ORPHAN DRUGS AND HIGH COST MEDICATIONS: CHALLENGES AND SOLUTIONS

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Abstract
There had been increased and strong public interests in rare diseases and orphan drugs as well as the issue of compulsory licencing for expensive medications in Malaysia in the mass-media and social media. We reviewed the issues of orphan drugs and the challenges faced in many countries in developing appropriate health financial modelling as well as getting accurate data on rare diseases. We also reviewed the old off-patent medications and the developments on how policy-makers can intervene to make expensive treatment affordable and sustainable for patients and the country.

Keywords: Rare Diseases, Orphan Drugs, Affordable Treatment, Non-Communicable Diseases

Introduction
Recently there had been strong public interests in rare diseases and orphan drugs as well as the issue of compulsory licencing for expensive medications in Malaysia. We reviewed the issues of orphan diseases and its treatment and the latest development on how the government can intervene to make expensive treatment affordable for patients.

Orphan diseases are non-communicable diseases
Rare diseases (RD), also called orphan diseases, tend to draw the short straw in the current climate of competing healthcare resources. While these diseases are a part of non-communicable diseases, there is little data on the prevalence and burden in Malaysia. Hence there is a need to develop strategies to obtain accurate data on burden of RD in Malaysia. This may include disease registries, population or newborn screening for RD and “quality-of-life” surveys or morbidity studies. The Ministry of Health of Malaysia (2016) published the National Strategic Planning for NCDs 2016-2025 where the report focussed on lifestyle risk factors such as hypertension, obesity, cancer and hypercholesterolemia, as well control of tobacco, salt and alcohol use (1). Yet there was no data on NCDs for population below 15 years old or the strategic planning for control and treatment needed for these orphan diseases in Malaysia in the above report.

World Health Organization (WHO) defines a rare disease as any disease which affects a small percentage of the general population. Although rare, collectively they numbered over 6000 types and this constituted a large number of patients. Indeed, they pose considerable medical and financial burden on the individual patient and extended family. EURORDIS, one of the largest non-governmental patient-driven alliance of patient organisations representing 761 rare disease patient organisations in 68 countries, reported that there are 8000 known rare diseases. About 80% of rare diseases are genetic in nature. The other rare conditions may be due to environmental factors, infections, and so on. About 30% of rare disease patients die before the age of 5 years. The survivors and the remaining patients with rare diseases often need long term medical care as a result of these chronic diseases. Children constitute 75% of them (2). About 9% or 45,000,000 people in Southeast Asia are afflicted by orphan diseases (3).

USA considers a condition rare if it affects less than 200,000 persons. For the European Union, it is fewer than 5 in 10,000 of the general population. There is no official definition for rare disease in Malaysia. The Malaysian...
Rare Disorder Society (http://www.mrds.org.my) defines it as a disease with a low prevalence of about 1 in 4,000 of the general population. Examples of rare diseases include many of the Inborn Errors of Metabolism such as lysosomal storage diseases, neuromuscular conditions such as Duchenne muscular dystrophy and spinal muscular atrophy; haemophilia, brittle bone diseases, achondroplasia and Huntington's Disease.

For practical reasons, rare or orphan diseases tend to get ignored. Most healthcare personnel do not recognize the symptoms and signs of rare diseases or know how to treat them. Diagnoses tend to be delayed, even in developed countries like USA and Britain by 5 to 7 years. Ironically it is well-known that medical students are fascinated by rare diseases because they are so interesting and distinct even though they may not encounter these diseases again as doctors. Both under-graduate and post-graduate examinations tend to use rare presentations of common diseases or common presentations of rare diseases for their clinical cases. However, as practising clinicians, reality sets in. Dr. Theodore Woodward, a former professor at the University of Maryland School of Medicine, Baltimore in the late 1940’s first alluded to, “When you hear hoof beats, think of horses, not zebras,” which means, “common diseases occur commonly.” This is practical as more patients are likely to be helped if a doctor is well-versed in common diseases which affect a lot of patients.

As Malaysia’s healthcare improved with reduction in mortality rates from malnutrition and infectious diseases, NCDs are now the main cause of morbidity and mortality. Whilst the public may be aware of NCDs such as hypertension and diabetes mellitus, very few members of the public or healthcare providers are aware of rare or orphan diseases. While treatment of rare diseases are best left in the hands of tertiary centres with personnel who have a special interest in them, there is a need for increased awareness and funding for research, screening, diagnosis, treatment and management of these orphan diseases (4).

