IJPSR (2019), Volume 10, Issue 2 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 June 2018; received in revised form, 13 August 2018; accepted, 18 August 2018; published 01 February 2019

ORPHAN DRUGS: OVERVIEW AND REGULATORY REVIEW PROCESS

Z. Thaker *, K. Jethva, D. Bhatt, M. Zaveri and S. Deshpande

K. B. Institute of Pharmaceutical Education and Research, Near GH - 6 Circle, Sector - 23, Gandhinagar - 382023, Gujarat, India.

Keywords:

Rare disease,
Orphan drugs, ODA

Correspondence to Author:
Z. Thaker

M. Pharm. Sem-III,
Department of Regulatory Affairs,
K. B. Institute of Pharmaceutical Education and Research, Sector - 23, Gandhinagar - 382023, Gujarat, India.

E-mail: zkthaker@gmail.com

ABSTRACT: Orphan drugs are medicines or vaccines intended to treat, prevent or diagnose a rare disease (*viz*., Huntington's disease, myoclonus disease, Tourette syndrome, *etc*.). The definition of rare diseases varies across jurisdictions but typically considers disease prevalence, severity, and existence of alternative therapeutic options. A rare disease is not universal and depends on the legislation and policies adopted by each region or country. In the last 35 years, ODA (Orphan Drug Act, 1983) has been adopted in several countries worldwide (USA, Australia, European Union, Japan, *etc*.) and has successfully promoted R and D investments to develop new pharmaceutical products for the treatment of rare diseases. The incidences of such diseases have been increasing at a greater pace than the speed with which drugs are researched and developed to treat such diseases. One of the major reasons is that the pharmaceutical industry is not very keen to research the development of orphan drugs as these drugs do not capture a bigger market. This is the current scenario in-spite of the various incentives provided in the orphan drug act. However, in this article, we have tried to focus on existing regulations and policies utilized by various countries namely USA, EU, Japan, and Australia. It has been noted, most importantly that the two largest populated countries- China and India, both lack national legislation for orphan medicines and rare diseases, which could have substantial negative impacts on their patient populations with rare diseases.

INTRODUCTION: A medicinal product designated as an orphan drug is one that has been developed specifically to treat a rare medical condition referred to as "orphan disease." It may be defined as drugs that are not developed by the pharmaceutical industry for economic reasons but which respond to public health need [1]. The spiralling cost of drug development in tune with stringent regulations, coupled with the low return on investment, often tends to discourage pharmaceutical innovators from developing products for extremely small patient populations.

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.10(2).505-18

The article can be accessed online on
www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(2).505-18

80% of rare diseases have been identified to genetic origins. Other rare diseases are the result of infections (bacterial or viral) and allergies or are due to degenerative and proliferative causes [1].

Orphan drugs are an important public health issue and a challenge for the medical community [2]. Modern society still has a lack of options for the effective treatment of patients with rare diseases. As one of the consequences of this, the demand for public health protection has increased the economic burden of a patient suffering from such diseases [3]. Scientific advances have given researchers a new tool to explore these orphan diseases, which are often more complex than common diseases. On the brighter side, these rare diseases when taken together cannot be called rare at all. There are approximately 7000 different types of rare diseases and disorders with more being discovered today. It has been reported that there are about 250 new rare

cases reported every year, however, the acceptable treatment is available only for 200-300 orphan diseases [4]. It is known that the 80% of these rare diseases are of genetic origin and the rest have environmental, bacterial, viral or unknown origin [4]. Overall orphan diseases are often chronic, progressive, disabling; even life-threatening and most of these have effective or curative treatment, having low prevalence and high complexity [5].

Evolution of Orphan Drug Act (ODA): The regulations resulting from the FD and C Act and the 1962 Amendment had especially negative consequences for orphan drugs. Because orphan drugs target small populations and yield lower returns, Asbury (1992) finds only four drugs that were on the market to treat rare diseases by 1965. Legislation significantly increased the costs associated with drug development and caused pharmaceutical companies to focus their attention on drugs that would maximize profits and the possibility of recouping their R and D costs.

Many people considered rare diseases to be "orphaned" or essentially ignored by drug manufacturers, due to the focus on profitable "blockbuster" treatments, defined as drugs that are expected to generate over $1 billion in sales annually. Because of their neglect, these treatments earned the label "orphan drug." Eventually, the influence of non-governmental organizations, like the National Organization for Rare Disorders (NORD) and patient advocacy groups, made orphan drug development a focus of public policy in the late 1970s and early 1980s. In 1980 Congress implemented the Bayh-Dole Act (PL No. 96-517, 1984), allowing the recipients of government-sponsored R and D to patent and licensed their research, followed by the Orphan Drug Act in 1983. [6]

The Orphan Drug Act (ODA) of 1983: Before the Orphan Drug Act (ODA) of 1983, the FDA had approved only 58 orphan designations, with fewer than 10 approved in the decade before the ODA was passed (Pharma, 2013). After the ODA, existing drugs that qualified had to be reapproved to gain market exclusivity and the benefits of the Act. The ODA has several parts, but its main purpose is to reduce costs and increase the returns to orphan drug production. Additionally, the ODA allows the FDA to expedite orphan drug designation approvals over other drugs, reducing the development time [7]. In 1997 Congress made a 50% tax credit on R and D expenditures a permanent feature of the Act. This credit goes towards clinical trial expenses of drugs that have received official orphan drug status by the FDA [6]. The most contested provision of the ODA is the seven years of market exclusivity rights that pharmaceutical companies can obtain for orphan products, which grants them a monopoly over the marketing of the drug for a particular indication.

Since the act has been enacted, it has been amended for numerous times by Congress. Initially, orphan status was only granted to drug manufacturers that demonstrated that the development of an orphan drug would be unprofitable and the costs would not be recouped through US sales. Orphan drugs could be profitable through worldwide sales as long as there were no "reasonable expectation" that US sales would exceed the development costs. Orphan drug exclusivity status was restricted to drugs that could not be patented, as some biotech drugs had difficulty in obtaining patents.

