Recent FDA Orphan Drug Designations I. Without Cancer Drugs (March 25, 2013, to May 30, 2013)

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ABSTRACT

In the United States, the US Food and Drug Administration (FDA) approves orphan drug designations before they are approved for marketing. Here we survey recently approved orphan drug designations for a variety of therapies for rare diseases. This survey covers the period between March 25 and May 30, 2013, and is limited to noncancer rare diseases. In this period, there were 33 designations. These designations and the diseases they are designed to treat are summarized based on information from the FDA. A further survey will focus on cancer therapies. In future issues of this journal, we will be updating new designations and commenting on trends in the field.

INTRODUCTION

The development of orphan drugs and their designations remains an active field despite slowed growth within the pharmaceutical industry.[1,2] At the time of the Orphan Drug Act of 1983, only 10 orphan drugs had received marketing approval from the US Food and Drug Administration (FDA).[3] Now, a total of 2899 orphan drug designations have been approved, and designations have increased since 2009.[3] Orphan drug designations are granted by the FDA to indicate approval to develop a drug as an orphan drug. Designations outnumber marketed drugs because of the many steps required between designation and marketing approval. However, a market assessment group, Evaluate Ltd., has estimated that the orphan drug industry will continue to grow, with a compound annual rate of 7.4% from 2013 to 2018.[4] According to the National Organization for Rare Disorders, 2 key factors contribute to this growth: 1) orphan drugs offer 1.7 times greater return on investment than nonorphan drugs, and 2) phase 3 clinical trial costs for orphan products are half those of standard drugs.[4] Furthermore, 20 to 30 million Americans are living with ~ 7000 rare diseases, so although the diseases are rare as a group, they pose a potentially large drug market.

One of the new trends in the survey is the appearance of 4 gene-based therapies that have received orphan designation. An adeno-associated virus vector to provide a missing enzyme has been designated for Tay-Sachs disease and one of its variants, Sandhoff disease. Both diseases require β-hexosaminidase, and this can be delivered by recombinant adeno-associated virus vector AAV2/rh8 expressing human β-hexosaminidase A and B subunits. Recombinant serotype 2 adeno-associated viral vector containing hAQP1 cDNA is designated for xerostomia resulting from radiotherapy for cancer of the oral cavity. Adeno- associated viral vector serotype rh.10 carrying the human SGSH and SUMF1 cDNAs has been designated for the treatment of mucopolysaccharidosis type III A (Sanfilippo type A syndrome).

Analysis of the first 25 years of the Orphan Drug Act of 1983 shows that cancer is the most common disease category with orphan disease indications.[3] A brief snapshot from 2013 continues that trend in orphan designations; but, with the greater understanding of genes and affordable gene sequencing, interest in and designations for genetic disorders are rapidly increasing (Figure).

Orphan Designations by Type (n=47)

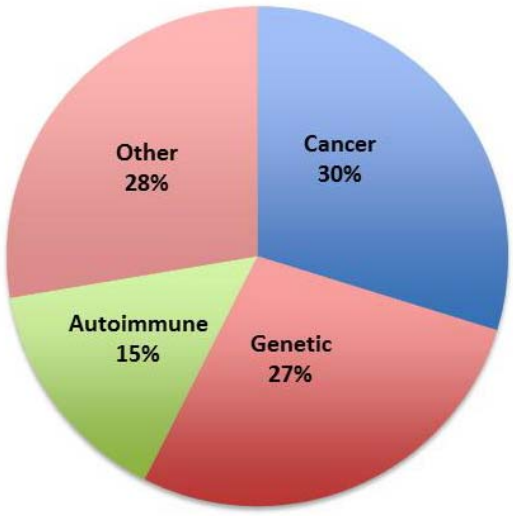

Figure. Orphan designations (March 25–May 30, 2013) categorized by types. The "other" category includes all non-autoimmune, non-genetic, and non-cancer diseases. [Data derived from http://www.accessdata.fda.gov/scripts/opdlisting/oopd/

FDA Orphan Designations Summary List (March 25–May 30, 2013) (http://www.accessdata.fda.gov/scripts/opdlisting/oopd/)

1. Recombinant adeno-associated virus vector AAV2/rh8 expressing human β-hexosaminidase A and B subunits

Active substance	Recombinant adeno-associated virus vector AAV2/rh8 expressing human β-hexosaminidase A and B subunits
Orphan designation	Treatment of Sandhoff disease
Designation date	March 25, 2013
Prevalence/total US cases	760
Existing therapies authorized	Palliative
US sponsor	National Tay-Sachs & Allied Diseases Association

