Orphan drug: Development trends and strategies

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Flow of Presentation

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- A comparison of essential medicines and orphan drugs.
- Orphan drug status: eligibility.
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- Indian Perspective.
- Market analysis of orphan drug: current and future.
- Incentives and Challenges faced by orphan drugs.
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Introduction to orphan drugs

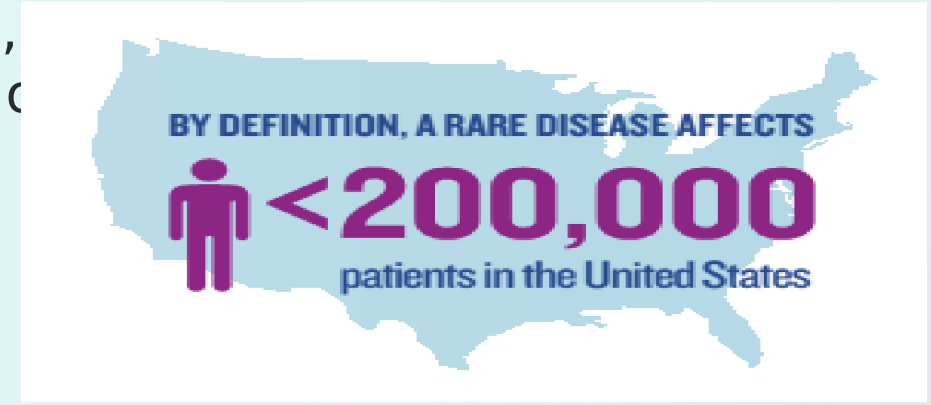
- A medicinal product designated as an orphan drug is one that has been developed specifically to treat a rare medical condition, the condition itself being referred to as “orphan disease.”
- Orphan Drug Definition in ODA: An orphan drug is defined in the 1984 amendments of the U.S. Orphan Drug Act (ODA) as a drug intended to treat a condition affecting fewer than 200,000 persons in the United States, or which will not be profitable within 7 years following approval by the FDA.
- Not developed by the pharmaceutical industry for economic reasons but which respond to public health need.
- Developing a orphan drug is extremely challenging for any pharmaceutical company because of :
    1. High cost intensive R&D initiatives
    2. Availability of a low return on investments

Introduction to orphan diseases

- Diseases that manifest in patient populations representing at the maximum 6–8% of the world population are defined as “orphan diseases”.
- E.g. glioblastoma multiforme, nocardiosis, Tourette syndrome, myeloid leukemia etc.
- Over 350 Million people world-wide are affected.
- There are between 5000-7000 orphan diseases.
- 1 in 20 Indians are affected.
- About 80% of RDs are genetic in origin.
- 50% of RDs are having onset at birth and remaining half are late onset.
- The prevalence distribution of rare diseases is skewed.
- 95 percent of rare diseases lack a single FDA approved treatment.

What is ‘Rare’:

- USA: <200,000 patients (<7.5 in 10,000, based on US population of 314m)
- EU: <5 in 10,000 (<250,000 patients, based on EU population of 506m)
- Japan: <50, on Japan population



A comparison of essential medicines and orphan drugs

Aspect	Essential medicines	Orphan drugs
Concrete policies in place since	1977 worldwide	1983 in USA, 2000 in EU
Primary focus	Public health: bringing effective medicines to as many patients as possible	Individual patient: even a single patient warrants all possible treatment
Initiated and developed by	WHO, and Member States	Governments of USA, Australia, EU, Japan; patient groups
Criteria	Drug driven (i.e., drug to be listed on EML is efficacious, safe, cost effective, based on evidence based data, etc.)	Disease driven (i.e., disease to be classified as an orphan drug has low prevalence <5–7.5: 10,000, is life-threatening, etc.)
Policies aim to	Provide established medicines to patients	Provide new medicines to as yet untreatable patients
Target populations	Initially low-income countries, now all countries	High-income countries, developed countries

‘Orphan Drug’ Status: Eligibility

1. A previously unapproved drug: For which no treatment is currently available.
2. A new orphan indication for an approved drug: e.g. Humira
3. The “same drug” as one already approved but with a potential to be “clinically superior”
4. Products withdrawn from the market for economic or therapeutic reasons.

    e.g., thalidomide in rare diseases such as leprosy and lupus erythematosus.