However, in 1985 another amendment to the ODA dropped that restriction. In reality, most orphan products could obtain patents, but it was because of the lengthy approval process that many of the patents expired before the product was able to reach the market, making them redundant. In 1990 Congress passed a proposal to limit market exclusivity, but President George H. W. Bush vetoed the amendment. Most recently, the FDA amended the ODA on June 12, 2013, to "clarify, streamline, and improve the orphan drug designation process" [8].

"Orphan Drugs" - Denotation in Various Boundaries:

United States: As defined in the United States, any drug developed under the Orphan Drug Act of January 1983 (ODA) is an orphan drug. The ODA is a federal law concerning rare diseases (orphan diseases) that affect fewer than 200,000 people in the United States or are of low prevalence (less than 5 per 10,000 in the community) [9].

Europe: A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare in

Europe (Orphan Drug Regulation 141/2000). At first glance, this may seem a small number, but by this definition, rare diseases can affect as many as 30 million European Union citizens. According to EURORDIS (European Organization for Rare Diseases), the number of rare diseases numbers from about 6,000 to 8,000, most of which have identified genetic conditions, with medical literature describing approximately five new rare conditions every week. Twenty-five to Thirty million people is reported to be affected by these diseases in Europe [9].

Japan: A drug must meet the following three conditions to be considered for orphan drug designation in Japan. Any disease with fewer than 50,000 prevalent cases (0.4%) is Japan's definition of rare. The drug treats a 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 market. 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, a New Drug Application (NDA) can be submitted. It is important to keep in mind that while Japan has orphan drug legislation, this legislation has room for interpretation. The MHLW (Ministry of Health, Labour, and Welfare) 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 approval [9].

Australia: The Therapeutic Substances Regulations does not define a rare disease or orphan indication regarding the number of patients, but rather indicates that it must not be intended for use in more than 2000 patients a year if it is a vaccine or *in-vivo* diagnostic. To attain the orphan designation, "the application must show why the medicine is an orphan drug." In Australia, orphan drugs are drugs used to treat diseases or conditions affecting fewer than 2,000 individuals at any one time (0.2%) [9].

India: The need for such an act is thus evident from the initiative by the Indian Pharmacists and the Government to implement Laws, which would strengthen the health infrastructure and provide relief to the numerous rare disease sufferers throughout the country. A group of pharmacologists at a conference held by the Indian Drugs Manufacturers Association in 2001 requested the Indian Government to institute the Orphan Drug Act in India [9].

Review Process for Orphan Drugs in Various Countries:

USA: To address these challenges, and help enable continued progress toward more treatments and even potential cures for rare diseases, FDA is undertaking a new effort to examine where it can help create a more efficient, scientifically advanced, predictable, and modern approach to the approval of safe and effective treatments for rare diseases.

This is beginning with a modernization of the process for granting Orphan Drug Designations by our Office of Orphan Products Development. With their leadership and hard work, we will be modernizing the processes in OOPD to make sure we continue to provide timely review of orphan drug designation requests. This will provide more certainty to sponsors, and simplify and ultimately reduce some of the time and costs associated with orphan drug development.

As part of this new plan, by September 21, 2017, FDA will complete reviews of all orphan drug designations that are older than 120 days. Following those 90 days, the agency is committing to respond to 100 percent of all new orphan drug designation requests within 90 days of their receipt by FDA. Program improvements and a renewed commitment to timely review to these critical products will ensure we do not build a backlog of designations again.

The few of programmatic improvements that are further described below in Orphan Drug Designation Plan:

1. In 90 days, FDA will complete reviews of all orphan drug designation requests that are older than 120 days (the backlog) while maintaining consistent, scientifically rigorous reviews; and

2. After 90 days, 100 percent of all new orphan drug designation requests will receive a response by the agency within 90 days of receipt. FDA will adhere to this 90-day timeline going forward [10].

PLAN:

Goal-1
In 90 days (by September 21, 2017) complete reviews of all requests older than 120 days
1. Created a Backlog SWAT Team of senior, experienced, proficient OOPD reviewers to focus solely on reviewing orphan drug designation requests, starting with the oldest ones first 2. Create and implement a new streamlined Designation Review Template to increase consistency, efficiency, and predictability of orphan designation reviews 3. Minimize discretionary work – i.e., FDA will reduce non-designation and non-grant-specific duties and assignments – for all other reviewers to enable the review teams to focus on core activities 4. OOPD will collaborate with FDA's Medical Product Centers to complete a CDER-CBER Orphan Designation Pilot Project – CDER and CBER reviewers will conduct preliminary primary reviews of a subset of drug designation requests, with OOPD conducting secondary reviews 5. OOPD will collaborate with the Office of Paediatric Therapeutics (OPT) to jointly review rare paediatric disease (RPD) designation requests. In these cases, OPT will conduct the paediatric review and OOPD will conduct the rare disease review. This policy began as of May 15, 2017. 6. OOPD transitioned secondary review of FOIA requests to the FOIA office, as of May 18, 2017 7. Continue to track weekly progress, adjust as necessary, and report on progress to the public