Sandhoff disease is the more aggressive form of Tay-Sachs disease–individuals rarely survive past 3 years of age. The disease is autosomal recessive and is characterized by deterioration of the central nervous system caused by loss-of-function mutation in the B subunit of the β-hexosaminidase enzyme. Without a functioning enzyme, GM2 ganglioside lipids accumulate within the neurons and other tissues. AAV2/rh8 gene therapy treats Sandhoff disease by providing individuals with functional copies of the hexosaminidase A and B subunits.[5]

2. Recombinant adenovirus vector AAV2/rh8 expressing human β-hexoaminidase A and B Subunits

Active substance	Recombinant adenovirus vector AAV2/rh8 expressing human B-hexosaminidase A and B subunits
Orphan designation	Treatment of Tay-Sachs disease
Designation date	March 25, 2013
Prevalence/total US cases	100 affected Jews 3000 total cases per year
Existing therapies authorized	Palliative
US sponsor	National Tay-Sachs & Allied Diseases Association

Tay-Sachs disease is a lysosomal storage disorder, and affected individuals rarely survive past 15 years of age. It is an autosomal recessive mutation in the hexosaminidase enzyme, which causes a loss of function. Consequently, GM2 ganglioside lipids begin to accumulate within cells, resulting in cellular death. A characteristic symptom of the disease is the cherry-red spots that develop in the eyes. Treatment for the disease focuses on palliative care and genetic screening for prevention. The recombinant adenovirus vector AAV2 received designation for its ability to provide a functional copy of the β-hexosaminidase A and B subunit genes.[6]

3. Acamprosate

Active substance	Acamprosate
Orphan designation	Treatment of fragile X syndrome
Designation date	March 25, 2013
Prevalence/total US cases	39,000–44,000 affected males 26,000–39,000 affected females 65,000–83,000 total cases
Existing therapies authorized	Training and education
US sponsor	Confluence Pharmaceuticals LLC

Fragile X syndrome is a genetic condition with a wide variety of symptoms and disabilities, the most common of which is mental retardation. Because males have a single copy of the X chromosome, they are at higher risk for the disease than are females. The disease is caused by a genetic change in the *FMR1* gene, and it is possible to develop fragile X syndrome without a family history of the disease. Acamprosate received designation based on a small clinical trial which found that individuals receiving the drug had improved communication and social behavior than those in the control group.[7]

4. Neridronate

Active substance	Neridronate
Orphan designation	Treatment of complex regional pain syndrome (CRPS-I, CRPS-II, CRPS-NOS
Designation date	March 25, 2013
Prevalence/total US cases	66,000
Existing therapies authorized	Rehabilitation therapy, psychotherapy, NSAIDs, corticosteroids, botox, opioids, NMDA receptor antagonists, topical anesthetics, calcitonin, antidepressants, antiseizure medications
US sponsor	Grunenthal USA, Inc.

Complex regional pain syndrome (CRPS) is a condition in which individuals experience prolonged pain or dramatic changes in skin color, temperature, and/or swelling in the affected area. In certain individuals the pain may be constant, and in others it may be extremely uncomfortable and severe. The pain can vary from a burning sensation to "pins and needles"; it also can feel as if someone is squeezing the affected limb. CRPS is believed to be caused by damage to, or malfunction of, the peripheral and central nervous systems. Those with CRPS-II (previously called causalgia) have confirmed nerve damage, whereas those with CRPS-I do not have confirmed nerve damage. A third category, CRPS-NOS , was added to address patients who appear to have CRPS but do not meet the diagnostic criteria of CRPS-I or CRPS-II. Neridronate received designation based on early clinical studies in which the treatment group's visual analog scale decreased significantly from baseline.[8,9]

5. Liposomal amikacin

Active substance	Liposomal amikacin
Orphan designation	Treatment of infections caused by nontuberculous mycobacteria
Designation date	March 25, 2013
Prevalence/total US cases	150,000 cases
Existing therapies authorized	Multiple antibiotic therapies
US sponsor	Insmed, Inc.

