Orphan Drugs and Orphan Drug Policies in Selected Countries

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1. What is an orphan drug?

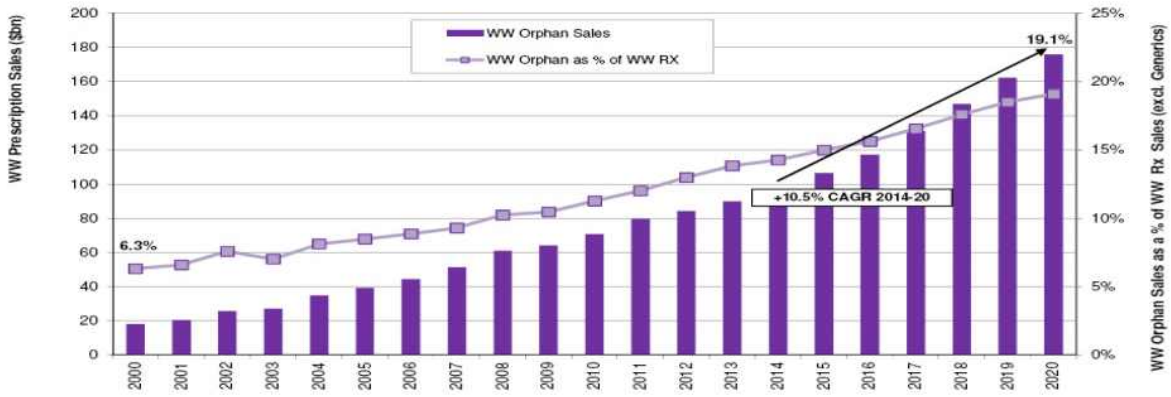
An orphan drug is a pharmaceutical product that is developed to diagnose, prevent or treat a rare disease afflicting a very small fraction of the population. A rare disease is defined as a medical condition affecting not more than 20,000 people in Korea, fewer than 200,000 people in the United States, not more than 50,000 in Japan, and not more than 5 in 10,000 people in the EU region.

One of the prominent characteristics of these rare diseases is that some 80 percent of them, most of which are life-threatening or chronically debilitating, are of genetic origin. There are more than 6,000 rare diseases known today, with to the tune of 100 million affected by one or more of them in the OECD countries. ("Patients' Needs, Medicines Innovation and the Global Public Interests", 2014, UCL School of Pharmacy Drugs) As they are for a small number of patients with gravely serious medical conditions that have few, if any, alternative treatments, orphan drugs tend to be very expensive.

2. Orphan drugs market

The global orphan drugs market, at USD97 billion as of 2014 (14.3 percent of prescription drugs), is expected to grow apace at an annual rate of 10.5 percent to an estimated USD176 billion in 2020, taking up 19.1 percent of the prescription drugs market.

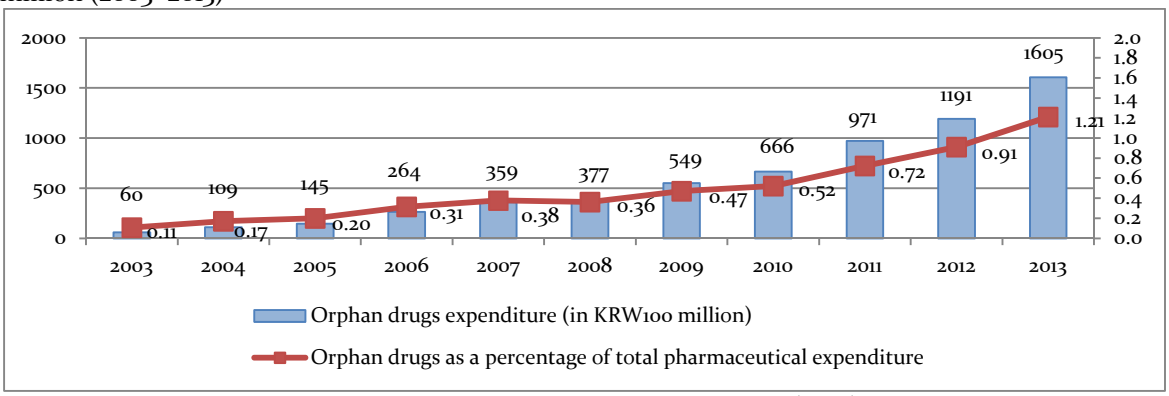
<Figure 1> Share of orphan drugs worldwide in the prescription drugs market (2000~2020)