Goal-2
After 90 days, 100 percent of all new orphan drug designation requests made to FDA will receive a response from the agency within 90 days of receipt and consistently thereafter
1. FDA will establish an "FDA Orphan Products Council" to address scientific and regulatory issues related to orphan products to ensure a consistent approach to regulating these products 2. FDA will work to establish and implement a future state including the below changes. We will report on a full timeline of the progress on these activities within the next two months. 3. Organizational re-structuring to maximize expertise and improve workload efficiencies 4. Leverage the inter-center consult process, involving the medical product centers, that was developed for combination products to develop a streamlined process for consistent and timely orphan consults 5. Designation and Exclusivity Programs (Orphan Drug, RPD, Humanitarian Use Device (HUD)) • Centralize orphan exclusivity review and determinations • Continue to enhance the information technology infrastructure, e.g., automating more of the administrative processes for designation reviews • Improve and implement streamlined "Designation Review Template" across all designation programs to bring more efficiency, consistency, and predictability to these activities • Complete development of web-based training for sponsors to enhance quality of submissions. 6. Grant Programs: With respect to the Orphan Products (OPD) Grant Program (Clinical Trials + Natural History) and Paediatric Device Consortia (PDC) Grant Program; FDA will: • Revise grant monitoring processes by increasing utilization of desk-top and virtual tools and by implementing a new risk-based approach for conducting in-person site visits to grant recipients • Modify and modernize reporting requirements so that FDA can continue to give a high assurance related to appropriate monitoring of federal funds and efficiently measures program success • Continue to enhance IT infrastructure for continued efficiency and better monitoring 7. Reduce OOPD office-wide workload • Modify Orphan Cluster meetings with EMA from monthly to quarterly o The impact of the reduction in frequency of meetings with EMA is mitigated by our well established and long-standing relationship with our EMA counterparts, which will allow us to have ad hoc meetings should they become necessary in the intervening months. • Modify FDA Rare Disease Council meetings from monthly to quarterly o The RDC was established in 2012 to serve as a forum to communicate and collaborate across the agency on rare disease issues. It is chaired by OOPD and includes representatives CDER, CBER, CDRH, OHCA, OL, and OOPD. Quarterly meetings would ensure continuity of cross-agency communication but would help reduce workload in administering monthly meetings. The implementation of more joint reviews and closer regular, ongoing collaboration should reduce the need for the larger, RDC meetings. • Minimize outreach activities and discretionary projects to only those deemed most meaningful 8. OOPD will create a new "Tracking Dashboard" to monitor and facilitate its efforts to meet the new designation goals and FDA will report on overall workload and progress more regularly

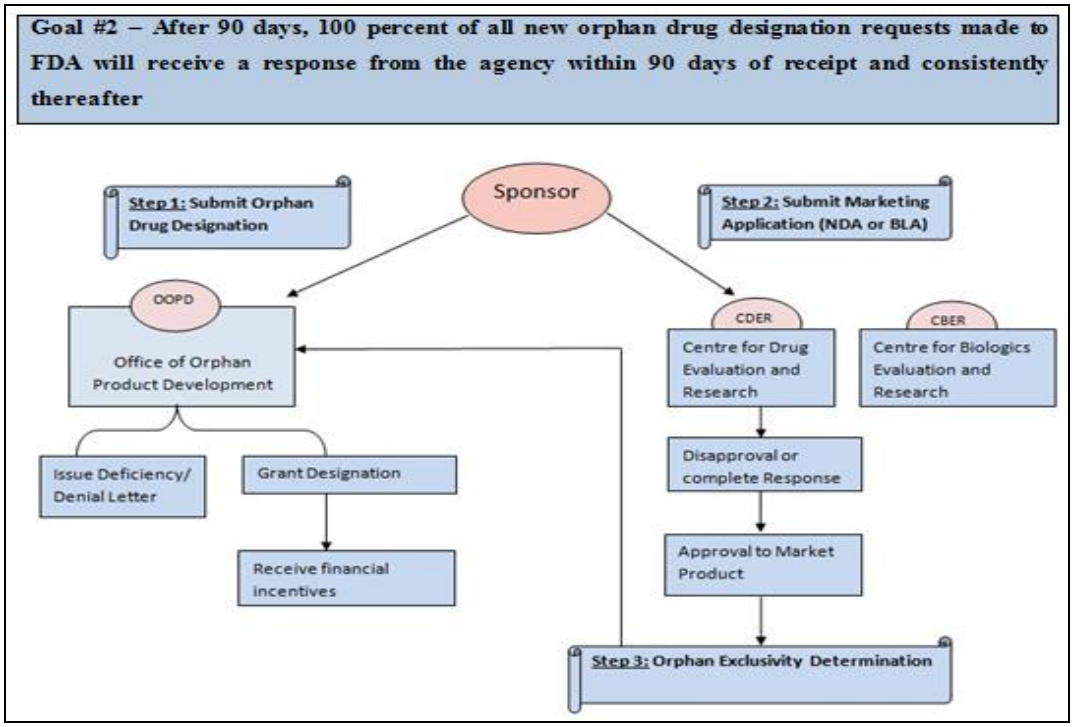


FIG. 1: ORPHAN DRUG REVIEW PROCESS IN USA

European Union: Sponsors are no longer required to send a notification of intent to file an orphan drug application for designation to the EMA. Sponsors should follow one of the two options listed below instead: [11]

