BioSpectrum the business of Bio & Health Sciences ASIA EDITION

Asia needs a legal framework to combat rare diseases

08 February 2018 | Analysis | By Aishwarya Venkatesh

Feb 28, 2018 will be observed as International Rare Disease Day. To generate more awareness about rare diseases and to emphasize the need for legal policies, Bio Spectrum Asia analyses trends, opportunities and challenges in Asia's orphan drug market.

Orphan diseases, once rare, are now affecting larger populations, with one in every 5000 people suffering from a rare genetic disorder. The World Health Organization defines it as a disease with 6.5 to 10 cases in every 10,000 people. About 6000 to 8000 rare diseases, mostly genetic in nature have been identified across the world and only around 500 of them have known therapies. Half of the population of orphan disease patients are children as most of the genetic orphan diseases occur at birth or childhood. Generally, orphan diseases are considered to be severe, progressive, degenerative, life-threatening or chronically debilitating diseases. Despite knowing the causes of orphan diseases, most of these diseases are still non-curable as they lack satisfactory treatments.

A rare disease affects a small number of people in comparison to the general population and the classification of a rare disease varies across continents, regions and countries. For instance, the FDA classifies a disease as rare if it affects less than 200,000 out of about 315 million Americans. In Japan, the Ministry of Health, Labor and Welfare states that a disease must affect less than 50,000 of the country's 127 million citizens in order to be considered rare. And, while a disease may be classified as rare in one country, the disease may be more prevalent in another country. Furthermore, the status of a disease may change over time, becoming more prevalent as doctor awareness and diagnosis abilities improve. Also, for the past three decades big pharma has not showed much interest in orphan drug space as they would not lead to substantial sales under normal market conditions because of the high costs and risks of drug development, insufficient knowledge of pathophysiological mechanisms of rare diseases that the drugs diagnose or treat, and difficulties in conducting clinical trials with small patient populations and a small potential market. However, nearly two-thirds of the world's population reside in Asia and hence even the rarest disease will have many patients seeking treatment.

Speaking to BioSpectrum Asia, Dr. Timothy Low, Head of Medical Affairs Asia Pacific, Shire, said that despite medical advancements, many patients suffering from a rare disease still lack access to appropriate medical interventions. "Effective therapies are still not available to more than 95 percent of the patients suffering from rare diseases option – that means only

a privileged one in 20 people living with rare diseases today can potentially take medication to sustain their lives – if they can access or afford it to begin with."

The need for orphan treatments in Asia is huge and with little in place so far, Asia represents a lucrative market for orphan operations. Also, with increasing un-met need, government and regulatory authorities are also encouraging orphan drug research. According to National Organization for Rare Diseases NORD estimates, close to half (41%) of the new medications approved by the FDA in 2016 were orphan drugs. In 2017 nearly 60 orphan drugs were approved by the USFDA. Since the introduction of Orphan Drug Act (ODA) in 1983 in a few countries across the globe, there has been a steady upward trend in orphan drug approvals. In each of the past 2 years, over 300 drugs were designated as being orphan drugs by the FDA.

Speaking to BioSpectrum, Dr Meenakshi Bhat, consultant in clinical genetics at the Center for Human Genetics in India accentuated, "India never had enough awareness and organized approach towards rare diseases. We have the talent and the money, however, it is not coordinated into actual deliverables. We have the largest biotech companies in India. Many are interested in investing in rare disorders R&D. But the moment they think in terms of marketing and business, which is where the hesitancy is."

Taking the lower limit of global prevalence estimate, populous nations like India and China should have more than 70 million rare disease cases each. Currently, drug developers in these countries are receiving no formal incentives from the government. Hence orphan drugs need to be imported which makes them highly unaffordable. As the Asian pharmaceutical markets are still in nascent stage, the opportunities for orphan drugs in Asia are also immense and getting increasingly popular.

