

Access to orphan drugs in the Middle East: Challenge and perspective

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Summary

An orphan drug is a drug developed specifically to treat a rare medical condition. With a combined population of less than 400 million, about 2.8 million patients are estimated to be suffering from a rare disease in the Middle East. Some disorders such as hemoglobinopathy, glucose-6-phosphate dehydrogenase deficiency, autosomal recessive syndromes, and several metabolic disorders have a presence throughout the Middle East. In order to promote the treatment of these diseases, Middle Eastern governments need to facilitate education and training of healthcare personnel; develop and execute a method for obtaining and paying for orphan drugs; and, finally, provide tax, marketing, and other incentives to domestic and international firms to develop drugs specifically for the diseases of most importance to Middle Eastern patients.

Keywords: Orphan drug, rare disease, genetic disorder, Middle East

1. Introduction

An orphan drug is a drug developed specifically to treat a rare medical condition (1). Because the high cost of drug development tends to discourage pharmaceutical companies from developing products for very small populations of patients, public-sector involvement becomes critical to the success of orphan-drug markets. Legislation has been implemented by the United States, the European Union, Japan, Singapore, Taiwan, South Korea, and Australia that offers subsidies and other incentives to encourage the development of orphan drugs (2). Some companies, such as Genzyme, acquired by Sanofi-Aventis in 2011, have even thrived under such legislation, focusing their efforts on developing treatments for rare diseases as a profitable business strategy (3). Myozyme (alglucosidase alfa, recombinant human GAA) and Lumizyme (alglucosidase alfa), both Genzyme products and the first two therapies available for Pompe disease, were approved as orphan drugs by the U.S. Food and Drug Administration (FDA) in

2006 and in 2010, respectively (4,5). They significantly improve survival for those patients suffering from this rare condition, affecting 5,000-10,000 people worldwide (6). Other recently approved orphan drugs include Glaxo's Lexiva (fosamprenavir) for HIV infection, Genzyme's Fabrazyme (agalsidase beta) for Fabry disease, and Novartis's Visudyne (verteporfin) for age-related macular degeneration (2).

As high-quality healthcare becomes a growing priority in developing countries, it is not surprising to see a rising interest in rare diseases and potential treatments in those countries as well. Public awareness of rare diseases is growing in China, where at least 10 million people (out of over 1.3 billion), *i.e.*, approximately 0.7% of the Chinese population, are estimated to be living with osteogenesis imperfecta, Fabry disease, hemophilia A and B, albinism, acromegaly, and other rare conditions (7). At this point in time, however, Chinese patients do not have good access to orphan drugs, nor are Chinese pharmaceutical companies participating in new orphan drug development (7). Meanwhile, rare-disease patients and their advocates in a number of Middle Eastern countries are finding themselves in a similar situation to those in China. As living standards improve in the Middle East, healthcare providers face higher expectations for better quality healthcare products and services (8). With a combined population of less than 400 million, about

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2.8 million patients are estimated to be suffering from a rare disease in the Middle East (7,9).

2. Rare diseases in the Middle East

The Middle East, in its "narrow" definition, consists of 16 countries (in declining order by population: Egypt, Iran, Turkey, Iraq, Saudi Arabia, Yemen, Syria, United Arab Emirates or UAE, Israel, Jordan, Lebanon, Oman, Kuwait, Qatar, Bahrain, and Cyprus) plus the Palestinian territories of the West Bank and the Gaza Strip. Using the 0.7% prevalence rate for China and the United Nations' population estimates for countries in the Middle East, estimated numbers of patients with rare diseases are shown for the Middle Eastern countries in Figure 1.

The population of the region is characterized by large family size, older maternal and paternal age, and a high rate (25-60%) of consanguineous marriages (10). Hence, the risk for genetic disorders may be higher than in other regions of the world. Indeed, such disorders

account for the majority of rare diseases in the Middle East and are responsible for the lion's share of infant mortality, morbidity, and handicaps in Arab countries (10). Genetic disorders such as hemoglobinopathy, glucose-6-phosphate dehydrogenase deficiency, autosomal recessive syndromes, and several metabolic disorders have a presence throughout the Middle East (10). Patients and their advocates have pushed for awareness of hypoparathyroidism (lack of parathyroid hormone) (11) and beta thalassemia (a blood disorder that reduces the production of hemoglobin) (12). Other genetic disorders, *e.g.*, glutaric aciduria type I (an organic acid disorder where individuals cannot metabolize the amino acids lysine, hydroxylysine, and tryptophan), may be more specific to certain countries and subpopulations (in this case, Israel) (13).

