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CARE FOR RARE: SPOTLIGHT ON MARKET EXCLUSIVITY FOR ORPHAN DRUGS

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Abstract:

Orphan drug are remedial product developed for the management of a rare disease. Rare disease is defined as a state that affects a very small percentage of the inhabitants and is severely debilitate. This rare condition should be looked into the deeper for the welfare of population. The term" orphan" is introduced because of the lack of any diagnosis, prevention and treatment. As these orphan drugs have a very low prevalence in the community due to which they are still kept untouched in dark and no any superior research is being provided by legislation and no any Advancement tools are to get through these orphan diseases so to catalyse the process economic incentives are given for development of specific treatment including tax credits. Rare diseases provide a challenge in the valuation of new therapies Orphan drug development is of increasing interest because of protection of the molecules with orphan designation. Market exclusivity provides monopoly for orphan drugs. There are different time periods of the market exclusivity for various countries. Rather than giving special benefits and incentives in market for orphan drugs the pathways can be drawn to increase the optimization and scope for research development so the pricing can also be in all the rational means. Various ways such as patent auctions and dose modification studies will help in rationalizing the cost of drug. Various new strategies can be pipelined with the collaboration with market players and the concern regulatory authorities to speed up the process and to bring the new medical evolution in coming decades.

Keywords: Market Exclusivity, Orphan Drug, Rare diseases,

Introduction: -

There is some specifically designed Drug product which is only intended /designated to treat a rare medical condition which show its rareness these conditions are referred as "orphan disease." These are the drugs which are not meant for any profitability to pharma companies but to provide a good and quality life for public. The high cost of drug development joined with strict regulations; along with the low return on investment are some important factors that discourage pharmaceutical innovators from developing orphan drug products.[1] Rare diseases are seem to be very important public-health and welfare issue and a task for the medical field. The other most important reason of addressing "orphan health" is high negligence and lack of development and the treatment option available for these rare conditions.[2] Maximum rare diseases are genetic disorders or autoimmune diseases and rest of them bacterial, viral or unknown origin, which hamper the life expectancy, and also substantially disables physical and mental health. In an all-orphan disease are having chronic, progressive, disabilities and can even have life threatening effects with high complexity and curative therapy.[4] Many of the times even physicians, are facing some issues in diagnosing and treating the condition, which reminds of the lack of knowledge and available treatment options to cure the medical condition. However, the saddest part is that patients who are suffering against the enemy don't even know about the treatment and the future life style with the diseased condition.[5]

The Brighter side is that there is increased public awareness of these rare diseases in recent year and all the thanks goes to work done by "patients support groups" established in 1983, the National Organisation of Rare Disorders (NORD) in the USA was instrumental in the approval of the Orphan Drug Act.[2] Due to the upfronting of various organisation the Orphan diseases have not only seek attention in scientific community's but also shown interest in the general public, which includes developed countries in last few years, But story still remains same in shaded dark developing countries like India, which experience the lack of knowledge and awareness in both the public community as well and Concerned authority and medical fraternity.[5]

Hence, we tried to take some insight review, on the current global and Indian situation with respect to orphan drugs. Further, there are some suggestions and few recommendations that can be adopted and inculcated in the respective streams to improve the drowning down situation in India by the authorities.

Orphan Diseases

The tenure "orphan" was actually invented in relative to the paediatric community, as they were being constantly side lined from the clinical trials because of the issues of safety and efficacy which was not so stringent which become hard for developer to develop the medical product to treat the condition, and this is the reason when the children's and infants got the status of "Pharmaceutical orphans". In orphan drug production there is no as such commercial benefits and no profit expense is been raised by the companies if they invest their capital in developing the products, as they are to be marketed in rare population.[3] However, there are two core elements that can possibly define the rare or orphan diseases which can be stated as Total prevalence of the disease (in ratio to the population) Non-availability of the treatment for the disorder [5]

What is the Need for an orphan drug regulation?

As such there is no any legit treatments available in market for the orphan diseases and this is due to the lack of the marketed and manufactured products by the pharma companies in India. However, this is because of none of the pharmaceutical company wants to invest their time and funds with insufficient knowledge and the facilities with no expected outcome to develop the product. In other words, the rarity of a particular disease limits drug development.[26] Therefore to encourage the research and development of these orphan drugs the regulatory authorities should provide incentives to Pharmaceutical companies so that they will invest in the development of new medicines, and are expected to be rewarded with a reasonable return on their investment [27]

Evolution of Orphan drug acts 1983.

There was some finding to bring this act into the action for the benefit of the pharmaceutical companies and for public welfare.

- The incentives and the clinical development epitome criteria given by the orphan drug act was found fascinating to many of the pharmaceutical companies which motivated them to produce and manufacture orphan products this led to the approval of more than 1000 designation by FDA
- Some agencies and authorities found out in their study and survey and reported that these orphan drugs are readily got accessible to the patient who are in the search of the therapy; though they cost

high amount and limited supply of the treatment to market, but due to insurance pays and incentives to companies this help patients to obtain their drug products.

- The quality service and required help was been provided by the OOPD to various companies and patient which ultimately lead to the information of the disease and its prevalence to the public and market.[35]

When is the drug designated to be an orphan drug?

The drug must follow some criteria which can are governed by the concern authorities who grant the designation. The drug must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening and prevalence of the condition should be according to the country limits and there should no satisfactory indication for the diagnosis, inhibition or treatment of the desired rare condition and, if there is any method available for the same, then that medicine must show more significant and effective benefit than the previous one present which will be boon for the affected population. They can also be classified which some basic criteria shown in table.1[7]

What is the difference between the Essential medicines and Orphan drug?

