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Review Article

A REVIEW ON RECENT ORPHAN DRUGS

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ABSTRACT

The drugs or biological products for the diagnosis, treatment, or, prevention of a rare disease or condition are orphan drugs. Even though the drugs intended to treat common disease where revenue is not expected by pharmaceutical manufacturer are as well categorized as orphan. United State of America (USA) was the first nation to propose a legal framework to encourage development and availability of orphan drugs. The orphan drug act was passed on January 28, 1983 by U.S.A.to stimulate the research, development, and approval of those products that treat orphan diseases. The regulation for orphan drugs varies in different countries. Orphan diseases are a spectrum of medical conditions with very different etiologies, the common denominator being the infrequency of their occurrence in the population. The new business model of orphan drugs could offer an integrated healthcare solution that enables pharmaceutical companies to develop newer areas of therapeutics, diagnosis, treatment, monitoring, and patient support. Incentives for drug development provided by governments, as well as support from the FDA and national organizations in special protocols are a further boost for the companies developing orphan drugs. Although there may still be challenges ahead for the pharmaceutical industry, orphan drugs seem to offer the key to recovery and stability within the market

KEYWORDS: *Orphan drugs, Orphan/rare diseases, Neglected disease, Orphan drug act.*

INTRODUCTION

Orphan drugs (ODS) are drugs indicated for prevention, treatment or diagnosis of rare diseases. The numbers of orphan drugs are growing steadily since the enactment of orphan drug act in the U.S.A.in year 1983, and the European Union (EU) regulation on orphan medicinal products in year 1999[1,2]. A disease is an impairment of health or a condition of abnormal functioning. It is a pathological condition of a part, organ, or system of an organism resulting from various causes, such as infection, genetic defect, or environmental stress, and is characterized by an identifiable group of signs or symptoms.

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The designation of orphan disease varies in different countries depending upon the ratios viz. EU: 5 per 10,000 individuals, USA: 7.5 per 10,000 individuals, Japan: 4 per 10,000 individuals, Australia: 1 per 10,000 individuals [3]. Almost 5,000 to 8,000 distinct rare diseases exist today, affecting 6% to 8% of the population in the European Union. Symptoms of some rare diseases may appear at birth or in childhood, including infantile spinal muscular atrophy, lysosomal storage disorders, patent ductus arteriosus (PDA), familial adenomatous polyposis (FAP) and cystic fibrosis [4].

DEFINITIONS

The concepts of rare diseases, neglected diseases, orphan diseases and orphan drugs are not clearly defined and used as interchangeable

concepts. This situation has led to misperception and confusion as to precisely what each of these concepts refers to and/or as to what reality each of them covers [5].

Rare diseases

Rare diseases are characterized by their low prevalence (less than 1/2000) and their heterogeneity. Because rare disease patients are a minority, there is a lack of public awareness; these diseases do not represent a public health priority. The market is so narrow for each disease that the pharmaceutical industry is reticent to invest in research to develop and to develop treatments for rare diseases. There is therefore a need for economic regulation, such as national incentives [6].

Neglected Diseases

Neglected diseases are conditions that inflict severe health burdens on the world's poorest people. Many of these conditions are infectious diseases that are most prevalent in tropical climates, particularly in areas with unsafe drinking water, poor sanitation, substandard housing and little or no access to health care[6].

Orphan Drugs

Orphan drugs are medicinal products intended for the diagnosis, prevention or treatment of rare diseases. These drugs are called "orphan" because, under normal market conditions, it is not cost-effective for the pharmaceutical industry to develop and market products are intended for only a small number of patients suffering from rare conditions. For drug companies, the cost of bringing an orphan medicinal product to the market would not be recovered by the expected sales of the product. For this reason, governments and rare disease organizations have emphasized the need for economic incentives to encourage drug companies to develop and market medicines intended for the "orphaned" rare disease patients [7].

LIST OF RECENT ORPHAN DRUGS

Row Num	*Generic Name*	*Trade Name*	*Designation Date*	*Orphan Designation*	*Contact Company/ Sponsor*
01	Expanded human allogeneic neural Retinal progenitor cells extracted From neural retina	N/a	8/22/2013	Treatment of Retinitis pigmentosa.	Re Neuron Ltd
02	Pomalidomide	N/a	8/22/2013	Treatment of systemic Sclerosis.	Celgene Corporation.
03	Ruxolitinib	Jakafi	8/16/2013	Treatment of Pancreatic cancer.	Incyte Corporation.
04	Syntheticdouble-stranded sirnaOligonucleotide against Antithrombin (AT) mrna	N/a	8/16/2013	Treatment of Hemophilia A.	Alnylam Pharmaceuticals.
05	Deflazacort	N/a	8/16/2013	Treatment of DuchenneMuscular dystrophy.	Marathon Pharmaceuticals, LLC.
06	Dantrolene sodium suspension forInjection	N/a	8/16/2013	Treatment of Malignant	Eagle Pharmace