Nontuberculous mycobacteria (NTM) infections manifest in 4 types of disease: localized cutaneous lesions, pulmonary disease, lymphadenitis, and disseminated disease. These infections are of growing interest because, in populations where tuberculosis rates have declined, NTM infections have become an increasing portion of granulomatous disease cases. Also, these infections are becoming increasingly more common among patients with AIDS. Like infections with *Mycobacterium tuberculosis*, NTM infections are difficult to treat and poorly characterized. Liposomal amikacin received designation for the novel preparation of packing amikacin within phospholipid vesicles, which greatly improved its microbiologic and pharmacologic activity over free amikacin.[10,11]

6. Kre-Celazine

Active substance	Kre-Alkalyn (US Patent 6,399,661) bonded to esterified fatty acid carbons
Orphan designation	Treatment of juvenile rheumatoid arthritis joint and related tissue inflammation in the pediatric population
Designation date	April 1, 2013
Prevalence/total US cases	11,700–69,000 aged ≤18 years 10,300–60,900 aged ≤16 years
Existing therapies authorized	NSAIDs, DMARDs, immunosuppressants, TNF blockers, exercise
US sponsor	All American Pharmaceutical & Natural Foods Corporation

Juvenile rheumatoid arthritis (JRA) is a chronic disease that affects children 6 months to 16 years of age and persists throughout their lifetime. The exact cause of JRA is unknown; however, experts suspect that it is an autoimmune disorder. In patients with JRA, the immune system attacks and destroys healthy body tissues within joints, which left untreated results in long-term damage. Existing therapies focus on decreasing inflammation, slowing progression of disease, suppressing the immune response, decreasing pain, and maintaining joint flexibility. Kre-Celazine received designation for its ability to reduce inflammation and pain in arthritic joints.[12-14]

7. Recombinant human tripeptidyl-peptidase 1 (rhTTP1)

Active Substance	rhTTP1
Orphan designation	Treatment of neuronal ceroid lipofuscinosis type 2
Designation date	April 1, 2013
Prevalence/total US cases	450–2800
Existing therapies authorized	Palliative
US sponsor	BioMarin Pharmaceutical Inc.

Neuronal ceroid lipofuscinosis type 2 (CLN2) is also known as late-infantile neuronal ceroid lipofuscinosis or Jansky-Bielschowsky disease. It is caused by an autosomal recessive mutation in the tripeptidyl-peptidase 1 gene (*TPP1*), which inactivates the lysosomal enzyme. Patients with CLN2 first develop symptoms around age 2 to 4 years and have a life expectancy from age 6 years to early teens. These symptoms begin with epilepsy and are followed by regression of developmental milestones, myoclonic ataxia, and pyramidal signs. Visual impairment accompanies the disease and rapidly progresses to light/dark awareness only. Current treatment options are palliative and symptomatic only, and individuals with a family history of the disease are encouraged to receive genetic counseling. Recombinant human tripeptidyl-peptidase 1 received designation for its ability to replace the inactive form of *TPP1* in ailing patients.[15]

8. Feiba NF

Active substance	Anti-inhibitor coagulant complex
Orphan designation	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A and B patients with inhibitors
Designation date	April 12, 2013
Prevalence/total US cases	30,000 hemophilia A 15,000 hemophilia B 45,000 total cases
Existing therapies authorized	Prophylaxis or intermittent, on-demand factor therapy
US sponsor	Baxter Healthcare Corporation

Within the United States, hemophilia A and B affects 30,000 and 15,000 individuals, respectively. Both diseases are characterized by the inability to form proper blood clots at the sites of injury or bleeding. Owing to the lack of specific clotting factors, spontaneous surface bleeding may occur, which typically requires a hospital visit for proper treatment and cessation of bleeding. Feiba NF received designation as a portable prophylaxis unit for patients with hemophilia.[16,17]

9. Givinostat

Active substance	Givinostat
Orphan designation	Treatment of Duchenne muscular dystrophy and Becker muscular dystrophy
Designation date	April 12, 2013
Prevalence/total US cases	4000–6000 cases in males aged 4–24 years
Existing therapies authorized	Palliative
US sponsor	Italfarmaco SpA

Duchenne muscular dystrophy is an X-linked recessive, rapid onset, rapidly progressing form of muscular dystrophy caused by a defective gene for dystrophin. It often occurs in people without a known family history of the disease. Individuals with Duchenne muscular dystrophy display reduced intelligence, rapidly progressing muscle weakness, and intellectual disability. Persons with Becker muscular dystrophy display symptoms similar to Duchenne muscular dystrophy cases; however, disease progression is slower.[18,19] Gavinostat helps treat these patients by inhibiting histone deacetylase, resulting in beneficial epigenetic changes.[20]

10. Melatonin

Active substance	N-acetyl-5-methoxytryptamine
Orphan designation	Treatment of neonatal hypoxic ischemic encephalopathy
Designation date	April 12, 2013
Prevalence/total US cases	5200–6800 cases per year
Existing therapies authorized	Hypothermia or stabilizing care
US sponsor	Scharper SpA