Source: "Orphan Drug Report 2014", EvaluatePharma

Orphan drugs expenditure in Korea has also been on the rapid increase, from KRW6 billion in 2003 to KRW160.5 billion in 2013, at an average annual rate of 41.0 percent, with its share in the National Health Insurance's pharmaceutical spending growing from 0.11 percent to 1.21 percent.

<Figure 2> Orphan drugs as % of National Health Insurance's pharmaceutical expenditure, in KRW100 million (2003~2013)



Source: Sung-ok Kim *et al.*, *Rational Management of Reimbursement for Rare Diseases* (p. 167), Health Insurance Policy Research Institute; *2013 Health and Welfare White Paper* (pp. 620~621), Ministry of Health and Welfare

Orphan drugs in the past were usually given short shrift in research and development because of their low market profitability and the difficulties associated with their clinical trials. Over the more recent years, however, interests in the research and development of orphan drugs have grown substantially worldwide, galvanized by new legislations in the US (1983) and the EU (2000) that provided incentives such as direct subsidies for research and development costs, tax breaks, fast-track marketing approval, and marketing exclusivity. Also, as recent advances in molecular genetic techniques have made it possible to segment diseases into subtypes, it is more than likely that more number of rare diseases will be identified and that the number of orphan drugs will correspondingly increase. For example, while in 1999 there were as few as less than 1,000 diseases with an identified mechanism, today the diseases with known mechanism number more than 5,000. The diseases that used to be lumped together into the category of lymphoma are now differentiated into tens of subgroups and, as a result, the US Food and Drug Administration (FDA) designated orphan drugs for more than 20 different lymphoma subtypes in 2013. Of all drugs approved by the FDA in 2013, more than one-third were orphans. (Reardon S., "Regulators adopt more orphan drugs", 2014, *Nature*, 508, pp. 16~17)

Developed to treat patients with highly serious diseases and often granted exclusive marketing rights, orphan drugs are usually extremely expensive for both individuals and public health insurance systems.

<Table 1> Per-patient annual cost of high-priced orphan drugs

Orphan drug (trade name)	**Indication**	**Annual cost per patient (USD)**
Agalsidase	Fabry disease	239,000
Lomitapide	Homozygous familial hypercholesterolemia	250,000
Rilonacept	Cryopyrin-associated periodic syndrome	250,000
Teduglutide	Short bowel syndrome	295,000
Imigluderase	Type 1 Gaucher disease	300,000
Ivacaftor	Cystic fibrosis	325,000
Galsulfase	Mucopolysaccharidosis VI	441,000
Idursulfase	Mucopolysaccharidosis I and II	475,000
Eculizumab	Paroxysmal nocturnal hemoglobinuria	486,000
C1 esterase inhibitor	Hereditary angioedema prophylaxis	487,000
Alglucosidase alfa	Pompe disease	575,000

Source: Joshua P. Cohen and Abigail Felix (2014), "Are payers treating orphan drugs differently?", *Journal of Market Access and Health Policy*, 2; 23513

3. Orphan drug policies in selected countries

As is the case with all other drugs, decisions as to the pricing and reimbursement of orphan drugs are made in the system of national health insurance regulations. Despite their high prices, most orphan drugs, as they usually are intended for those with highly serious diseases who have no alternatives, have a high chance of being covered by health insurance plans. For some of these orphan drugs, however, reimbursement may well be denied by existing reimbursement rules, in which case the patient may have to bear high out-of-pocket costs or face limited access to the drug she needs.