				hyperthermia Syndrome.	uticals, Inc.
07	Pentamidine	N/a	8/12/2013	Treatment of liver And intrahepatic Bile duct cancer.	Oncozyme Pharma, Inc.
08	Pentamidine	N/a	8/12/2013	Treatment of Ovarian cancer.	Oncozyme Pharma, Inc.
09	Synthetic double-stranded Sirna oligonucleotide against Antithrombin mrna	N/a	8/12/2013	Treatment of Hemophilia B.	Alnylam Pharmaceuticals.
10	Uridine triacetate	N/a	8/9/2013	Treatment of Hereditary orotic Aciduria.	Wellstat Therapeutics, Inc.
11	Bispecific antibody (monoclonal antibody)	N/a	8/8/2013	Treatment of HER2-Expressing advanced Adenocarcinoma of The stomach and Gastroesophageal Junction.	Merrimack Pharmaceuticals, Inc.
12	Recombinant human nerve Growth factor	N/a	8/8/2013	Treatment of Retinitis Pigmentosa.	Dompe s.p.a.
13	Small molecule inhibitor of Histone methyltransferase dot1l	N/a	8/8/2013	Treatment of acute Lymphoblastic leukaemia(ALL).	Epizyme Inc.
14	Bispecific antibody (monoclonal antibody)	N/a	8/8/2013	Treatment of HER2-Expressing Adenocarcinoma of theOesophagus.	Merrimack Pharmaceuticals,Inc.
15	Human hemin	N/a	8/6/2013	Prevention ofIschemia reperfusionInjury in patientsUndergoing solid organ Transplantation.	Borders Technology Management Ltd.
16	Conjugate of a dengue virus SpecificSmall chemical Ligand and An Amphiphilic PEG based Polymer	N/a	8/6/2013	Treatment of dengue Fever(includes dengue hemorrhagic fever	Nanoviricides Incorporated.

				and Dengueshock syndrome)	
17	L. Reuteri	N/a	8/1/2013	Prevention of necrotizing Enterocolitis in preterm Infants with birth weight Less than or equal to 1,500 grams.	Infant Bacterial Therapeutics.
18	(S)-3-(1-(9H-purin-6-ylamino)Ethyl)-8-chloro-2-PhenylisoQuinolin-1(2H)-one	N/a	8/1/2013	Treatment of follicular Lymphoma.	Infinity Pharmaceuticals,Inc.
19	Angiotensin (1-7)[A(1-7)]	N/a	7/25/2013	Treatment of Duchenne Muscular dystrophy.	US Biotest,Inc.
20	Sulthiame	N/a	7/25/2013	Treatment of patients With benign epilepsy Of childhood with c Entrotemporal spikes (BECTS) also known asRolandic epilepsy.	Marathon Pharmaceuticals, LLC.
21	Hydroxycarbamide (hydroxyurea)	Siklos(R)	7/24/2013	Treatment of sickle Cell disease in patients Under 18 years of age .	Addmedia Laboratories.
22	Topiramate injection	N/a	7/24/2013	Treatment of partial Onset or primary Generalized tonicclonicSeizures for hospitalized Epilepsy patients who are unable to take oral topiramate	Ligand Pharmaceuticals, Inc.
23	(5R)-5-(4-{[2-fluorophenyl)methyl]oxy}phenyl)-Lprolinamide,Hydrochloride.	N/a	7/24/2013	Treatment of trigeminalNeuralgia.	Convergence Pharmaceuticals Ltd.
24	Bezafibrate Bezalip		7/24/2013	For therapeutic Treatment of Barth syndrome	Barth Syndrome Foundation, Inc.

25	Granulocyte-macrophage colonystimulating factor-coding oncolytic adenovirus, Ad5/3-D24-GMCSF	N/a	7/24/2013	Treatment of soft tissue sarcoma	Oncos Therapeutics Ltd.
26	N-methyl-4-({4-[({3-Methyl(methylsulfonyl)amino]Pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-Yl}amino)benzamideHydrochloride.	N/a	7/18/2013	Treatment of Mesothelioma.	Verastem, Inc.
27	Allopregnanolone	N/a	7/12/2013	Treatment of Neimann-Pick disease, type C.	Lajolla Pharmaceutical company Inc.
28	Alisertib	N/a	7/12/2013	Treatment of small cell lung cancer.	Millenniu m Pharmaceuticals, Inc.
29	Pertuzumab	N/a	7/12/2013	Treatment of gastric Cancer.	Genentech , Inc.
30	Denileukin diftitox	N/a	7/12/2013	Treatment of cutaneous T-cell lymphoma.	Eisai Inc.
31	Repository corticortropin injection	H.P. Acthar Gel	6/28/2013	Treatment of Amyotrophic lateral sclerosis.	Questor Pharmaceuticals, Inc.
32	Moxetumomab pasudotox	N/a	6/28/2013	Treatment of acute Lymphoblastic leukaemia.	Medimmune, LLC.
33	Intravenous carbamazepine	N/a	6/27/2013	Treatment of epilepsy patients who cannot take anything by mouth (NPO).	Lundbeck, LLC.
34	Human platelet antigen-1a Immunoglobulin (anti-hpa-1a)	Trompl ate	6/27/2013	Prevention of foetal and neonatal alloimmune thrombocytopenia prophylix.	Pharma AS.
35	Eculizumab	Soliris	6/24/2013	Treatment of neuromyelitis optica.	Alexion Pharmaceuticals, Inc.
36	Cyclo(-y-aminobutyryl-Lphenylalanyl-L-tryptophanyl-Dtryptophanyl-L-lysyl-L-threonly-Lphenylalanyl-N-3-carboxypropyl)-Glycine amide, acetate salt	N/a	6/24/2013	Treatment of a Cromegaly.	Aspireo Pharmaceuticals Limited.
37	Flunarizine hydrochloride	N/a	6/24/2013	Treatment of alternating	Marathon Pharmace

				hemiplegia.	uticals, LLC.
38	Liposomal busulfan	Busulipo	6/24/2013	For use as a Conditioning regimen for patients with malignancies undergoing autologous or allogenic hematopoietic stem cellTransplantation	Pharmalink AB.
39	Humanized 3F8-igg1 monoclonal Antibody	N/a	6/24/2013	Treatment of neuroblastoma	Memorial Sloan-Kettering Cancer Centre.
40	(S)-4-(5-chloro-2-(isopropyl amino)pyridin-4-yl)-N-(1-(3-chlorophenyl)-2-Hydroxyethyl)-1H-pyrrole-2-carboxamide hydrochloride .	N/a	6/24/2013	Treatment of Stage iib through Stage IV BRAF mutant melanoma.	Biomed Valley Discoveries, Inc.
41	IL-12 secreting dendritic cellsLoaded with autologous tumourLysate .	N/a	6/24/2013	Treatment of malignant glioma.	Activartis Biotech gmbh.
42	Sodium phenylbutyrate	Phebur ane	6/6/2013	Treatment of urea cycledisorders.	Lucane Pharma SA. .
43	Human interleukin-3 genetically Conjugated to diphtheria toxin Protein	N/a	6/6/2013	Treatment of blastic Plasmacytoid dendritic cell neoplasm.	Stemline Therapeutics, Inc.
44	(1-methyl-2-nitro-1H-imidazole-5-Yl)methyl N,N'-bis(2-broethyl) Diamidophosphate	N/a	6/5/2013	Treatment of pancreatic cancer.	EMD Serono.
45	Ibrutinib	N/a	5/30/2013	Treatment of small lymphocytic lymphoma.	Pharmacyclics, Inc.
46	Abatacept	Orencia	5/30/2013	Treatment of type I diabetes mellitus patients with residual Beta cell function.	Orban Biotech LLC.
47	Diazepam auto-injector	N/a	5/30/2013	Management of selected, refractory patients with	Meridian Medical Technolog

				Epilepsy on stable regimens of antiepileptic drugs, who require intermittent use of Diazepam to control bouts of increased seizure activity.	ies-a Pfizer subsidiary .
48	Modified recombinant humanFactor VIIA (rFVIIA) molecule	N/a	5/30/2013	Treatment of bleeding episodes in hemophilia A or B subjects with inhibitors.	Bayer healthcare Pharmaceuticals, Inc.
49	Terguride	Mysalfon , Teluron	5/17/2013	Treatment of systemic sclerosis.	Serodapharm UG.
50	Ibrutinib	N/a	5/16/2013	Treatment of multiple Myeloma.	Pharmacyclics, Inc.
51	Hirmab-IDS	N/a	5/15/2013	Treatment of Mucopolysaccharidosis Type II (Hunter Syndrome).	Armagen Technologies, Inc.
52	2-[4-Methoxy-3-(2-m-tolyl-ethoxy)-benzoylamino]-indian-2-carboxylic acid	N/a	5/14/2013	Treatment of patients with systemic sclerosis.	Sanofi U. S., Inc.
53	N-{3-[(2-{[4-(4-acetylpiperazin-l-yl)-2-methoxyphenyl]amino}-5-(trifluoromethyl) pyrimidin-4-yl)amino]phenyl}prop-2-enamide	N/a	5/14/2013	Treatment of non-small cell lung cancer and mutations in the epidermal growth factor receptor.	Clovis Oncology, Inc.
54	3,5-diiodothyropropionic acid	N/a	5/14/2013	Treatment of Allan-Herndon-Dudley syndrome.	Zarion Pharmaceuticals P/L.
55	DCVAC OvCa	N/a	5/14/2013	Treatment of ovarian cancer.	SOTIOS a.s.
56	H-Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-alys-aleu-Ser-Ser-Ile-Glu-Ser-Asp-Val-OH	N/a	5/14/2013	Treatment of subarachnoid Haemorrhage.	NoNo, Inc.
57	Teprotumumab	N/a	5/6/2013	Treatment of active (dynamic) phase Grave's orbitopathy.	River Vision, Inc.

58	Zoledronic acid	Zometa, Reclast, Aclasta	5/6/2013	Treatment of complex regional pain syndrome (CRPS).	Axsome Therapeutics, Inc.
59	Recombinant fusion protein linking Coagulation factor VIIa with Albumin (rVIIa-fp)	N/a	5/6/2013	Treatment of congenital factor VII deficiency which includes treatment and prophylaxis of bleeding episodes in patients With congenital factor VII deficiency	CSL Behring.
60	Isavuconazonium sulphate	N/a	5/6/2013	Treatment of invasive Aspergillosis.	Astellas.
61	Daratumumab	Humax (R) -Cd38	5/6/2013	Treatment of multiple Myeloma.	Janssen Research & Development, LLC.
62	Adeno associated viral vectorSerotype rh.10 carrying the human SGSH and SUMF1 cDNAs	N/a	5/6/2013	Treatment of Mucopolysaccharidosis type IIIA (Sanfilippo type A syndrome) .	Lysogene.
63	Pexastimogene devacirepvec	N/a	5/6/2013	Treatment of hepatocellular carcinoma.	Jennerex, Inc.
64	Pazopanib	N/a	5/6/2013	Treatment of ovarian cancer.	Glaxo Wellcome Mfg. Pte Ltd.
65	Budesonide	Uceris	5/6/2013	Treat of ulcerative colitis paediatric patients aged 0 through 16 years.	Santarus, Inc.
66	Hepatitis B virus neutralizingHuman monoclonal antibody	Hepabig Gene	5/6/2013	Prevention of hepatitis B recurrence following liver transplantation.	Green Cross Corp.
67	Replication-deficient recombinantSerotype 2 adeno-associated viral Vector containing hAQP1 cDNA	N/a	5/3/2013	Treatment of symptoms of Grade 2 and Grade 3 late xerostomia from parotid gland	John A. Chiorini, phd.

				hypofunction caused by radiotherapy for cancer of the oral cavity.	
68	Tocilizumab	Actemra	4/17/2013	Treatment of systemic sclerosis to be a separate disease or Condition from localized scleroderma.	Genentech, Inc.
69	Opioid growth factor	N/a	4/16/2013	Treatment of liver and intrahepatic bile duct cancer.	Primocure Pharma,Inc.
70	sdTD-k6a.513a.12; smallInterfering RNA composed of 2 Strands of hybridized RNAs	N/a	4/15/2013	Treatment of pachyonychia congenital.	Trans Derm, Inc.
71	Sodium ascorbate and menadione sodium bisulfite	N/a	4/15/2013	Treatment of autosomalDominant polycystic liver disease.	IC-Medtech Corporation.
72	Daunorubicin citrate	N/a	4/15/2013	Treatment of cutaneous T-cell lymphoma.	Shape Pharmaceuticals, Inc.
73	Methylparaben suberohydroxamicAcid phenyl ester	N/a	4/15/2013	Treatment of acute myeloid leukemia.	Galen Limited.
74	4-(6-(4-(piperazin-1-yl) Phenyl_pyrazolo[1,5a]pyrimidin-3-yl)quinoline hydrochloride	N/a	4/15/2013	Treatment of fibrodysplasia ossificans progressive.	La Jolla Pharmaceutical Company, Inc.
75	(S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one	N/a	4/15/2013	Treatment of chronic Lymphocytic leukemia and small lymphocytic lymphoma.	Infinity Pharmaceuticals.
76	Brentuximab vedotin	Adcetris	4/15/2013	Treatment of patients with peripheral T-cell lymphoma, not otherwise specified.	SeattleGenetics, Inc.

77	Recombinant human alpha-N-acetylglucosaminidase	N/a	4/15/2013	Treatment of Mucopolysaccharidosis IIIB(Sanfilippo B syndrome)	Synageva biopharma Corp.
78	Sodium ascorbate and menadione Sodium bisulfite	Apatone	4/15/2013	Treatment of autosomal dominant polycystic kidney disease.	IC-medtech Corporation.
79	Anti-inhibitor coagulant complex	Feiba Nf	4/12/2013	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A and B patients with inhibitors Baxter.	Healthcare Corporation.
80	Melatonin	N/a	4/12/2013	Treatment of neonatal hypoxic ischemic encephalopathy .	Scharper S.p.A.
81	Recombinant humanized IgG1kMonoclonal antibody to humanInvariant T cell receptor (iTCR)	N/a	4/12/2013	Treatment of sickle cell disease.	NKT Therapeutics, Inc.
82	Givinostat	N/a	4/12/2013	Treatment of Duchenne Muscular Dystrophy and Becker Muscular Dystrophy	Italfarmaco spa.
83	Transforming growth factor-betaReceptor 1 kinase inhibitor	N/a	4/1/2013	Treatment of hepatocellular Carcinoma	Eli Lilly and Company.
84	Recombinant human tripeptidylpeptidase1(rhTPP1)	N/a	4/1/2013	Treatment of neuronal ceroid Lipofuscinosis type2.	Biomarin Pharmaceutical, Inc.
85	Kre-Celazine	N/a	4/1/2013	Treatment of juvenile Rheumatoid arthritis joint and related tissue inflammation in the paediatricpopulation.	All American Pharmaceutical & Natural Foods Corpor.
86	Recombinant adenovirus vectorAAV2/rh8	N/a	3/25/2013	Treatment of Tay-Sachs disease.	Na't Tay-Sachs &

	expressing human Bhexosaminidase A & B subunits				Allied Diseases Association.
87	Acamprosate	N/a	3/25/2013	Treatment of fragile XSyndrome.	Confluence Pharmaceuticals, LLC.
88	Inotuzumab ozogamicin	N/a	3/25/2013	Treatment of B-cell acute lymphoblastic leukemia.	Pfizer, Inc.
89	liposomal amikacin	Arikace	3/25/2013	Treatment infections caused by Non-tuberculous mycobacteria.	Insmed Incorporated.
90	Recombinant adeno associatedVirus vector AAV2/rh8 expressing Human B hexosaminidase A and B Subunits	N/a	3/25/2013	For the treatment of Sandhoff disease.	Nat'l Tay-Sachs & Allied Diseases Association.
91	Neridronate	N/a	3/25/2013	Treatment of complex regional pain syndrome (CRPS1-, CRPSII, CRPS-NOS).	Grunenthal USA, Inc.
92	N-tert-butyl-3-[(5-methyl-2-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}pyrimidin-4-yl)amino] benzenesulfonamide Dihydrochloride monohydrate	N/a	3/21/2013	Treatment of polycythemiaVera.	Sanofi-AventisU.S. LLC.
93	Sirolimus	N/a	3/18/2013	Treatment of pachyonychiaCongenita.	Trans Derm, Inc.
94	Neostigmine	N/a	3/18/2013	Treatment of acute colonic Pseudo-obstruction.	Luitpold Pharmaceuticals, Inc.
95	40K pegylated recombinant factorIX	N/a	3/18/2013	Routine prophylactic Administration for preventionof bleeding in patients	Novo Nordisk, Inc.

				with hemophilia B (Christmas disease).	
96	Autologous CD34+ hematopoieticStem cells transduced withlenti Globin BB305 lentiviral vectorEncoding the human BA-T87Qglobin gene	N/a	3/18/2013	Treatment of B-thalassemia major and intermedia.	Bluebird bio, Inc.
97	Cell based therapeutic composed of allogeneic donor apoptotic cells	Apocell	3/18/2013	Prevention of graft versus host disease.	Enlivex Therapeutics Ltd.
98	Recombinant elafin	N/a	3/18/2013	Prevention of inflammatory Complications of transthoracic Esophagectomy.	Proteo Biotech AG.
99	Recombinant fusion proteinConsisiting of a modified form of extracellular domain of human Activin receptor IIB	N/a	3/18/2013	Treatment of myelodysplastic Syndrome.	Acceleron Pharma, Inc.
100	Chimeric monoclonal antibodyAgainst Claudin 6	N/a	3/18/2013	Treatment of ovarian cancer.	Ganymed Pharmaceuticals AG.
101	Transforming growth factor-beta receptor 1 kinase inhibitor	N/a	3/11/2013	Treatment of glioma	Eli Lilly and Company.
102	AAV-G6Pase vector	N/a	3/11/2013	Treatment of glycogen storage disease type Ia.	Glygenix Therapeutics, Inc.
103	His-His-Ile-Tyr-Leu-Gly-Ala-Val-Asn-Tyr-Ile-tyr	N/a	3/11/2013	Treatment of retinal Detachment.	ONL Therapeutics, LLC.
104	Aerosolized beractant	N/a	3/11/2013	Treatment of respiratory distress syndrome.	Beena G. Sood, MD, MS.
105	C66H100N6O27	N/a	3/11/2013	Treatment of hepatocellular carcinoma.	Genspera, Inc.
106	Recombinant fusion proteinConsisting of a modified form of the extracellular domain of human active receptor IIB	N/a	3/11/2013	Treatment of B-thalassemia.	Acceleron Pharma, Inc.

	(actRIIB) linked to a human igg1 Fc domain.				
107	Plasminogen (human)	N/a	3/5/2013	Treatment of Hypoplasminogenemia, or type I plasminogendeficiency.	Prometic Biotherapeutics, Inc.
108	Recombinant human Naglu-insulin-like growth factor II	N/a	3/5/2013	Treatment of Mucopolysaccharidosis type IIIB (Sanfilippo syndrome type B).	Shire Human Genetic Therapies, Inc.
109	3-bromopyruvate	N/a	3/5/2013	Treatment of liver and intrahepatic bile duct cancer	Primocure Pharma, Inc.
110	2-hydroxypropyl-B-cyclodextrin	Kleptose	2/18/2013	Treatment of Niemann-Pick disease type C.	National Institutes of Health.
111	Minnelide (Tm)		2/18/2013	Treatment of pancreatic cancer.	Minneamrita Therapeutics, LLC
112	Allogeneic ex-vivo expandedPlacental adherent stromal cells	N/a	2/18/2013	Treatment of Aplastic Anemia. .	Pluristem Therapeutics, Inc.
113	Testosterone undecanoate (oral)	N/a	2/13/2013	Treatment of constitutional Delay in growth and puberty in Adolescent boys (14-17 yrs of age).	SOV Therapeutics, Inc.
114	Idursulfase beta	N/a	2/11/2013	Treatment of Hunter Syndrome (mucopolysaccharidoses).	Green Cross Corp.
115	Human insulin beta chain peptideWith incomplete Freund's adjuvant Vaccine	N/a	2/11/2013	Treatment of Type 1 diabetes patients with residual beta cell Function.	Orban Biotech, LLC.
116	Enalapril maleate (powder for oral Solution) .	Epaned	1/30/2013	Treatment of hypertension in Pediatric patients.	Silvergate Pharmaceuticals, Inc.
117	[met5]-enkephalin	Opioid Growth Factor	1/24/2013	Treatment of pancreatic cancer.	TNI biotech, Inc.