Orphan drugs according to indications and countries

Drug	Indications	Country
Acetylsalicylic acid	Polycythemia Vera	Europe
Tobramycin Inhalational Powder/ Solution	Cystic Fibrosis Pneumonia due to Pseudomonas Aeruginosa	US Europe
Desipramine Chlorhydrate	Rett Syndrome	Europe
Indomethacin	Patent Ductus Arteriosus	Japan
Histamine Dihydrochloride	Acute Myeloid Leukemia Acute Erythroid/Promyelocytic Leukemia	Europe USA

Requesting Orphan Designation

- The sponser must submit the request for orphan designation to OOPD before filing the NDA.
- If OOPD grants orphan designation, then the drug is said to have “orphan status”.
- Sponsors may use FDA Form3671 to apply for orphan designation in both Europe and the US at the same time.
- Orphan status does not mean that FDA has approved the drug.

Legislation related to orphan drugs:Orphan Drugs Act

- The Orphan Drug Act (ODA) was passed on January 28, 1983.
- USA was the first nation to propose a legal frame work to encourage development and availability of orphan drugs.
- Following the same policy as the US, Australia (1998), Japan (1993) and Europe (2000) passed laws with aim to promote research and development in the field of rare diseases .
- A group of pharmacologists requested the Indian government to institute ODA at the conference held by the Indian Drug Manufacturing Association in November 2001, but nothing concrete has materialized so far.

Comparison of the various policies on orphan drugs worldwide

Parameters	USA	Japan	Australia	EU
Legal framework	Orphan Drug Act (1983)	Orphan Drug Regulation (1993)	Orphan Drug Policy (1998)	Regulation (CE) N°141/2000 (2000)
Administrative authorities involved	FDA /OOPD	MHLW(Orphan Drug Division)	TGA	EMEA/COMP
Prevalence of the disease (per 10,000 individuals), justifying the orphan status	7.5	4	1.1	5
Estimation of the population affected	20 millions	No information	No information	25–30 millions
Marketing exclusivity	7 years	10 years	5 years	10 years
Tax credit	Yes: 50% for clinical studies	Yes: 6% for any type of study +10% of the company’s corporate tax	No	Managed by the member states
Grants for research	Programs of NIH and others	Governmental funds	No	“FP6”, Horizon 2020 + national measures
Reconsideration of applications for orphan designation	No	Yes	Yes (every 12 months)	Yes (every 6 years)
Technical assistance for the application file	Yes	Yes	No	Yes

Orphan drug market exclusivity

Countries	Market exclusivity
USA	7 Years
Europe	10 Years
Japan	10 Years
Korea	6 Years
Singapore	10 Years
Taiwan	10 Years

Impact Of ODA

- Since the introduction of ODA, nearly 2900 drugs and biological products have been designated as orphan products.
- 300 orphan drugs and devices approved in the last 25 years.
- The FDA has approved over 231 of these for marketing, thereby facilitating treatment for an estimated 11 million patients in the USA.
- A decade after in 1993, Japan took similar initiative followed by Australia in 1998. Currently, Singapore, South Korea, Canada, and New Zealand are also having their country specific ODA.
- But India has still not inacted the Orphan Drug ACT.

Indian Perspective

- India does not have its own orphan drugs act so far.
- Rare disease population estimated to be around 72,611,605 (70 million, more than the US and EU rare disease populations combined).
- India represents a lucrative market to developers and pharma.
- Close to 400 US FDA approved orphan drugs and about 80 EMA approved orphan drugs are available in India.
- Most of them are either not accessible to most patients in India or are unaffordable.
- ORDI aims to work between the Government of India and the Pharma/Biotech/Diagnostic industry to enact an orphan drugs act in india.

Contd…

- Three biggest hurdles to improving patient access to orphan drugs in India

    1. Awareness
    2. Affordability and Accessibility
    3. Enactment of the Orphan Drug Act

ORPHAN DRUGS IN INDIA

- The Hyderabad based **NATCO Pharma's** novel anti-cancer drug,
- NRC-AN-019 has received " Orphan Drug Designation" from the
- US-FDA for 3 indications-
- Glioma
- Pancreatic Cancer
- Chronic Myeloid Leukemia

contd…

ORPHAN DRUGS IN INDIA- Contd..