With the recent surge in the number of orphan products entering the pharmaceutical market, many countries in the developed world have put in place programs whereby one can apply for additional funding for the use of unauthorized orphan products or authorized orphans that are not covered by the existing reimbursement system. Examples of these programs include France's Temporary Authorizations for Use (ATU), Italy's Fondo AIFA 5%, Belgium's Special Solidarity Fund (SFF), and Australia's Life Saving Drugs Program (LSDP).

The UK has instituted in April 2013 a process for the Highly Specialized Technologies (HST), through which to decide the reimbursement of "ultra-orphan drugs," medicines that are developed to treat highly rate diseases with prevalence of fewer than one in 50,000 people. In carrying out the process, the National Institute for Health and Care Excellence (NICE), the responsible authority, factor in the new technology's quality-of-life impact on patients and their carers, the clinical effectiveness and evidence, budget impact, efficiency, impact other than direct health benefits, and impact on the delivery of other services. ("Interim Process and Methods of the Highly Specialised Technologies Programme", NICE, 2013) Yet another example is Scotland's Patient and Clinician Engagement (PACE). Established under the Scottish Medicines Consortium (SMC) in 2014, the PACE system is designed to give greater consideration to the views and needs of patients and clinicians when making reimbursement decisions for drugs used in the treatment of ultra-rare diseases and end-of-life conditions. The use of new drugs that have yet to be approved by the SMC can be financed by the New Medicines Fund if the treating physicians deem it necessary to use them for their patients.

Policies for strengthening the evidence of orphan drugs

Most orphan drugs get authorized based on short-term clinical trials conducted on a limited number of subjects and thus without much evidence for their clinical effectiveness. Also, decisions as to reimbursement for orphan drugs are often made in the absence of alternatives, leaving their cost-effectiveness in need of further review. Despite all this, orphan products are sold at high prices, and thus have an immense impact on national health spending, which calls for evidence-based, post-approval evaluation of the effectiveness—both cost-wise and clinical—of these drugs.

There have been a growing number of patient registries which provide databases on how effective orphan drugs are in real clinical settings. According to a report by the EU Expert Group on Rare Diseases (Report on the State of the Art of Rare disease Activities in Europe), there were, as of January 2014, 641 rare disease registries in Europe, of which 446 were national, 47 global, and 40 European. Mostly housed in universities or research institutes and in some cases managed by pharmaceutical firms or patient organizations, these registries pertain to diseases for which a pharmaceutical treatment is being developed or marketed.

<Table 2> National registries of rare diseases: registered data

Country	Registered data
France	Patient ID, demographic data, familiarity of the disease, drug treatment data, diagnosis, fetus and newborn data, data on research participation, data on biological sample donations, death date and cause, patient consent
Belgium	Patient ID, demographic data, registering center and treating physicians codes, first onset date, diagnosis, death date, patient consent
Italy	Patient ID, demographic data, diagnosis, diagnosis date, diagnosis center data, first symptom onset date, prescribed drug, cost exemption code, death date

Source: Taruscio D. (2014.11.9) National Registries of Rare Diseases in Europe: An Overview by the EPIRARE Project, ICORD

Policies for the timely and efficient use of orphan drugs

Using orphan drugs in timely and adequate manner for patients who need them requires management interventions which ensure best treatment outcome with least waste. Rare diseases are by definition low in prevalence, yet they come in many kinds and in many cases their mechanisms are insufficiently understood at best. For these reasons, it is critical that the use of orphan drugs be based on prescription by physicians with relevant expertise and experience. In addition, with the impact of orphan drugs increasing on national health expenditures, the importance of how to keep financing the cost of these special drugs is growing over time. In these circumstances, several countries have placed controls on the distribution of orphan drugs. France, the UK, Spain, Italy, and the Netherlands are among the European countries where orphan drugs are prescribed and distributed only through government-designated "centers of expertise." (Denis A *et al*., "A comparative study of European rare disease and orphan drug markets," *Health Policy*, 97, pp.173~179)