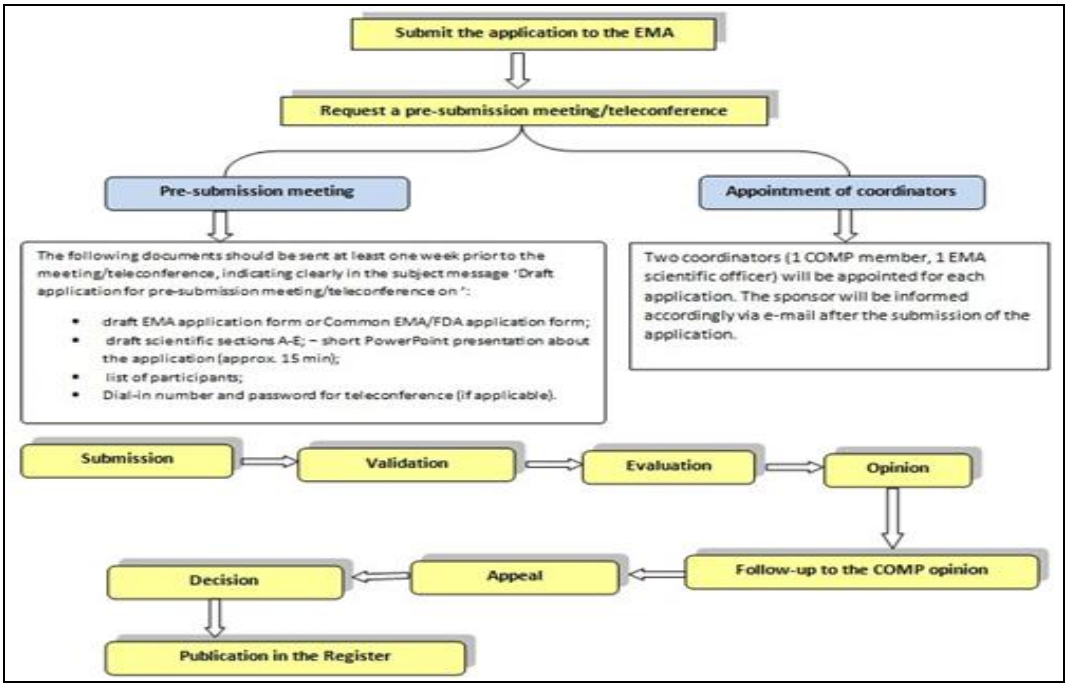


FIG. 2: ORPHAN DRUG REVIEW PROCESS IN EU

Applications for orphan designation are examined by the EMA's Committee for Orphan Medicinal Products (COMP), using the network of experts that the Committee has built up. The evaluation process takes a maximum of 90 days from validation [12].

Japan: The major regulatory authorities involved in the designation system are described as below:

- MHLW- Ministry of Health, Labour, and Welfare

- PMDA- Pharmaceuticals and Medical Devices Agency
- NIBIO- National Institute of Biomedical Innovation
- PFSB- Pharmaceutical and Food Safety Bureau
- PAFSC- Pharmaceutical Affairs and Food Sanitation Council [13].

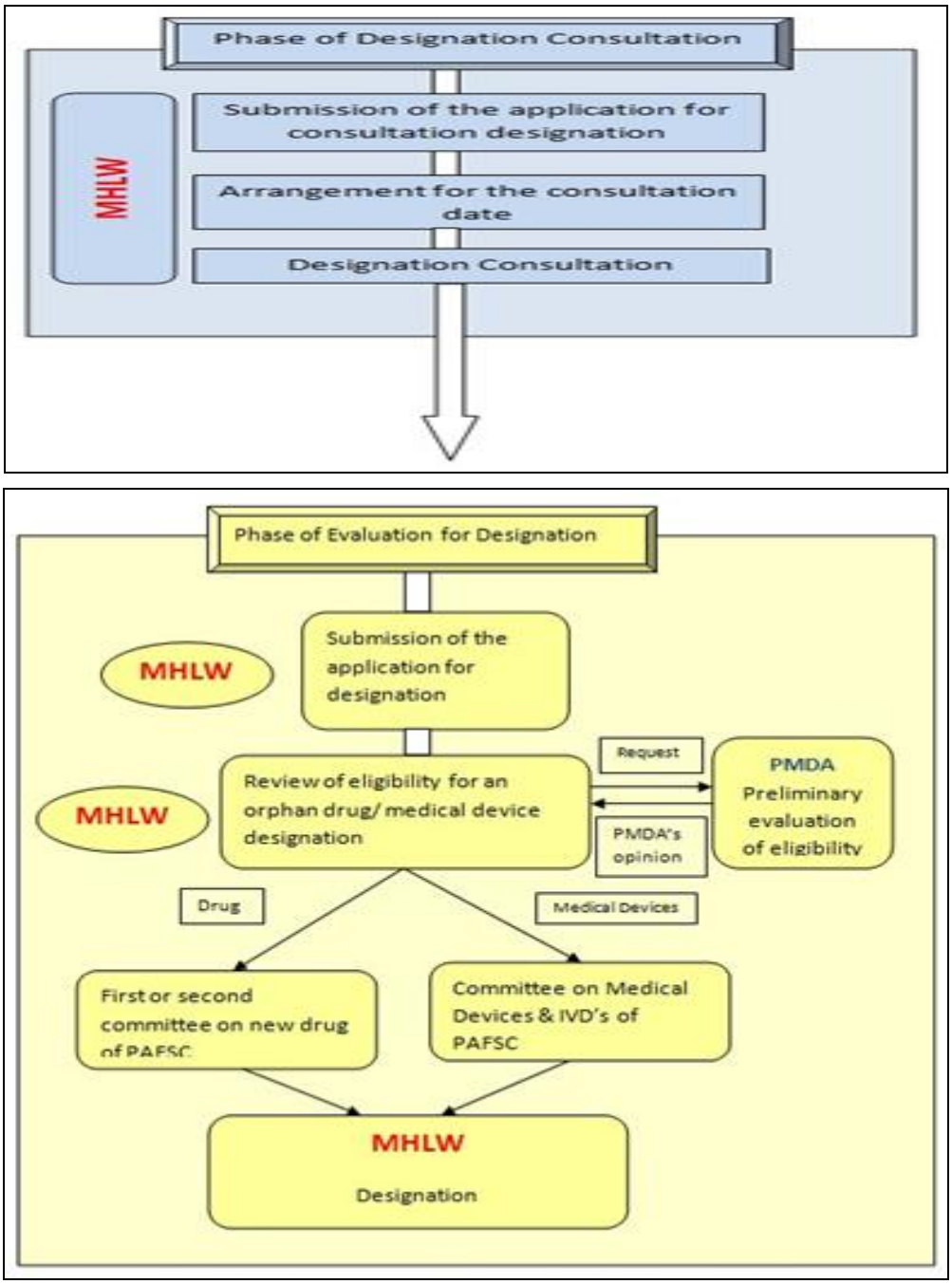
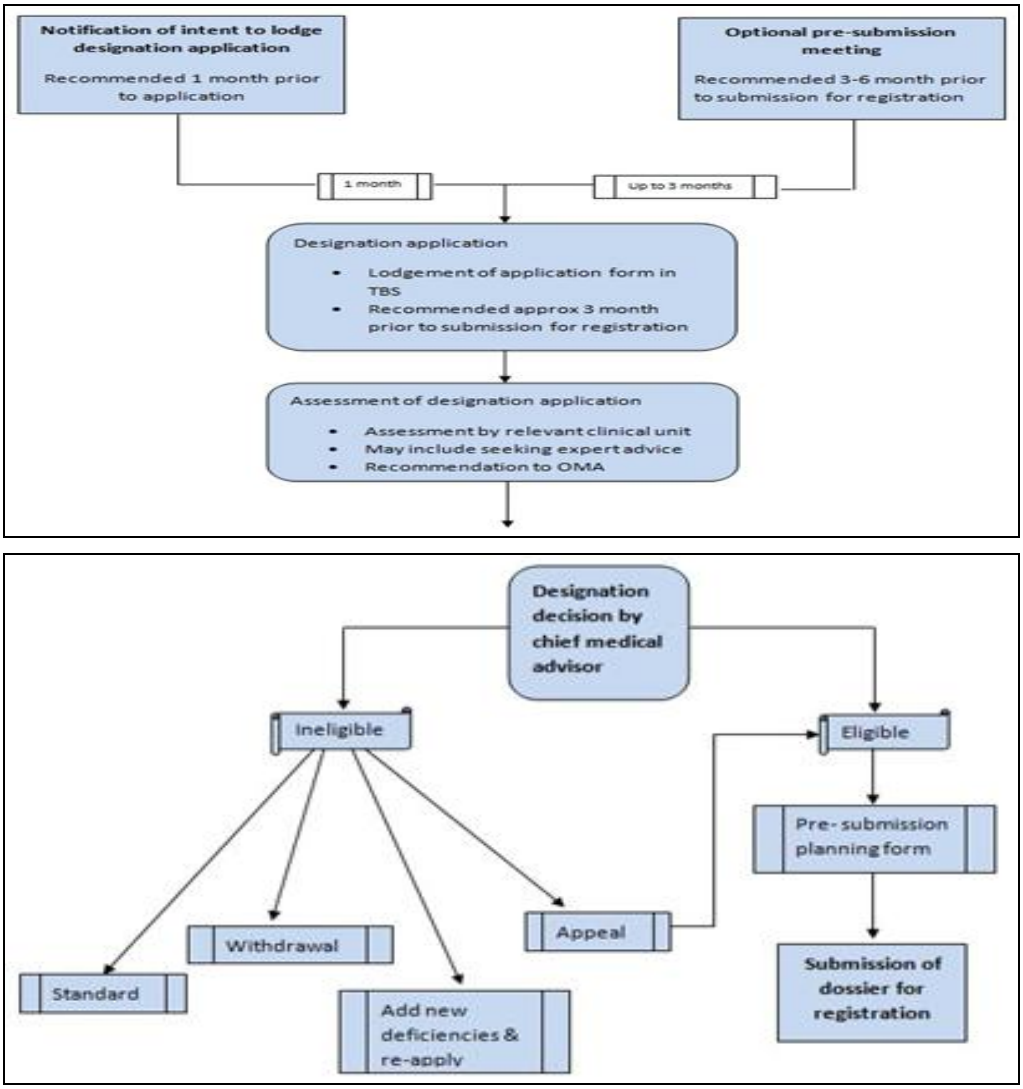


