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The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity?

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ABSTRACT

Objectives: This study investigates issues associated with the United States Orphan Drug Act.
Methods: A comprehensive orphan drug database was compiled from FDA data and corporate annual reports of major pharmaceutical companies. Analysis allowed the generation of a descriptive orphan drug portrait as well as documentation of orphan drugs along their lifecycle.
Results: Currently, 2002 products have obtained orphan drug designation with 352 drugs obtaining FDA approval. Approximately 33% of orphan drugs are oncology products. On average, products obtain 1.7 orphan designations with approximately 70% obtaining a single designation. At least 9% of orphan drugs have reached blockbuster status with two-thirds having two or more designations. An additional 25 orphan drugs had sales exceeding US$ 100 million in 2008 alone. Since 1983, at least 14 previously discontinued products have been recycled as orphan drugs.
Conclusions: The United States Orphan Drug Act has created issues which, in some cases, have led to commercial and ethical abuses. Orphan Drug Act reform is necessary but current incentives, including 7 year market exclusivity, should be maintained in order to favour patients as well as economic prosperity. Suggested reforms include price regulation, subsidy paybacks for profitable drugs and the establishment of an International Orphan Drug Office.

1. Introduction

The United States Drug Act was implemented as a direct result of the political and social context following the thalidomide scandal of the late 1950s. The Kefauver–Harris amendments of 1962 mandated that pharmaceuticals demonstrate their innocuity and therapeutic efficacy resulting in substantially increased drug development costs. In order to maximize returns, the pharmaceutical industry focused on large disease populations while smaller rare disease populations were "orphaned" [1]. NGOs, such as the National Organisation for Rare Diseases, shed light onto the plight of rare disease sufferers and public pressure influenced political thinkers and health policy of the late 1970s [2]. With the objective of stimulating rare disease research as well as the development of pharmaceutical agents for the treatment of rare conditions, President Ronald Reagan signed the Orphan Drug Act (ODA) into law in 1983.

At the heart of the ODA, is the concept of "orphan disease" defined as a disease with a U.S. patient prevalence of less than 200 000 and/or for which drug development costs are unlikely to be recovered through sale in the United States [3,4]. The ODA created a number of incentives for the pharmaceutical industry which include: (i) 7

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year market exclusivity for orphan drugs; (ii) tax credits totalling half of development costs; (iii) research and development grants; (iv) fast-track development and approval; (v) access to Investigational New Drug Program and pre-approval; (vi) waived drug application fees [2,3]. Orphan drug status is granted through the FDA and is independent of the patent system [2]. In addition, orphan drug market exclusivity periods come into effect at the date of market approval and are not expended during product development [1,2].

With over 2000 orphan designations and an excess of 300 currently approved orphan drugs, the US Orphan Drug Act appears highly successful. Nonetheless, the current political, social and economic context has evolved over the 25 years since its implementation. Mean patient populations for orphan diseases are consistently rising [5] and technological advances forecast an era of personalised medicine. According to the National Institutes of Health, a total of 6819 rare diseases are presently registered in the United Sates [6]. These diseases afflict an estimated 20–25 million Americans and approximately 250 new rare diseases are described annually [6]. Manufacturers are increasingly interested in orphan designation as orphan drugs often face less competition and are more likely to demonstrate "proof of concept" [3,6]. In addition, the ODA may potentially provide manufacturers with non-economic advantages as a company's ethical profile may benefit from the association to a rare disease [4]. As a result, orphan drugs are likely to seize an increasingly greater proportion of the annually approved pharmaceutical products and occupy larger fractions of healthcare budgets. In effect, sales of biopharmaceutical drugs, which include many orphan drugs, have increased by over 100% in the US and over 200% in most European nations during 2001–2005 [7].

Few studies have exposed the issues surrounding the orphan drug act. In addition, most of these investigations have based their conclusions on a relatively small number of exceptional and controversial orphan drugs. Few studies have used a quantitative approach or addressed orphan drugs in general along with extreme cases. Yin [8] is among the first studies to investigate the effects of ODA incentives on pharmaceutical innovation through mathematical analysis of an orphan drug database. Seoane-Vazquez et al. [6] investigated the effect of orphan drug status on market exclusivity length and provided a descriptive portrait of designated and approved orphan drugs. The present investigation attempts to expand ODA knowledge and stimulate discussion. Through the analysis of a comprehensive database, this study quantitatively characterises and describes the multiple outcomes of orphan drug products along their lifecycles. Advantages and disadvantages of the ODA are identified and presented. The frequency, extent and impact of ODA flaws are exposed and enumerated. Issues such as the validity of the currently accepted definition of orphan drug and rare diseases, the perceived profitability of orphan drugs, the vulnerability of patient populations and the potential need for ODA reform are addressed.

2. Methods

2.1. Data sources and database construction

Orphan drug data was obtained from the online List of Orphan Drug Designations and Approvals of the US Food and Drug Administration (last updated 5/5/2009; http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm). Designation date, market authorisation date, indication, sponsor, name of active ingredient and trade name of all drugs with orphan designations were entered into a Systat 8.0 data file (SPSS Inc, Chicago, USA). Data relating to the designation and approval date as well as product names for orphan drugs of the European Union were obtained from the online Register of Designated Orphan Medicinal Products of the European Commission-Enterprise and Industry (last updated 5/5/2009; http://ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm).

Based on the indication of each orphan designation, products were classified by therapeutic class (e.g. neurological disorders) according to the Merck Manual Online Medical Library (http://www.merck.com/mmpe/index.html). An additional therapeutic class was included to encompass oncology related orphan drug designations. For the purposes of this study, the WHO's International Classification of Diseases for Oncology (http://www.who.int/classifications/icd/en/) was used as a guide.

For each orphan drug, the presence of generic and/or brand name competitors was verified through an active ingredient search of the Drugs@FDA database (http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/). Competing products were classified as either having been previously launched or launched following the market approval of the earliest orphan drug for each respective pharmaceutically active ingredient. The current market status of products (available or discontinued) was also recorded.

In order to investigate the potential relationship between economic conditions and orphan drug approvals, economic data (United States annual GDP growth) was obtained from online databases of the Bureau of Economic Analysis of the US Department of Commerce (http://www.bea.gov/).

Online annual reports of major companies which sponsor/manufacture one or more orphan drugs were analysed in order to obtain global annual sales data for specific orphan drugs. Orphan drugs were also classified according to their manufacturer/sponsor type (e.g. biotechnology or pharmaceutical). For the purposes of this study, biotechnology companies are generally defined as "emerging firms with limited cash reserves which develop novel, often first-in-class, large molecule-based drugs" as described by Malik [9]. To obtain this classification, biotech research must be the core activity of the specified company.

The resulting comprehensive orphan drug database was analysed using Systat 8.0 graphic and descriptive statistics tools (SPSS Inc, Chicago). No data transformations were required or used during analysis. Resulting trends were summarized and presented as figures and tables

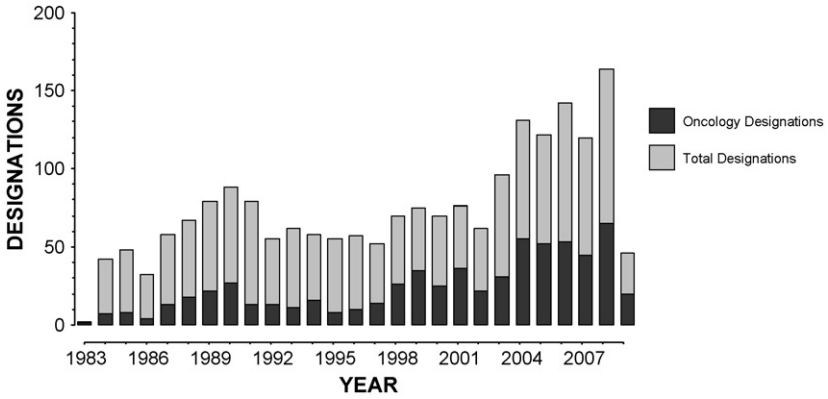

Fig. 1. Number of orphan drug designations granted each year in the United States by the Food and Drug Administration during the period of 1983–2009. The number of oncology products (black bars) which obtained orphan designation during this period is indicated as a fraction of the total annual orphan drug designations (grey bars).

constructed using Microsoft Office (Microsoft Corporation, Washington).

3. Results

3.1. Orphan designations granted in the United States

As of 5 May 2009, the FDA has granted 2002 orphan designations since the creation of the Orphan Drug Act. During its first year of implementation, only two products obtained orphan designation. In 2008, at its current highest point, 164 products were granted an orphan designation in this single year (Fig. 1). Over the last quarter century, the FDA has generally granted increasingly more orphan designations on an annual basis (Fig. 1). On average, 47 products per year were granted orphan designations during the period from 1983 to 1989. During the period of 1990–1999, this average had increased to 65 products per year and further increased to 109 products per year during the period of 2000–2008 (Fig. 1). These findings point to the success of the ODA in stimulating research into rare diseases especially in the current context of pharmaceutical R&D inefficiency. While the number of orphan designations granted yearly is increasing over time, this trend can be described as a three stage distribution rather than a continuity. In effect, the first phase, characterized by fast growth, appears to peak in 1990 (Fig. 1). This is soon followed by a second more uniform low growth phase, ending around 2001, and then succeeded by a third phase again characterized by fast growth (Fig. 1).

As demonstrated in Fig. 2, oncology products account for the greatest number of orphan designations (650 designations). Infectious and respiratory diseases as well as neurological, endocrine/metabolic, haematological and immunologic disorders are also major therapeutic classes which include more than 100 orphan designations per class

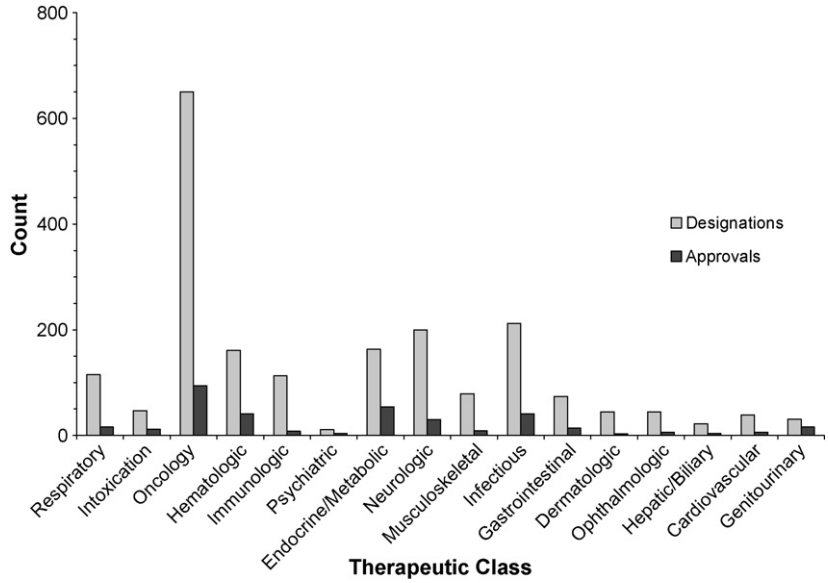

Fig. 2. Classification according to therapeutic class of orphan drug designations (grey bars) and orphan drug approvals (black bars) granted in the United States during the period of 1983–2009.

Table 1
Descriptive classification of orphan designated products with a trade name. Number of orphan designations, number of pharmaceutically active agents and number of new molecular entities which have obtained an orphan designation in the United States are indicated.

Designations per agent	Active agents	Orphan NMEs	Total designations with trade name
1	423	354	423
2	101	81	202
3	35	27	105
4	28	24	112
5	12	8	60
6	7	6	42
7	3	2	21
8	2	2	16
9	1	0	9
10 or more	4	2	80
Total	616	506	1070

(Fig. 2). Within these 6 therapeutic classes, only infectious diseases and neurological disorders account for 200 or more designations per class (212 and 200 designations, respectively). The other therapeutic classes, which include psychiatric, musculoskeletal, gastrointestinal, dermatologic, ophthalmologic, hepatic/biliary, cardiovascular and genitourinary disorders as well as drugs for the treatment of intoxications/envenomations, inclusively account for less than 20% of all orphan designations (Fig. 2).

As well as accounting for the majority of orphan designations, oncology products are a major contributor to the yearly growth of orphan designations. On average, 10 oncology related orphan designations per year were granted during the period from 1983 to 1989 (Fig. 1). During the period of 1990–1999, this average had increased to 17 oncology related orphan designations per year and to 43 oncology related orphan designations per year in the 2000–2008 period (Fig. 1). The distribution of oncology related orphan designations granted yearly is increasing over time and is also best described as a three-staged distribution (Fig. 1). No other therapeutic class demonstrated similar growth over time.

Of the 2002 orphan designations, 1070 have been given a trade name and are therefore likely progressing in their development process. A total of 616 unique pharmaceutically active agents account for the 1070 brand name products which have obtained orphan designations. Within these, 423 active agents have a single orphan designation, 101 have two designations, 35 have three designations, 28 have four designations, 12 active agents have five orphan designations and a total of 17 active agents have six or more orphan designations (Table 1). Most notably, interferon (alfa-2a/b, beta-1a/b and gamma-1b combined) with its nine brand name products accounts for 33 orphan designations including various cancers, idiopathic pulmonary fibrosis, papillomatosis, hepatitis, AIDS, multiple sclerosis and rheumatoid arthritis. The active agent, somatropin, with its eight brand name products accounts for 24 orphan designations related to either growth failure or cachexia. Coagulation factor, which is sold under the names MonoNine, AlphaNine, Benefix and NovoSeven, accounts for 13 orphan designations related either to haemophilia, thrombasthenia or blood factor deficiency. The active agent, levocarnitin, also known as Carnitor, accounts for 10 orphan designations of which the majority are related to carnitine deficiency. Of the 616 active agents with orphan designations, 82% are new molecular entities (NMEs) with no prior generic and/or brand name competitors (Table 1). Of these orphan designated NMEs, 70% have only one designation, 26% have two to four designations while 4% have five or more orphan designations per pharmaceutically active agent (Table 1).

The majority of orphan designated products (73%) are sponsored by biotechnology companies and these same companies sponsored 64% of all trade name products with orphan designations. Nonetheless, the top 10 biotechnology companies of 2008 account for only 12% of all biotechnology sponsored orphan drug designations and 15% of all biotechnology sponsored trade name products with orphan designations (Table 2). Most active are Genzyme and Amgen (35 and 33 orphan designations, respectively) as well as Genentech and Biogen (23 orphan designations each). The top 10 pharmaceutical companies, on the other hand, account for 51% of all orphan drugs sponsored by pharmaceutical companies and 49% of pharma sponsored trade name products with orphan designations (Table 2). Six of these pharmaceutical companies, notably Novartis, Johnson & Johnson, GlaxoSmithKline, Pfizer, AstraZeneca and Roche, individually account for 25 or more orphan designations (Table 2). As previously described [10,11], earlier orphan drug research and development is usually conducted by smaller start-up biotechnology enterprises. It also appears that pharmaceutical companies prefer to focus on marketing and relatively few, mostly large, pharmaceuticals conduct early stage orphan drug research and development.

3.2. Approved orphan drugs in the United States

Taking into account both the List of Orphan Drug Approvals as well as the Drugs@FDA database, 352 orphan drugs have been approved in the United States as of 5 May 2009. During the 1983–1989 period, 8 orphan drugs per year obtained FDA approval on average. From 1990 to 1999, this average had increased to 14 orphan drug approvals per year and in the 2000–2008 period, 15 orphan drugs per year obtained approval (Fig. 3). In common with the distribution of orphan designations granted yearly, the distribution of approved orphan drugs appears to be three phased and is marked by lows in the early 1990s and early 2000s (Fig. 3). In the early 1990s, ODA amendments, which would strip pharmaceuticals of their status if patient pop-

Table 2
Number of orphan drug designations, trade name orphan drugs and approved orphan drugs sponsored by the top 10 pharmaceutical and biotechnology companies. Indicated totals include products obtained as the result of previous company mergers.

Rank	Company	2007 Revenue (US$ million)	Orphan designation	Designated branded	Orphan approval
1	Pfizer	44,424	36	25	9
2	GlaxoSmithKline	38,501	41	27	18
3	Sanofi-Aventis	38,452	14	4	3
4	AstraZeneca	28,713	31	16	5
5	Merck	26,532	8	6	3
6	Novartis	25,477	50	34	21
7	Johnson & Johnson	24,866	48	35	7
8	Roche	21,988	25	22	7
9	Eli Lilly	17,638	9	7	4
10	Wyeth (acquired by Pfizer in 2009)	17,179	14	11	7
Top 10 Pharma Total			276	187	84
Pharmaceutical Total			541	382	175
1	Amgen	14,771	33	18	14
2	Genentech (acquired by Roche in 2009)	11,724	23	19	8
3	UCB SA	4972	7	1	0
4	Gilead Sciences	4230	6	3	2
5	Genzyme	3814	35	19	9
6	Biogen Idec	3172	23	8	1
7	CSL Ltd	2788	8	5	1
8	Cephalon	1773	14	11	3
9	Celgene	1406	17	12	5
10	Actelion	1098	8	6	3
Top 10 Biotech Total			174	102	46
Biotechnology Total			1461	688	177
Grand total		2002	1070	352	

ulations exceeded 200 000 and/or sales reached US$ 200 million, were proposed [12,13]. While these bills did not become law, it appears the associated uncertainty was significant enough to postpone growth of orphan drug designations and approvals for at least 5 years. The growth of orphan drug designations and approvals was also adversely affected during another occasion. The economic recession of the early 2000s and the associated shattered investor confidence made life much harder for start-up biotechnology companies and rare disease research. Additionally, the current recession most likely will have negative effects on orphan drug developments for 2009. Such events should remind potential ODA reformers of the sensitivity of rare disease research.

Oncology related products, at 27%, account for the majority of the approved orphan drugs (Fig. 2). Haematological (41), endocrine/metabolic (54) and neurological disorders (30) as well as infectious diseases (41) are the

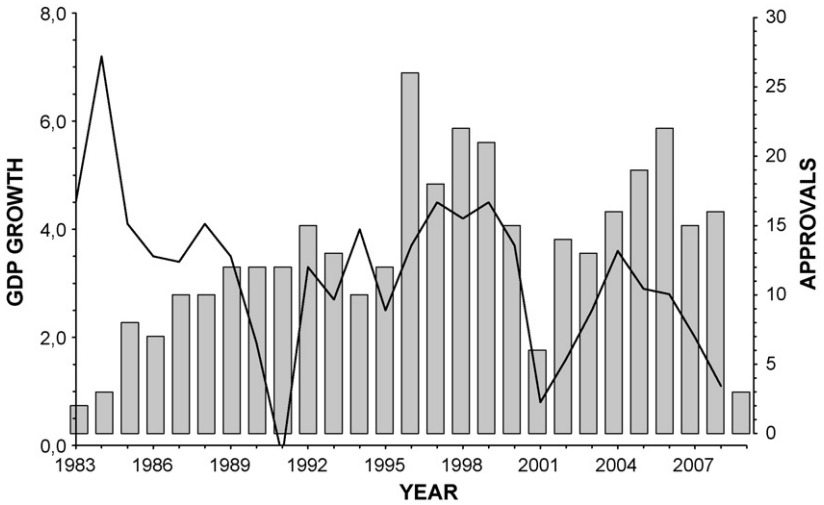

Fig. 3. Number of orphan drug market approvals granted each year in the United States by the FDA during the period of 1983–2009. The left *y*-axis indicates the annual gross domestic product growth rate (bold line) for the United States while the right *y*-axis indicates the annual number of orphan drug approvals (bars).

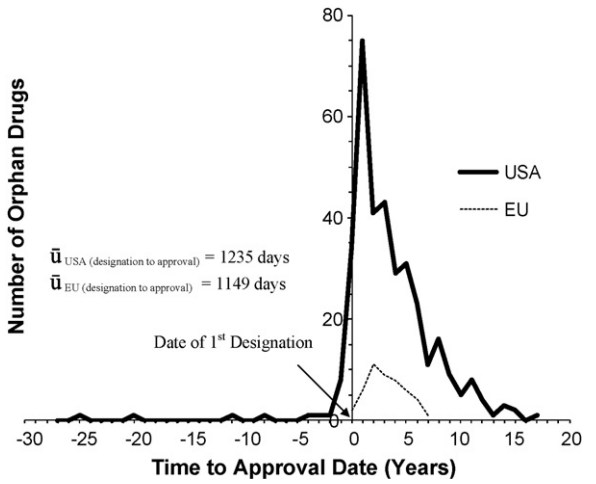

Fig. 4. Duration of product research and development for orphan drugs which have obtained market approval in the United States and the European Union. The time difference (nearest year) between approval date and orphan designation date is indicated with the *y*-axis assigned as the date of first orphan designation. Orphan drugs plotted left of the *y*-axis therefore obtained market authorisation prior to orphan drug designation.

only other therapeutic classes which account for 30 or more approved orphan drugs per class (Fig. 2). The other 11 therapeutic classes account for the remaining 26% of approved orphan drugs. As indicated in Table 2, pharmaceutical and biotechnology companies each roughly sponsor half of all approved orphan drugs. The top 10 pharmaceutical companies account for 48% of pharma sponsored approved orphan drugs while the top 10 biotechnology companies account for 26% of approved orphan drugs sponsored by biotech companies (Table 2). Within the biotechnology companies, only Amgen accounts for more than 10 approved orphan drugs while two pharmaceutical companies, namely GlaxoSmithKline and Novartis, account for 10 or more of pharma sponsored approved orphan drugs. These findings reflect the core activities of both biotechnology and pharmaceutical companies.

As can be seen in Fig. 4, 72% of the approved orphan drugs obtained market authorisation within 5 years of their orphan designation. The majority of products (21%) obtained market authorisation the year following their orphan designation and 34 products were approved in the same year they obtained their orphan designation (Fig. 4). These findings suggest that ODA incentives are effective in promoting the swift development of orphan drugs. Alternatively, the short development periods may merely reflect the reduced duration and complexity of orphan drug clinical studies due to small subject populations and difficulties associated with locating and recruiting candidates. Orphan drug incentives also appear to have had similar effects in the European Union with approximately 90% of approved orphan drugs reaching market authorisation within 5 years of orphan designation (Fig. 4). Nonetheless, the number of designated and/or approved orphan drugs in the European Union is much lower (Figs. 4 and 5) despite a common application form and slight variations in the definitions of orphan drugs. These differences cannot be attributed solely to the European Union's later enactment of orphan drug policies but are likely the result of multiple factors including lack of harmonization between EU member states, necessity to apply for tax credits in individual states, potential exclusively withdrawal for profitable drugs (although never invoked), higher patenting costs and relatively smaller market importance [11,14,15].

3.3. Blockbuster drugs with orphan designations

A total of 43 brand name drugs with global annual sales of greater than a billion US$, were identified to have orphan designations and are presented in Table 3. Of these blockbusters, 18 were approved solely as orphan drugs in the United States. Within these 18 orphan blockbuster drugs, 11 have reached blockbuster status within the 7 year orphan drug market exclusivity period (Table 3).

Only one product, Prograf, was designated prior blockbuster status and later obtained orphan drug approval (Table 3). Additionally, 7 drugs have obtained orphan designations in the years during or following their first

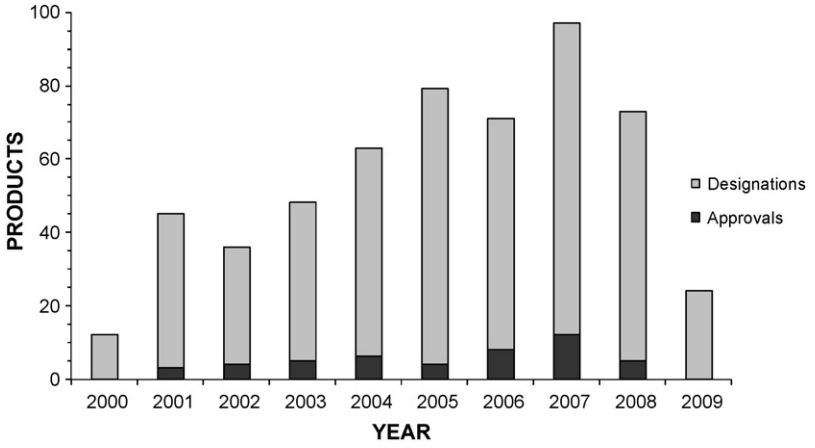

Fig. 5. Orphan drug designations and approvals in the European Union during the period covering 2000–2009. Number of orphan drug approvals (black bars) is indicated as a fraction of the total annual number of orphan drug designations (grey bars).

Table 3
Blockbuster drugs which have obtained orphan drug designation. For each pharmaceutical product, the earliest orphan designation date and approval date, as well as the first year where global annual sales surpassed 1 billion US$ is indicated. Brand name, generic name, approval type (new molecular entity), total number of orphan designations as well as the number of previous launches under the same brand name are also indicated.

Brand Name	Generic name	Sponsor	NME	Designation	Orphan approval	Designations	Prior launch[a]	First year blockbuster
Humira	Adalimumab	Abbott	Yes	2005	2008	2	1	2005
Fosamax	Alendronate	Merck	Yes	2001		2	3	2001
Ceredase	Alglucerase	Genzyme	Yes	1985	1991	2	0	2008
Abilify	Aripiprazole	Bristol-Myers Squibb	Yes	2006		1	4	2004
Avastin	Bevacizumab	Genentech	Yes	2003		4	1	2005
Velcade	Bortezomib	Millennium Pharma	Yes	2003	2003	2	0	2008
Tracleer	Bosentan	Acetelion	Yes	2000	2001	2	0	2007
Botox	Botulinum toxin	Allergan	Yes	1984	1989	4	0	2007
Novoseven	Coagulation factor	Novo Nordisk	No	1988	1999	10	3	2006
Epogen	Epoetin alfa	Amgen	Yes	1986	1989	2	0	1996
Procrit	Epoetin alfa	Johnson & Johnson	No	1987		3	1	1998
Enbrel	Etanercept	Amgen	Yes	1998	1999	2	1	2003
Neupogen	Filgrastim	Amgen	Yes	1990	1994	6	1	1997
Neurontin	Gabapentin	Pfizer	Yes	1995		1	7	2000
Copaxone	Glatiramer acetate	Teva Pharmaceuticals	Yes	1987	1996	2	0	2005
Gleevec	Imatinib	Novartis	Yes	2001	2001	7	0	2003
Cerezyme	Imiglucerase	Genzyme	Yes	1991	1994	1	0	2006
Remicade	Infliximab	Centocor	Yes	1995	1998	6	0	2002
Betaseron	Interferon beta-1b	Chiron	No	1988	1993	2	0	2004
Avonex	Interferon beta-1a	Biogen	No	1991	1996	2	0	2002
Rebif	Interferon beta-1a	Pfizer/Serono	No	1992		2	1	2004
Lamictal	Lamotrigine	GlaxoSmithKline	Yes	1995	1998	1	1	2004
Revlimid	Lenalidomide	Celgene	Yes	2001	2006	4	0	2008
Lupron	Leuprolide	Tap Pharmaceuticals	Yes	1988	1993	1	3	2002
Mobic	Meloxicam	Boehringer Ingelhein	Yes	2002	2005	1	2	2005
Provigil	Modafinil	Cephalon	Yes	1993	1998	1	0	2009
CellCept	Mycophenolate	Hoffmann-La Roche	Yes	2006		1	4	2002
Sandostatin	Octreotide	Novartis	Yes	1998	1998	3	1	2007
Kogenate	Octocog	Bayer Schering	Yes	1989	1993	2	0	2006
Taxol	Paclitaxel	Bristol-Myers Squibb	Yes	1997	1997	1	1	1998
Pegasys	Peginterferon alfa-2a	Hoffmann-La Roche	No	1998		2	1	2004
Alimta	Pemetrexed	Eli Lilly	Yes	2001	2004	1	0	2008
Mirapex	Pramipexole	Boehringer Ingelheim	Yes	2008		1	1	2008
Evista	Raloxifene	Eli Lilly	Yes	2005	2007	1	1	2004
Rituxan	Rituximab	Genentech	Yes	1994	1997	4	0	2002
Vioxx	Rofecoxib	Merck	Yes	2004		1	3	2000
Prograf	Tacrolimus	Astellas	Yes	1998	2006	2	2	2004
Cialis	Tadalafil	Eli Lilly	Yes	2006		1	1	2007
Temodar	Temozolomide	Schering-Plough	Yes	1998	1999	2	0	2008
Spiriva	Tiotropium	Boehringer Ingelheim	Yes	2008		1	1	2005
Topamax	Topiramate	Johnson & Johnson	Yes	1992	2001	1	3	2003
Herceptin	Trastuzumab	Genentech/Roche	Yes	1999		1	1	2003
Zometa	Zoledronic acid	Novartis	Yes	2000	2001	1	0	2004

[a] *Note*: Prior launch does not include new indications or new dose formulations.

blockbuster year and two of these blockbusters (Humira and Evista) have obtained orphan approval.

Of the remaining 17 blockbuster drugs with orphan designations, 9 have reached blockbuster status during or following the year of their orphan drug approval. For 7 of these cases, blockbuster status was achieved within the 7 year exclusivity period. The final 8 blockbuster drugs with orphan designations had been previously launched under the same brand name, have obtained orphan designation prior or during their first blockbuster year but have not currently been approved as orphan drugs (Table 3).

Within the 43 orphan designated blockbuster drugs, 18 had a single designation, 15 had two designations and 10 had three or more orphan designations (Table 3). The blockbusters, Epogen and Procrit, share the same pharmaceutically active agent (epoetin alfa) and have multiple orphan designations each. Betaseron, Avonex and Rebif also have the same pharmaceutically active agent (interferon-beta) and have each obtained two orphan designations (Table 3). Novoseven, Neupogen, Gleevec and Remicade are all examples of blockbuster drugs with five or more orphan designations each.

3.4. Orphan designated products with 2008 global sales of US$ 100–999 million

Through an investigation of corporate annual reports, 33 orphan designated drugs with 2008 global annual sales between US$ 100 and 999 million were identified. Of these commercially profitable products, 19 have been approved solely in the U.S. as orphan drugs and 6 have been approved as orphan drugs but previously launched under the same trade name (Table 4). Humatrope, Genotropin and Nutropin share the same pharmaceutically active agent

Table 4
Examples of commercially profitable drugs (100 to 999 million US$ in global annual sales) with orphan designations. For each pharmaceutical product, the earliest orphan designation date, the earliest orphan drug approval and the 2008 global annual sales are indicated. Brand name, generic name, approval type (new molecular entity), total number of orphan designations as well as the number of previous launches under the same brand name are also indicated.

Brand name	Generic name	NME	Orphan designation	Orphan approval	Designations	Prior launch[a]	Sponsor	2008 Sales (million US$)
Replagal	Alpha-galactosidase A	N/A	1998		1	N/A	Shire	176
Myozyme	Alpha-glucosidase	Yes	1997	2006	1	0	Genzyme	296
Activase/Cathflo Activase	Alteplase	Yes	2003		1	2	Genentech	286
AmBisome	Amphotericin B	No	1996	1997	3	0	Astellas	290
Strattera	Atomoxetine	Yes	2003		1	1	Eli Lilly	580
Vidaza	Azacitidine	Yes	2001	2004	2	0	Celgene	207
Dysport	Botulinum toxin A	No	1989		3	1	Ipsen	199
Subutex/Suboxone	Buprenorphine	No	1994	2002	1	0	Schering-Plough	230
Fabrazyme	Ceramide trihexosidase	Yes	1988	2003	1	0	Genzyme	500
Erbitux	Cetuximab	Yes	2000	2006	2	1	Bristol-Myers	749
Sensipar	Cinacalcet	Yes	2003	2004	1	0	Amgen	597
Exjade	Deferasirox	Yes	2002	2005	1	0	Novartis	531
Sprycel	Desatinib	Yes	2005	2006	2	0	Bristol-Myers	310
Pulmozyme	Dornase alfa	Yes	1991	1993	1	0	Genentech	305
Marinol	Dronabinol	Yes	1991	1992	1	1	Unimed	190
Aromasin	Exemestane	Yes	1991	1999	1	0	Pfizer	465
Fludara	Fludarabine phosphate	Yes	1989	1991	2	0	Bayer	140
Elaprase	Idursulfase	Yes	2001	2006	1	0	Shire	305
Intron A	Interferon alfa-2b	Yes	1987	1988	10	1	Schering-Plough	234
Somatuline	Lanreotide	Yes	2000	2007	1	0	Beaufour Ipsen	170
Aldurazyme	Laronidase	Yes	1997	2003	1	0	Biomarin	151
Lialda	Mesalamine	No	2008		1	1	Shire	140
Pegintron	Peginterferon alfa-2b	Yes	2008		1	1	Schering-Plough	914
Rebetol	Ribavirin	No	2003	2003	1	1	Schering-Plough	260
Actonel	Risedronate	Yes	2006		1	2	Sanofi-Aventis	462
Humatrope	Somatropin	No	1986	1987	3	1	Eli Lilly	441
Genotropin	Somatropin	No	1994	1997	3	2	Pharmacia	898
Nutropin	Somatropin	Yes	1987	1985	5	0	Genentech	375
Nexavar	Sorafenib	Yes	2004	2005	3	0	Bayer	647
Thalomid	Thalidomide	Yes	1995	1998	4	0	Celgene	505
Tobi	Tobramycin	No	1994	1997	2	0	Novartis	295
Remodulin	Treprostinil	Yes	1997	2002	1	0	United Therapeutics	270
Decapeptyl	Triptorelin pamoate	N/A	1990		1	N/A	Ipsen	347

[a] *Note*: Prior launch does not include new indications or new dose formulations.

(somatropin) and account for multiple orphan designations (3 or more each). A total of 20 profitable orphan designated products have a single orphan designation, 5 have two designations and another 5 have three orphan designations (Table 4). Thalomid, Nutropin and Intron A account for 4, 5 and 10 orphan designations each respectively. Genotropin, Nexavar, Erbitux and Pegintron each had global annual sales in excess of US 600 million $ in 2008 and another five products had global annual sales of US$ 500–599 million (Table 4).

3.5. Products given a new life as orphan drugs

A product history search revealed a total of 26 previously approved pharmaceutically active agents that were discontinued and later obtained orphan designations under the same or different trade name (Table 5). Of these, 14 obtained market authorisation as orphan drugs. First approved in 1969, aminosidine was discontinued and later obtained orphan designations, as Gabbromicina and Paromomycin, in 1993 and 1994, respectively. Baclofen, first launched in 1977 was discontinued, obtained orphan designation in both 1987 and 1991, and was later approved as an orphan drug under its original trade name; Lioresal (Table 5). First launched in 1982, cromolyn was discontinued and later approved as the orphan drugs Gastrocrom and Opticrom. Somatropin, first launched in 1976 was discontinued and later granted orphan designation under eight different trade names of which seven obtained market authorisation as orphan drugs (Table 5). Also notable are aminosidine and fluorouracil, which were previously available as generic brand name drugs, discontinued and later granted orphan designations.

3.6. Discontinued orphan drugs

A total of 33 previously approved orphan drugs were found to have been later discontinued (Table 6). Of these, 12 were found to have no currently approved chemically identical alternatives. Of the remaining 21 discontinued orphan drug products with alternatives, 13 have currently approved alternatives with the same brand name as the discontinued orphan drug product (Table 6). In 9 cases, currently approved alternatives to discontinued orphan drugs are generic products. Interestingly, Cibacalcin, Chenix, Numorphan, Metrodin and Fertinex, which are presently discontinued, are among the few products which obtained approval prior to orphan designation (Table 6). A third of products which obtained approval prior to orphan designation have been discontinued (data not shown). Pre-

Table 5
Examples of discontinued pharmaceutical agents given a new life as orphan drugs. Trade name, approval date and drug type of previously discontinued products as well as trade name, designation date and approval date of later orphan products is provided for each pharmaceutical agent.

Generic name	Prior discontinued product	Drug type	Approval	Orphan brand	Orphan designation	Orphan approval
Aminosidine	Humatin	Generic	1969; 1981	Paromomycin	1994	
Aminosidine	Humatin	Generic	1969; 1981	Gabbromicina	1993	
Baclofen	Lioresal	Brand	1977	Lioresal	1987	1992
Baclofen	Lioresal	Brand	1977	Neuralgon	1991	
Benzylpenicillin	Pre-Pen	Brand	1974	Pre-Pen	1987	
Brimonidine	Alphagan	Brand	1996; 1997	Alphagan	2000	
Citric acid	Irrigating Solution; Urologic G	Brand	1982; 1983	Renacidin	1989	1990
Cromolyn sodium	Intal	Brand	1982	Gastrocrom	1984	1989
Cromolyn sodium	Intal	Brand	1982	Opticrom	1985	1984
Daunorubicin	Cerubidine	Both	1979; 1980	DaunoXome	1993	1996
Fluorouracil	Adrucil	Generic	1991	Adrucil	1989	
Mazindol	Sanorex; Mazanor	Brand	1973; 1980	Sanorex	1986	
Perflubron	Imagent	Brand	1993; 2002	LiquiVent	2001	
Pergolide	Permax	Brand	1988	Permax	1997	
Rofecoxib	Vioxx	Brand	1999	Vioxx	2004	
Somatropin	Crescormon; Asellacrin	Brand	1976; 1979	Humatrope	1986	1987
Somatropin	Crescormon; Asellacrin	Brand	1976; 1979	Norditropin	1987	1995
Somatropin	Crescormon; Asellacrin	Brand	1976; 1979	Biotropin	1993	
Somatropin	Crescormon; Asellacrin	Brand	1976; 1979	Genotropin	1994	1997
Somatropin	Crescormon; Asellacrin	Brand	1976; 1979	Serostim	1991	1996
Somatropin	Crescormon; Asellacrin	Brand	1976; 1979	Nutropin	1987	1985
Somatropin	Crescormon; Asellacrin	Brand	1976; 1979	Saizen	1987	1996
Somatropin	Crescormon; Asellacrin	Brand	1976; 1979	Zorbtive	1995	2003
Sulfadiazine	Sulfadiazine	Brand	1941; 1978	Sulfadiazine	1994	1994
Thyrotropin	Thytropar	Brand	1953	Thyrogen	1992	1998
Urea	Sterile Urea; Ureaphil	Brand	1966; 1976	Neurosolve	2005	

Table 6
Approved orphan drugs which have been later discontinued. Chemically identical alternatives, orphan approval date and orphan designation date are indicated for each discontinued orphan drug.

Brand name	Generic name	Designation	Approval	Sponsor	Available alternatives[a]
Cordarone	Amiodarone	1994	1995	Wyeth	Cordarone, Nexterone, Generics
Mepron	Atovaquone	1990	1992	GSK	Mepron
Ucephan	Benzoat/phenylacetate	1986	1987	B Braun	Ammonul
Cibacalcin	Calcitonin	1987	1986	Novartis	Miacalcin, Calcimar, Fortical, Generics
Phos-Lo	Calcium acetate	1988	1990	Fresenius	Phos-Lo, Generics
Exosurf	Colfosceril	1989	1990	GSK	
Gastrocrom	Cromolyn sodium	1984	1989	Fisons	Gastrocrom, Opticrom, Intal, Generics, OTC
Chenix	Chenodiol	1984	1983	Sigma-Tau	
Ornidyl	Eflornithine	1986	1990	Hoechst Mari	Vaniqa
Didronel	Etidronate	1986	1987	MGI	Didronel, Generics
Supprelin	Histrelin	1988	1991	Shire	Supprelin, Vantas
Idamycin	Idarubicin	1988	1990	Pharmacia	Idmaycin, Generics
Gleevec	Imatinib	2001	2001	Novartis	Gleevec
Lutrepulse	Gonadorelin	1987	1989	Ferring Labs	
Halfan	Halofantrine	1991	1992	SmithKline	
Wellcovorin	Leucovorin	1988	N/A	Glaxo Wellco	Leucovorin, Generics
Iplex	Mecasermin	2002	2005	Insmed	
Lariam	Mefloquine	1988	1989	Roche	Generics
Numorphan	Oxymorphone	1985	1960	Endo	Opana
Orlaam	Levomethadyl	1985	1993	Roxane	
Moctanin	Monoctanoin	1984	1985	Ethitek	
Geref	Sermorelin	1988	1997	EMD Serono	
Protropin	Somatrem	1985	1985	Genentech	
Nutropin	Somatropin	1999	1999	Genentech	Multiple brands
Norditropin	Somatropin	1987	1995	Novo Nordisk	Multiple brands
Parathar	Teriparatide	1987	1987	Sanofi-Aventis	
Eldepryl	Selegiline	1984	1989	Somerset	Eldepryl, Zelapar, Generics
Cyklokapron	Tranexamic	1985	1986	Pharmacia	Cyklokapron
Neutrexin	Trimetrexate	1986	1993	Medimmune	
Metrodin	Urofollitropin	1987	1986	EMD Serono	Bravelle
Fertinex	Urofollitropin	1997	1986	EMD Serono	Bravelle
Secreflo	Secretin	2000	2002	ChiRhoClin	Secreflo, Chirhostim
Hivid	Zalcitabine	1988	1992	Roche	

[a] Alternatives refer to pharmaceutically identical agents and do not consider specific therapeutic indications.

vious data have reported that 16.7% (2 out of 12) orphan drug NMEs have been discontinued due to safety reasons in comparison to 34.7% (25 out of 72) for other NMEs [6]. While this suggests enhanced safety for orphan drugs, the relatively small size of the evaluation database for orphan drugs limits this analysis.

4. Discussion

4.1. Issues with the United States Orphan Drug Act

Once a product has obtained orphan drug exclusivity, the FDA cannot approve a new brand name or generic drug application for the same product and for the same rare disease indication [6]. On the other hand, the same drug can obtain approval for a different disease indication and there is no limit on the number of drugs that may be designated for a specific disease [2,6]. Allowing multiple products for specific rare diseases potentially benefits patients through the increased availability of therapeutic options as well as competitive pressures which lower prices. In addition, multiple orphan designations per product could be justifiable for therapeutic indications, preferably outside the same therapeutic class, where significant clinical research effort is required to demonstrate innocuity and efficacy. Nonetheless, these circumstances create additional issues.

The vast majority of orphan designations (32%) were found to relate to cancer. No other therapeutic class was found to account for more than 10% of orphan designations. In effect, oncology was the only identifiable therapeutic class to demonstrate growth and this growth appears to be the major contributor to the yearly increase in orphan drug designations. As stated by Abbey S. Meyers, executive director for the National Organisation of Rare Diseases, "all cancers but four are considered to be rare diseases" [12]. Chemotherapy drugs are often effective in several different cancers and off-label use is frequent in the field of oncology [12,16]. In addition, oncology is among the most lucrative and fastest growing therapeutic classes [17]. Therefore, sponsors appear to concentrate their orphan drug research investments in lucrative fields, such as oncology, to the detriment of other previously unaddressed or under-addressed rare diseases. Such findings question whether so many oncology products should qualify for orphan drug designation and whether so many cancers should be considered as rare diseases. Applying molecular tools and techniques for the classification of cancer as increasingly suggested in literature, rather than relying on traditional morphological classification, could have substantial effects on orphan drug attributions and the size of rare disease patient pools with the potential combination of different cancers (i.e. breast and prostate tumours) under a single fundamental mechanism [18].

In addition, pharmaceutically active agents such as interferon, somatropin and levocarnitin, among others, can obtain up to 33 orphan designations each. Orphan drugs, intended to treat small patient populations, become drugs which treat large populations through the addition of orphan drug niches and thereby violate the "less than 200 000 patient population" clause. Hence, initially unprofitable orphan drugs potentially reach blockbuster status due to multiplication and extension of indications. In effect, out of the 18 blockbuster drugs which are solely approved as orphan drugs, only 4 had a single indication. This problem is not only limited to blockbuster orphan drugs but also extends to non-blockbuster profitable orphan drugs. Out of the 19 profitable drugs of 2008 which were approved solely as orphan drugs, 8 had two or more orphan designations. Alternatively, other orphan drugs, such as Epogen, have been reported to reach blockbuster status as the result of off-label use [19].

Orphan drugs can bring in significant revenues for pharmaceutical companies. In 2006, a quarter of products which reached blockbuster status that year had one or more orphan designations [20,21]. These orphan drugs brought in global sales of US$ 58.7 billion in 2006 [20,21]. Products such as Cerezyme, Provigil, Alimta and Zometa have reached blockbuster status as orphan drugs with a single orphan designation. Additionally, 11 products with global annual sales of over US$ 100 million in 2008 were orphan drugs with a single orphan designation. Considering the small patient populations of such orphan drugs, these findings fuel criticisms of high treatment costs [19]. Individual costs appear even more dramatic considering that many biologic agents, and therefore expensive orphan drugs, are "tier 4" medications which require patients to contribute 20–33% of overall costs within the increasingly more common private coinsurance-like plans of the United States [22]. In contrast, most European countries provide universal healthcare drug coverage [23,24]. While patient advocacy organisations aggressively persuade third-party payers, namely private and state-funded insurance, to provide full reimbursement of products and some pharmaceutical manufactures, such as Genzyme, offer product discounts [5,11], the accessibility and availability of orphan drug products in the U.S. can be questionable. Additionally, patients can find themselves paying twice for the same drug as public funds potentially financed orphan drug R&D and market cost of essential treatments must be assumed, at least partially, by patients [6]. The high price of orphan drugs in the United States is even perceived to subsidize orphan drugs abroad where prices can be significantly lower due to regulation [23].