Yet other rare diseases may not have a genetic cause but rather result from viral or bacterial infections or allergies. Behcet's disease, characterized by genital ulcers, skin lesions, and uveitis, though very rare in the United States, is more common in the Middle East and

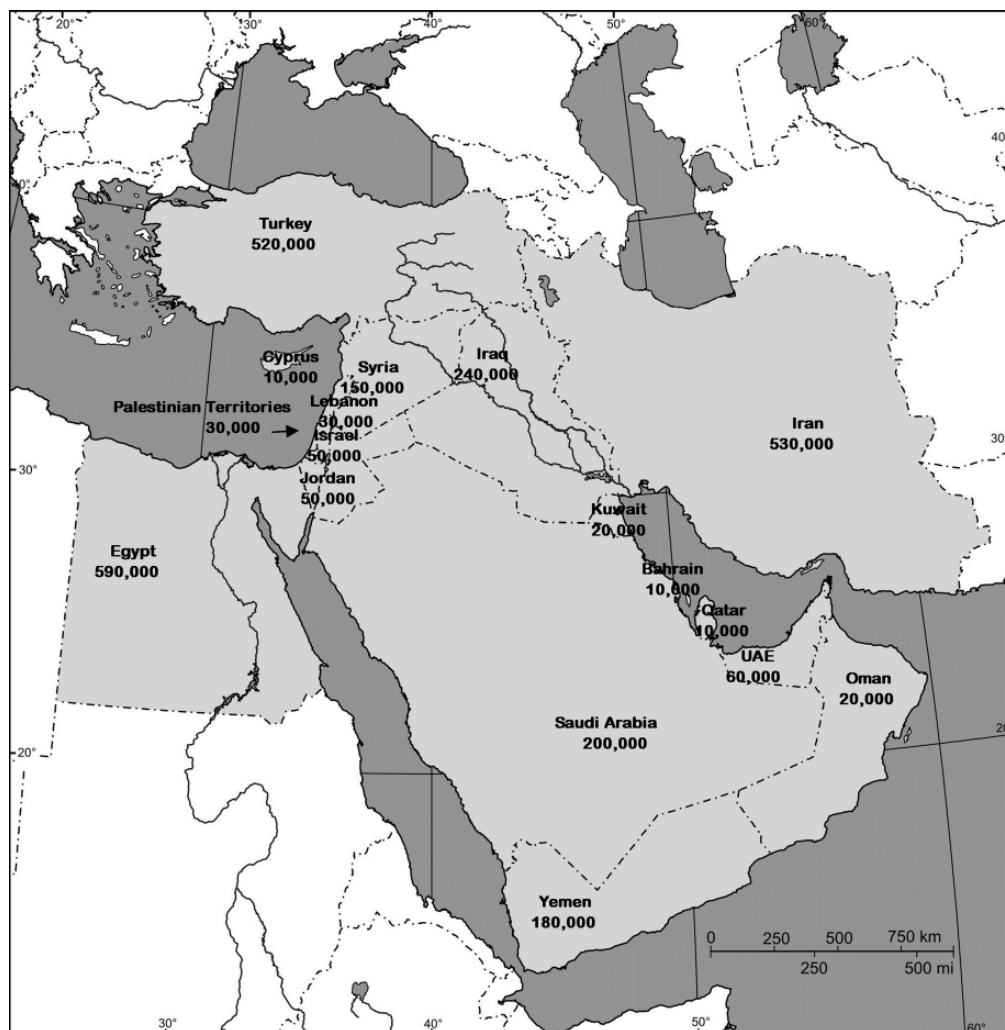


Figure 1. Estimated number of individuals with a rare disease in the Middle East (estimates obtained by multiplying United Nations' 2012 population estimates by 0.7% and rounding to the nearest 10,000). Source: Middle East outline map available at <http://www.zonu.com/fullsize-en/2009-11-17-11130/Middle-East-outline-map.html>. Accessed on September 21, 2012.