FIG. 3: ORPHAN DRUG REVIEW PROCESS IN JAPAN

Australia: A valid designation must be held for benefits resulting from designation to apply. Orphan drug designation of medicine can:

- facilitate orphan drug access to the Australian marketplace
- help offset orphan drug development costs
- Provide consistency and transparency to the orphan drug program.

Medicines with orphan drug designation have the same evidence requirements as other prescription medicines and will be evaluated by TGA for quality, safety, and efficacy in the same way [14].



Incentives: There are financial and non-financial incentives to ensure availability and access to orphan drugs. We summarize these below:

1. Financial Incentives.
2. Non-Financial Incentives.

Financial Incentives: Financial incentives utilized worldwide include: research grants, tax credits / corporate tax reductions, marketing exclusivity, and user fee waivers [15]. These provisions exist as a means to allow firms to recover research and development costs, which would not be possible with sales of orphan drugs given the small market sizes.

These incentives generally help to increase the availability of orphan drugs; Blankart *et al*., found that only 10% of clinical trials for orphan drugs would have been conducted without such financial incentives [16].

Non- Financial Incentives: Non-financial incentives we identified include: fast track approval, pre-licensing access (in the form of compassionate or off-label access) and scientific advice, that is, free protocol assistance and development consultation [17]. Garau *et al*., investigated a selection of seven EU member states and found four countries (France, Italy, Spain and the Netherlands) allow pre-licensing access to orphan drugs but encourage the collection of additional clinical data to prove a therapeutic benefit.

Pre-licensing allows importation of orphan drugs available in other countries but currently unauthorized in the country. Pre-licensing access is often the most common method for patients accessing orphan drugs in many countries, often through procedures such as ‘named patient procedures.’ Such use may be granted to an

individual or a group of patients with a serious or life-threatening disease where there is no alternative therapeutic option [18]. Free scientific advice including protocol assistance is provided by regulatory authorities to increase the quality of clinical trials and study protocols, and increase the likelihood of successful marketing authorization and subsequent reimbursement application [19].

Marketing Exclusivity: Orphan drug exclusivity applies to those vaccines and diagnostic or preventive drugs either designed to affect conditions that afflict a relatively small number of people or for which there is no reasonable expectation of the recovery of research and development costs [20]. The approval of an application for orphan designation is based upon the information submitted by the sponsor. A drug that has obtained orphan designation is said to have "orphan status" [21]. Sponsors need to follow the "standard regulatory requirements and process for obtaining market approval" [22]. A sponsor may request orphan drug designation for a previously unapproved drug or an already marketed drug. More than one sponsor may receive orphan drug designation for the same drug for the same rare disease or condition. A drug with orphan status enjoys exclusive approval and market exclusivity [6].

Worldwide Sales: Over the five years to 2017, industry revenue is anticipated to grow at an annualized rate of 2.1% to $1.2 trillion, including 2.7% revenue growth in 2017 that was realized.