Early diagnosis reduces long term complications in the patients, allows genetic counselling to be provided for the family and the option for prenatal diagnosis and support services can be made available. Very often, empowering patients and families with knowledge have multiple beneficial effects – the caregivers will take charge of treatment regimes, improved medication compliance and play an active role in advocacy and support for each other. Patient support groups like the Malaysian Rare Disorders Society played a major role in dissemination of information to increase awareness, provide advisory services, fund-raising and patient advocacy.

**Orphan drugs are expensive**

Orphan drugs are treated by orphan drugs. Orphan drugs are economically not viable to produce because of their small patient pool. Research and development (R & D) in the treatment of rare diseases is likely to be costly and not worthwhile financially for the pharmaceutical industry.

The United States Congress passed the Orphan Drug Act (ODA) in early 1983. The Orphan Drug Act (ODA) provides for granting special status to a drug or biological product (“drug”) to treat a rare disease or condition upon request of a sponsor. For a drug to qualify for orphan designation both the drug and the disease or condition must meet certain criteria specified in the ODA and FDA’s implementing regulations. Since 1983, more than 600 drugs and biologic products have been approved for treatment of rare diseases (5). Orphan designation qualifies the sponsor of the drug for various development incentives including tax credits for qualified clinical testing. The Orphan Drug Tax Credit (ODTC) under ODA gives pharmaceutical companies credit for half their clinical trial expenses, that resulted in the approval of 486 orphan products (6). Unfortunately, ODTC has recently been amended as a result of the Tax Cuts and Jobs Act (TCJA) approved by the US Senate (6). Critics said the ODTC and other provisions in the ODA have been abused (7). It is estimated that there would be 33% fewer orphan drugs on the market today without the enactment of the ODTC (6). While the ODA incentives help companies get orphan drugs to the market, they do not protect the consumer by regulating orphan drug prices. Part of the ODA ensures market exclusivity for 7 years after FDA approval (8). Drugs that are already approved for a non-orphan use can be approved for orphan drug use and receive orphan drug designation (9). When this occurs, the price for non-orphan and orphan use may increase tremendously due to the market exclusivity and non-competitive pricing for designated orphan products.

Since the year 2000, over 1,950 orphan medical product designations have been issued by the European Commission, of which so far 142 have resulted in authorised medicinal products (10). One of the most challenging issues identified was how to apply health technology assessment (HTA) for orphan drugs to support the evidence base of pricing and reimbursement decisions. Due to the high cost of these medicines, small patient cohorts and the limitations in clinical evidence, the standard methodology and decision criteria of HTA seem to be difficult to use regarding most of the ODs (11).

While these efforts have brought many new treatment options to patients with rare diseases, they were still unaffordable to many patients in low and middle income countries. In a systematic review of 35 countries, it was found that the availability of orphan drugs depends on individual country’s legislation (only 23/35 countries) and national orphan drug policies and designation, marketing authorization, marketing exclusivity and incentives as well as tax credits to support research, development and marketing. High prices and lack of evidence often limit orphan drugs from meeting the HTA criteria, especially cost-effectiveness, which may influence access (12). There are two health financing models often used as a modelling choice for a chronic disease: a patient-level simulation model such as discrete event simulation (DES) and a cohort-level modelling approach such as a Markov state-transition model, of which both allow for a more detailed...
representation of the disease course. In the patient-level simulation model, each patient is represented individually and the final outcomes are calculated by aggregating over all individuals. In contrast, the Markov model represents the study population as a homogeneous cohort and reflects the continuous risk of a disease over a long time period. The choice of which model to use is dependent on the type of disease, the amount of data available and the experience of the researcher. A Markov-state transition model seems to be most suitable model for economic evaluations of orphan and ultra-orphan drugs.

There are no specific legislations pertaining to orphan drugs in Malaysia. It was reported that challenges faced by Malaysian patients with rare diseases included delayed treatment due to late diagnosis, limited availability to genetic medicine services and expensive treatments which reduced access to these medicines. The National Medicines Policy states that there shall be appropriate procedures to enhance accessibility of orphan medicines and Ministry of Health (MOH) has prepared the Malaysian Guidelines for the Management of Orphan Drugs which will provide a framework for all stakeholders the management of orphan drugs. Issues related to the designation, regulation, marketing and procurement procedures for orphan drugs are addressed and aim to increase availability of non-commercially viable products without compromising on safety. The study stated that the major hurdle faced by MOH is on the question of affordability. The majority of orphan drugs are not listed in the MOH formulary and are procured through special approval processes.