"Asia Pacific is currently way under-represented in the area of rare diseases," highlighted, Dr Low. "If you simply look at the market potential >2B population, >16T GDP, and >230B market, and estimated of 100 million people affected by rare diseases, we see a significant opportunity to build a leading rare disease and specialty business in the region."

Few Asian countries have implemented the ODA and have a well-defined system for orphan drugs. They provide health insurance coverage, expedited registration, and exclusive marketing periods and provide many such incentives to woo pharma companies. However, other Asian countries are only now beginning to look at rare diseases, and what they can do to help their citizens afflicted with them. Recently, China's FDA, long criticized for its slow drug-review process, is offering to grant conditional approvals for orphan meds already approved abroad, even without in-China trial data.

Dr Low explained, "In Asia barring Australia and Japan, only South Korea, and Taiwan have established systematic economic and regulatory incentives to encourage the development of drugs for rare diseases. China is also actively promoting the regulation of rare diseases and orphan drugs. However, a rare disease framework doesn't really exist in Southeast Asia. The current regulations only set forth general criteria to accelerate the registration and approval of orphan drugs, but detailed rules have not been implemented and further incentives have not been proposed. Thus, the pressing issue for such Asian countries without orphan drug legislation is to establish domestic legislative regulations and incentives to encourage the development of orphan drugs. Take Singapore for example, the Orphan Drug Act which came into force in 1991 gave a definition of orphan drugs and of the legal framework for imports. But it lacks a formal regulatory framework for orphan drugs; therefore working with clinicians to increase the understanding of disease; as well as with payers, policymakers, patients to commit to finding pricing solutions for medicines that are sustainable is absolutely critical."

Need for a legal policy

FDA estimates that around 200 drugs enter development every year and a third of them receive approval. However, these drugs also present significant challenges including difficulty in execution of clinical trials, regulatory hurdles, and a changing reimbursement environment. With proper strategic planning, sponsors seeking orphan drug designation and approval can more skillfully navigate these clinical, regulatory and financial challenges.

Lack of a policy or a legal framework in many Asian countries is deterring the development of these drugs and thus many rare diseases patients die of the disease. Increasing number of people falling prey to these diseases have reiterated the need for a sound legal policy and framework to support drug development for diseases.

Mr Chul-Woong, Regional Team Lead, Rare Disease, Emerging Markets, Asia, Pfizer, observed, "Recently in some Asian countries, we have witnessed various governments seeking policy changes with the goal improve their existing healthcare systems in relation to the treatment of rare diseases. This is encouraging, however improved patient access still remains a challenge across Asia. Medicines are among the most powerful tools for patients to cure, treat, and prevent illness and disability. All patients should have access to the medicines their doctors prescribe."

For long, Orphan Drug Act (ODA) has been considered as a key game changer that can alter the dynamics of orphan drugs and rare diseases in any country. The ODA, formulated by the US, in 1983 can be rightly termed as the catalyst that fostered the development of these drugs. Following the example of the U.S. FDA's Orphan Drug Act established in 1983, some Asian countries have developed orphan drug legislation, such as Singapore's Orphan Drug Exemption to the Medicines Act and Japan's Orphan Drug Amendment to the Pharmaceutical Affairs Law. Under this Act, orphan drugs enjoy many regulatory and commercial incentives such as tax credits, grants, waived FDA fees, reduced timelines for clinical development and higher probability of regulatory approval, coupled with commercial drivers such as premium pricing, faster uptake, lower marketing costs and longer market exclusivity. Only five Asian countries have so far implemented this Act- Taiwan, Korea, Australia, Japan, and Singapore. Programs encouraging orphan drug development are available in many countries in Asia that address such unmet medical needs, but these programs are known by different terminologies in different countries in Asia and they are not addressed under a policy or a legal framework. Also, countries with a huge population like China and India do not have a policy that can attract global players to show corporate interest in this area. If the governments in these countries do not formulate a policy to address these rare disorders, orphan diseases will unfortunately remain orphan.