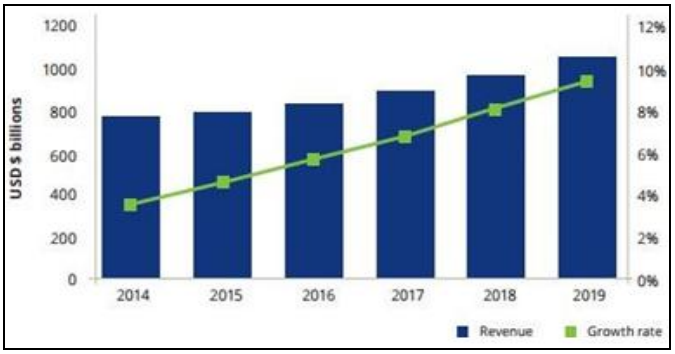


FIG. 4: WORLDWIDE PHARMACEUTICALS SALES, 2011- 2020

As more pharmaceutical manufacturers expand to serve emerging markets, industry revenue is expected to grow, especially as manufacturers target prevalent region-specific diseases. Profit is increased from 22.9% of industry revenue in 2012 to 24.1% in 2017, driven by rising global consumer demand for high-margin biologic drugs [23].

Global Trade and Regulations: The industry contended with global governments seeking to reduce drug costs. This trend has been particularly popular in Europe, with austerity measures resulting in many countries announcing reimbursement reductions. In response, many pharmaceutical companies have altered their drug portfolios from primary-care blockbusters to specialities such as oncology, immunology, and inflammation, where the medical need is so high that regulators more-readily accept prices.

TABLE 1: REVENUE GROWTH

Year	Revenue (in mm)	Growth (%)
2007	867,156	
2008	905,801	4.46
2009	956,928	5.64
2010	1,007,008	5.23
2011	1,050,625	4.33
2012	1,042,338	-0.79
2013	1,051,157	0.85
2014	1,047,579	-0.34%
2015	1,103,644	5.35%
2016	1,126,549	2.08%
2017	1,156,516	2.66%

While this trend provided the industry with stable need-based demand, counterfeit drugs have hampered industry revenue growth. According to the World Health Organization, counterfeit drugs currently account for 10.0% of the global market, but in some emerging countries, this proportion is as high as 30.0% to 40.0%. Recent data from the World Customs Organization puts the drug counterfeiting business at $250.0 billion a year. Protection and enforcement of intellectual property rights remain a difficult issue in many emerging markets, with forgery and first-copy products widespread.

TABLE 2: LIST OF APPROVED ORPHAN DRUGS, 2018

Trade Name	Generic Name	Company	Designation	Indication	Marketing Approval Date
Azedra Ultratrace	Iobenguane I 131	Progenics Pharmaceutical, Inc.	Treatment of neuroendocrine tumors	AZEDRA is indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive,	07/30/2018

				unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy	
Omegaven	Omegaven emulsion	Fresenius Kabi USA, LLC	Treatment of parenteral nutrition-associated liver disease	Omegaven is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC)	7/27/2018
n/a	Tafenoquine	Glaxo Group Limited, England	Treatment of malaria	KRINTAFEL is indicated for the radical cure (prevention of relapse) of Plasmodium vivax malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection	7/20/2018
n/a	Ivosidenib	Agios Pharmaceutical, Inc.	Treatment of acute myeloid leukemia (AML)	TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test	7/20/2018
n/a	Gemcitabine ready-to-use	Sun Pharmaceutical Industries Ltd.	Treatment of ovarian cancer	INFUGEM in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy	7/16/2018
Tpoxx	Tecovirimat	SIGA Technologies, Inc.	Treatment of smallpox	TPOXX® is indicated for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients weighing at least 13 kg	7/13/2018
Signifor	Pasireotide	Novartis Pharmaceuticals Corporation	Treatment of Cushing's disease	SIGNIFOR® LAR is indicated for the treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative	6/29/2018
n/a	Encorafenib + binimetinib	Array BioPharma, Inc.	Treatment of Stage IIB-IV melanoma positive for the BRAF mutation.	BRAFTOVI™ is indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test	6/27/2018
n/a	Encorafenib + binimetinib	Array BioPharma, Inc.	IIB-IV melanoma is positive for the BRAF mutation.	MEKTOVI® is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test	6/27/2018
Epidiolex	cannabidiol	GW Research Ltd.	Treatment of Lennox-Gastaut syndrome	EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older	6/25/2018
Epidiolex	Cannabidiol	GW Research Ltd.	Treatment of Dravet syndrome	EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older	6/25/2018
Ablysinol	Dehydrated alcohol	Belcher Pharmaceutical, LLC	Treatment of hypertrophic obstructive cardiomyopathy	ABLYSINOL® is indicated to induce controlled cardiac septal infarction to improve exercise capacity in adults with symptomatic hypertrophic obstructive	6/21/2018

