Policy Towards

Finding Cure and Management of Rare Diseases

Recommendations of a Workshop

February 23rd, 2017

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Preamble

Rare diseases when taken together affect as much as 72 million of our population (http://www.censusindia.gov.in/2011-prov-results/data_files/india/Final_PPT_2011_progresstables.pdf). They deserve attention due to the high level of morbidity and mortality faced by a large number of patients. Though worldwide effort to find cure for these diseases through research and policy initiatives is very encouraging, the efforts in this direction in India have begun only recently.

In India roughly 450 of the 7000 rare diseases have been seen and recorded. It is being increasingly recognised that rare diseases are not that rare and there are many more rare diseases in India than the number recorded so far. The capability of diagnosis and management of these diseases has been augmented in both public and private sector. ICMR and DHR played a key role in this area by supporting a number of groups through a special task force. Civil society has played a key role in all these developments by forming patient groups (specific for a disease, as well as rare diseases in general) that are working on a unified approach towards policy development on rare diseases. In order to assess the current status of rare disease diagnosis and research, a workshop "To develop a scientific agenda for research in rare diseases" was organized at the Indian National Science Academy, New Delhi on April 22-23, 2016 by Dr. V.M. Katoch, former DG Indian Council of Medical Research, Dr. P.P. Majumder, Director, National Biomedical Genomics Institute, Kalyani and Dr. Alok Bhattacharya, Professor, Jawaharlal Nehru University, New Delhi. The Workshop was attended by over 100 clinicians, researchers, Government officials, representatives of the pharmaceutical industry and NGOs, patients and students working in this area and from across the country. A number of action points were raised during this meeting and a summary of the recommendations is attached as **Annexure 1**. The current meeting has been organized following one of the recommendations of the workshop to hold a separate meeting on formulating a policy for research on rare diseases.

A national policy for rare diseases is required because rare diseases have different needs and priorities than common medical conditions. Rare diseases are given special policy preference in many jurisdictions through the enactment of laws like the Orphan Drug Act, 1983 in the US. The Orphan Drug Act is said to have facilitated pharmaceutical interest in rare diseases to a great extent. There is a need for a unifying policy that incorporates special provisions for supporting diagnosis and development/availability of therapeutics at a rapid scale using expertise from both public and private sector.

In order to evolve a policy framework a discussion meeting was organized on February 23, 2017 at Jawaharlal Nehru University, New Delhi. The discussion meeting was jointly organized by Dr. V.M. Katoch (former secretary DHR), Prof. Madhulika Kabra, AIIMS New Delhi and Prof. Alok Bhattacharya, JNU New Delhi. The meeting was attended by the stakeholders, that is, clinicians, researchers, Government agencies, social scientists, lawyers and patient groups. Dr. Soumya Swaminathan, DG ICMR and Secretary DHR initiated the discussion with her opening talk and this was supported by a brief talk by Dr. A.K. Pradhan, Deputy Drugs Controller of India. A list of all participants is appended at the end of the report.

Recommendations from the meeting

General Comments

ICMR, other agencies and many State Governments have set up sub committees/groups for looking at different aspects of Rare Diseases. It was felt that all these different organizations should work co-ordinately and the Secretary, DHR should take the initiative in chalking out a plan for tackling rare diseases.

Definition of a rare disease

It was agreed to define rare diseases in India at <1 per 4000 births. This number is based on several factors, including WHO recommendation, and the current estimates for some of the common rare diseases such as Down's syndrome, thalassemia, sickle cell anaemia etc. A formal definition of Rare disease will help to bring all rare diseases under a common umbrella, and will be necessary to generate resources for working towards therapies and common goals. Currently it is not clear how many of the estimated 7000 rare diseases affect Indian population. There is some record of about 452 diseases in India. It was felt that definition of rare disease should have flexibility, and as more data is available about disease prevalence the definition may undergo a change. An analysis of rules and policies followed by different countries is given in **Annexure 2**. For now, the most acceptable definition seems to be <1 in 4,000 individuals. Generally expert groups who have previously deliberated on definition of rare disease in India have extrapolated from the numbers in USA and suggested that a disease may be considered rare in India if the total number of affected individuals is less than 300,000. That would mean less than one in 4,000 individuals. Further, it was felt that frequency of some rare diseases in India may be higher than expected due to factors like consangenuity. Thus, some of the more frequently reported diseases like Down's syndrome, beta-thalassemia and hemophilia, may not be categorized under rare diseases in India. For these diseases there are already some schemes and programs in place for diagnosis and management.