Challenges in Orphan Drug Space:

There are many challenges faced in the orphan drug space. There is little known about the natural history of rare diseases and hence diagnosis and development of a drug is a huge challenge. There are over 7000 rare diseases which occur over a broad spectrum of illnesses that have little or nothing in common with each other. The disease affects a very small population of the society and mostly young children and hence structuring clinical trials is very difficult. Many a times the disease is localized to one country and is not prevalent in other countries. Hence, without adequate financial assistance by the government, Pharma companies will reap very little or no profits through their orphan business.

Dr Low said, "Major challenges for R&D in the rare disease field stem from the impact of the unique characteristics of the small patient populations; high risk of failure inherent in developing breakthrough medicines in areas of high unmet need; exceptionally complex science and clinical/manufacturing process; and the commitment to invest in the necessary services required to support patient outcomes, which include training and education, treatment administration and targeted diagnostic approaches. Also, only 1-2 percent of every 10,000 substances synthetized in a laboratory will go through all stages of R&D to be launched on the market. In case of Europe, of the 1,360 potential treatments evaluated as orphan medicines to date, only 143 have gained a marketing authorization by EMA. This means that almost 9 out of every 10 treatments that make it all the way to orphan status have not yet made it to or even failed to get to patients."

Mr Chul-Woong, added, "Patient Access remains the biggest challenge faced by the pharmaceutical industry. We believe all patients should have access to the medicines their doctors prescribe and are committed to partnering with Governments and other stakeholders to find novel solutions for overcoming access challenges in underserved communities. We need to work on holistically addressing the complicated barriers to access."

In 2014, cost of R&D for new chemical or biological entity was estimated at > $2bnIn 2014, cost of R&D for new chemical or biological entity was estimated at > $2bn

Lucrative market, looming patent cliff attracting Big Pharma

Despite the inherently small market, these drugs have gained momentum over the years. Many reports indicate that orphan drugs are the next blockbusters and many pharmaceutical companies want them in their product portfolio. Analysts estimate that the Orphan Drugs market is expected to grow at a CAGR of 11.4% during the forecast period 2017–2023 to touch an aggregate of $246.55 billion by 2023. According to a study published by Reuters, the orphan oncology drug Rituxan (generic: Rituximab) is the world's second most profitable drug.

As reported by total biopharma, it is estimated that biological patents worth $67 billion is due to expire by 2020. With many blockbuster drugs losing protection, big pharma companies have now gravitated towards specialty drugs, orphan drugs, and the biologics market. If proper legislation and framework is enacted, orphan businesses may swell in this patent pool and thus can eventually treat many potential rare disorders. The last decade had been the most productive period in orphan drug development, both in designations and approvals with many big biopharma companies having atleast one orphan drug in their pipeline. The extended period of exclusivity for these drugs means that they are insulated from generic competition for a potentially longer period than their non-orphan counterparts as orphan drug exclusivity does not have any association with patents. Celgene, BMS, Novartis, Roche, J&J, Shire, Abbvie, Merck &Co, Alexion, Pfizer are some of the top companies in orphan drug space.

However despite advancements, lack of a sound legal framework encouraging in-house orphan drug R&D in all Asian countries is a major deterrent to the development of drugs and many Asian countries still import these drugs. These imported

drugs are inaccessible to many patients as they are very costly and majority of Asia's population is below poverty line and cannot afford them. Orphan drug development provides ample opportunities for research and development and reducing the disease burden of the society and improving healthcare of the country at large. However, without a proper system and guidance from the regulatory bodies or pharmacological associations, it is challenging for a pharmaceutical company to invest in the development of orphan molecules from scratch. It is important to integrate orphan drugs into the healthcare system of Asia as with treatment, these patients lead a normal life but without treatment, one in three children will not live past their fifth birthday.