				cardiomyopathy who are not candidates for surgical myectomy	
Cinryze(R)	C1 esterase inhibitor (human)	ViroPharma Biologics, Inc.	Treatment of angioedema	CINRYZE is a C1 esterase inhibitor indicated for routine prophylaxis against angioedema attacks in adults, adolescents and pediatric patients (6 years old and above) with Hereditary Angioedema (HAE)	6/20/2018
Avastin	Bevacizumab	Genentech, Inc	Treatment of fallopian tube carcinoma	the combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection	6/13/2018
Avastin	Bevacizumab	Genentech, Inc	Treatment of patients with ovarian cancer	In combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection	6/13/2018
Keytruda	Pembrolizumab	Merck, Sharp & Dohme Corp.	Treatment of primary mediastinal B cell lymphoma	KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy	6/13/2018
n/a	Moxidectin	Medicines Development Limited	Treatment of onchocerciasis volvulus in children and adults	Moxidectin Tablets are indicated for the treatment of onchocerciasis due to Onchocerca volvulus in patients aged 12 years and older	6/13/2018
Avastin	Bevacizumab	Genentech, Inc	Treatment of primary peritoneal carcinoma	In combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection	6/13/2018
Venclexta	Venetoclax	AbbVie, Inc	Treatment of chronic lymphocytic leukemia	VENCLEXTA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) without 17p deletion, who have received at least one prior therapy	6/08/2018
Rituxan(R); Mabthera (R)	Rituximab	Genentech, Inc	Treatment of pemphigus vulgaris	RITUXAN is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris	6/07/2018
Palynziq	Pegvaliase-pqpz	BioMarin Pharmaceutical Inc.	Treatment of hyper phenylalaninemia	Palynziq is indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management	05/24/2018
n/a	Tacrolimus granules for oral suspension	Astellas Pharma Global Development, Inc.	Prevention of rejection in kidney, liver or heart transplant in pediatric patients	PROGRAF Granules (tacrolimus for oral suspension) for the prevention of rejection in heart, kidney or liver transplant in pediatric patients	05/24/2018
Actemra	Tocilizumab	Genentech, Inc	Treatment of pediatric patients (age 16 years and younger) with polyarticular-course juvenile idiopathic arthritis	ACTEMRA® (tocilizumab) for subcutaneous injection is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older	05/11/2018
Darzalex	Daratumumab	Janssen Biotech, Inc	Treatment of multiple myeloma	In combination with bortezomib, melphalen, and prednisone for the	05/07/2018

				treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	
Tafinlar(R) Capsules A Nd Mekinist(R) Tablets	Dabrafenib and trametinib	Novartis Pharmaceuticals Corporation	Treatment of patients with anaplastic thyroid cancer and locally advanced or metastatic papillary thyroid cancer whose tumors harbor a BRAF V600 mutation	TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options	05/04/2018
Tafinlar(R) Capsules A Nd Mekinist(R) Tablets	Dabrafenib and trametinib	Novartis Pharmaceuticals Corporation	Treatment of patients with anaplastic thyroid cancer and locally advanced or metastatic papillary thyroid cancer whose tumors harbor a BRAF V600	MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment	05/04/2018
Andexxa	Coagulation factor Xa (recombinant), inactivated-zhzo	Portola Pharmaceutical, Inc.	For reversing the anticoagulant effect of direct or indirect factor Xa inhibitors in patients experiencing a serious uncontrolled bleeding event or who require urgent or emergent surgery	Coagulation factor Xa (recombinant), inactivated-zhzo is indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding	05/03/2018
Kymriah	Tisagenlecleucel -T	Novartis Pharmaceuticals Corporation	Treatment of diffuse large B-cell lymphoma	KYMRIAH is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of patients with diffuse large B-cell lymphoma, high-grade B-cell lymphoma, or DLBCL arising from follicular lymphoma who received two or more lines of systemic therapy	05/01/2018
Mekinist And Tafinlar	Trametinib and dabrafenib	Novartis Pharmaceuticals Corporation	Treatment of Stage IIb through IV melanoma.	MEKINIST is indicated, in combination with dabrafenib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection	04/30/2018
Mekinist And Tafinlar	Trametinib and dabrafenib	Novartis Pharmaceuticals Corporation	Treatment of Stage IIb through IV melanoma.	TAFINLAR is indicated, in combination with trametinib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection	04/30/2018
Jynarque	Tolvaptan	Otsuka Pharmaceuticals Co., Ltd.	Treatment of autosomal dominant polycystic kidney disease	JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)	04/23/2018
Tagrisso	Osimertinib	AstraZeneca Pharmaceuticals LP	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	TAGRISSO® is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test	04/18/2018
n/a	Fostamatinib	Rigel	Treatment of immune	TAVALISSE is indicated for the	04/17/2018

	disodium hexahydrate	Pharmaceutical, Inc.	thrombocytopenic purpura	treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to previous treatment.	
Crysvita	Burosumab-twza	Ultragenyx Pharmaceutical, Inc.	Treatment of X-linked hypophosphatemia (formerly known as vitamin D-resistant rickets)	CRYSVITA is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older	04/17/2018
n/a	Recombinant von Willebrand factor (rhVWF)	Baxalta US, Inc.	Treatment of von Willebrand disease.	Indicated for use in adults (age 18 and older) diagnosed with von Willebrand disease (VWD) for perioperative management of	04/13/2018
Afinitor	Everolimus	Novartis Pharmaceuticals Corp.	Treatment of tuberous sclerosis complex including TSC-associated subependymal giant cell astrocytoma (SEGA), TSC-associated angiomyolipoma and TSC-associated lymphangioleiomyoma tosis (LAM)	For the adjunctive treatment of adult and pediatric patients, age 2 years and older with tuberous sclerosis complex (TSC)-associated partial-onset seizures	04/10/2018
Rubraca	Rucaparib	Clovis Oncology, Inc.	Treatment of ovarian cancer	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.	04/06/2018
Leukine	Sargramostim	Partner Therapeutics, Inc.	Treatment of individuals acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome)	LEUKINE® is indicated to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS])	03/29/2018
Blincyto	Blinatumomab	Amgen, Inc.	Treatment of acute lymphocytic leukemia	BLINCYTO® is indicated for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children	03/29/2018
Tasigna	Nilotinib	Novartis Pharmaceutical Corporation	Treatment of chronic myelogenous leukemia	TASIGNA® (nilotinib) is indicated for the treatment of pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase and pediatric patients greater than or equal to 1 year of age with chronic phase Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior tyrosine kinase inhibitor (TKI) therapy.	03/22/2018
Adcetris	Brentuximab vedotin	Seattle Genetics, Inc.	Treatment of Hodgkin's lymphoma	ADCETRIS® is indicated for the treatment of adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with chemotherapy.	03/20/2018