Asia, suggesting a tropical-area cause (14). The lichen planus pigmentosus presents with hyperpigmented, dark-brown macules in sun-exposed areas of the body and is more common in the Middle East than in Europe. It may be caused by a viral infection or topical agent (15). Leishmaniasis, a sand-fly-transmitted disease, leads to symptoms ranging from cutaneous lesions to fatal visceral disease. It has been designated as one of the most neglected tropical diseases by the World Health Organization (16). Pemphigus is the general designation for a group of autoimmune skin diseases that cause ulceration and crusting of the skin (17). It is present in people of Middle Eastern or Jewish descent (18).

3. Diagnosis of rare diseases in the Middle East

Orphan diseases are so rare that a physician will not observe a case often. In order to diagnose accurately a rare disease, doctors rely on the published literature and rare-disease registries, which vary considerably in volume and availability across rare diseases. Misdiagnosis or delayed diagnosis is very risky for rare-disease patients. For example, delaying the treatment for infantile-onset Pompe disease until the patient is 6 months old is already too late (19). Another problem with diagnosis is that there is no special coding system for rare diseases. The International-Classification-of-Diseases system that is used in most countries is not suitable for rare diseases. The absence of a universally recognized coding system is an obstacle for reliable registration of patients in national or international databases (20).

On top of the worldwide difficulty in diagnosing rare diseases, Middle Eastern countries generally have a shortage of trained medical professionals, partly due to the lack of medical schools in some of the countries and partly due to limited training in certain medical specialties including diagnostic medicine. The growing demand for physicians and other medical workers is currently being met in the Middle East partly by expatriates from the West, as well as from the Indian subcontinent and the Philippines, all of whom are unlikely to be trained in Arab rare diseases (8). However, Bahrain employs a relatively high proportion of nationals in healthcare; Dubai has attracted Harvard Medical School to Dubai Healthcare City where nationals will be trained; and Qatar is building a specialty teaching hospital run in association with Weill Cornell Medical College. Saudi Arabia is sending nationals abroad for training while it builds more teaching hospitals with the help of private investment (8). Basic training and continuing professional development are needed to ensure that all doctors have the ability to detect a rare disease, especially one more likely to occur in the Arab countries.

Meanwhile, efforts are being organized to keep track of patients with rare diseases. The Centre for Arab

Genomic Studies (CAGS) launched a pilot project to construct the Catalogue of Transmission Genetics in Arabs (CTGA) database. This database helps Middle Eastern governments educate the medical community and raise public awareness in at-risk populations (21). In addition, Kuwait University established the Molecular Genetics Diagnostic Service Division, within the Faculty of Medicine, Department of Pathology, which focuses on delivering state-of-the-art genetic analysis for the Kuwaiti population. This service includes autozygosity (homozygosity in which two alleles are identical by descent) mapping in families with consanguineous marriages (22). Pre-marital genetic screening is offered in a number of countries, including Saudi Arabia, Bahrain, the UAE, and Jordan (10). A comprehensive program for thalassaemia screening and genetic counseling was started in Iran in 1996 (10).

4. Availability of orphan drugs in the Middle East

Orphan drugs are very expensive. Insurers in the United States have traditionally covered these therapies because only a small number of patients have needed them. However, as more new products are launched, payers will become more and more sensitive to cost, potentially affecting utilization (23). Some countries in the Middle East with per-capita income approaching or exceeding that of the United States should be able to pay for the drugs through public or private health insurance, though they will eventually face the same problems that United States payers are facing. Patients in other lower-income Arab countries, however, may have to rely on charitable organizations. Several of the countries in the region, including Qatar, Saudi Arabia, and Bahrain, are committed to increasing the role of the private sector in the public-private mix. The first private hospital in Qatar opened in 1999 (8). In 2008, expatriate health insurance became mandatory in Saudi Arabia for firms employing foreigners (8).

Orphan Europe, established in 1990, is a pharmaceutical company that develops and distributes orphan drugs. Today, the company provides 9 orphan products to patients all over the world. One of its products, Cystadane (betaine anhydrous), has marketing authorization in the United States, Canada, Australia, and Israel (24). It treats homocystinuria (an inherited rare condition where the body is unable to metabolize certain amino acids properly). This condition seems to be more common in some countries, including Qatar, where it is estimated that 1 in 1,800 people is affected (25). Orphan Europe has an office in Dubai Healthcare City. This move should help to increase awareness of rare diseases and orphan drugs in the Middle East.