Registries for rare diseases

Some initiatives have been taken to make registries of rare diseases. A comprehensive registry of rare diseases should be set up to provide informed estimates of different rare diseases in India. ICMR/DHR can look into the possibility of setting up a comprehensive pan India genome database with tools for analysis. A mechanism may be evolved to collect data from across the country involving medical colleges and hospitals, particularly medical genetics, Paediatrics and Neurology departments of medical colleges in all states of the country so that maximum population is covered. The 22 medical bioinformatics centres across the country could also be involved in data handling and analysis. Confirmed diagnosis of genetic disorders may be obtained in collaboration with accredited DNA sequencing labs. Database should be generated for pathogenic and normal variants and algorithms/computational tools should be developed for prediction of pathogenic variants. Scattered information through NGS data is available with various groups. If this is pooled it could give good information about common variants and founder mutations. In addition to creation of comprehensive registries, we need a large effort in epidemiology of rare and genetic disorders. For this effort we may need to initiate extensive training for generating human resources in the area of rare disease epidemiology. Depending on

incidence rate, different states of the country could be asked to do new born screening for selected diseases (for example, Gujarat is doing for sickle cell anemia).

Lists of rare diseases, shared by Indian Pharmaceutical Industries Association (**Annexure 3**), is enclosed. Currently, the list is not India-centric. Once registry is functional it may be possible to get India-centric data.

Research Initiatives

There was a strong support for creation of research resources that will help in development of new low-cost therapies, diagnostic methods and assistive devices. These resources are necessary not only for generating preclinical data for eventual clinical trials, but also necessary for screening for therapeutic molecules as well as basic research for understanding pathophysiology of a disease. It was also felt that all efforts should be made to get pharmaceutical companies to partner these development efforts by providing necessary incentives. Some of the recommendations are:
Creation of research consortium involving different aspects listed below. Since development of therapies against rare diseases will involve multidisciplinary approach requiring different expertise and resources, a consortium approach may be required.

a. Setting up biobanks: These depositories should store and distribute well characterized and documented tissues and cells (dermal fibroblasts) from as many rare disease patients as possible.
b. Setting up of animal model facility: Animal models are available only for a few rare diseases. Unfortunately, even these models are rarely available for Indian researchers. There should be dedicated centres that will develop and characterize these models (rodents, Zebra fish, Fly). Effort should be made to generate models that closely resemble the corresponding human disease. The centres can either distribute these models or closely work with researchers in utilizing these models.
c. Setting up of centres for research reagents and cell lines: Many platform technologies (gene therapy, stem cell, small molecule library, molecule delivery systems) can be the basis for development of therapies for large number of rare diseases. Focussed funding to groups with relevant expertise can help us to develop and make these technologies available within our country. To establish a network of all Institutes and research labs working on rare diseases a Consortium of Rare Diseases should be set up.
d. Encouragement through funding mechanism for basic studies to understand the pathophysiology of different rare diseases. There is a gap in knowledge in this area, particularly in our understanding regarding relationship between different mutations and disease phenotype. This is essential for diagnosis and development of therapy.
e. Development of cost-effective therapies. Repurposed drugs could also be studied for possible treatment options.

During the discussion it became apparent that a number of ICMR Institutions already have expertise and resources to provide support towards rare disease research and training. For example, National Institute of Epidemiology at Chennai, National Animal Resource Facility for Biomedical Research etc. can participate in rare disease activities.

Policy

General

1. Currently there are very few centres in the country that cater to diagnosis and subsequent care for patients with rare diseases. Most of these centres tend to specialise in particular type of diseases (for example, hemoglobinopathies). Therefore, it is very important that a number of Centres of excellences in the diagnosis and treatment be set up around the country to cover more rare diseases. These COEs could specialise along the following lines.

Neuro-muscular diseases

Metabolic diseases

Hemoglobinopathies and immunological

Neurodevelopmental Disorders etc.

   There could be multiple such centres spread across the country involving clinical, academic and commercial groups. Given that private agencies are taking the lead today in NGS and newborn screening – the COE concept should also be extended to private agencies. This may help to provide wider coverage and higher quality diagnosis.

2. There is an urgent need of suitable training of medical and paramedical persons in different aspects of rare diseases, from diagnosis to management. Training modules may be developed in collaboration with MCI and implemented in our educational and training Institutes. A joint task force of Health Ministry/DHR along with MCI may be set up for this purpose.

Specific issues

A number of policy issues were discussed with respect to two different categories of rare diseases.

Diseases for which no therapy is currently available: It was felt that the major emphasis should be in developing therapies and making these available as rapidly as possible. Alternate medical systems should also be explored and scientifically proven good practices should be made available. A task force of the concerned ministry should be formed to expedite this. If any of the medical systems can stop or reduce progression of these diseases it will be a great boon to the patients.

Diseases for which therapies are available: The major effort should be to identify these patients and provide therapy. A number of initiatives can be taken in this regard.

a. Screening of new born using inexpensive tools for those diseases for which therapy is available. This screening should be part of child care schemes similar to our vaccination strategies.

b. If the treatments are below a certain cost and the income of the parents is below a certain limit, the whole expenses for the treatment should be borne by the Government. For other cases (as in case of ERT) a proper transparent policy for Government support should be drawn (similar to Malaysian Government).
c. Government should provide financial and other incentives for pharmaceutical companies/interested groups to produce these drugs in India. Till the time it happens the Government should waive import duty and service tax on these drugs.
d. Government can also negotiate with the companies manufacturing drugs for rare diseases to reduce the cost .

Policy regarding approval of new drugs

It was strongly felt that India needs an orphan drug act that should spell out policies regarding approval of all therapies that can benefit rare disease patients. The act should also include incentives for companies and other public and private Institutions for investment into projects for development of therapies against rare diseases. The act should empower DCGI to set up a fast track dedicated system for approval, and lay robust policy guidelines that will allow easy filing for approval even by smaller organizations with less financial resources. Many countries have come up with legislative frameworks and we could consult these to formulate our policy.

For majority of rare diseases there are not enough patients to carry out a trial in almost any country. Moreover, due to lack of financial resources/rewards there are only a few trials being conducted and many registered trials do not even take off. If some of the trial sites are in India and if DCGI can accept data from such trials it will be highly useful to patients. Best practices followed/tried internationally should be considered, debated and adapted to frame our guidelines and regulations. A special section on rare diseases – definition and procedures must be incorporated in the new Drug and Cosmetics act.

Humanitarian issues

We need to understand the impact of different diseases on society and societal contribution to care and management of rare disease patients in order to formulate proper policy. Rare Disease Act must acknowledge this important aspect and set aside special funding for studies in this area. 'Genomics Information Nondiscrimination' being followed in some countries should be introduced in India so that insurance companies and employers would not discriminate on the basis of genetic data. There is need for a fundamental reform of IRDA act – which specifically lists genetic pre-existing conditions as exempt from coverage.

Funding initiatives

ICMR needs to form consortium with other agencies like DST, DBT to dedicate a percentage of their funds for rare diseases (for example, 3% of ICMR funds are earmarked for disability research).

NITI Aayog can be approached if we can come up with Grand Challenges for Rare Diseases. Indian diaspora all over the world should be roped in for expertise.

Role of Civil Society and Patient Groups

Many patients and families have set up special interest groups and organizations that work for the welfare of patients. These are great resources and their support can be crucial for proper implementation of the Act and to bring down drug pricing. Moreover, many patient groups already have database of specific diseases. Their participation can also help in preparation of rare disease registry. Patients groups must be made a stakeholder in the Act which will ensure their participation. These groups can also sensitize parliamentarians to push policy. Disability due to rare diseases and the disadvantages suffered by these patients should be recognized when formulating policies.

Advocacy : The patient organisations could play a very important role in this aspect and help in evolving a comprehensive Government policy. In this regard Civil Society and Patient Groups should set up a common platform to use media, access to law makers and any other approaches for fighting the cause of all rare diseases. Some of the specific issues that patient groups can positively help to formulate are:

a. Inclusion of various aspects of the policy from the patients perspective
b. Adoption by Central and State governments that include ensuring proper budgetary allocations

Awareness : The patient groups can use different approaches to enhance awareness about different rare diseases and the Government should use these organizations to spread basic knowledge and information about different schemes of the Government. A lot of awareness events are being organised by individual organisations to raise awareness around specific rare diseases but a concerted effort has been lacking. A multicentric event with participation of all stakeholders may be a good idea.

LIST OF PARTICIPANTS

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ANNEXURE 1

Recommendations of the Workshop

"To Develop a Scientific Agenda for Research on Rare Diseases"

Indian National Science Academy

April 22-23, 2016

Rare diseases are defined by the number of patients afflicted in a given country based on population. There are no clear universal criteria for defining a disease as rare. Different countries follow different cut off numbers. For example, USA uses less than 200, 000 patients while the EU follow 4/10,000 for identifying a rare disease. It is estimated that there may be roughly 7000 rare diseases occurring worldwide, though the basis of this estimate is unclear. In India only about 400 of the rare diseases have been documented. Given the problem about diagnosis of these diseases, the number of patients appear to be grossly under estimated. Children are the major sufferers of rare diseases as about 50% of the patients are below the age of 5years. Though these diseases may be rare individually, all together they are estimated affect 5-7% of the population.

More than 80% of the rare diseases have a genetic basis. It varies from monogenic with simple Mendelian inheritance to the involvement of multiple genes with complex inheritance. The problem is compounded by the fact that there is extensive diversity of mutations in the same gene even for the same disease. This causes major problems in diagnosis. Moreover, there is no therapy available for majority of these diseases leading to substantial morbidity and mortality. Somerare diseases may also be caused bypathogens. Though a substantial number of people may get infected with these organisms, only a handful display disease symptoms.

Most of the problems faced by patients suffering from rare diseases are due to the ignorance about these diseases, not only within the general public, but also within the clinical and research community. Lack of interest among companies in developing diagnostic methods and therapies due to low patient numbers is hampering emergence of newer methods and technologies for benefit of the patients. Moreover, stringent and inflexible regulatory system do not allow rapid transfer of treatment from lab to the patients. Since most of these diseases are degenerative, the patients become worse every passing day that they do not get proper treatment. The rarer the disease, the more serious are these problems. Since the causal factors vary from one disease to another, a single solution may not apply for management of all of these diseases.

In order to develop a strategy to help patients with rare diseases, a Workshop was organized at the Indian National Science Academy, New Delhi on April 22-23, 2016. The meeting was organized by Dr. V.M. Katoch FNA, former DG Indian Council of Medical Research and Secretary, Health Research, Dr. P.P. Majumder FNA, Director National Biomedical Genomics Institute, Kalyani and Dr. Alok Bhattacharya FNA, Professor, Jawaharlal Nehru University, New Delhi. The Workshop was inaugurated by Prof. P.N. Tandon and was attended by over 100 clinicians, researchers, Government officials, representatives of the pharma industry and NGOs, patients and students working in this area, from across the country. List of participants is appended (Annexure 1). Deliberations during the workshop resulted in the following set of recommendations.

a. There should be an effort to estimate the number of patients suffering from variousrare diseases. These estimates will be helpful in defining a rare disease in India and also to recognize the total burden of these diseases. This should be aided by producing information/booklet for identification and diagnosis of such diseases. Since rare diseases constitute a large number of diverse group of diseases, disease specific patient groups and clinicians should come together to produce this document. Moreover, social media and new communication devices can be used in conjunction with crowd sourcing for finding patients. Establishing a registry/ registries of important rare diseases is recommended as a long term measure.

b. One of the major problems in rare diseases is lack of awareness not only among common people, but also clinicians and researchers. A concerted effort should be made to increase awareness. Examples of modalities of increasing awareness include:
    1. Development of training/information modules for the public, teaching institutions, doctors/specialists, other practitioners, health care providers, policy/ law makers etc.
    2. TV, radio and newspaper articles that depict and explain rare diseases.
    3. School and college students across the country should be made aware through mechanisms formulated by CBSE and NSS.
    4. Introducing suitable content for MBBS/MD/ other specializations through Medical Council of India (MCI)
    5. Attending different medical conferences and making appropriate presentations.
    6. Publishing editorial and review articles in Indian Medical Journals.
    7. Organising CMEs for clinicians and regular workshops for researchers on a regular basis

c. Majority of rare diseases are due to genetic alterations. For a rare disease for which the genetic alteration is unknown, a confirmed diagnosis can be made by analyzing the DNA sequence of a patient in relation to those of other patients and normal individuals. As genotype-phenotype correlation may be influenced by epigenetics and other factors, generation and analysis of India specific data was emphasized for this purpose. For a rare disease for which the genetic defect is known, diagnosis can be made by targeting and assessing specific DNA changes or DNA changes in small regions of the human genome. Implementation of these methods requires access to technologies that are available with a small number of organizations, many of which are not mandated to provide clinical service. Further, even though costs of DNA analysis are gradually decreasing, the costs are still beyond the reach of most patients. It was recommended that the Government should set up a network of DNA/ Genetic diagnostic centres across the country and subsidize costs of DNA analysis for patients. Sample collection centers can be placed in each districts and these can be send to the nearest sequencing center for analysis. This is now possible as sample collection has become much easier.

d. Recommendations regarding management of rare diseases.
    1. It is proposed that Centres of Excellence (COEs) for research and patient-servicemay be set up on different groups of rare diseases in different Institutions. These COEs will work as referral and research centers and will be involved in developing therapeutics and diagnostics. Moreover, these COEs will have interdisciplinary, multiple specialty

expertise to tackle different aspects of patient care which should include disease management, physiotherapy and counselling. Examples of possible areas of specialization for COEs are neuromuscular diseases, lysosomal storage diseases, hemoglobinopathies, immunological deficiencies, dementia etc.

2. Alternate forms of therapy, such as Ayurveda/ other alternate systems should be explored to investigate their potential role in preventing progression and enhancing quality of life of patients. Specific yogic practices should be developed for the physical and mental wellbeing for different types of patients.
3. In order to enhance quality of life of patients with rare diseases we need to provide better assistive devices and there is a need to set up a few COEs on different types of assistive devices, such as those that help patients with degenerative physical disability, people with hearing disorders, visual defect etc. Different COEs can specialize in a specific area. The COEs will include an interdisciplinary team consisting of experts from engineering, medicine, physical rehabilitation, material science and work in close collaboration with patient group to develop useful devices.

e. Development of therapies for rare diseases

There should be a concerted effort to develop therapies for these diseases and make these accessible and available to all patients. Different agencies should come together and work jointly in mission mode to develop molecules, biologicals and platform technologies. Some of the areas that need special attention are listed here, there could be other approaches as well. Since many of these approaches have wider applications in other diseases including cancer, the effort to develop may be commercially attractive.

1. Development of model systems: Animal and other models will be needed for development of therapeutics. It is recommended that Government should set up a few centers that will have a bank of different models of rare diseases. Some of the organisms that can be used are the fruit fly Drosophila, Zebra fish and rodents. These models should be characterized and made available to researchers and drug development organizations.
2. Stem cells: bank of embryonic stem cell lines; bank of iPSCs from normal individuals; development of technology for corrected iPSCs from patients; high efficiency transformation of stem cells into cells of interest; Gene therapy: A bank of different gene therapy vectors; development of gene therapy vectors with long term survival in target tissue, high expression and minimum side effect that includes off target effects and immune response.
3. Gene editing and mRNA therapy: Both in vivo and in vitro gene editing technologies with off target and minimum side effects; production of large amounts of non-degradable mRNAs.
4. Protein or enzyme therapy: Production methods to reduce cost of production; stabilization with respect to storage and stability inside the body.

5. Specific delivery to target tissues and cells: stem cells, gene delivery vectors, proteins and mRNAs.
6. Small molecules: Molecules that activate various chaperones and help in correctly folding mutated proteins; allow skipping of stop codons; enhance activities of proteins by allosteric regulation. Besides these small molecules can be designed for preventing pathology in specific diseases.

f. Rare Disease Policy

The major recommendation is to formulate and implement a comprehensive rare disease policy that will take care of different issues related to rare disease and welfare of patients with these diseases. About 27 countries have specific policies in place and it is time that India should also develop its own policy.
Specific recommendations are:

1. Creation of a dedicated administrative and financial organizational structure (e.g. Rare Disease Authority) that will oversee all aspects of rare diseases.
2. Evolving an India centric definition of rare diseases by taking into account opinion of all stake holders.
3. Enactment and implementation of Orphan and Rare Disease Drug Act/amendment of Drug and Cosmetics Act to include special provisions to help faster development of diagnostic methods and therapeutics both by public and private sector. The new law should modify drug approval mechanisms for rare diseases and allow applications for new drug (s) /diagnostic method(s)to be reviewed in a fast forward manner. It should also allow automatic approval of drugs for rare diseases that have received approval in well-regulated countries.
4. Since number of patients of a particular rare disease are few, special financial incentives should be provided to drug developers for their participation in drug development in line with rare disease policies in other countries. Financial and other incentives to pharma companies are required to make drug development viable.
5. Rare disease policy should ease clinical trial rules, recommend removal of restrictionsfor joining global clinical trials and allow use of multicentric global data for approval of any therapy.
6. Drugs/devices for rare diseases should be exempt from taxes/duties and allowed to be imported freely. Present policy should be made more patient friendly and need for repeated permission for import of drugs and devices should be relaxed.
7. A comprehensive state insurance policy should be formulated for patients with rare diseases. This insurance scheme should be able to support assistive devices and care takers in addition to medical help.
8. The policy should also include support for building assisted living facilities for people with rare diseases.
9. Government should earmark funding for development of new diagnostics/therapeutics through different agencies, such as DST, DBT, ICMR/DHR,

CSIR/DSIR and other science agencies. Researchers and clinicians should be encouraged to work collaboratively on rare diseases.

10. Patient advocacy groups should be part of development and implementation of the policy and their suggestions should be sought at every stage.
11. A policy should create and strengthen networks involved in treatment and research of rare diseases with participation of various stakeholders. Research/ academic institutions including science academies should play a leading role in rare disease research.

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ANNEXURE 2

Rare disease policies: A snapshot of policies and plans across countries

Out of 350 million people suffering from rare diseases worldwide, approximately 70 millionare in India. Organisation for Rare Disease (ORDI) study estimates that 1 in every 20 Indian is suffering from a rare disease. In this case it is very pertinent that rare diseases should feature in the health priority of the government. Such a Largenumber of rare diseased population in Indiaposes a challenge for the policy makers.

Rare diseases require active public support. The very name sugests that there is only inadequate market incentives for private sector to invest for the cure and management of these diseases. The absence of any significant scale economics in production and distribution of health care of rare diseases, again arising out of small market size, makes it susceptible to high production costs, translating into higher prices of drugs and health care. Public support, over and above what is obvious for health care in general, is, therefore, needed to ensure that people who need health care for rare disease demand for it.

The current document is a snaposhot of the policies being formulated/followed in various countries on this issue. This document has been prepared by analysing the country plans published in the various journals, country documents, online resource centres, and official reports given by the expert committees (see table). The boxes left blank indicate lack of sufficient data for the respective field.

We observed that definition of rare diseaseis an empirical/policy question. Countries such as USA, Japan, and EU have defined rare diseaseskeeping in mind the patterns of disease prevalence and population size. Countries in the EU follow the definition given by the EU based on share of disease (prevalance of 1 in 2000 people),while the USA uses the gross number of people affected by a disease to define a rare disease. In their policy, …“any disease or condition that affects less than 200000 persons” is a rare disease. We have tabulaed the country wise varioation in definiiton in the attached table.

From the tableone could also observe that the countries are at different phase of policymaking for rare diseases. While some countries are at the stage of guideline formulation, few others have passed the stage of formulation, and are currently at the stage of implementation. As the table shows,the policy framework, broadly, covers the dimensiosn of creation of registries, research promotion, awareness generation, neonatal screening, genetic testing, put in place legislations and policies for orphan drug research, distribution and reimbursement. Some countries include drug repurposing, compassionate use policies as well. Almost all countries in the list, except Denmark, have a system of public registry for documenting the cases of rare disease. Denmark and Italy also do not have any orphan drug legislation or incentives but they do have a policy of

reimbursement for orphan drugs[1]. The modes of implementation also vary. Some are implementing the national plan through various legislative supports in the form of legislation for the orphan drug, reimbursement etc. While the US framed its Orphan Drug Act in 1983, the EU Act came only on the year 2000.

Orphan drug policies have included incentives for the pharmaceutical companies to promote drug discovery and research for rare disease. Incentive are both financial as well as non financial in nature. These include 'pull' incentives such as guaranteed market exclusivity (up to 7 years in the US and up to 10 years in the EU) and 'push' incentives such as tax credits for clinical research in the US, or reduction of licensing fees, scientific advice and protocol assistance in both the US and EU.

The policy framework for orphan drugs often adopts "Compassionate use polices".[2] This **is a treatment option that allows the use of medicines, which are yet to be cleared by the country's drug regulatory authority. The European Medicine Agency (EMA) states that "under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter** clinical trials"**.** By virtue of their development for the treatment of very rare and seriously debilitating diseases, Orphan Medical Products may qualify under the compassionate use policy, and can be used as treatment options that allow the use of unauthorised medicines in patients (Rapulu, 2015). More than 50 notifications of compassionate use programmes have been submitted to the EMA by Member States since 2006 out of which about 40% relate to orphan drugs (Hyry et al. 2015).It can be observed that though EU has a policy for compassionate use, it is not binding on the member countries. This nonbinding nature has provided member countries flexibility to use their discretion in the provision for the compassionate use for orphan drugs.

[1]The mechanism of reimbursement seems to vary across countries. While some countries reimburse through insurance companies, others transfer it directly to treating organisations.
[2]Also known as Expanded Access Programme, Early Access Scheme etc.

Table 1 Rare disease policies across countries

country	Policy stage	Rare disease definition	Registries	Neonatal screening	Genetic Testing	Orphan Drug legislation	Orphan Drug Reimbursement	Orphan drug incentives	Orphan drug in the market	Compassionate use	References
Canada	Formulation			yes		No					17,18
USA	Fully implemented	yes	yes	yes		yes	Yes	yes	yes	yes	1,2,3,15,16
Russia	Implementation stage	a disease where not more than 10 cases per 100,000 people is considered rare	Yes at the development stage			yes	Yes	yes	available		5,6
UK		no official definition	yes	yes	yes	Only at European level		No specific incentives	No specific information	yes	7,
France			yes	yes	yes	yes	Yes	yes	available	yes	8
Germany	2009	yes	Incipient stage	yes	yes	yes	Yes	yes	available	yes	9
Italy	1998 at the implementation stage	yes	yes	yes	yes	No	Yes	Yes	available	yes	10
Netherland	At implementation stage	yes	yes	yes	yes					yes	11
Denmark	Discussion stage	yes	No public registeries	yes	yes	NO	No	yes	yes	yes	
China	Developing guidelines	No	No	No		NO	NO	NO			12,13,14,
Japan		yes	yes			yes		yes	yes	yes	15
Taiwan	Implementation stage	yes	yes	yes	yes	yes	Yes	yes	yes		19,20
South Korea		yes				yes	Yes	yes	yes		19
Switzerland		yes	yes	yes	yes		Yes but no market exclusivity.	yes			26
Singapore	Formulation stage	Yes	YES	Yes			Yes	yes	yes		21
Norway		yes	yes	yes	yes	yes	Yes	yes	yes		22
Spain		yes	yes	yes							27,28
Estonia		yes	yes	yes			yes	yes	yes		29,30
Australia		< 2000 affected individuals									15
Malaysia	In the process of formulation	No				No	No	No	No		21,23

Source: own compilation

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