118	Nivolumab	N/a	1/23/2013	Treatment of Stage IIb to IV melanoma.	Bristol-Myers Squibb Co.
119	Onartuzumab	N/a	1/23/2013	Treatment of gastric cancer including gastroesophageal Cancer.	Genentech, Inc.
120	Exon 45 specific phosphorothioate Oligonucleotide	N/a	1/23/2013	Treatment of DuchenneMuscular Dystrophy patients bearing mutations that can beCorrected by skipping exon 45.	Prosensa Therapeutics B V.
121	Exon 53 specific phosphorothioate Oligonucleotide	N/ a	1/23/2013	Treatment of DuchenneMuscular Dystrophy patients Bearing mutations that can beCorrected by skipping exon 53.	Prosensa Therapeutics B.V.
122	10 synthetic peptides targeting 5 tumor asociated antigens	N/a	1/23/2013	Treatment of non-small cell lung cancer in patients expressing HLA-A2.	Orphan Synergy Europe Pharma (OSE Pharma.
123	Exon 55 specific phosphorothioate Oligonucleotide	N/a	1/23/2013	Treatment of DuchenneMuscular Dystrophy patients bearing mutations that can beCorrected by skipping exon 55.	Prosensa Therapeutics B.V.
124	Exon 52 specific phosphorothiate Oligonucleotide	N/a	1/23/2013	Treatment of DuchenneMuscular Dystrophy patients bearing mutations that can beCorrected by skipping exon 52.	Prosensa Therapeutics B V.
125	Eflornithine plus sulindac	N/a	1/22/2013	Treatment of familial Adenomatous polyposisCancer Prevention	Pharmaceuticals, Inc.
126	Apremilast	N/a	1/17/2013	Treatment of Behcet's disease.	Celgene Corporation.

127	Modified recombinant human Ctype natriuretic peptide (CNP)	N/a	1/17/2013	Treatment of achondroplasia.	Biomarin Pharmaceutical, Inc.
128	lisuride	N/a	1/17/2013	Treatment of pulmonary arterial hypertension.	Sinoxa Pharma.
129	5-aminolevulinic acid	Gliolan	1/15/2013	Visualization of malignant tissue during surgery for malignant glioma (WHO garde III and IV).	NX Development Corporation.
130	Tafenoquine	N/a	1/15/2013	Treatment of malaria.	Glaxo Group Limited, England.
131	Syntheticpeptide; cyclo-Cys-Gly-Gln-Arg-Glu-Thr-Pro-Glu-Gly-Ala-Glu-ALA-Lys-Pro-Trp-Tyr-Cys	N/a	1/15/2013	Treatment of high altitude pulmonary edema.	Apeptico Forschung und Entwicklung gmbh.
132	Beloranib	N/a	1/15/2013	Treatment of Prader-Willi Syndrome.	Zafgen, Inc.
133	O-(3-piperidino-2-hydroxyl-1-Propyl)-nicotinic acid amidoximeHydrochloride	N/a	1/15/2013	Treatment of DuchenneMuscular Dystrophy.	N-Gene Research Laboratories, Inc.
134	Efdispo	N/a	1/15/2013	Treatment of Ewings Sarcoma.	TDP Biotherapeutics, Inc.
135	Rilonacept	Arcalyst	1/9/2013	Treatment of familial Mediterranean fever Philip.	J Hashkes, MD, msc.
136	Ezatiostat hydrochloride .	Telintra	1/9/2013	Treatment of myelodysplastic Syndrome.	Telik, Inc.
137	P140K MGMT transduced human CD34 cells	N/a	1/9/2013	For bone marrow protection in the treatment of Glioblastoma Multiforme.	Lentigen Corporation.
138	Paclitaxel nanoparticles	N/a	1/3/2013	Treatment of pancreatic cancer.	CIRJ Co., Ltd.

ORPHAN DRUG REGULATIONS

Inaccessibility of specific treatment for orphan disease leads the patient and their family into mental stress & depression. Many diseases lacking specific therapy are important targets for unreliable therapy. Thus the unproven therapies and wrong beliefs prevail in seek out of some relief. Orphan drugs generally follow the same regulatory development path as any other pharmaceutical product, in which testing focuses on pharmacokinetics and pharmacodynamics, dosing, stability, safety and efficacy. However, some statistical burdens are lessened in an effort to maintain development momentum. For example, orphan drug regulations generally acknowledge the fact that it may not be possible to test 1,000 patients in a phase III clinical trial, as fewer than that number may be afflicted with the disease in question. Since the market for any drug with such a limited application scope would be small and thus largely unprofitable, government intervention is often required to motivate a manufacturer to address the need for an orphan drug.

USA was the first nation to propose a legal framework to encourage development and availability of orphan drugs. The Orphan Drug Act (ODA) was passed on January 28, 1983, which was an amendment of Federal Food, Drug and Cosmetic Act of 1938, to stimulate the research, development, and approval of products that treat orphan diseases. ODA exists in various countries like USA, Japan, Singapore, Australia, Canada, France, Sweden, and United Kingdom. The basis of the initiative of other countries being the US ODA, with variations like marketing exclusivity rights to the marketing company for 7 years in USA, 10 years in Japan, and 5 years in Australia [8].

THE USA ORPHAN DRUG ACT

The U.S. Orphan Drug Act was signed in 1983 and provided incentives for the pharmaceutical industry to develop drugs that otherwise had minimal commercial return on investment, but which are necessary, and often life-saving, for patients with rare diseases [9].The Orphan Drug Act is codified in 21 CFR Part 316. Since 1983, Congress has amended the Orphan Drug Act several times. Amendments to the Orphan Drug Act were passed in 1984, 1985, 1988, 1990 and 1992 [10]. The distinctive purpose of the 1983 Orphan Drug Act was to provide incentives in the development of drugs for the treatment of rare diseases that would normally be unprofitable or unpatentable. The manufacturers had to demonstrate, to qualify for orphan drug status, that the development of a particular orphan drug would be unprofitable. As per the amendment to the Act in 1984, to qualify for orphan drug status, a rare disease or condition was defined as any disease or condition either affecting less than 200,000 persons in the United States or affecting more than 200,000 persons in the United States, but for which there is no reasonable expectation that the sales of the drug will recover the costs. Prior to this amendment, a drug sponsor was required to provide financial information regardless of the size of the proposed target patient population [11].

In 1985, the act was amended again, to extend marketing exclusivity for both patentable and unpatentable products. The purpose was to protect those products that were patentable, but whose patents would expire before or shortly after marketing approval. Many of these drugs were biotech drugs that had difficulties in obtaining patents. The earlier assumption about most orphan drugs being unpatentable was found to not always be true. Patents had been issued for many potential orphan products, but because of prolonged research, the patent protection had sometimes expired before marketing approval was obtained. In 1988, an amendment to the Act changed the requirement for submitting applications for orphan drug status. The application for orphan drug designation now has to be made prior to the submission of an application for marketing approval, New Drug Application (NDA) or Product License Application (PLA). Prior to the1988 amendment, the designation request could be filed at any time before the U.S. Food and Drug Administration's (FDA) approval to market the product [12].

JAPAN ORPHAN DRUG REGULATION

After the first national orphan drug policy in United States, It took ten years for the second country, Japan, to follow with a similar, although less generous amendment to its drug regulatory and taxation laws. On 1 October 1993, the Japanese government revised the pharmaceutical law by introducing special provisions relative to research and development of orphan drugs. According to provisions, orphan drug status can be granted to a drug, provided it fulfils the two criteria. The disease for which use of the drug is claimed must be incurable. There must be no possible alternative treatment; or the efficacy and expected safety of the drug must be excellent in comparison with other available drugs. The number of patients affected by this disease in Japan must be less than 50000 on the Japanese territory, which corresponds to a maximal incidence of four per ten thousand. Japanese orphan drugs system offered new opportunities both for multinational and small-size and medium-size companies. Public institutes and universities, and biotechnology companies are less active than in the USA [13].

AUSTRALIAN ORPHAN DRUGS ACT

The Australian orphan drugs policy was set up in 1997. This orphan drugs program aims to ensure the availability of a greater range of treatments for rare diseases and allows the Australian Therapeutic Goods Administration (TGA) to use information from the US Food and Drug Administration (FDA) Orphan Drugs Program as part of the Australian evaluation process. To be eligible for designation as an orphan drug the product must not have been rejected on safety grounds by the TGA, the Food and Drug Administration of the United States of America (FDA), the Medicines and Healthcare Products Regulatory Agency of the United Kingdom (MHRA), the Therapeutic Products Directorate of Canada (TPD), the Medical Products Agency of Sweden (MPA), the Medicines Evaluation Board of the Netherlands (MEB) or the European Medicines Agency (EMEA) for use for the disease in question. Orphan designation is intended for drugs which aim to treat diseases with a prevalence of 2000 patients or less in the Australian population (18 million)/ a maximal of twelve to per ten thousand. Another alternative criterion which leads to orphan designation consists in combining the fact that the drug is not commercially available, when used in the patient population it is indicated for [14].

EUROPEAN ORPHAN DRUG ACT

Efforts have been jointly made at national and European levels by industry and health authority, European Medicines Evaluation Agency (EMEA), in order to offer the incentives required to stimulate the development of orphan drugs. The goal was to rapidly make available, for rare diseases, drugs with a level of quality equivalent to that required for any other drug. A policy was implemented much later in Europe than in the USA. The reason lies mainly in the fact that its territory is split-up and its competencies as regard to health are scattered. Since 1 January 1995, with the new system of EU marketing authorisation that is valid for the whole territory and the free circulation that goes with it, Europe can be considered now as a territory with a population of about 377 million inhabitants that is a population greater than that of the United States where a common regulation is enforced. On 16 December 1999, the European Parliament and the Council adopted regulation (CE) No. 141/2000 on orphan drugs [15]. The goals were to encourage the pharmaceutical and biotechnological industry to develop and market orphan drugs, create a Committee of Orphan Medicinal Products (COMP) within the European Medicines Evaluation Agency (EMEA). This committee is responsible for studying the applications for orphan designation and to advise and assist the Commission in discussions on orphan drugs [16].

ORPHAN DRUG ACT IN INDIAN PERSPECTIVE

The established and developed countries have captures the importance of orphan drug regulation offering several incentives along with fast approval process for the pharmaceutical manufacturers. The developing countries like

India would be affected a lot during third world war with rare disease. Need for such an act is evident, initiative from the Indian Pharmacists and the Government to implement such Laws would strengthen the health infrastructure, manufacturers and provide relief to the numerous rare disease sufferers across the country. A group of pharmacologists at a conference held by the Indian Drugs Manufactures Association (IDMA) in 2001, requested the Indian Government to establish the Orphan Drug Act in India [17]. If such legislation could be implemented, it will be a benefit not only to pharmaceutical and biotechnological Industry but will also bring relief to the unlisted very possibly large groups of rare disease sufferers, in the country. The national orphan drug regulation should offer lucrative incentive, economic outcome and market exclusivity rights to the rare drug manufacturer to enjoy the reasonable profit and interest for investment in the R&D of rare drugs [18].