- **Troikaa Pharmaceuticals**, Ahmedabad manufactures following orphan preparations:

1. Tachyban (Adenosine injection)
2. Hemaprot (Aprotinin injection)
3. Neopam (Pralidoxime injection)
4. Narcotam (Naloxone hydrochloride injection)
5. Cyan SOS (Cyanide antidote kit)

Tachyban

HAEMAPROT

Neopam

NARCOTAN

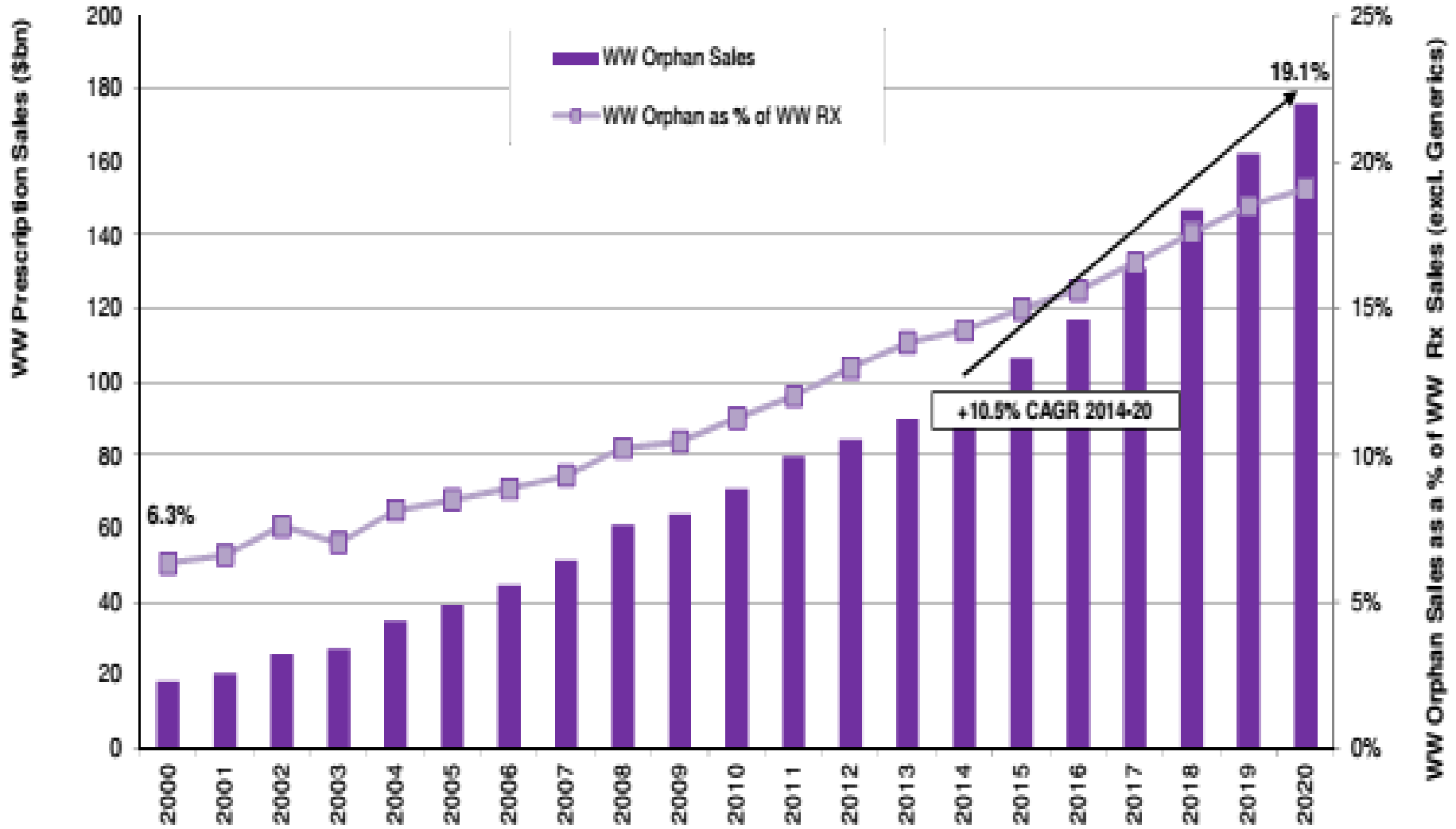
CYAN SOS

Market analysis of orphan drug: current and future

- EvaluatePharma's *2014 Orphan Drug Report* reveals that orphan drugs are now showing a greater return on investment than products aimed at larger patient pools.