On the 27th July 2017, the Deputy Health Minister replied in the Parliament of Malaysia that the Ministry of Health allocated a budget of RM8.5 million annually for the treatment of 28 patients with lysosomal storage diseases with each patient needing between RM500,000 to RM1 million a year. A Technical Committee for ERT was established and a guideline on the indications and use of enzyme replacement therapy for lysosomal diseases in Malaysia was issued by the MOH in 2009. However, with the increasing number of patients and the chronic nature of these rare diseases, the funding allocated to the MOH has become insufficient. Many patients are not receiving sufficient dose for their treatment and some new patients are awaiting treatment. Clearly, much more is needed to be done to improve the situation. On the 27th October 2017, Prime Minister Datuk Seri Najib Razak, in his 2018 Budget announcement said the government had also allocated a total of RM10 million to accommodate the medical costs for rare diseases, which was on an upward trend. Prior to the 14th General Election, the Pakatan Harapan (PH) coalition issued a manifesto declaring in one of its promises (Promise 9) that it “will increase budget allocation and will provide incentives for the participation of private companies and charitable bodies to tackle rare diseases.” Specific measures and actions by PH government to follow through with this promise are highly anticipated.

There are many other orphan drugs for other rare diseases in the pipeline and other alternative funding sources are needed. A Rare Disease and Orphan Drug Act is urgently needed in Malaysia to facilitate adequate funding for treatment of rare diseases. In addition, under this proposal, biotechnology companies may be able to produce generic drugs and biosimilars for rare diseases not only for Malaysia but export to regional countries. It is expected that a holistic approach to obtain adequate funding for rare disease in Malaysia include getting accurate date on the burden of diseases, prevalence and incidence data of RD, cost-benefit and cost-effectiveness studies using a Markov-state transition health model. Studies had shown that owing to the high cost of these medicines, small number of patients and the limitations in clinical evidence, the standard methodology and decision criteria of HTA may be an inappropriate approach for evaluation of these orphan drugs for rare diseases. Other innovative strategies such as outcomes-based managed entry agreements were used for products with a conditional marketing authorization or authorized under exceptional circumstances.

Another group of orphan drugs: the old off-patent drugs

There is another group of orphan drugs where the cost of R & D had been borne by the original parent company. These are the old off-patent drugs whose patient pools are again small. But should any pharmaceutical company acquire the exclusive manufacturing and marketing rights to these old, off-patent under-utilized but nevertheless essential drugs, they would have the monopoly and patients, albeit few, will be at their mercy.

“Drug profiteering” is a strategy where an astute pharmaceutical company purchase the rights to old off-patent drugs and squeeze high profits out of them. The methods of drug profiteering included the following scenarios:

1. Savvy investors spot drugs with only one manufacturer or single-source drugs as opportunities to earn monopoly profits.
2. Price hike of multi-source generic drugs through mergers and acquisitions of pharmaceutical companies.

A recent example is the acquisition by Turing Pharmaceutical of the marketing right to pyrimethamine in August 2015. Pyrimethamine is used to treat malaria and toxoplasmosis. Its patient pool includes pregnant women, HIV/AIDS patients, post-organ transplant patients on immune-suppressants and patients on chemotherapy. Within a month of this venture, Turing hiked the price per tablet of pyrimethamine from USD13.50 to USD750, an increase of 5500%. Bear in mind that pyrimethamine has been in the market for more than 60 years and has been off-patent since the 1970′s. Its initial R & D cost had been borne...
by GlaxoSmithKline, its original manufacturer. The small patient pool, the absence of a competitor and a lack of alternatives, all contributed to an effective monopoly. For a while, Turing’s then-CEO, Martin Shkreli was the most hated man on social media. This “drug profiteering” by Turing was further put in perspective when a group of Sydney Grammar School students managed to produce 3.7 g of pyrimethamine in the school laboratory for a paltry sum of USD20 (17).

Similarly, Valeant Pharmaceuticals, a Canadian company, acquired 2 drugs commonly used to treat cardiovascular diseases, isoprenaline and sodium nitroprusside, and overnight increased their prices by up to 500%. Multidrug-resistant tuberculosis is an emerging worldwide problem. Hence it was indeed disturbing when Rodelis Therapeutics purchased cycloserine from an affiliate of non-profit Purdue University and hiked the price for a course of treatment from USD500 to USD10,800, an increase of 2,160% (17).

