emphasizes on commercialization of a drug. The goal in this model is to get approval of the newly discovered drug in the market. Sometimes, the discovery may only result in dissemination of data for clinical use without regulatory approval. Last model involves industrial collaborations or partnerships with academic institution providing research and specialized services and pharmaceutical companies as sponsor of the program.

There are several research centers in the United States applying above structures; The Center for Rare and Neglected Diseases at the University of Notre Dame, the Manton Center for Orphan Disease Research at Children's Hospital in Boston, the Center for Orphan

Drug Research at the University of Minnesota, the Center for Rare Disease Therapies at the Keck Graduate Institute of Applied Life Sciences, and Raymond and Ruth Perelman School of Medicine at the University of Pennsylvania.⁴⁰⁻⁴³⁾

However, lack of experiences with regulatory process and financial support challenge the establishment of academic centers for orphan drug research and development. Lack of infrastructure, gaps in research funding, issues with career progression, internalization of clinical research, collaboration of commercial sponsors also pose challenges.³¹⁾

FUTURE DIRECTIONS

Rare diseases need more attention due to lack of proper diagnosis and treatment options. The patients suffering from rare diseases also deserve the same quality of care as other patients with general diseases. Large amount of cost required for such developmental process is not recovered within short period of time when compared to drugs for non-rare diseases. Recently, in parallel with economic growth, increasing numbers of countries are showing interest in rare disease research and orphan drug development and starting government-level supports on them. As Asian pharmaceutical markets grow, Asian governments focus more on the development and reimbursement of orphan drugs. Therefore, the future of rare disease research and orphan drug development has an international dimension.

Reflecting the growing global orphan drug market, more and more governments are taking action to promote orphan drug development, especially in Asia. Australia, Japan, Singapore, Taiwan, and Korea have already implemented legislation for promoting research on orphan drugs.¹⁾ India and New Zealand are in the process of establishing similar regulatory processes. Governmental promotions of orphan drug research include both financial and academic assistance throughout the development process. Advantages such as relatively easier discovery of treatment target, shorter clinical trials, and more likelihood to receive market approval make rare disease research and orphan drug development an attractive challenge on top of

many governmental incentives.

Government's stimulation policy would lead rare disease research and orphan drug development so that, even with many difficulties, the future growth of orphan drug market remains positive. From an industry standpoint, orphan drug development would be lucrative business under government's stimuli. Government and industry funding would help the rare disease research flourish in universities and research hospitals. It is forecasted that biologics would lead future orphan drug market. Academic institutions will play a significant role in orphan drug research taking advantage of its resources and expertise. There are several different model types that may be applied in designing research structures depending on each institution's characteristic. Thorough and strategic planning of orphan drug research based on basic principles of research design would be the key to succeed.

Even with many barriers and challenges along the new drug discovery process, it will be worthy at the end. It is important to focus on the uniqueness of rare diseases and orphan drugs and to take advantage of collaborative efforts of different academic institutions and industries and government's stimulation policies. Thus, we should do it before someone else takes it. However, the patients should be the primary beneficiary.

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