- Worldwide orphan drug market set to reach $176 billion by 2020, accounting for nearly 19% of total prescription drug sales.
- Soliris (eculizumab) highest revenue per patient orphan drug in the USA.
- Median cost per patient differential 19 times higher for orphan drugs compared to non-orphan.
- Expected return on investment of phase III/ filed orphan drugs 1.89 times greater than
  non-orphan drugs.
- Imbruvica most promising new orphan drug approved by FDA in 2013.
- Non-Hodgkin Lymphoma (NHL) is indication with most filed orphan drug
- designations in EU

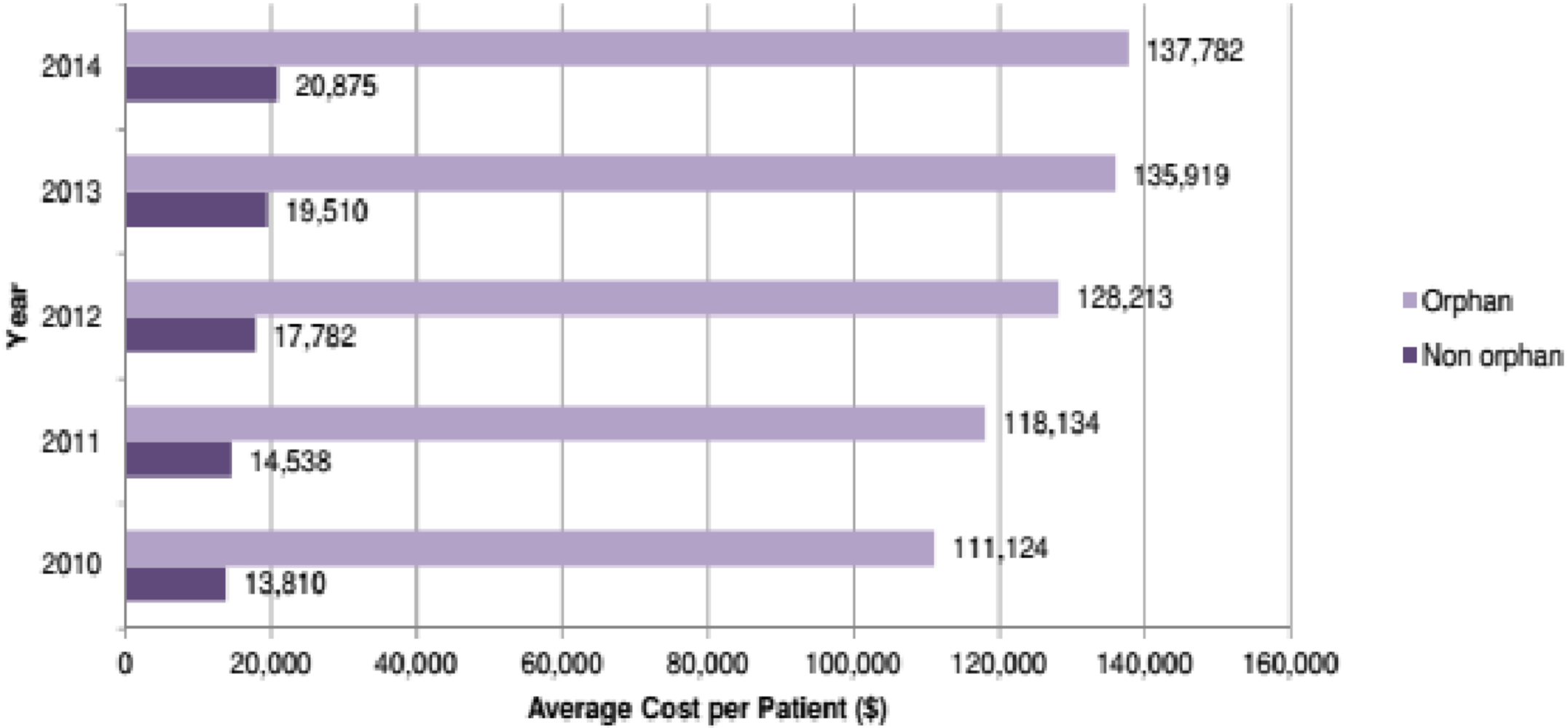
Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2000-20)

Source: EvaluatePharma® (27 OCT 2014)



Average Cost per Patient per Year 2010-14

Source: EvaluatePharma® (27 OCT 2014)



Companies involved in the manufacture of orphan drugs

Big pharma and established biotech
Pfizer
GlaxoSmithKline
Novartis
Sanofi-Aventis
Roche
Johnson and Johnson
Merck and Co
Eli Lilly
Bayer
Orphan drug specialists
Genzyme
Actelion

Orphan drugs and market players

Drug	Company	Therapeutic indication
Zavesca (miglustat)	Actelion Pharmaceuticals US, Inc	Type 1 Gaucher disease
Ventavis (iloprost)	Actelion Pharmaceuticals US, Inc	Pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III or IV symptoms.
Trisenox (arsenic trioxide injection)	Cephalon, Inc.	Acute promyelocytic leukemia (APL)
Tracleer (bosentan)	Actelion Pharmaceuticals US, Inc	Pulmonary arterial hypertension (WHO Group I) in patients with WHO Class II–IV symptoms
Somavert (pegvisomant for injection)	Pfizer Limited	Acromegaly
Replagal (agalsidase alfa)	Transkaryotic Therapies, Inc.	Fabry's disease (alpha-galactosidase A deficiency)
Onsenal	Pfizer	Familial adenomatous polyposis (FAP)
PhotoBarr (porfimer sodium)	Axcan Pharma International	High-grade dysplasia (HGD)
Litak (cladribine)	Lipomed	Hairy cell leukemia
Glivec (imatinib mesylate)	Novartis	Philadelphia chromosome positive chronic myeloid leukemia
Fabrazyme (agalsidase beta)	Genzyme Europe	Fabry disease

Top Revenue Generating Orphan Drugs

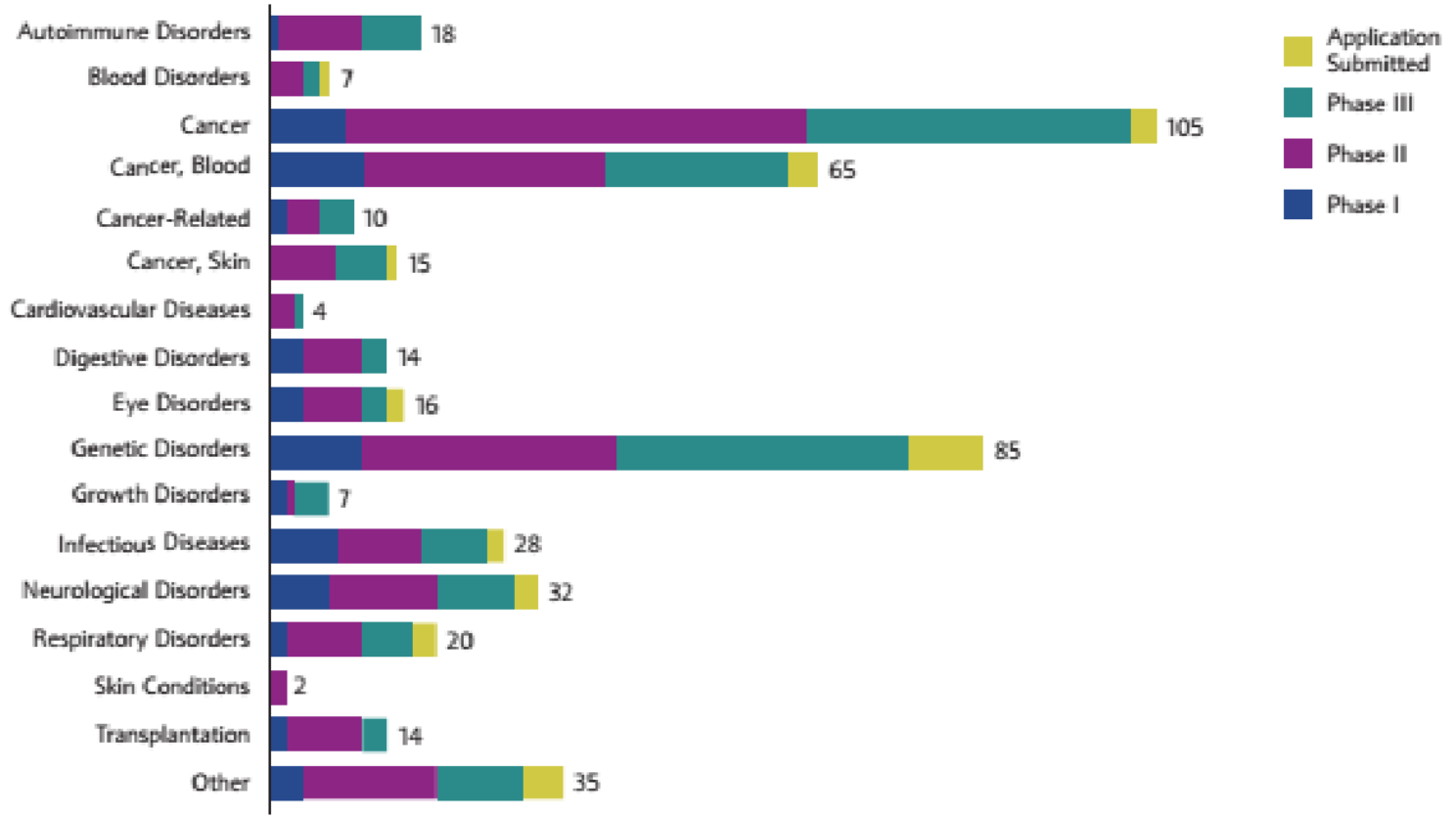
Generic name	Indication	Manufacturing Company	Peak sales value
Rituximab	Follicular lymphoma	Roche	$7 billion
Ranibizumab	Opthalmology	Celgene Corp.	$5 billion
Lenalidomide	Multiple myloma	Celgene Corp.	$5 billion
Imatinab mesylate	GI stromal Tumours	Novartis	$5 billion

The orphan drug pipeline

Brand name	Generic name
Oncology	
Istodax	Romidepsin
Yondelis	Trabectedin
Omapro	Omacetaxine
Clolar	Clofarabine
TM601	
EGEN – 001	
Central nervous system	
Zenas	Amifampridine
H P Acthar Gel	
Respiratory system	
Surfaxin	
Anti-infectives	
Cayston	Aztreonam lysine
Abthrax	Raxibacumab
Autoimmune and inflammation	
EN 101	

Medicines in Development By Disease and Phase

Some medicines are listed in more than one category.



Top 20 orphan drugs by 2018

1 Rituxan	11 Rebif
2 Revlimid	12 Kalydeco
3 Soliris	13 Jakavi
4 Afinitor	14 Sutent
5 Tasigna	15 Kyprolis
6 Velcade	16 Kogenate
7 Avonex	17 NovoSeven
8 Alimta	18 Nexavar
9 Yervoy	19 Copaxone
10 Sprycel	20 Ibrutinib

Incentives

- The incentives include:
- Funding towards investigation
- Tax credit for clinical research
- Waiver of fees for new drug application
- Market exclusivity of “Orphan drugs”
- Accelerated approval or fast track or priority review, may also be available for sponsors of orphan drugs.
- Enhanced patent protection.

Challenges faced by orphan drugs

- Difficulties in attracting public and private funding for research and development
- Insufficient numbers of research participants for clinical studies
- Lack of knowledge and training for many rare diseases
- Lack of adequate expertise and review by authorities
- Deficient diagnostic systems
- High price of "orphan drugs"
- Small patient population
- Limited public awareness

Conclusion

- Orphan drugs may help pharma companies to reduce the impact of revenue loss caused by patent expiries of blockbuster drugs.
- The new business model of orphan drugs offer an integrated healthcare solution that enables pharma companies to develop newer areas of-

  Therapeutics

  Diagnosis

  Treatment

  Monitoring and

  Patient Support

Contd....

- The Government of India should visualize this scenario sooner, and come out with an appropriate ODA combating the challenges, hence the domestic pharmaceutical industry of India will be able to emerge as a force to reckon with, in this important global space, much faster than what one would currently anticipate.
- Such legislation would bring relief to large groups of rare diseases sufferers, in India.


Thank You