The essential drug and orphan drugs have their own importance and prevalence in the population irrespective of its marketing and development for the different market scale what is the target population and its importance is shown in table.2 [28]

Why shift paradigm to Orphan drugs?

From very long time, orphan drugs were neglected and was treated with the status of the "poor cousin" of the non-orphan drugs. This was because of the fewness of orphan diseases anticipated with less yield income which deprived the companies to look into the area of rare condition. Although in few years, there has been a drastic shift in imagining taking a chance to do some innovation by companies in this "pharmaceutical touch me-not" entities [5]. This shift is due to the higher profit margin, shorter clinical development time, incentives related to development, reduced tax and marketing costs and finest pricing. However, it is unclear whether this necessarily translates to higher company profit [6.] There are also Concerns which are benign articulated that orphan drug policies are being demoralized by the big shot pharma players as they initially file application for orphan designation and after approval they are used broadly. Rituximab, was approved as

an orphan drug by the FDA for the treatment of follicular non-Hodgkin's lymphoma whereas now it is used in various other condition so these things should also be considered while we are raising voice for orphan designation development so this misuses also should be taken into consideration[6]. There are various regulating agencies across worldwide which support the Orphan drug development and give necessary helps and information some of these are listed in table.3 [4]

Orphan drug regulation around the worldwide.

Various countries are having their own orphan drug policies with some application and enrolment formalities with some provision made for the designation approval and with some incentives and marketing rights. Some regulatory condition and approval criteria are described in table-4. [7]

Application filing Process for the essential drugs and orphan drugs

The application filling process of orphan and non-orphan drug is more over the same but only the approval authorities and the review process is having basic difference and have some less complication with regards to the orphan drugs evaluation as compared to non-orphan drugs. In the application Filling of orphan drug, the sponsor can file the application at any step of the drug development with enough evidence of its orphan status and minimal clinal and pre-clinical data in special cases are approved and given grant after knowing the efficacy of the drug on the medical condition in fig.1 and fig.2 the process of filling application is shown.

What are the types of Application which can be designated as the Orphan drug?

To apply for authorization as an orphan drug a centralized European procedure should be followed.

There are two different types of approval:

- **Normal Conditional:** when the data are still incomplete. The manufacturer obliged to carry out additional studies and approval is renewed annually until the studies are completed and then the drug will attain normal status
- **Under exceptional circumstances**: when an applicant shows that it is not possible to provide complete data on efficacy and safety of the drug. This usually occurs when the disease is extremely rare, there is little scientific knowledge in the field, or due to ethical reasons on data collection.[8]

Review process of application of Orphan drug in various countries:

USA:

There are some new goals are laydown in US for the review of application programmatic improvements that are taken in Orphan Drug Designation Plan:

- In 90 days, FDA will complete the consistent evaluation and rigours scientific reviews formalities of all the application for orphan drug designation
- After 90 days, new orphan drug designation requests will receive a response by the agency receipt of acknowledgement. FDA strictly adhere to this 90-day timeline [9.] The process of filing application is shown in fig.3

European Union:

- The EMA's (COMP) Committee for orphan medical product Agency is the one responsible for reviewing and evaluating applications from sponsors for designation. This agencies with the help of expert network committee speed up the process of review and takes maximum 90 days to validate the given proof of designation. Sponsor have to follow the two option which is shown in fig.4 [10-11]

Australia:

- An effective designation must be giving the designation approval and can lend so benefit to the owner in various means and also facilitate orphan drug access to the Australian market which can help drug development costs with abided consistency and transparency towards the program. TGA will review all the clinical proofs in knowing the safety and quality of drug product Medicines before the allow the marketing rights.[12] diagrammatic representation of filling application is shown in fig.5

Japan:

- In Japan, drugs products and medical devices can be applied for orphan status designated by proving its quality, safety and effectiveness regarding any desired products or therapy. Minister of Health, Labour and Welfare in alliance with Pharmaceutical Affairs and Food Sanitation Council can grant them the marketing authority by evaluating and reviewing the application and necessary evidences, this application and evaluation process is shown in Fig.6 [13-36]

Incentives in favour for the orphan designated drugs:

1. **Financial Incentives** : They receive research grants, tax/ credits/ corporate tax reduction, market monopoly rights and fees waviers and protocol access. This provission is given to firms to recover the research cost and the development revenue which was uesd in the application and development of drug which is any ways not possible with the scale of orphan drug in the small market. This helps to increase the availability of orphan drug in the market domain.[14-15]
2. **Non-Financial Incentives**: They are favoured by the fast track processes,pre-licensing, scientific advice and protocol assistance which is provided by the regulatory authorities which improves and increases the quality of the clinical trials and the processof the development of te drugs.[16-17-25]
3. **Market Exculsivity**: The exclusivity applies to the vaccines or diagnosis or drugs that prevent the rare condition/ disesses in the prevalent group of people so there is no margin of cost recovery and the capital invested for the development of the drug and to gain such benefits the drug has to acchieve the "orphan status" and to get the the designation the sponsors have to do the needful process designed by the regulatory authorites the sponsors can file the application for the drug which was previously unpporved or which is already approved and being marketed in public domain and even one or more than one sponsor is eligible for the same drug or diferent rare condition.Drug witthe orphan status isgiven exclusive approval and have the exclusivity market monopoly.[18-19-20]
4. **Extension of market exclusivity period**: The regulatory authorities can even extend the period of marketing right for 2 yrs for orphan designated condition which is being addresing for paediatric population and completed in accordance with fully compliant paediatric investigation plan(PIP) [21]
5. **Expiry of marketing** : As soon as the exclusivity period for an dication ends/ expires the regulatory authorites remove it from the community register of orphan medical products. Then medicine ceases to be classifed as an orphan medicines and is no longer under any favour or benefits. [21]
6. **Centralised Procedures**: Direct access to the centralised procedure for marketing authorisation.[24] comparision table for incentivesis are shown in table.5 [31-32]

Depriving Challenging factors for the development of orphan drug designation.