Hizentra	Immune Globulin Subcutaneous (Human), 20%	CSL Behring	Treatment of chronic inflammatory demyelinating polyneuropathy	Indicated for the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIPD) as maintenance therapy to	03/15/2018
Trogarzo	Ibalizumab	TaiMed Biologics, Inc.	Treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy	TROGARZO, in combination with another antiretroviral (s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen	03/06/2018
n/a	Tezacaftor and Ivacaftor combination therapy	Vertex Pharmaceuticals Inc.	Treatment of cystic fibrosis (CF)	SYMDEKO a combination of tezacaftor and ivacaftor, is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on *in-vitro* data and/or clinical evidence	02/12/2018
n/a	Tezacaftor and Ivacaftor combination therapy	Vertex Pharmaceuticals Inc.	Treatment of cystic fibrosis (CF)	YMDEKO a combination of tezacaftor and ivacaftor, is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on *in-vitro* data and/or clinical evidence	02/12/2018
n/a	lutetium Lu 177 dotatate	Advanced Accelerator Applications	Treatment of gastro-entero-pancreatic neuroendocrine tumors	Treatment of somatostatin receptor positive GEP-NETs including foregut, midgut, and hindgut neuroendocrine tumors in adults	01/26/2018
Trisenox	Arsenic trioxide	Teva Branded Pharmaceutical Products R&D, Inc	Treatment of acute promyelocytic leukemia	In combination with tretinoin for treatment of adults with newly-diagnosed low-risk acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression	01/12/2018

CONCLUSION: The orphan drug programs relating to rare diseases have met success only in some countries. In a market where first-mover advantages are small, it is difficult to find the appropriate incentive system.

The system created by the ODA has led to an increase in the development, approval, and availability of orphan products. While the market exclusivity provision has expanded access to orphan drugs, it may be erroneously providing exclusive market protection for other products.

A country should try to produce important drugs for the benefit of the whole world, depending on the R and D investment, the return on such investment, the tax and patent incentives, and its regulatory policies. Agreement of these points might lead to beneficial changes in our national thinking and prevent "orphanisation of new drugs."

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Jyothi G, Venkatesh M, Kumar PT, Radhadevi N, Gundavaram R and Sharma KK: Orphan Drug Act: History, Perspective and Challenges for Future. Am J PharmTech Res 2012; 2249-3387.
2. Schieppati A, Henter JI, Daina E and Aperia A: Why rare diseases are an important medical and social issue. The Lancet 2008; 371(9629): 2039-41.
3. Haffner ME: Adopting orphan drugs-two dozen years of treating rare diseases. New England Journal of Medicine 2006; 354(5): 445-7.
4. Stakisaitis D, Spokiene I, Juskevicius J, Valuckas KP and Baiardi P: Access to information supporting the availability of medicines for patients suffering from rare diseases looking for possible treatments: the European Service. Medicine (Kaunas, Lithuania) 2007; 43(6): 441-6.
5. Wästfelt M, Fadeel B and Henter JI: A journey of hope: lessons learned from studies on rare diseases and orphan drugs. Journal of Internal Medicine 2006; 260(1): 1-10.
6. Smith and Sara HD: Orphan Drug Development: Incentives Under the Orphan Drug Act. Senior Theses, Trinity College, Hartford, CT 2015.
7. DiMasi JA, Hansen RW, Grabowski HG and Lasagna L: Cost of innovation in the pharmaceutical industry. Journal of Health Economics 1991; 10(2): 107-42.
8. Eichler HG, Bloechl-Daum B, Brasseur D, Breckenridge A, Leufkens H and Raine J: The risks of risk aversion in drug regulation. Nature reviews Drug discovery 2013; 12(12): 907.
9. Sharma A, Jacob A, Tandon M and Kumar D: Orphan drug: development trends and strategies. Journal of Pharmacy and Bioallied Sciences 2010; 2(4): 290.
10. https://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/FINAL Orphan Drug Designation Plan.
11. Antoniu S: Fresh from the designation pipeline: orphan drugs recently designated in the European Union. Expert Opinion on Orphan Drugs 2013; 1(3): 249-53.
12. http://ec.europa.eu
13. Yano K, Watanabe N, Tsuyuki K, Ikawa T, Kasanuki H and Yamato M: Regulatory approval for autologous human cells and tissue products in the United States, the European Union, and Japan. Regenerative Therapy 2015; 1: 45-56.
14. https://www.tga.gov.au/node/758474
15. Franco P: Orphan drugs: the regulatory environment. Drug Discovery Today 2013; 18(3-4): 163-72.
16. Blankart CR, Stargardt T and Schreyögg J: Availability of and access to orphan drugs. Pharmacoeconomics 2011; 29(1): 63-82.
17. Picavet E, Cassiman D and Simoens S: Evaluating and improving orphan drug regulations in Europe: a Delphi policy study. Health Policy 2012; 108(1): 1-9.
18. Garau, Martina and Mestre-Ferrandiz, Jorge, Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries, OHE Briefing, No. 52, 2009.
19. Kamusheva M, Stoimenova A, Doneva M, Zlatareva A and Petrova G: A cross-country comparison of reimbursed orphan medicines in Bulgaria, Greece and Romania. Biotechnology and Biotechnological Equipment 2013; 27(5): 4186-92.
20. Mitsumoto J, Dorsey ER, Beck CA, Kieburtz K and Griggs RC: Pivotal studies of orphan drugs approved for neurological diseases. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society 2009; 66(2): 184-90.
21. Stolk P, Willemen MJ and Leufkens HG: Rare essentials: drugs for rare diseases as essential medicines. Bulletin of the World Health Organization 2006; 84(9): 745-51.
22. Fischer A, Borensztein P and Roussel C: The rare European diseases therapeutic initiative. PLoS Medicine. 2005; 2(9): e243.
23. https://www.ibisworld.com: IBIS World, Healthcare and Pharmaceuticals Industry NAICS.

How to cite this article:
Thaker Z, Jethva K, Bhatt D, Zaveri M and Deshpande S: Orphan drugs: Overview and regulatory review process. Int J Pharm Sci & Res 2019; 10(2): 505-18. doi: 10.13040/IJPSR.0975-8232.10(2).505-18.