Taiba is a leading regional specialty healthcare company, focused on marketing and distribution of pharmaceutical products for rare diseases. It acquires

and licenses innovative orphan drugs by building a strong network with international partners (26). The head office is in Muscat, Oman, and there is a regional office in Dubai. Indeed, leading pharmaceutical companies are turning to Taiba to help grow their business. For example, Dyax Corporation has given exclusive distribution rights to Taiba for the distribution of Kalbitor (ecallantide) in the Middle East (27). Kalbitor is used for the treatment of hereditary angioedema (a genetic defect that results in episodes of swelling in various parts of the body).

5. Development of orphan drugs in the Middle East

Orphan drug development in the United States took off after the passage of the Orphan Drug Act (ODA) of 1983. Under the ODA, drugs, vaccines, and diagnostic agents would qualify for orphan status if they were intended to treat a disease affecting fewer than 200,000 American citizens (28). Orphan drug designation means that the drug-company sponsor qualifies for certain benefits, including 7-year market exclusivity, tax incentives, and grants for drug development (28). Furthermore, the Food and Drug Administration (FDA) has been expediting the marketing approval for many orphan drugs (29). In 1982, only 34 drugs were marketed in the United States to treat orphan diseases (30). From the passage of the ODA until May 2010, the FDA approved 353 orphan drugs and granted orphan designations to 2,116 compounds (31). The European Union enacted legislation similar to the ODA in 1999. In Europe, an orphan designation is granted only if "... it is unlikely that the revenue after marketing of the medicinal product would cover the investment in its development" (32). Because of the nature of orphan drugs, no country can expect private-sector firms to embrace their development without public-sector legislation offering companies a potential return on their investment. It is simply much more profitable for them to develop drugs that can benefit large numbers of people globally.

Short of encouraging the growth of a domestic pharmaceutical industry, of course, attracting foreign investment is another option for countries in the Middle East. Indeed, the Dubai Biotechnology & Research Park (DuBiotech) provides an environment for life sciences companies to set up operations in the Middle East and to collaborate in productive partnerships, potentially with local firms (33). Pharmaceutical companies in DuBiotech include Pfizer, Genzyme, Merck-Serono, Amgen, Maquet, and Fimenich. Pharmax Pharmaceuticals, a "home-grown" pharmaceutical company in the United Arab Emirates that manufactures oral solid dosage products including tablets and capsules, will develop a 90,000-square-foot manufacturing facility, becoming the first pharmaceutical production unit at DuBiotech (33).

Eventually, a successful development effort will require education and training in pharmaceutical sciences at Middle Eastern or foreign universities. The size of the global orphan-drugs market was about \$84.9 billion in 2009, and the market is expected to reach \$112.1 billion by 2014 (34). There will be profit-making opportunities for firms from all over the world, including from the Middle East, provided that some governmental incentives are in place.

Not all orphan drug development has to be executed by private pharmaceutical companies, with incentives from the government, although this has been the development model in the West. In the Middle East, public-private partnerships (PPPs) are public-health-driven, not-for-profit organizations that encourage pharmaceutical companies to develop new orphan drugs for rare diseases in partnership with them. Even large, multinational pharmaceutical companies may find it in their long-term interest to participate in the neglected-disease market provided that they can partner with experts in distribution and patient needs in developing countries. As of 2004, eight neglected-disease projects (Artemotil, Paluther, Coartem tablets pediatric label extension, Lapdap, Biltricide, Impavido, Ornidy, and Mectizan) had been conducted in public-industry collaboration (35). One of the resulting products that had a major impact in the Middle East is Biltricide (praziquantel), which helps to control schistosomiasis (a parasitic disease). The PPPs model may, in at least some situations, be able to deliver better health care, both more efficiently and less expensively, than either the (primarily Western-based) private drug companies or the not-for-profit or public sector acting alone (35).

6. Conclusion

As healthcare improvement rises in priority in Middle Eastern countries, as a natural consequence of economic development, a focus on rare diseases and orphan drugs is to be expected. Although some diseases, cultural environment, and health-system features are uniquely Arab, ideas for government legislation and an optimal public-sector-private-sector mix in orphan-drug distribution and development can come from other countries that are currently paving the way. Ultimately, the rare-disease-and-orphan-drug problem is global. International discourse and cooperation should be at the top of every country's list of relevant policies.

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