As private corporations, pharmaceutical companies are legally obliged to act in the interests of their shareholders to maximize profits. However modern corporate law does not require for-profit corporations to pursue profit at the expense of everything else, and many do not. There is always a tension between public interests and private incentives, and both are legitimate (18). Keeping the costs of off-patent drugs low despite monopoly, should be a social obligation of the pharmaceutical industry.

**Direct acting antivirals in Hepatitis C: The case in Malaysia**

Similar argument could also be applied to advocate lowering the prices of expensive state-of-the-art drugs with clear public health benefits. A case in point is the new oral Direct Acting Antivirals (DAA) in the treatment of chronic hepatitis C. When DAAs were first marketed in Malaysia in 2016, only few could afford it. The price of RM150,000 to RM175,000 for a 12-week course of treatment was the cost of a low-cost house. Despite their close to 100% cure rate, the outcome is suboptimal because not many patients could afford it to benefit from it. When cheap generic DAAs from India and Bangladesh, where patent laws are very lax, were introduced into the local market, Abbvie voluntarily slashed the price of their DAAs, Viekirax and Exviera by 1/3 to RM50,000. Merck, Sharp & Dohme also priced its 12-week course of Zepatier (elbasvir and grazoprevir) at a similar cost.

In the face of these challenges, Gilead Science, the American manufacturer of Sofosbuvir, announced its decision on August 24th 2017 to expand its HIV and Hepatitis C generic licensing agreement to Malaysia. This means that it will be possible for lower-cost generic versions of this life-saving drug to be made available in Malaysia through volunteer licensing. It is really a case of “if you can’t beat them join them.” Previously Malaysia was not given special pricing for DAAs by pharmaceutical companies as it was considered a middle-income country (19).

Prior to this announcement, the Geneva-based Drugs for Neglected Diseases initiative (DNDI) has been conducting clinical trials in partnership with the Malaysian Health Ministry and Egyptian drug manufacturer, Pharco Pharmaceuticals to test a combination treatment of sofosbuvir and ravidasvir. Pharco has agreed to set the price of the combination treatment at USD300 (RM1,260) per 12-week course once ravidasvir is registered. Dr Bernard Pécout, DNDi executive director in a statement on 20th September 2017 said that Malaysia’s landmark decision to invoke a “government-use” licence to get access to affordable hepatitis C treatment will embolden other poor countries to follow suit. International trade rules allow countries to issue government-use licences when pharmaceutical companies fail to avail affordable patented medicines. (20) This is known as compulsory licensing.

**How can the government intervene?**

The government could rein in the cost of expensive off-patent single-source drugs by:

A. **Price control**

B. **Promote competition**

Switzerland, home to pharmaceutical giants like Novartis and Roche, sets maximum allowable prices on drugs for sale within its borders (21). The government of many Organization for Economic Co-operation and Development (OECD) nations frequently use government authority and bargaining strength to lower the cost of prescription drugs, be they original or generic, patented or off patent (17).

**Strategies for Price Control include:**

a. **Reference pricing** is a method of calculating the cost of a drug in relation to its cost in several peer nations and the average price of therapeutically comparable drugs in that country itself.

b. **Value-based pricing** relates drug prices to quality-adjusted life years (QALYs), a metric of disease burden that measures improved health due to treatment. One year in perfect health equals one QALY. Four years in moderate health equals 2 or 3 QALY. By applying cost-per-QALY to therapeutically comparable drugs, Norwegians pay 71% less than the US Medicare for the same osteoporosis treatment (22).

c. **Profit controls** - The United Kingdom caps the annual expenditure of pharmaceutical companies in order to limit their profits, requiring them to foot the bill or cut drug prices if expenditure exceeds this cap.

**Strategies to Promote Competition include** applications by generic companies to produce these drugs should be expedited as well as waiver of some fees in the application process. This step will help the government to ensure and minimize patient endangerment caused by either orphan drug shortages or lack of accessibility to these old off-patent drugs.
Conclusions

Government policymakers clearly have a role to play to ensure inclusiveness when developing national strategies for NCDs such as rare disease and providing healthcare treatment for children who needed orphan drugs. Similarly, legitimate private profits must not be procured at the expense of public interests. Indeed the landmark World Trade Organization (WTO) Ministerial Declaration on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and Public Health not only recognized the legality but also the need for countries to take pro-public health measures and not let patents or monopoly get in the way of public health interests (23,24).

Competing Interest

The authors declare no competing interest.

References: