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Research Article

Orphan Drugs " Empowering Hope : Bridging Gaps With Orphan Drugs ".

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ORPHAN DRUGS

- "THE ORPHAN DRUG DESIGNATION PROGRAM ASSIGNS ORPHAN DESIGNATION TO MEDICINES AND BIOLOGICS THAT ARE DESIGNED FOR THE SAFE AND EFFECTIVE TREATMENT, DIAGNOSIS, OR PREVENTION OF UNCOMMON DISEASES/DISORDERS.
- THE SO-CALLED "ORPHAN DRUGS" ARE MEANT TO CURE ILLNESSES THAT ARE SO UNCOMMON THAT THEIR SPONSORSARE HESITANT TO PURSUE THEM UNDER NORMAL COMMERCIALIZATION GUIDELINES.
- THE DEMAND FOR ECONOMIC FEASIBILITY PREVENTS EVEN PRIORITIES OF RESEARCH INTO THESE DISORDERS.
- THEY WERE DEVELOPED IN REACTION TO PUBLIC HEALTH NEEDS, NOT BY THE PHARMACEUTICAL INDUSTRY FOR ECONOMIC REASONS.
- DEVELOPING ORPHAN DRUGS IS A SIGNIFICANT CHALLENGE FOR PHARMACEUTICAL COMPANIES.

ORPHAN DISEASES

- ORPHAN DRUGS ARE NEGLECTED DISEASES INCLUDE RARE AND TROPICAL DISEASES.
- DISEASES AFFECTING A SMALL PERCENTAGE OF THE POPULATION ARE CONSIDERED AS ORPHAN DRUGS
- APPROXIMATELY 250 NEW RARE DISEASES ARE DISCOVERED EACH YEAR.
- MEDICAL LITERATURE DESCRIBES OVER 7000 REAR DISEASES, OF WHICH APPROXIMATELY 650 HAVE BEEN OFFICIALLY DESIGNATED AS RARE.
- SOME ORPHAN DISEASES: CYSTIC FIBROSIS, LOU GEHRIG'S DISEASE ,TOURETTE'S SYNDROME

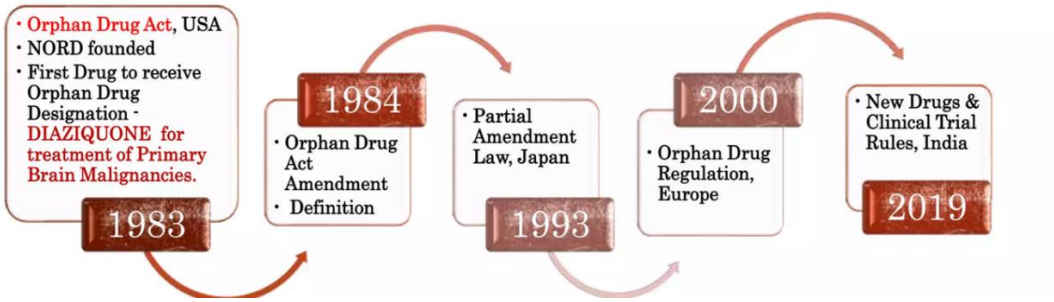
CHARECTERISTICS OF ORPHAN DRUGS

Clinical trial characteristics	Orphan drugs	Non-orphan drugs
Sample size	Small (n = 96)	Large (n = 290)
Randomization	Less likely (30%)	More common (80%)
Double blind	Less common (4%)	Common (33%)
Primary endpoint	Measure disease response	Measure disease progression
Comparator	None in 70% trials	Present in 80% trials
Serious adverse events	Higher (48%)	Lesser (36%)
Median duration clinical trial	Shorter (5 years)	Longer (6.9 years)
Post marketing efficacy assessment	Done in 60% cases	Done in 92% cases

ORPHAN DRUGS ACT

- THE ORPHAN DRUG ACT OF 1983 IS A LAW THAT WAS PASSED IN THE UNITED STATES TO FACILITATE THE DEVELOPMENT OF ORPHAN DRUGS, WHICH ARE DRUGS FOR RARE DISEASES THAT AFFECT SMALL NUMBERS OF RESIDENTS IN THE UNITED STATES, INCLUDING HUNTINGTON'S DISEASE, MYOCLONUS, ALS, TOURETTE SYNDROME, AND MUSCULAR DYSTROPHY.
- THE LONG TITLE WHICH DESCRIBES ORPHAN DRUGS ACT IS"An Act to amend the Federal Food, Drug, and Cosmetic Act to facilitate the development of drugs for rare diseases and conditions, and for other purposes".
- THE ORPHAN DRUGS ACT WAS ENACTED BY 97THCONGRESS OF UNITED STATES.
- THIS ORPHAN DRUG ACT CAME INTO ACTION ON "January 4 1983"
- • THE NATIONAL ORGANIZATION FOR RARE DISORDERS (NORD) AND OTHERS, AN INFORMAL COALITION OF SUPPORTERS AND FAMILIES OF PATIENTS WITH RARE DISEASES, CALLED FOR A CHANGE IN LAW TO SUPPORT THE DEVELOPMENT OF ORPHAN DRUGS, OR DRUGS FOR TREATING RARE DISEASES.

HISTORY OF ORPHAN DRUGS



1974-The "Interagency Committee on Drugs of Limited Commercial Value" was formed by the FDA.
1977-The Commission to Manage Huntington's Disease and Its Aftereffects.
Late 1970s-Legislation Reforming Drug Laws with Orphan Drug Provisions
1982, March- Orphan Products Board
1982, May-Development Office for Orphan Products in United States
1985-Japan initially recognized the problem.
1993-A Japanese regulation is implemented on orphan drugs
1995-Resolution on Orphan Drugs by the EU Council
1997- The Australian Orphan Drug Policy is launched.
1999-Published: EU Regulation on Orphan Medications
2000- REGULATION OF ORPHAN DRUGS IN EUROPE
2019- REGULATION OF NEW DRUGS AND CLINICAL TRIAL RULES IN INDIA

ROLE OF FDA IN ORPHAN DRUG DEVELOPMENT

- THE MISSION OF THE FDA'S OFFICE OF ORPHAN PRODUCTS DEVELOPMENT (OOPD) IS TO PROMOTE THE EVALUATION AND DEVELOPMENT OF PRODUCTS (DRUGS, BIOLOGICS, DEVICES, OR MEDICAL FOODS) THAT SHOW PROMISE FOR TREATMENT OR DIAGNOSIS OF RARE DISEASES OR CONDITIONS.
- COORDINATION OF FDA INITIATIVES PERTAINING TO RARE DISEASES IS DONE BY THE OFFICE OF ORPHAN PRODUCTS DEVELOPMENT. OVERSEES THE DESIGNATION PROGRAMS FOR HUMANITARIAN USE DEVICES, RARE PEDIATRIC DISEASES, AND ORPHAN DRUGS. FUNDS GRANTS AND COOPERATIVE AGREEMENTS FOR RARE ILLNESS RESEARCH. THE PRIMARY POINT OF CONTACT FOR INQUIRIES CONCERNING THE FDA'S WORK IN RARE DISEASES FROM PATIENTS, CAREGIVERS, AND ADVOCACY GROUPS.
- A DRUG OR BIOLOGICAL PRODUCT MAY BE GRANTED AN ORPHAN DRUG DESIGNATION BY THE FDA IN ORDER TO PREVENT, DIAGNOSE, OR TREAT A RARE DISEASE OR CONDITION. THE ORPHAN DRUG DESIGNATION ELIMINATES SPONSORS FROM TAX CREDITS FOR APPROVED CLINICAL TRIALS, AMONG OTHER INCENTIVES. EXEMPTION FROM USER FEES.
- • AFTER 90 DAYS, THE AGENCY WILL RESPOND TO 100% OF NEW ORPHAN DRUG DESIGNATION REQUESTS WITHIN 90 DAYS OF RECEIPT. MOVING FORWARD, FDA WILL COMPLY WITH THIS 90-DAY TIMELINE.
- THE FDA FOCUSESONTHE FOLLOWING AREASTOADDRESSPARTICULAR FACTORS WHILECREATINGANDAPPROVINGMEDICALTREATMENTSFORUNCOMMONDISEASES:

1. Provide FDA employees with specialized training on rare disease subjects.
2. Provide industry guidelines to promote the development of medicinal products for uncommon conditions.
3. Organize and take part in patient-focused gatherings and conversations around uncommon diseases.
4. To enhance the regulatory science for rare diseases, award contracts, cooperative agreements, and research funds and carry out specific data analysis and pilot programs.
5. Oversee the compassionate use or expanded access program for investigational medicinal goods in their particular location.
6. Engage in discussions about rare disease issues with the FDA's Rare Disease Council.
7. Participate in the FDA's yearly Rare Disease Day celebration.

ORPHAN DRUGS DEVELOPMENT

ORPHAN DRUGS DEVELOPMENT CAN BE DONE BY **START** CHECK LIST

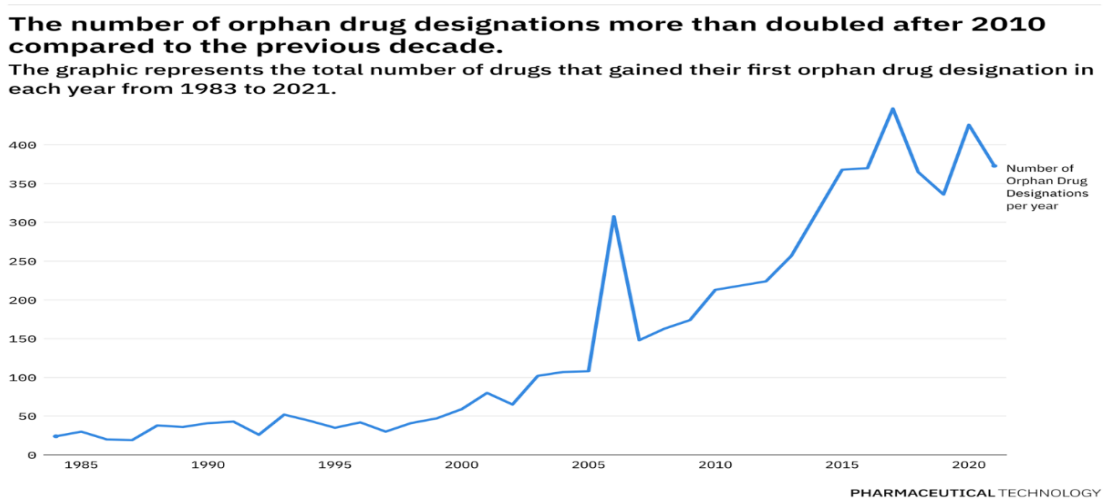
1. STACK HOLDER MAPPING

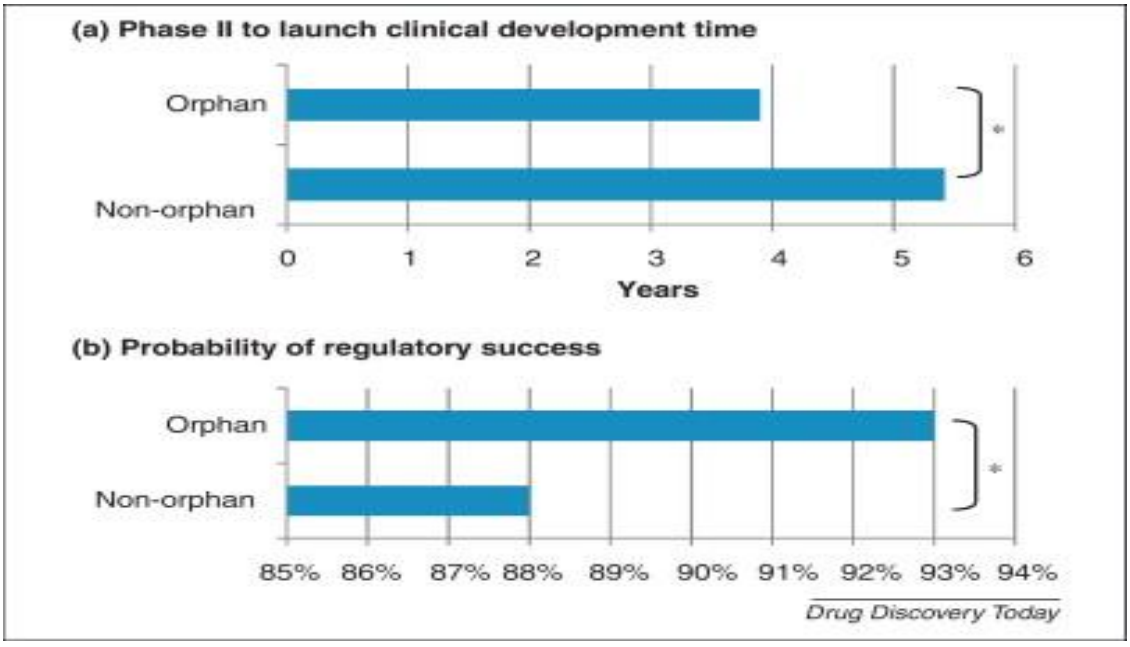
- EXIST ANY PATIENT ASSOCIATIONS?
- EXIST ANY COMMUNITY ADVISORY BOARDS? -CABS
- DO STAKEHOLDER NETWORKS EXIST?-ERNS AND/OR CRNS, - IRUD
- EXIST ANY INFRASTRUCTURES OR PLATFORMS FOR BROAD DEVELOPMENT SUPPORT? -C4C, EJP-RD
- ANALYSIS OF THE DEVELOPMENT LANDSCAPE AND HORIZON SCANNING

2. AVAILABLE DISEASE INFORMATION
- STUDIES OF NATIONAL HISTORY
- TOOLS FOR DIAGNOSIS
- PCOMS
- DETERMINED BIOMARKERS
- CODING OF UNCOMMON ILLNESSES

3. FUNDING RESOURCES
- PRIVATE FUNDING
- PUBLIC FUNDING

4. TARGET PATIENT VALUE PROFILE





INDIAN SCENERIO IN ORPHAN DRUGS DEVELOPMENT

AN EXTRAPOLATION FROM THE RARE ILLNESS ESTIMATE FOR THE WORLD INDICATES THAT AROUND 70 MILLION PEOPLE ARE IMPACTED BY UNCOMMON DISEASES.BECAUSE THERE ARE SO MANY RARE DISEASES, MANY OF WHICH GO UNDETECTED, AND THERE ARE NOT ENOUGH RESOURCES AVAILABLE FOR RESEARCH AND DEVELOPMENT, MANAGING RARE DISEASES IS THEREFORE EXPECTED TO BE EXTREMELY DIFFICULT. ON THE OTHER HAND, A NUMBER OF IMPORTANT INITIATIVES HAVE BEEN ANNOUNCED BY DIFFERENT GROUPS.

IN ORDER TO ESTABLISH THE FIRST-EVER "INDIAN RARE DISEASE REGISTRY," THE INDIAN COUNCIL OF MEDICAL RESEARCH (ICMR), IN COLLABORATION WITH AIIMS, JNU, AND PRESIDE, INITIATED THE NATIONAL INITIATIVE FOR RARE DISEASES IN 2017.
SUCH A REGISTRY AIMS TO IDENTIFY PATIENTS WITH RARE DISEASES IN ORDER TO FACILITATE RELEVANT UNDERSTANDING OF PATIENT AND DISEASE CHARACTERISTICS. THIS, IN TURN, OPENS THE DOOR TO THE USE OF SUCH DATA FOR RESEARCH AND POLICY FORMULATION.
THE NATIONAL POLICY FOR RARE ILLNESSES, 2021 HAS REAFFIRMED THAT IT WILL ALLOW ICMR TO ESTABLISH A HOSPITAL-BASED NATIONAL REGISTRY WITH THE PARTICIPATION OF CENTERS ENGAGED IN THE DIAGNOSIS AND TREATMENT OF RARE ILLNESSES, DESPITE THE FACT THAT IT HAS NOT YET MADE ANY SIGNIFICANT CONTRIBUTIONS.

SUCCESSFUL ORPHAN DRUGS

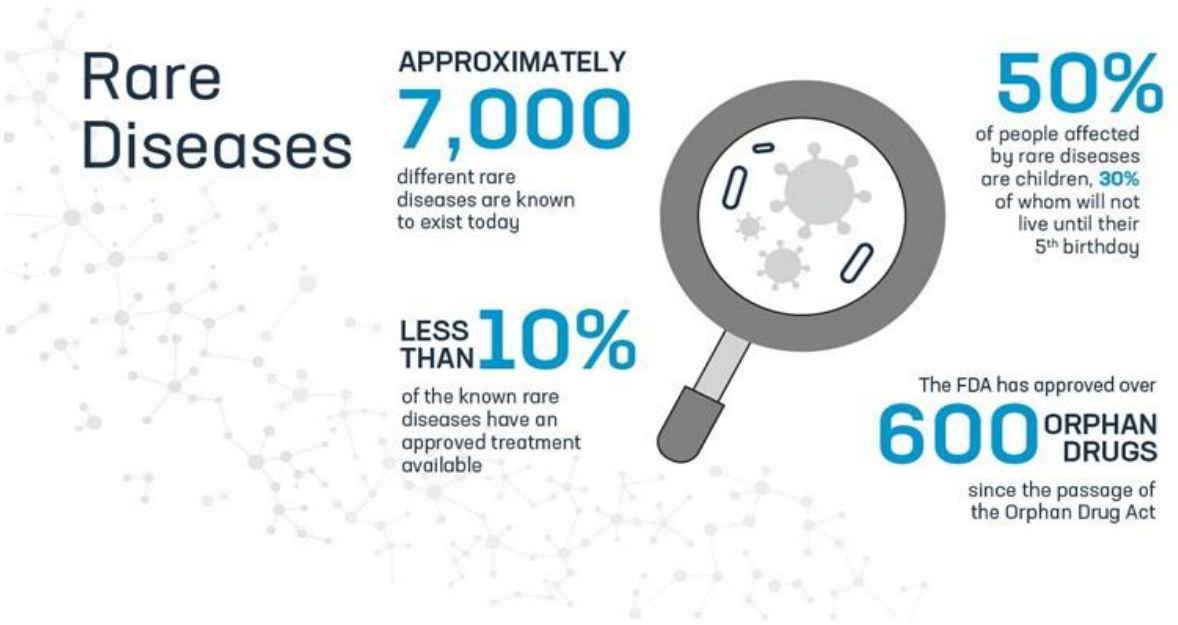
Drug	Company	FDA Approval	Indication	2021 Sales
Trikafta	Vertex Pharmaceutical	2019	Cystic Fibrosis	US$ 5.69 Billion
Imbruvica	AbbVie	2015	Mantle Cell Lymphoma; Chronic Lymphocytic Leukemia; Waldenström's Macroglobulinemia; Small Lymphocytic Lymphoma; Marginal Zone Lymphoma	US$ 5.4 Billion
Venclexta	Abbvie	2016	Chronic Lymphocytic Leukemia, Acute Myeloid Leukemia	US$ 934 Million

SUCCESSFUL CASE STUDY OF ORPHAN DRUGS

1.Thrombotic thrombocytopenic purpura (TTP) and thrombosis are the two thrombotic single-domain antibody (VHH) appearing in Capalcizumab (trade name Cablivi). A TTP has an annual incidence of 0.15-0.22 per 1,00,000. It is an ultra rare disease.

- A TTP states urgent medical emergency and is an ultra-rare life-threatening blood disorder. A TTP carries a life-time risk of regression and is an acute onset disease of an episodic nature. Patients who survive acute TTP episodes seldom fully recover due to long-term complications failure to achieve rapid control of acute ttp episodes can be fatal.
- Caplacizumab is suggestible for adults going through a TTP episode, when used along with plasma exchange and immunosuppression. Clinical trails show that, in comparison to standard case alone, caplacizumab with standard care reduced the time to platelet count normalization, the amount of time spent hospitalized, the risk of respiratory disease, the risk of acute mortality, and the requirements for plasma exchange.
- During august and November of 2019 and appropriated by "nice" (ta667)an application for Caplaczinumab to be considered via the HST route was denied because ATTP was not regarded as chronic and severely crippling; instead, caplaczinumab was evaluated via the STA route in accordance with standard wtp thresholds, despite the fact that "nice" acknowledged the rarity of ATTP and a significant unmet need.
- The appraisal process took 461 days, 156 days longer than Nice's expected duration of 305 days, from invitation to participate to final appraisal determination, recommendation.
- 2.Teduglutide for short bowel syndrome (SBS)
- Due to the removal of a significant portion of the stomach by surgery, SBS is a chronic and potentially life-threatening condition in which nutrients and fluids are not properly absorbed by the gut [28]. Long-term parental (intravenous) nutrition is necessary for individuals with intestinal failure caused by sickle cell disease (SBS), and it is linked to severe complications.
- Revestive®; shire/Takeda, teduglutide, has a license to treat SBSin adults and children above one year [28]. Teduglutide reduced parenteral support in adults and children, shown by clinical trial results [29, 30]. The estimated prevalence of SBSin adults and children in England is 7.2 and 0.5 per 100,000, respectively. SBSis an extremely rare disease.
- A full year expired between the HST draft scope and the STA final scope, after teduglutide was rejected from the HST Programme. The company was invited by nice to participate in may 2017. A full resubmission was initiated in April 2021, for which two committee meetings have already been required, following the termination of the appraisal process (ta690) [31, 32].

- when the two appraisals were combined, their combined duration exceeded 1700 days, which is more than five times longer than what nice had anticipated. Additionally, the current appraisal consultation document has an optimized recommendation that should only be used for pediatric patients (those under the age of 17).
- 3.Pirfenidone for idiopathic pulmonary fibrosis (IPF)
- IPF is a chronically progressive lung disease characterized by scarring, or fibrosis. Patients endure a reduction in their quality of life and a decline in lung function before passing away from the illness. IPF is a severe disease with a median survival from diagnosis of roughly three years, while the severity of the illness determines life expectancy [33].
- Pirfenidone (Esbriet®; Roche) was shown in clinical trials to reduce the decline in forced vital capacity, a measure of lung function, vs placebo [33]. It is indicated for adults for the treatment of mild to moderate IPF. It has a designated orphan status and its prevalence in England is 7.2 and 12.4 per 100,000, respectively for mild and moderate IPF [33].
- in April 2013, nice recommended pirfenidone for patients with moderate IPF, which is defined as a predicted forced vital capacity of 50–80%. A second appraisal, starting late in 2015 (ta504), centered on removing the stopping rule defined within the original recommendation and extending the recommendation to patients with mild disease. The final appeal was dismissed [34]; the second appraisal process involved three committee meetings and two appeals on the grounds that nice failed to consider the totality of the data. The appraisal process took 776 days, longer than double Nice's expected duration, from invitation to participate to publication of the final guidance.



TOP SELLING ORPHAN DRUGS

Drug	Indication
Rituximab	Oncology
Ranibizumab	Ophthalmology
Somatropin	EPR, Metabolism
Lenalidomide	Oncology
Imatinib Mesylate	Oncology
Filgrastim	Hematology
Glatiramer Acetate	MSP
Recombinant Factor VIII (Octocog alfa)	Hematology
Bosentan Monohydrate	Cardiovascular
Bortezomib	Oncology
List courtesy of Thomson Reuters	

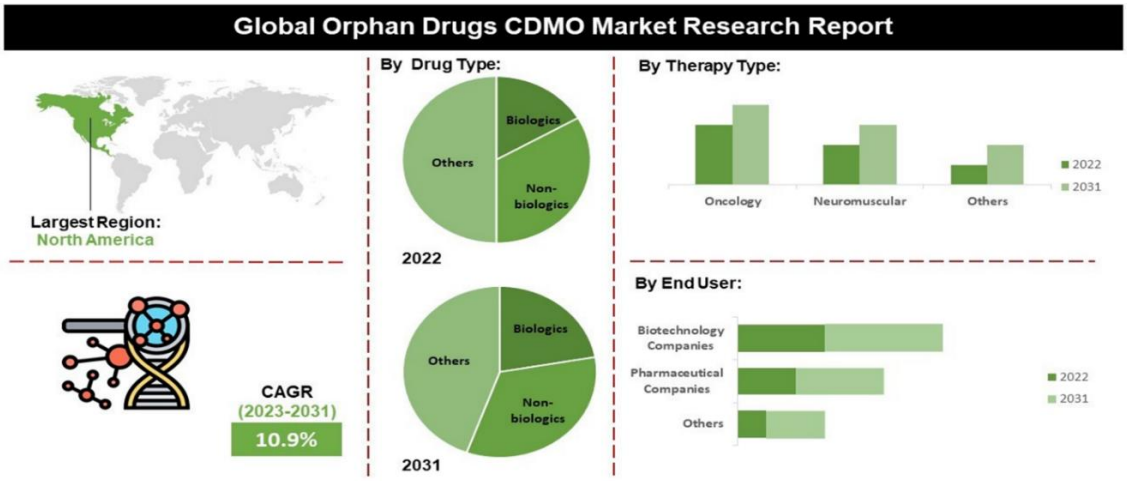
RITUXIMAB:- IT IS USED TO TREAT A KIND OF CANCER KNOWN AS NON-HODGKIN'S LYMPHOMA (NHL), EITHER BY ITSELF OR IN COMBINATION WITH OTHER MEDICATIONS.
RANIBIZUMAB:-MEDICATION USED FOR DIABETIC MACULAR EDEMA, MYOPIC CHOROIDAL NEOVASCULARIZATION, DIABETIC RETINOPATHY, AND NEOVASCULAR AGE RELATED MACULAR DEGENERATION ARE ALL TREATED WITHIN THIS MEDICATION.
SOMATROPIN:-IN ADULTS AND CHILDREN WITH GROWTH HORMONE DEFICIENCY, IT IS USED TO REPLACE GROWTH HORMONE, A NATURALLY OCCURRING HORMONE PRODUCED BY OUR BODIES.
LENALIDOMIDE :- IT IS USED TO TREAT PATIENTS WITH PARTICULAR TYPES OF MYELODYSPLASTIC SYNDROME (MDS) FOR ANEMIA (LOW RED BBLOOD CELLS).
IMATINIB MESYLATE :-PHILADELPHIA CHROMOSOMES POSITIVE ADULTS AND CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA ARE APPROPRIATE FOR TREATMENT.
FILGRASTIM:- LOW WHITE BLOOD CELL NEUTROPENIA CAUSED BY CANCER MEDICINES IS TREATED WITH IT.
GLATIRAMER ACETATE:- ACTIVE SECONDARY PROGRESSIVE DISEASE IN ADULT, RELAPSING-REMITTING DISEASE, AND CLINICALLY ISOLATED SYNDROME ARE ALL TREATABLE WITH IT THROUGH RELAPSING FORMS OF MULTIPLE SCLEROSIS (MS).
BOSENTAN MONOHYDRATE :-IT IS USED TO TREAT PULMONARY ARTERIAL HYPERTENTION IN ADULTS AND CHILDREN 3 YEARS OF AGE AND OLDER (PAH,HIGH BP IN VESSELS THAT CARRY BLOOD TO LUNGS).
BORTEZOMIB:-IT IS USED TO TREAT BOTH MANTLE CELL LYMPHOMA AND MULTIPLE MYELOMA (BLOOD PLASMA CELL CANCER) IN PATIENTS WITH OR WITHOUT A PRIOR HISTORY OF TREATMENT.

CHALLENGES IN ORPHAN DRUGS DEVELOPMENT

SMALL POPULATIONS WITH LIMITED CHANCE TO PARTICIPATE IN THE STUDY AND REPLICATE THE RESULTS IN BIGGER TRIALS.
DISEASE AND PHENOTYPIC PRESENTATIONS IN A HETEROGENEOUS MANIFESTATION.
POORLY UNDERSTOOD PATHOLOGY AND DISEASE (A RARE DISEASE PATIENT TYPICALLY SEES SEVEN SPECIALISTS, AND IT CAN TAKE UP TO EIGHT YEARS TO GET A CORRECT DIAGNOSIS).
INSUFFICIENT AGREEMENT ON CLINICAL OUTCOME METRICS AND INADEQUATELY DEFINED ENDPOINTS.
LOW RETURN ON INVESTMENT & HIGH RESEARCH COSTS.
IT IS DIFFICULT TO DEVELOP ORPHAN MEDICATIONS DUE TO A LACK OF SCIENTIFIC AND FINANCIAL RESOURCES AS WELL AS A SHORTAGE OF PEOPLE FOR CLINICAL STUDIES.
FOR ORPHAN DRUGS DEVELOPMENT OBTAINING PUBLIC AND PRIVATE FUNDING FOR RESEARCH AND DEVELOPMENT IS DIFFICULT
THE REQUIREMENT TO DEMONSTRATE “SUBSTANTIAL EVIDENCE” OF SAFETY AND EFFECTIVENESS THROUGH SUFFICIENT, CAREFULLY MONITORED RESEARCH AND CLINICAL BENEFIT REMAINS UNCHANGED FOR APPROVAL.

INADEQUATE DIAGNOSTIC SYSTEMS AND DELAYED DIAGNOSIS

FUTURE DEVELOPMENT OF ORPHAN DRUGS



WITH NEW THERAPEUTIC HORIZONS AND EMERGING TECHNOLOGY CHANGING THE FACE OF RARE DISEASE TREATMENT, THE FUTURE OF ORPHAN PHARMACEUTICALS LOOKS BRIGHT.
SALES OF ORPHAN DRUGS WILL GROW ALMOST 13% BETWEEN 2023 AND 2028, WAY QUICKER THAN THE 7% EXPECTED FOR NON-ORPHAN INNOVATIVE DRUGS.
IT IS REASONABLE TO HOPE AND ANTICIPATE THAT A VARIETY OF OPIOID DRUGS WILL BE INTRODUCED TO THE MARKET IN THE NEAR FUTURE.
ORPHAN DRUGS, TARGETING A WIDE RANGE OF GENETIC DISEASES, WILL BECOME EVEN MORE PRECISE.
ACCORDING TO PROJECTIONS, THE GLOBAL ORPHAN DRUG MARKET WOULD REACH US$ 869.6 BILLION BY 2030, GROWING AT A COMPOUND ANNUAL GROWTH RATE OF 10.4%.

PUBLIC AWARENESS ON ORPHAN DRUGS

ABOUT 300 MILLION PEOPLE ARE LIVING WITH RARE DISEASES ABROAD, 70% OF WHICH START IN CHILDHOOD. THE MAJORITY OF RARE DISEASES ARE DEBILITATING, SOMETIMES EVEN FATAL. IN FACT, STUDIES SHOW THAT REDUCED LIFE EXPECTANCY IS LINKED TO BETWEEN 57.5% AND 65% OF RARE DISEASES.
OVER 7000 ORPHAN DISEASES ARE KNOWN TO EXIST, IMPACTING 6-8% OF THE GENERAL POPULATION.
MOST RARE DISEASES ARE INHERITED; SOME WELL-KNOWN EXAMPLES ARE HUNTINGTON'S DISEASE, SICKLE CELL DISEASE, CYSTIC FIBROSIS, AND OTHER MUSCULAR ATROPHIES AND DYSTROPHIES. EVEN THOUGH THESE CASES HAVE RECEIVED EXTENSIVE RESEARCH, THERE ARE A GREAT DEAL MORE UNCOMMON ILLNESS TYPES ABOUT WHICH NOTHING IS UNDERSTOOD.THE DRUGS WHICH TREAT OR DIAGNOSIS THESE DISEASES ARE CALLED ORPHAN DRUGS
ABOUT 400 ORPHAN-DESIGNATED MEDICATIONS UNDERGOING CLINICAL TRIALS AND 281 MARKETED ORPHAN PHARMACEUTICALS WERE AVAILABLE IN 2014. MORE THAN 60% OF ORPHAN MEDICATIONS WERE BIOLOGICS.
70% OF ORPHAN MEDICATIONS HAD BEEN APPROVED BY THE FDA, BUT SAFETY-RELATED LABELLING CHANGES WERE MORE OFTEN MADE TO THE MEDICATIONS THAT HAD BOXED WARNINGS.
THE RECENTLY APPROVED MEDICATION, IMBRUVICA, WILL BE AVAILABLE ON AUGUST 24, 2022, AND IS INTENDED TO TREAT SPECIFIC CANCERS, INCLUDING WALDENSTRÖM'S MACROGLOBULINEMIA AND CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA.

CONCLUSION

IN CONCLUSION, ORPHAN DRUGS OFFER ESSENTIAL SOLUTIONS FOR RARE DISEASES, GUIDED BY THE ORPHAN DRUG ACT. THEIR ACCELERATED REGULATORY PATHWAYS HAVE SPARKED TRANSFORMATIVE DEVELOPMENTS WHEN COMBINED WITH INCENTIVES. WE VIEW THE IMPACT OF THESE DRUGS, WHICH BRING HOPE TO OVERLOOKED PATIENT POPULATIONS, THROUGH INSPIRING CASE STUDIES. FORWARD-THINKING RESEARCH AND COLLABORATIONPLEDGE ONGOING PROGRESS, REINFORCING THE DEDICATION TO COMBATING UNCOMMON DISEASES. OPHAN DRUGS EMBODY THE COLLECTIVE DEDICATION TO INCLUSIVITY AND MEDICAL PROGRESS AS WELL AS RESHAPING TREATMENT LANDSCAPES.

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