As we know there is lack of knowledge in medical community and unawareness in population regarding the rare condition and concern regulatory authorities have improper pipeline to channelized the disease diagnosis and drug development protocol, clinical process pathways. The major 3 criteria which need to be study to bridge this gap are:

1. **The study population**: - As the diseased condition is addressed to be orphan the prevalence of suffering population with this condition is very less and the major factor is that they are heterogenous dispersed geographically, and individual response to this condition is different so, to get sufficient patient tracks is the biggest challenge.
2. **Disease condition**: - As the low number of patients and no substantial initiative by the patients for the clinical trials led to limited clinical manifestation and as these diseases are showing progressive degeneration it gets difficult to understand its chronology and creates poor and incomplete data to track the nature of diseases which is under investigation
3. **Efficacy and safety**: - As there is no collective data for the diagnosis it become issue to find the pathbreaker to conquer the diseases with the study protocol for the safety of drug and its effectiveness on the condition and very limited clinical response is obtained which makes difficult to predict patient's behaviour and drug behaviour on patient which may lead to life threatening condition some major strategies should be lined up by the major market players in collaboration with certain government agencies to rule out these challenges and to achieve bright future in the development so such challenging drug development.

List of the Approved orphan drugs.

After the continues evaluation and through check with all the submitted proofs and evidence of the developed drug products the agencies grant the permission for marketing these drugs in the public domain. These evidences can also be insufficient due to lack of insignificant cause in development and shortage of clinical manifestation or ongoing process with the valid supporting documents they may get grants in much emergencies by the regulatory authorities. In table.6 List of orphan drug approved by the authority is mentioned. [30]

The exorbitant prices of orphan drugs: Are we paying twice?

There is development in the area of the orphan drugs but are they affordable? Affordability of these orphan drugs is the new and major issue and cause of tension between different MNCs. Some companies have responded to this by developing programs to facilitate access to orphan drugs.[29] The high prices governing the orphan drugs is the serious issue which makes it difficult for the ordinary people to gain the benefits due to financial sustainability in the health care stream and uneven access for the therapy amongst the patient population. Though the elevated pricing is completely justified considering the development for limited market, in this case the drugs studies can be turn out to be bit cheaper if given focus on rare diseases and treatment at some government aided or at the centralised laboratories.[8]

Some of the proposals to control the pricing:

1. The provision of the diagnosis and laborious obedience to the clinical indications must be taken in consideration for rare diseases. There should be accountability of each prescription and the high-cost drug which should be strictly monitored for validated by authorised centre for treatment of the disease.
2. There also should be strategies regarding the registry of the diagnosis, and should be kept updated with all the necessary data. This will help to evaluate the efficacy and safety of the drugs and also will be helpful for patients to use the facilities in the desired manner.
3. Documenting the costs of orphan drug research, and estimation of profit margin should be based on ethical principles so that all the needful patient population can be benefited by the policy and the agenda is fulfilled by al the possible means. [8]

Pharmacovigilance

There is also the surge of the Post marketing surveillance for all the approved orphan designated status which helps to grade the safety and efficacy and also to rule out any desired and undesired side effects and risks in patients taking them. The purpose of this Pharmacovigilance survey is to check whether the drug is truly having the designation or orphan or no, so that the drug can be taken down from the market.[33] Therefore with the help of pharmacovigilance strategies all the necessary information about the diseased condition is gathered and kept under the supervision and is strictly followed by regulatory bodies to check

its pharmacokinetics and to study its safety profile and related issues these all can be treated as the precautions taken if there is any misuse or any risk in future.[34]

Where does India stand out in the orphan drug designation? What can be done to speed up the awarness in population and regulatory authorities?

The insight about orphan diseases and the awareness of drugs has not yet being entered into the population of developing countries. There is negligence amongst the Indian medical community and careless attitude towards orphan diseases, is leading us to the lack the good and quality system drugs to treat the rare diseases and India is becoming the victim of these life-threatening conditions. India is the most popular country in the world and it has around 70 million cases of orphan diseases.[22] The main reason that we are not able to combat the impact of orphan diseases in India is lack of proper registry authority of this epidemiology. By the virtues and initiatives of NGO's and ORDI we can at least address the issues related to these diseases.[23]

Each day there are millions of peoples who are suffering from the rare diseases due to lack of regulatory plans on orphan conditions. There is no any legit framework and stringent guideline to address these conditions and on the top of that they are highly non-accessible and not affordable to most of the orphan approved drugs. However, the pharmaceutical companies are also not having strategies to look into this condition due to the less or inadequate policies and infrastructures which is needed to develop the products. One more main key depriving factor is to ear profit from the market which is not coming from the orphan drugs. There is need of paradigm shift in the pharmaceutical industry toward orphan drugs which is very unexploited domain, so in the need of the hour India need to look into these issues urgently and devotedly.

In our opinion:

1. Some of the Special incentives should be provided for R&D of orphan drugs and also the agencies and NGO's can have the alliance with the government laboratories and can get the technical support and assistance from the expert.
2. There should be the awareness drive in the population with regards to orphan disease and their developments using various online portal and media platforms and health campus and drives

3. Tax incentives which can be benefits of taxation and fee waivers, even we can take a leaf out of EMEA's book and should also include patient advocacy group representatives in the entire process of approval of orphan drug given by authority.

Conclusion:

Despite of the small target market pool for the rare diseases the research and development of the orphan drug have increased potential for the commercialization due to some attractive incentives which are given by the regulatory authorities for the marketing of orphan drugs as compared to the non-orphan drugs/ essential drugs which is having the maximum scale in the market due to the increasing population suffering from the diseases. The economic driver such as Tax credits, regulatory grants, FDA fees waiver scheme, lower timeline for clinical trials and speedy regulatory approvals which comes hand in hand with some of the commercial joy which includes premium pricing, fast track review, regulatory portal access, reduction in the marketing cost and monopoly marketing rights and also given the extension of the marketing exclusivity in the applied cases. All these are the key driving factors to fuel the substantial widening the power of the orphan drug development.

Government should come up with the framework and stick to the plans to execute all the conducive to enable the manufacturing of orphan drug and also should have the collaboration with the indigenous growing pharmaceutical companies and the CRO to give them all the need help and funding to kick start the development strategies for the orphan drug production all the necessary information about the diseased condition should be provided so as the fulfil the gap between the diseased condition and its treatment. This can also help the pharma companies to create the revenue and to dig the cost invested into the development with the help of filling patients and getting grants.

The orphan designated should be easily accessible to all the patients how want to opt for the treatment within the cheap and affordable cost to all the population in developed and developing countries.

This insight will not only potentially uplift the millions of lives who haven being suffering from these diseased conditions, it will also increase the accuracy and correct diagnostic method to identify and treat these life-threatening diseased conditions.

Table-1: Classification of Orphan drugs. [7]

Type	Expected Profit	Available Medication.
Little/no commercial benefits	Poor	Inadequate
Commercial Benefits	Good to Excellent	Inadequate
For the rare diseases that can be treated.	Variable	Adequate
Unprofitable.	Poor	Inadequate
Orphan for both rare and common diseases	Variable	Variable

Table-2: Comparison between Essential drugs and Orphan drugs. [28]

Aspects	Essential Medicines	Orphan drugs
Concrete policies in place since	1997 World wide	1983 in US and 2000 in EU
Primary focus on	Taking Public health into consideration bringing effective medication to as many patients possible	Individual patients even if one patient is there they should be treated.
Initiated and Developed by	WHO and member states	Australia, Japan, USA, EU, patient group.
Criteria	Drug driven	Diseases driven
Policies aims to	Provide established medicines to patients	Provide new medicines to yet untreatable patients
Target population	All the countries population	High incomes countries, developed countries.
Economics	Cost effectiveness, sustainable and affordable access	Relatively higher prices per individual patients, cost maximization per patient population.

Table-3: Supporting agencies for the development of the rare diseases and orphan drugs. [4]

Regulatory Authorities	Agencies	Responsibilities
Special regulatory authorities	1) Office of orphan product development within USFDA in US 2) Committee of orphan medical product within European Medicines Agency (EMA) in EU 3) Ministry of Health, Labour, and Welfare (MHLW) in Japan 4) Korean Food and Drug Administration (KFDA) in South Korea. 5) Department of Health (DOH) in Taiwan	Their responsibility is examining applications for orphan drug designation and planning and regulating the development of rare disease and orphan drugs.
Special Research support	1) Office of Rare Diseases Research (ORDR) was established in 1993 within the National Institutes of Health (NIH) for US.	Coordinate and support rare disease research, explore opportunities to research rare diseases, and provide information on rare diseases.
	2) In EU, the Rare Disease Task Force (RDTF) was established in 2004 within the European Commission Public Health Directorate.	Provide evidence to support policymaking, provision of medical services, and community support for rare diseases and orphan drugs through European coordination.
	3) In Asia, the Specified Disease Treatment Research Program was established in Japan in 1972.	
	4) In South Korea, the Research Centre for Rare Diseases (RCRD) was established in 2008 with the support of the Ministry of Family Affairs, Health and Welfare.	
	5) In China, research support comes mainly from the National Natural Science Foundation of China (NSFC).	

Table-4: Orphan drug regulation around worldwide globe.[7]

Countries	Description
Australia	• No Orphan drug Policy • Special Access scheme (SAS) for unapproved drugs • Provision for fees and tax reduction
Canada	• No Orphan drug policy • Emergency drug release program/ IND Provide access to unapproved drugs. • SR and ED tax incentive program would support R and D in the Orpah drug • Reduction in fees • Process patent granted for biotechnology products.
France	• No orphan drug policy. • Temporary approval for Orphan drug may get granted based on the availability of the data for the time period for 3 months to 1 year
Japan	• Orphan drug program • Designation granted based on Prevalence of diseases in the population • Grants are given for R and D and Manufacturing of Orphan drug. • Tax incentive granted • NDA for Orphan drugs are given priority Review.
US	• Orphan drug Act (January 4th 1983) • Designation Granted based on the Prevalence of the disease. • Protocol assistance to design the research protocol • Market exclusivity. • Tax credits and funding for clinical research. • Penalty for intentionally false claim statement of orphan drugs status • Accelerated Approvals • Process patent granted for biotechnological products.

Table-5: Comparisons in incentives and marketing exclusivity rights across the globe for OD'S. [31-32]

Legislation and provisions	US	EU	CHINA	KOREA	JAPAN	TAIWAN
OD legislation policies	ODA 1983 (FDA)	European medicine evaluation agency (2000)	China food and drug administration (CFDA)	Korea food and drug administration (KFDC)	PMDA	TFDA/ CDE
Marketing Exclusivity	7 years	10 years (extended for OD'S in paediatric PIP)	7 years.	6 years (extended for OD'S in paediatric PIP)	10 years	10 years
Accelerated evaluation	yes	yes	yes	Yes	yes	Yes
Fees regulatory reductions	yes	yes	NA	Yes	yes	Yes
Scientific Advices	yes	yes	yes	Yes	yes	yes
Tax incentives	50% Tax credits for clinical research cost	Tax credits depend on the country.	NA	50% subsidized application in fees.	50% development cost 12% tax exemption 25% less review fees.	NA
Approval period.	6 months	5 months.	NA	10-12 months	5 months	6-10 months

Table-6: List or orphan drug approved. [30]

Trade name	Active substance	Authorised marketing indication.	Date of approval	Marketing authorisation holders.
AYVAKYT	Avapritinib	Used in Monotherapy for the treatment in adult patients suffering from metastatic gastrointestinal stromal tumours.	24/09/2020	Blueprint Medicines (Netherlands) B.V.
BLENREP	Belantamab mafodotin	Monotherapy for the treatment of multiple myeloma in adult patients.	25/08/2020	GlaxoSmithKline (Ireland) Limited
DAURISMO	Glasdegib	This is used in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML)in adults.	26/06/2020	Pfizer Europe MA EEIG
HEPCLUDEX.	Bulevirtide	Granted for the therapy of chronic hepatitis delta virus (HDV) infection in plasm HDVRNA positive adult patients with liver disease	31/07/2020	MYR GmbH
IDEFIRIX	Imlifidase	Indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor.	25/08/2020	Hansa Biopharma AB
KAFTRIO Vertex	Ivacaftor / Tezacaftor / Elexacaftor	Indicated in a combination with ivacaftor for the treatment of cystic fibrosis in patients aged 12 years.	21/08/2020	Pharmaceuticals (Ireland) Limited
PRETOMANID FGK	Pretomanid	Indicated for used when combined with bedaquiline and linezolid, for the	31/07/2020	FGK Representative Service GmbH

		treatment of pulmonary extensively drug resistant and TB.		
REBLOZYL	Luspatercept	Treatment of adult patients with transfusion-dependent anaemia associated with beta thalassaemia.	25/06/2020	Celgene Europe B.V.

Fig.1: Application filling and evaluation of Essentail drugs to FD.

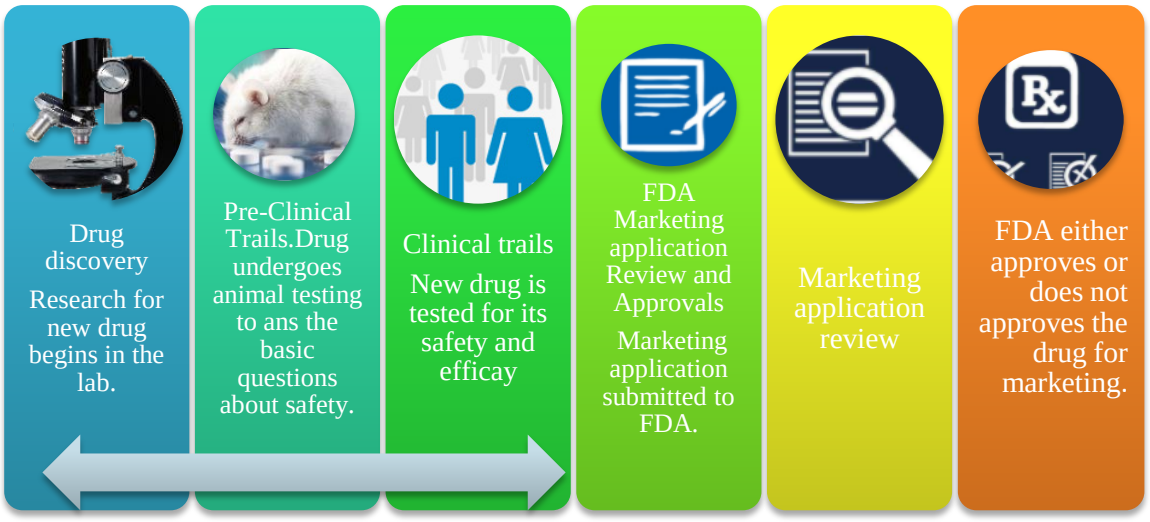


Fig.2: Application for orphan drug designation to OOPD.

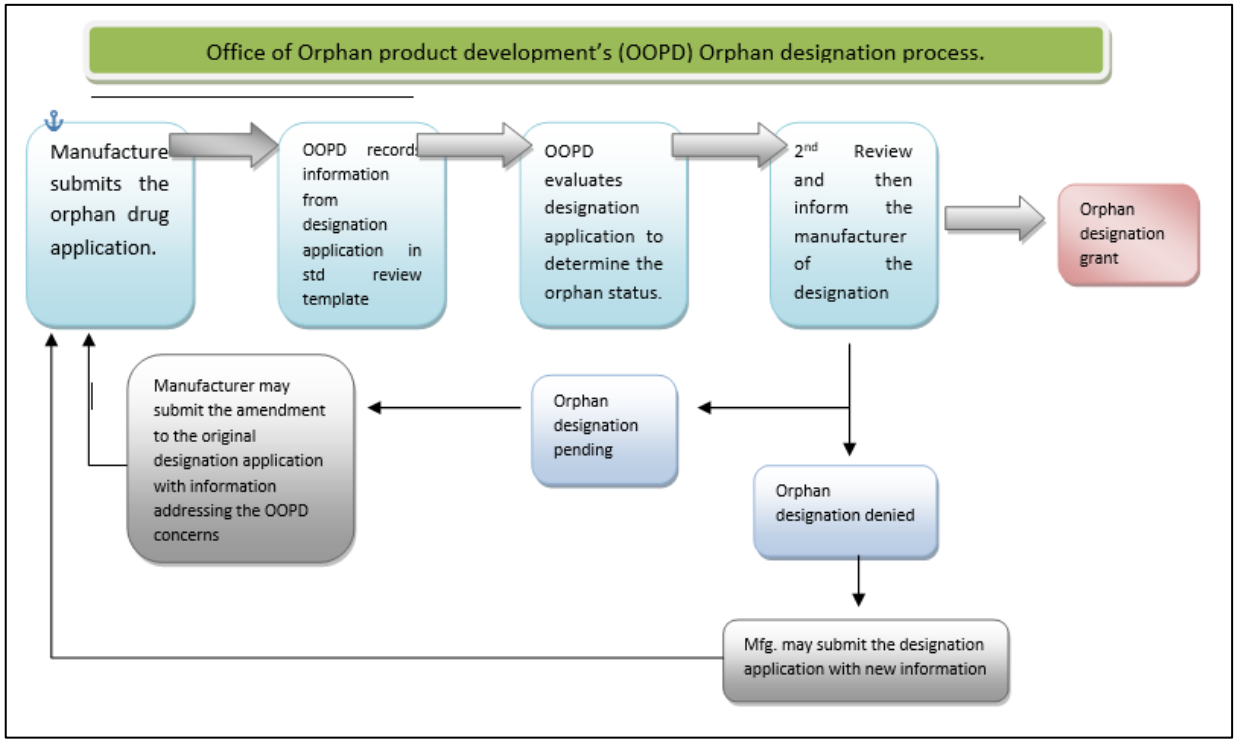


Fig.3: Filling application process and evaluation in USA. [9]

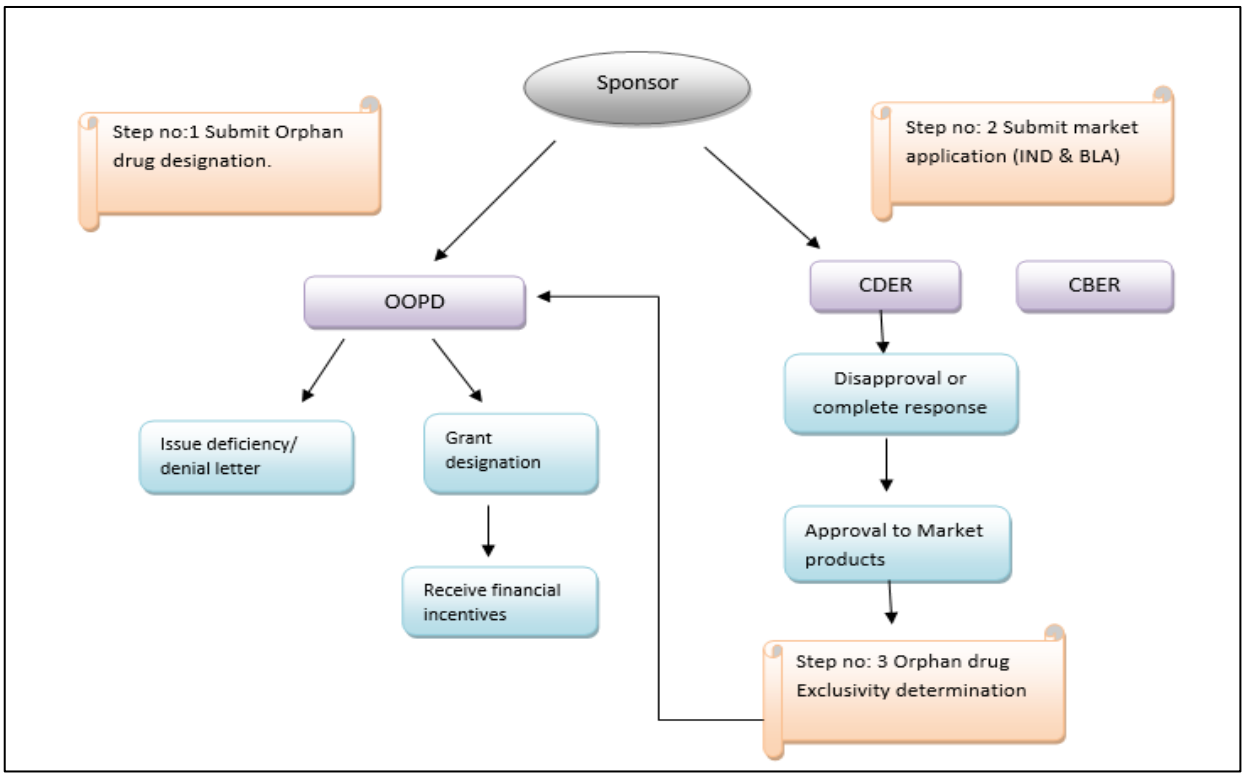


Fig.4: Filling application and evaluation for ODD in EU.[10-11]

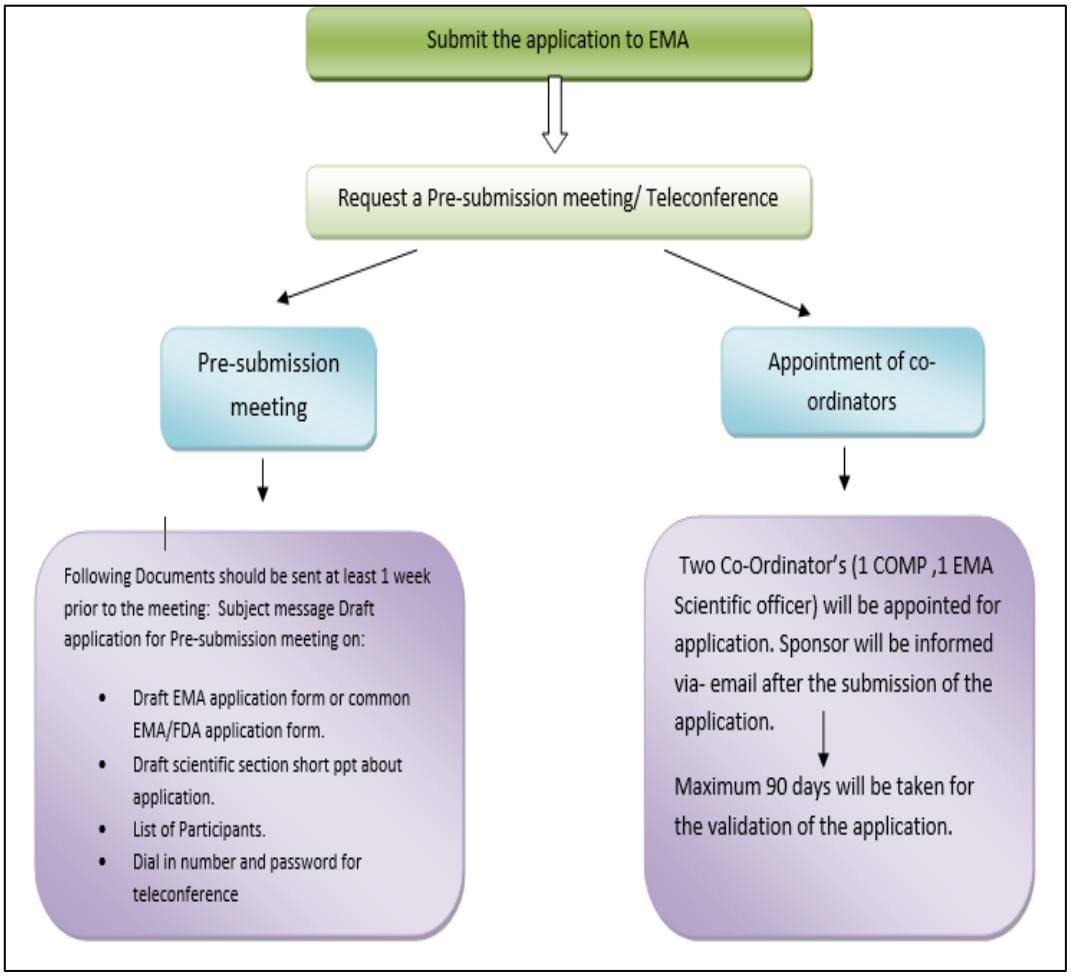


Fig.5: Filling application and evaluation of OOD in Australia. [1]

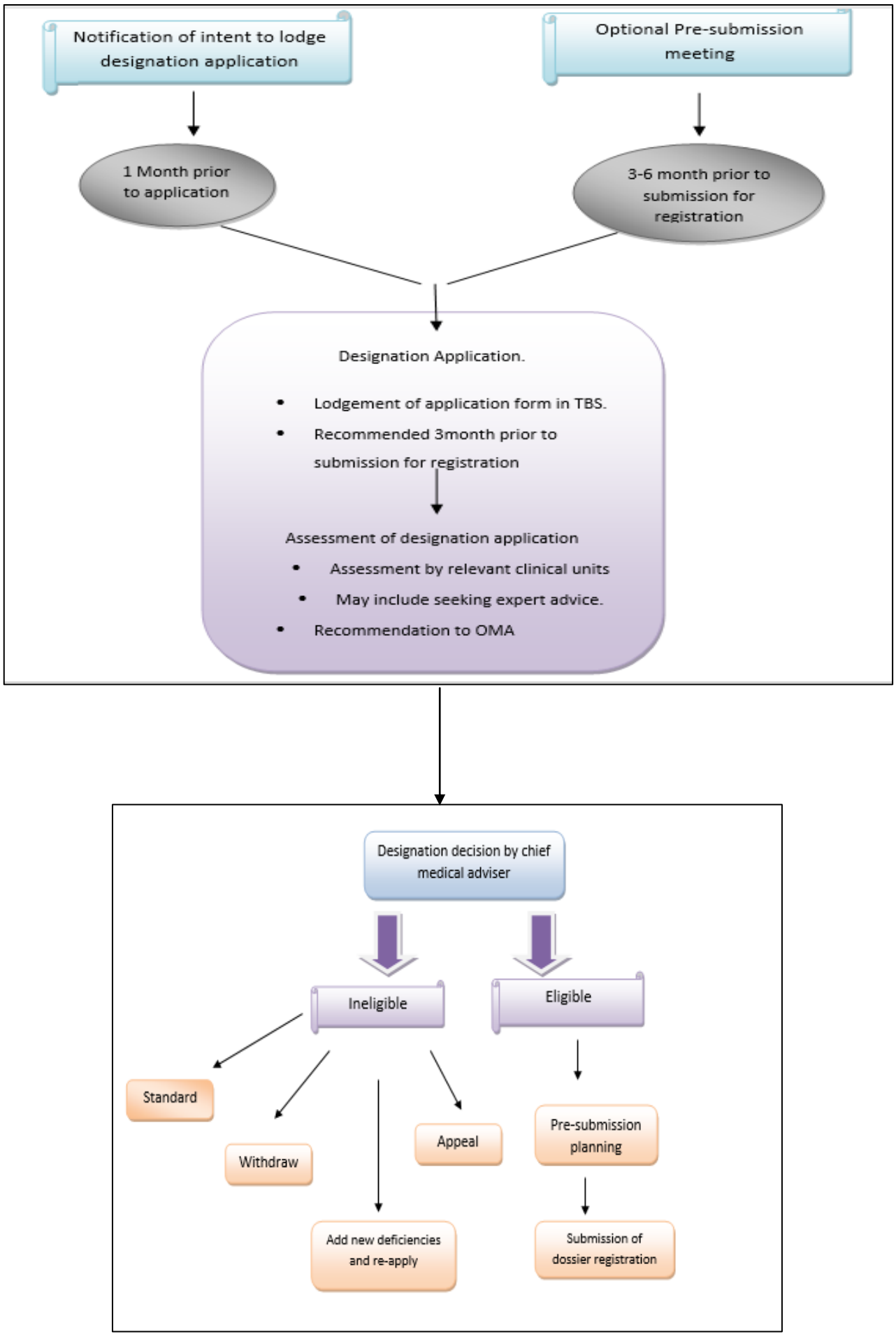
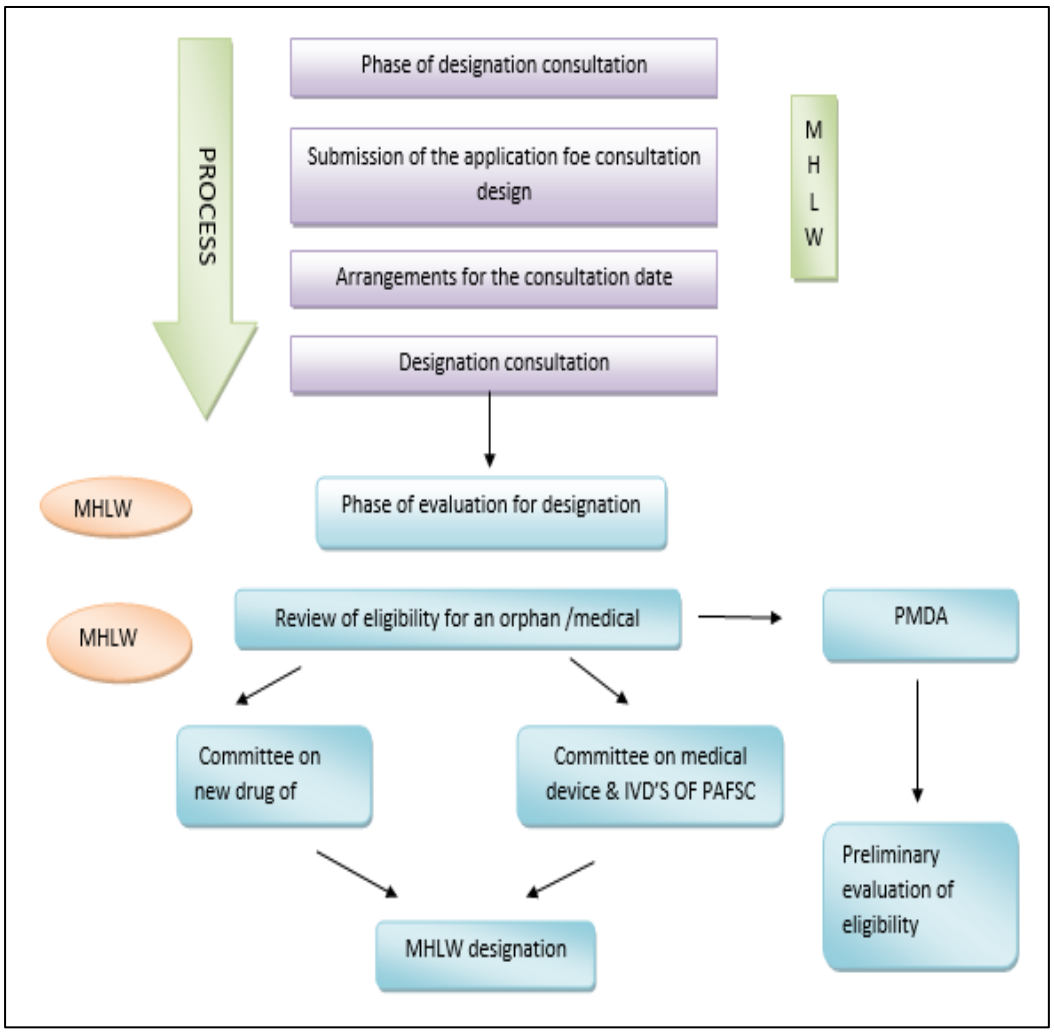


Fig.6: Application filling and evaluation of ODD in Japan.[13]



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