Neonatal hypoxic ischemic encephalopathy (HIE) causes long-term neurologic complications in newborns. Current treatments for neonatal HIE cases involve induced hypothermia and focus on palliative or stabilizing care. Melatonin is a powerful antioxidant capable of passing the blood-brain barrier, reducing the oxidative stress from an HIE event.[21]

11. Recombinant humanized IgG1k monoclonal antibody (mAb) to human invariant T-cell receptor (iTCR)

Active substance	Recombinant humanized IgG1k mAb to human iTCR
Orphan designation	Treatment of sickle cell disease
Designation date	April 12, 2013
Prevalence/total US cases	90,000–100,000 cases
Existing therapies authorized	Antibiotics, pain medication, hydroxyurea, transfusions, supplemental oxygen, bone marrow transplant
US sponsor	NKT Therapeutics, Inc.

Sickle cell disease (SCD) affects millions worldwide but only affects 100,000 cases in the United States. Individuals with SCD have less access to comprehensive health care than do people with genetic disorders (such as cystic fibrosis or hemophilia), and the average lifetime of a patient with SCD is 30 to 40 years less than the national average. Because sickle cell disease is a genetic condition, approved treatments focus on palliative care and reducing risks. Furthermore, patients with sickle cell disease suffer from chronic inflammation associated with the disease pathology. Recombinant humanized IgG1k monoclonal antibody to human invariant T cell receptor received designation for its ability to reduce the amount of invariant natural killer T cells (iNKT) thereby decreasing the damaging inflammation associated with the disease.[22,23]

12. Apatone

Active substance	Sodium ascorbate and menadione sodium bisulfite
Orphan designation	Treatment of autosomal dominant polycystic kidney disease
Designation date	April 15, 2013
Prevalence/total US cases	1 in 500–1000 live births
Existing therapies authorized	Treatment of manifestations
US sponsor	IC-MedTech Corporation

Autosomal dominant polycystic kidney disease (ADPKD) is the prevalent form of polycystic kidney disease. It is caused by a mutation in *PKD1* or *PKD2*; 95% of patients inherited the gene from their parents and 5% have a de novo mutation. About 85% of ADPKD patients have a mutation in the *PKD1* gene coding for polycystin-1. The disease affects multiple organs (liver, seminal vesicles, pancreas, vasculature, abdominal wall), and 50% of cases develop end-stage renal failure by age 60 years. The gene mutations have high penetrance, and all adults develop multiple bilateral cysts. Apatone received designation for its ability to target cell-cycle machinery and decrease cell hyperproliferation, and reduce hepatic and renal cyst formation.[24]

13. sdTD-K6a.513a.12; small interfering RNA composed of 2 strands of hybridized RNAs

Active substance	sdTD-K6a.513a.12; small interfering RNA composed of 2 strands of hybridized RNAs
Orphan designation	Treatment of pachyonychia congenita
Designation date	April 15, 2013
Prevalence/total US cases	<1 in 100,000 ~1000 registered worldwide
Existing therapies authorized	Palliative
US Sponsor	TransDerm, Inc

Pachyonychia congenita (Jackson-Lawler syndrome or Jadassohn-Lewandowski syndrome) is an extremely rare, autosomal dominant, genetic disorder that primarily affects the skin and nails. The symptoms manifest within the first few months of life and include hypertrophic nail dystrophy, painful blisters, palmoplantar keratoderma, oral leukokeratosis, follicular keratosis, cysts, palmoplantar hyperhidrosis, and steatocystomas. Researchers have identified mutations in keratin genes (*KRT6A*, *KRT6B*, *KRT16*, *KRT17*) that cause the disease. TransDerm's sdTD-K6a.513a.12; small interfering RNA composed of 2 strands of hybridized RNAs received orphan designation for being the only therapy for pachyonychia congenita and because it is specific to the mutation that causes the disease.[25]

14. Recombinant human α-N-acetylglucosaminidase

Active substance	Recombinant human α-N-acetylglucosaminidase
Orphan designation	Treatment of mucopolysaccharidosis IIIB (Sanfilippo B syndrome)
Designation date	April 15, 2013
Prevalence/total US cases	1600 cases
Existing therapies authorized	Palliative
US sponsor	Synageva BioPharma Corp.

Mucopolysaccharidosis IIIB (MPS IIIB, Sanfilippo syndrome type B) is an autosomal recessive, neurodegenerative disease of children. Mutation within the *NAGLU* gene leads to severe mental retardation and dementia, which appear after the first year of life. Long-term prognosis is poor, with few individuals surviving beyond their teen years. Recombinant human α-N-acetylglucosaminidase received designation as a treatment for MPS IIIB.[26,27]

15. Apatone

Active substance	Sodium ascorbate and menadione sodium bisulfite
Orphan designation	Treatment of autosomal dominant polycystic liver disease
Designation date	April 15, 2013
Prevalence/total US cases	3200–29,000
Existing therapies authorized	Aspiration, surgery, resection, transplantation
US sponsor	IC-Medtech Corporation

Autosomal dominant polycystic liver disease (ADPLD) is defined by having multiple bile duct–derived epithelial cysts scattered throughout the liver parenchyma. ADPLD was believed to be a result of autosomal dominant polycystic kidney disease until 2003, when researchers identified the *PRKCSH* and *SEC63* genes as causes of ADPLD. Apatone received designation for reducing cell hyperproliferation and hepatic cyst formation.[28,29]

16. 4-(6-(4-(piperazin-1-yl)phenyl pyrazolo[1,5-a]pyrimidin-3-yl)quinoline hydrochloride

Active substance	4-(6-(4-(piperazin-1-yl)phenyl pyrazolo[1,5-a]pyrimidin-3-yl)quinoline hydrochloride
Orphan designation	Treatment of fibrodysplasia ossificans progressiva
Designation date	April 15, 2013
Prevalence/total US cases	160–320 cases
Existing therapies authorized	Palliative
US sponsor	La Jolla Pharmaceutical Company

Fibrodysplasia ossificans progressiva (FOP) is an autosomal dominant disorder in which muscle and connective tissue are gradually replaced by bone (ossified). The process begins in the neck and shoulders and works its way downward and into the limbs. Injury to muscle, as well as bouts of influenza, accelerates the process. A characteristic sign of the condition is malformation of the great toes. La Jolla Pharmaceutical Company's product, 4-(6-(4-(piperazin-1-yl)phenyl pyrazolo[1,5-a]pyrimidin-3-yl)quinoline hydrochloride, is a kinase inhibitor that targets bone morphogenic protein type -1 receptor and has received designation for being the only treatment developed for FOP.[30,31]

17. Actemra

Active substance	Tocilizumab
Orphan designation	Treatment of systemic sclerosis to be a separate disease or condition from localized scleroderma
Designation date	April 17, 2013
Prevalence/total US cases	89,000 cases
Existing therapies authorized	Anti-inflammatories, NSAIDs, ACE inhibitors, palliative
US sponsor	Genentech, Inc.

Systemic sclerosis is characterized by accumulation of collagen in skin and other organs. It is classified as an autoimmune disease and its cause is unknown. Death occurs from pulmonary, heart, or kidney failure. Actemra received designation for its ability to suppress autoimmune responses by binding interleukin-6 receptor.[32]

18. Replication-deficient recombinant serotype 2 adeno-associated viral vector containing hAQP1 cDNA

Active substance	Replication-deficient recombinant serotype 2 adeno-associated viral vector containing hAQP1 cDNA
Orphan designation	Treatment of symptoms of grade 2 and grade 3 late xerostomia from parotid gland hypofunction caused by radiotherapy for cancer of the oral cavity
Designation date	May 3, 2013
Prevalence/total US cases	<200,000
Existing therapies authorized	Wetting treatments
US sponsor	John A. Chiorini, PhD National Institutes of Health

Xerostomia (dry mouth) is common in patients who receive radiotherapy for head or neck cancers. Half of the survivors develop irreparable damage to salivary glands and decreased saliva production–the parotid is a major salivary gland. Conventional therapies do little to alleviate or treat the symptoms of xerostomia. Saliva is an integral part of the maintenance and physiology of the upper gastrointestinal tract, serving as a lubricant and an antimicrobial with remineralizing and reparative functions. Patients with severe xerostomia have recurrent oral infections, mucositis, dysphagia, discomfort, decrease in quality of life, and a high morbidity rate. AAV gene therapy with the *hAQP1* (human aquaporin 1) gene provides promise for increasing salivary flow.[33,34]

19. Recombinant fusion protein linking coagulation factor VIIa with albumin (rVIIa-FP)

Active substance	rVIIa-FP
Orphan designation	Treatment of congenital factor VII deficiency, which includes treatment and prophylaxis of bleeding episodes in patients with congenital factor VII deficiency
Designation date	May 6, 2013
Prevalence/total US cases	640 cases
Existing therapies authorized	NovoSeven (eptacog alfa) and AryoSeven for uncontrolled bleeding
US sponsor	CSL Behring

Congenital factor VII deficiency (congenital proconvertin deficiency) is an extremely rare genetic disorder in which a key enzyme in the coagulation cascade is deficient or nonfunctioning. Patients with factor VII deficiency present similarly to people with hemophilia, and treatments to stop bleeding involve similar recombinant proteins or concentrates. CSL Behring's product, rVIIa-FP, received designation as a novel method for providing factor VII, which decreases immunologic response against recombinant factor VII .[35,36]

20. Teprotumumab

Active substance	Teprotumumab
Orphan designation	Treatment of active (dynamic) phase of Graves' orbitopathy
Designation date	May 6, 2013
Prevalence/total US cases	31,000 cases
Existing therapies authorized	Palliative, anti-inflammatory drugs, surgery
US sponsor	River Vision Development Corp.

Graves' disease is an autoimmune disease that commonly affects the thyroid and eyes. The 2 categories of Graves' ophthalmopathy are the dynamic or active phase, which occurs over a period of months, and the plateau phase, which lasts for years and displays the "bug-eyes" or "bulging eyes" characteristic of the disease. Aside from surgery, current treatments focus on prevention by treating the hyperthyroidism associated with Graves' disease. Recent studies have found elevated levels of insulin-like growth factor-1 receptor (IGF-R1) to be associated with disease pathology. Teprotumumab received designation for being a well-tolerated antibody against IGF-R1.[37]

21. Zometa (Reclast, Aclasta)

Active substance	Zoledronic acid
Orphan designation	Treatment of complex regional pain syndrome
Designation date	May 6, 2013
Prevalence/total US cases	~60,000 cases
Existing therapies authorized	Occupational/physical therapy, nerve blocks, surgery, analgesics, antidepressants, corticosteroids, muscle relaxants, sleeping medications, opioids, antiseizure drugs
US sponsor	Axsome Therapeutics, Inc

Complex regional pain syndrome (CRPS) is a chronic pain condition with unknown triggers. Experts believe that trauma–both major and minor–can trigger the condition in anyone, regardless of age, although it is more common in women. In mild or minor cases of CRPS, the symptoms gradually fade with time and patients return to normal functionality. However, in severe cases, patients may be left with long-lasting, crippling pain resulting in disability. Zolendronic acid was designated as a treatment for CRPS based on a successful case report.[8,38]

22. Hepatitis B virus neutralizing human monoclonal antibody (mAb)

Active substance	Hepatitis B virus neutralizing human mAb
Orphan designation	Prevention of hepatitis B recurrence following liver transplantation
Designation date	May 6, 2013
Prevalence/total US cases	~3000–6000
Existing therapies authorized	Alpha-interferon , viral replication inhibitors, antibody therapy
US sponsor	Green Cross Corp.

Liver transplant is the only treatment for hepatitis B infection that results in liver failure. However, the rate of recurrent infection within this patient population is high (70%–80%), which does not cure the patient of the disease and will ultimately result in another liver failure. Various practices have been applied to prevent the rate of reinfection, most aimed at halting viral replication or reducing viral load. Hepatitis B virus neutralizing human mAb received designation as a human antibody against hepatitis B that is administered post surgery.[39,40]

23. Uceris

Active substance	Budesonide
Orphan designation	Treatment of ulcerative colitis in pediatric patients aged 0–16 years
Designation date	May 6, 2013
Prevalence/total US cases	11,000–65,000
Existing therapies authorized	Aminosalicylates, steroids, immune modifiers, antibiotics, surgery
US sponsor	Santarus, Inc

Ulcerative colitis is an inflammatory bowel disease caused by an autoimmune response against the top layers of the colon. Children with the condition may not develop or grow properly. Symptoms include cramping abdominal pain, severe urgency to have a bowel movement, onset of sudden uncontrollable diarrhea, and loose stool. Most treatments aim toward inducing remission of the symptoms, followed by maintenance. Surgery is a curative option exercised when all other options have been exhausted. Uceris received designation for being a safe and specific drug therapy for ulcerative colitis in pediatric patients.[41,42]

24. Adeno-associated viral vector serotype rh.10 carrying the human SGSH and SUMF1 cDNAs

Active substance	Adeno-associated viral vector serotype rh.10 carrying the human SGSH and SUMF1 cDNAs
Orphan designation	Treatment of mucopolysaccharidosis type IIIA (Sanfilippo type A syndrome)
Designation date	May 6, 2013
Prevalence/total US cases	3200–4500
Existing therapies authorized	Palliative
US sponsor	Lysogene

Mucopolysaccharidosis type III (MPS III) is a rare genetic disorder resulting in the inability to break down heparan sulfate sugar chains. The systemic buildup of the glycosaminoglycans results in cell death that affects appearance, physical abilities, organ function, and mental development. There are 4 types of MPS III, each associated with a necessary enzyme for the degredation of heparan sulfate sugar chains. MPS IIIA (Sanfilippo type A syndrome) is the most common form of MPS III and is caused by a mutation in heparan N-sulfatase. Life expectancy is varied; however, most individuals succumb to the disease in their teens. Adeno-associated viral vector serotype rh.10 carrying the human SGSH and SUMF1 cDNAs received designation for having the potential to provide a lasting cure for patients with MPS IIIA.[26,43]

25. Isavuconazonium sulfate

Active substance	Isavuconazonium sulfate
Orphan designation	Treatment of invasive aspergillosis
Designation date	May 6, 2013
Prevalence/total US cases	3200–6400
Existing therapies authorized	Voriconazole, itraconazole, lipid amphotericin, caspofungin, micafungin, posaconazole
US sponsor	Astellas

Aspergillosis is rare in the general population but is common in patients with compromised immune function. With a growing number of patients with neutropenia or taking immunosuppressant medication, aspergillosis rates are on the rise. Invasive aspergillosis comes in a variety of forms, such as pulmonary, tracheobronchial, chronic necrotizing pulmonary, single-organ, extrapulmonary, central nervous system, sinonasal, endocarditis, pericarditis, and myocarditis, to name just a few. All forms of invasive aspergillosis prove difficult to treat and many result in death or disfiguring surgical interventions. Isavuconazonium sulfate received designation based on a completed clinical trial and for being a novel water-soluble, broad-spectrum antifungal effective against fluconazole-resistant aspergillus.[44,45]

26. H-Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-alys-aleu-Ser-Ser-Ile-Glu-Ser-Asp-Val-OH

Active substance	H-Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-alys-aleu-Ser-Ser-Ile-Glu-Ser-Asp-Val-OH
Orphan designation	Treatment of subarachnoid hemorrhage
Designation date	May 14, 2013
Prevalence/total US cases	19,000–52,000
Existing therapies authorized	Surgery, endovascular embolization
US sponsor	NoNO Inc

Subarachnoid hemorrhage is bleeding in the area between the brain and the thin tissues that cover it. Because of its close proximity to the brain, a host of complications can arise from this condition, such as stroke, brain damage, coma, and death. Treatment focuses on preserving the patient's life, repairing the cause of bleeding, alleviating symptoms, and preventing permanent brain damage such as strokes. In certain cases, however, the cause of bleeding cannot be ascertained, and the patient is closely monitored. NoNO, Inc's peptide sequence received designation for its ability to inhibit neuronal death by inhibiting PSD-95, a key protein in the prodeath pathway.[46,47]

27. 3,5-diiodothyropropionic acid

Active substance	3,5-diiodothyropropionic acid
Orphan designation	Treatment of Allan-Herndon-Dudley syndrome
Designation date	May 14, 2013
Prevalence/total cases	<25 worldwide
Existing therapies authorized	Palliative
US sponsor	Zarion Pharmaceuticals P/L

Allan-Herndon-Dudley syndrome is an extremely rare, X-linked recessive genetic disorder in which the *SLC16A2* gene, a key receptor-transport protein (MCT8), is disrupted. Males with this condition have moderate to severe mental retardation, hypotonia (weak muscle tone), and muscle hypoplasia (underdeveloped muscles), and joint deformities called contractures form as they age. *SLC16A2* forms a protein that facilitates transfer of triiodothyronine (T3) into developing brain cells; T3 is a necessary hormone for normal function and growth of neurons, and plays a critical role in the development of synapses. 3,5-dilodothyropropionic acid was designated for being a weak agonist for α and β thyroid hormone receptors and because it is able to enter cells without aid of the MCT8 receptor.[48-50]

28. 2-[4-Methoxy-3-(2-m-tolyl-ethoxy)-benzylamine]-indian-2-carboxylic acid

Active substance	2-[4-Methoxy-3-(2-m-tolyl-ethoxy)-benzylamine]-indian-2-carboxylic acid
Orphan designation	Treatment of patients with systemic sclerosis
Designation date	May 14, 2013
Prevalence/total US cases	89,000
Existing therapies authorized	Anti-inflammatories, NSAIDs, ACE inhibitors, palliative
US sponsor	Sanofi U.S., Inc.

Systemic sclerosis is characterized by accumulation of collagen in skin and other organs. It is classified as an autoimmune disease and its cause is unknown. Death occurs from pulmonary, heart, or kidney failure. In mouse models of the disease, scientists have found overexpression of the LPA-LPA1 pathway, which results in recruitment of fibroblasts and vascular leaking, to be strongly correlated to the disease state. Sanofi's 2-[4-Methoxy-3-(2-m-tolyl-ethoxy)-benzylamine]-indian-2-carboxylic acid received designation for preclinical studies in which oral doses of up to 1000 mg of LPA1 inhibitor were well tolerated by patients for 14 days.[32,51]

29. HIRMAb-IDS

Active substance	HIRMAb-IDS
Orphan designation	Treatment of mucopolysaccharidosis type II (Hunter syndrome)
Designation date	May 15, 2013
Prevalence/total US cases	2100 males
Existing therapies authorized	Management of symptoms, palliative
US sponsor	ArmaGen Technologies, Inc.

Mucopolysaccharidosis II (MPS II, Hunter syndrome) is the only X-linked MPS disease. It is caused by a deficiency of the lysosomal enzyme iduronate-2-sulfatase, which leads to the accumulation of glycosaminoglycans in all tissue types. Death typically occurs in the patients' 20s, although those with mild symptoms can live until their 50s. HIRMAb-IDS received designation for being a combination insulin receptor monoclonal antibody fused to iduronate 2-sulfate designed to cross the blood-brain barrier (BBB) through use of the existing insulin receptors on the BBB.[52,53]

30. Terguride

Active substance	Terguride
Orphan designation	Treatment of systemic sclerosis
Designation date	May 17, 2013
Prevalence/total US cases	89,000
Existing therapies authorized	Anti-inflammatories, NSAIDs, ACE inhibitors, palliative
US sponsor	Serodapharm UG

Systemic sclerosis is characterized by accumulation of collagen in skin and other organs. It is classified as an autoimmune disease and its cause is unknown. Death occurs from pulmonary, heart, or kidney failure. Elevated levels of serotonin have been found in patients with systemic sclerosis. Serotonin, in addition to being a neurotransmitter, binds receptors on the surfaces of cells and induces connective tissue proliferation. Terguride received orphan designation from the FDA as a serotonin antagonist capable of inhibiting the production of fibrous connective tissue.[32,54]

31. HIRMAb-IDS

Active substance	rFVIIa molecule
Orphan designation	Treatment of bleeding episodes in hemophilia A or B subjects with inhibitors
Designation date	May 30, 2013
Prevalence/total US cases	~15,000 (1/3 of all people with hemophilia)
Existing therapies authorized	High-dose clotting factors, bypassing agents, immune tolerance induction therapy (stop inhibitor response)
US sponsor	Bayer HealthCare Pharmaceuticals Inc.

Patients with hemophilia use recombinant clotting factors or clotting factor concentrates. Eventually, an immunologic response against these beneficial agents develops, and patients become susceptible to uncontrolled bleeding events. Treating patients with hemophilia with inhibiting agents proves to be challenging and cost-inefficient, owing to the staggering amounts of clotting factors needed to stop bleeding incidents. Inhibitors typically develop within the first year of therapy in immune-naive patients with hemophilia. rFVIIa received designation for being able to circumvent specific steps in the coagulation pathway, thereby reducing dosing frequency compared with the available recombinant bypassing agent.[36,55,56]

32. Diazepam auto-injector

Active substance	Diazepam auto-injector
Orphan designation	Management of selected, refractory patients with epilepsy on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity
Designation date	May 30, 2013
Prevalence/total US cases	2 million with epilepsy 20%–40% become refractory <200,000
Existing therapies authorized	
US sponsor	Meridian Medical Technologies, Inc

Epilepsy is a chronic neurologic condition of recurrent seizures. It affects 2 million Americans and accounts for $15.5 billion in direct and indirect costs annually. Most patients respond to drug therapy; however, 20% to 40% of these patients become refractory, having either partial or no response to therapeutics. Diazepam auto-injector for the management of select refractory patients with epilepsy received designation as a portable administration system for those with epilepsy, which promises help in minimizing symptoms for refractory patients.[57-59]

33. Orencia

Active substance	Abatacept
Orphan designation	Treatment of patients with type 1 diabetes mellitus and residual β-cell function
Designation date	May 30, 2013
Prevalence/total US cases	25,000–55,000
Existing therapies authorized	Insulin therapy
US sponsor	Orban Biotech, LLC

Type 1 diabetes mellitus (T1DM) is primarily caused by an autoimmune-mediated destruction of a patient's β cells. Almost 100% of patients with T1DM retain β-cell function for the first 2 years after diagnosis; however, after 15 to 35 years, only 15% have residual function. Orencia, originally approved for rheumatoid arthritis, received designation for T1DM after clinical trials ascertained that abatacept helped preserve β-cell function in patients by inhibiting T-cell response by way of T-cell anergy.[60,61]

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