<Table 3> Centers of expertise for rare disease in selected EU member states

	Country							
	France	UK	Spain	Italy	Netherlands	Sweden	Norway	Denmark
Number of Centers	131	50~60	78	215	8	18	10	100~120

Source: "2014 Report on the State of the Art of Rare Disease in Europe", EUCERD, p.34

Some countries have raised out-of-pocket payments and imposed prescription limits for orphan drugs as a way to curb their impact on pharmaceutical spending. In 2010, in a total of 1,620 stand-alone Part D prescription drugs, 95 were reimbursable orphan drugs, of which 76 were placed on Tier 4, where copayment is high at 25~33 percent of the drug cost. Also, as a way to restrict the prescription of high-priced specialty pharmaceuticals like orphan drugs, health insurers in the US as a rule require "prior authorization," which means that a given drug treatment must obtain approval from the insurer before it is used. Another cost containment instrument employed in the US is the quantity limits policy, which puts a ceiling on the reimbursable amount of a given orphan drug. Of the 95 orphan products under the stand-alone Medicare Part D prescription drug plan, 80 were subject to prior authorization by one or more plans and quantity limits were imposed on 56 orphan drugs by at least one plan. (*Rare Diseases and Orphan Products: Accelerating Research and Development*, National Academic Press, 2010, pp. 184~197)

As a response to the growing cost of orphan drugs, many countries around the world have in place policies for encouraging the use of cheaper alternatives. As many of the high-priced orphan drugs are biologics, their cheaper biosimilars can be brought out after their patent

expires. Switching from reference products to their biosimilars can help save costs, but the issue of interchangeability remains an open question globally.

Earlier this year, the national drug authorities of the Netherlands, Portugal, and Finland have announced that they support and permit physician-overseen switching between reference biologics and their biosimilars. Currently 8 states in the US have legislated biosimilar interchangeability, and 13 more states are on the move to do the same. For example, Utah, one of the 8 states, pharmacists are allowed to substitute a reference product with a biosimilar, if the later is approved as interchangeable by the FDA, while the prescribing physician has the right to reject substitution. In a similar move, the Australian government in May this year announced the Pharmaceutical Benefits Scheme (PBS) Access and Sustainability Package—a set of measures designed to promote sustainable drug reimbursement and to ensure the quality of drug use—which, as per recommendations from the Pharmaceutical Benefit Advisory Committee, included measures that permit substitution of reference biologics with biosimilars at pharmacies. In 2014, both France and Italy put into effect legislation that promotes their national healthcare systems to reimburse off-label use (use of medications for an unapproved indication), for economic reasons, of an cheaper therapeutic alternative to expensive options. Before this, off-label use of alternative products had been restricted only to cases where there were no approved drugs for a specific medical condition.

4. Policy implications

With the continued advancement of medical technologies, the orphan drugs market is expected to continue growing in the coming years. As this will exert a considerable cost impact on both patients and the National Health Insurance, ways should be sought to make drug reimbursement more sustainable and beneficial for patients. Korea's policy on orphan drugs has been moving toward increasing reimbursement levels for individual medicines. This study suggests that drug coverage under the National Health Insurance should be expanded based on patient-oriented evidence. While still keeping the National Health Insurance as the frame of reference for orphan drugs reimbursement, case-by-case programs will need to be added to existing coverage to help cover the cost of non-reimbursable or unapproved orphan drugs for patients who, due to individual drug response, have to use them. How to finance these new programs should be decided by social consensus. The prescription of orphan drugs of significant clinical and financial implications will have to be limited to medical institutions with doctors who specialize in treating specific conditions for which these drugs are indicated. The use of cheaper alternatives is worth promoting with policy incentives. Also, data should collected in a systematic fashion on the how effective orphan drugs are in clinical settings, so that they can be used as an evidence base in making decisions about future reimbursement of those drugs.