STATISTICS OF RARE DISEASES

About 6000-8000 rare diseases have been affecting 7% of population worldwide. 95% of medical conditions included in rare list have no FDA approval treatments [19]. 80% of rare diseases have been identified to genetic origins. Other rare diseases are the result of infections (bacterial or viral) and allergies, or are due to degenerative and proliferative causes According to San Orphan SA, Geneva, Switzerland, around 65 per cent of rare diseases are serious and disabling. More interestingly, about 250 new rare diseases are discovered each year, corresponding to five new rare diseases per week [20].

Orphan Designation

The Orphan Designation is a legal procedure that allows for the designation of a medicinal substance with therapeutic potential for a rare disease, before its first administration in humans or during its clinical development. The Office of Orphan Products Development (OOPD) evaluate requests for orphan drug designation, and once a drug is designated, acts as an internal FDA advocate interfacing with the FDA review division to help facilitate progress. The OOPD is separate from the FDA therapeutic review divisions [21]. A sponsor may request orphan drug designation for a previously unapproved drug or anew indication for an already marketed drug. The drug product may be a new formulation and the requisite information for a new drug product required by International Conference on Harmonization (ICH)/FDA would need to be provided in a marketing application. If the sponsor is able to provide valid evidence that their drug may be clinically superior to the drug already has orphan drug status, the new drug can be designated as orphan drug. In either of the above scenarios, the sponsor would need to include patent certification in the marketing application that demonstrates that there are no patent infringement issues [22].

LIST OF SOME ORPHAN DISEASES

Retinitis Pigments

Retinitis pigmentosa is an inherited retinal aldystrophy caused by the loss of photoreceptors and characterized by retinal pigment deposits visits on fundus examination. The most common form of retinitis pigmentosa (RP) is a rod-cone dystrophy, in which the first symptom is night blindness, followed by the progressive loss in the peripheral visual field in day light, and eventually leading to blindness after several decades [23].

The probable order for the development of degenerative changes in retinitis pigmentosa patients is as follows:

- Migration of nuclei from the outer nuclear layer to the rod and cone layer.
- Degeneration and loss of photoreceptors and their nuclei in the outer nuclear layer.
- Loss of connecting fibers in the outer plexiform layer.
- Migration of the retinal pigment epithelium (RPE) into the retina.
- Adhesion of the retinal to the retinal pigment epithelium in broad areas and possible transneuronal degeneration of some cells in the inner nuclear and ganglion cell layers [24].

Cystic Fibrosis

Cystic fibrosis (also known as CF or mucoviscidosis) is an autosomal recessive genetic disorder that affects most critically the lungs, and also the pancreas, liver, and intestine. It is characterised by abnormal transport of chloride and sodium across an epithelium, leading to thick, viscous secretions [25]. The name *cystic fibrosis* refers to the characteristic scarring (fibrosis) and cyst Formation within the pancreas. Difficulty breathing is the most serious symptom and results from frequent lung infections that are treated with antibiotics and other medications. CF is caused by a mutation in the gene for the protein membrane (CFTR). This protein is required to regulate the components of sweat, digestive fluids, and mucus. CFTR regulates the movement of chloride and sodium ions across epithelial membranes, such as the alveolar epithelia located in the lungs.

Pompe disease

Pompe disease also referred to as acid maltase deficiency (AMD) or glycogen storage disease type II (GSDII) is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid-glycosidase (GAA). It was the first recognized lysosomal storage disease and is the only glycogen storage disease that is also a Lysosomal storage disease. In Pompe disease, lysosomal glycogen accumulates in many tissues with skeletal, cardiac and smooth muscle most prominently involved [26].

Mutations in the *GAA* gene cause Pompe disease. The *GAA* gene provides instructions for producing an enzyme called acid alpha glycosidase (also known as acid maltase). This enzyme is active in lysosomes, which are structures that serve as recycling centres within cells. The enzyme normally breaks down glycogen into a simpler sugar called glucose, which is the main energy source for most cells[27]. Mutations in the *GAA* gene prevent acid alpha glycosidase from breaking down glycogen effectively, which allows this sugar to build up to toxic levels in lysosomes. This build up damages organs and tissues throughout the body, particularly the muscles, leading to the progressive signs and symptoms of Pompe disease [28].

Raynaud's phenomenon

Reynaud's phenomenon (RP) is a condition resulting in a particular series of discolorations o the fingers and/or the toes after exposure to changes in temperature (cold or hot) or emotional events. Skin discoloration occurs because an abnormal spasm of the blood vessels causes a diminished blood supply to the local tissues. Initially, the digit(s) involved turn white because of the diminished blood supply. The digit(s) then turn blue because of prolonged lack of oxygen. Finally, the blood vessels reopen, causing a local "flushing" phenomenon, which turns the digit(s) Red. This three-phase color sequence (white to blue to red), most often upon exposure to cold temperature, is characteristic of RP.

CONCLUSION

The success of orphan drug designation for neglected rare diseases shows that companies using orphan drug programs can generate profits and recoup their R&D investments even with relatively small markets in the developed world. The orphan drug designation mainly encourages investments and initiatives by small science-oriented companies. In general, orphan drugs have been developed by small biotech firms focused on niche markets or by academic investigators combining solid scientific expertise in a specific medical area with good entrepreneurial skills. The orphan drug designation should be promoted in various countries, not having their regulations for such categories of diseases, to promote the treatment for sufferers with rare diseases.

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