The investigation of blockbuster drugs with orphan designations also revealed other issues. While the Orphan Drug Amendment of 1988 excludes the designation of products following the submission of their marketing authorisation application, this does not extend to previous non-orphan drug marketing authorisations. Therefore, a product can be launched under a non-orphan indication, obtain orphan designation prior or following the non-orphan approval and later receive market authorisation as an orphan drug. Thus, 12 out of the 30 blockbuster drugs with orphan approvals had been previously launched under the same brand name. While "after the fact" discovery of an orphan application can justify this succession of events, there exists a potential risk that orphan drug incentives were used to develop non-orphan drugs. Alternatively, an already profitable product can later obtain orphan designation and/or approval as appears to be the case for Prograf and Evista.

The 1988 amendment, in combination with the 7 year exclusivity period of the ODA, can permit the extension

of the effective patent life of specific products. Nonetheless, it should be noted that such occurrences are relatively uncommon. As demonstrated in a previous investigation, orphan drug market exclusivity increased effective patent exclusivity of products by merely 0.8 years on average [6]. In addition, the ODA's 7 year market exclusivity incentive is an indispensable tool for start-up biotechnology businesses desiring to attract investors. As indicated in the May 2001 report from the United States Office of Inspector General, the ODA assists biotechnology companies in attracting venture capital and growth of biologic orphan drug products mirrors the growth of the biotechnology industry [5]. ODA incentives, such as waived fees, tax credits and research grants, are beneficial for start-up firms but only orphan drug exclusivity can assist these companies in obtaining funding to cover operational costs and continued product research and development. Policies structured as tax credits are relatively ineffective at stimulating innovation in markets with small revenue potential [8]. Finally, stimulating rare disease research can often lead to scientific breakthroughs applicable to common conditions as was the case with the study of homozygous familial hypercholesterolaemia which lead to the development of statins [25].

The ODA also permits enough freedom of movement for sponsors to recycle previously discontinued products. Wide application pharmaceutical products, such as Vioxx, which were discontinued due to safety concerns, can be given a new life as orphan drugs with much more restricted applications. Twenty-six discontinued products were found to have later obtained orphan designations with 14 of these achieving orphan drug approval. Favourable patient benefit to risk ratios may potentially justify some of these products. Nonetheless, old pharmaceutical agents could potentially benefit from drug development incentives as later orphan drugs and demand higher market prices even though these pharmaceutically active agents were once available either as brand name or generic drugs.

Finally, orphan drugs, which are presumably the only therapeutic treatment available, can be discontinued for safety or even financial reasons. A total of 33 previously available orphan drugs were identified as currently discontinued. In such cases, already vulnerable patients can be left to search for suitable alternatives. For 12 of these products, no chemically identical alternatives appear to be available. Such findings lead to ethical concerns on the continued accessibility of approved orphan drugs once manufacturing begins. The probability of losing a treatment alternative appears even greater when unexpected hazards of orphan drugs are considered. During clinical testing, 31% of orphan drugs had more pronounced side effects than non-orphan drugs and 13% of FDA approved orphan products provoked more side effects than anticipated [26].

4.2. Potential reform of the Orphan Drug Act

In 1990, the US senate attempted to pass bills which would remove orphan drug status from products with sales exceeding US$ 200 million or with markets exceeding 200 000 patients but these were finally vetoed under President Bush [12,13]. While these bills were designed to address legitimate issues of the ODA, the approach taken may not have been ideal. In effect, the threat of stripping drugs of their orphan status created uncertainty and hindered orphan drug development for multiple years after. An alternative remains the establishment of a federal regulatory agency, such as the Patented Medicine Prices Review Board (PMPRB) of Canada, to regulate the price of pharmaceutical products entering the United States market place. In fact, manufacturers of products registered as orphan drugs in the United States are among those which have been ordered to reduce their prices by the PMPRB on the Canadian market [23]. Currently, the United States is the only major industrialized country which does not regulate prescription drug prices [23,27,28]. In 2008, European drug prices averaged 40% less than U.S. prices with prices in Italy and Germany respectively averaging 55% and 70% of U.S. prices [29]. In the United States, drug manufacturers negotiate with associations, such as Medicaid, Veterans Health Administration and Pharmacy Benefit, but remain free to set their own introductory prices and competition between manufactures has little regulatory effects in comparison to imposed price restrictions [27]. Even when exclusivity protections expire, many orphan drugs and especially biotechnology products face little competition due to difficulties in demonstrating equivalence and since generic manufacturers rarely invest in large scale trials [30]. The impact of biogeneric drugs on orphan drug prices may also be limited since these generics remain relatively costly (20–25% discount relative to branded biologics while 75–85% discount for traditional generics relative to branded pharmaceuticals) [31]. In addition, the few available biogeneric/biosimilar drugs have not yet reached the American market due to the absence of a clear FDA approval process [32]. Orphan drug research and development would not be hindered by price regulation since all pharmaceuticals, rather than orphan drugs alone, would be affected. Additionally, the issues of excessively priced and profitable orphan drugs would be addressed. The seven year orphan drug exclusivity period, which is the major incentive for the development of orphan drugs, would remain untouched. Finally, manufacturers would maintain the potential to make significant gains allowing returns on investment and economic growth.

In order to address the issue of profitable drugs which have benefited from orphan drug incentives (namely R&D grants, waved fees and tax credits), initiatives from Japan could be considered. In Japan, pharmaceutical manufacturers are mandated to pay a one-percent sales tax on orphan drugs with annual profits exceeding 100 million yen until government subsidies received by manufacturers have been repaid [2]. This clause does not appear to have negatively affected orphan drug development in Japan since the Japanese Orphan Drug Act has resulted in the approval of nearly 100 orphan products in the 12 years following its 1993 enactment [23,33,34]. Considering that both Japan and the EU offer 10 year market exclusivity, the Japanese Orphan Drug Act appears to be more successful in stimulating orphan drug R&D, as deduced by drug approvals, than its European counterpart which has threatened to revoke orphan drug status for profitable drugs.

This tax clause could also be transferable with incentives provided to one R&D company and later repaid by the marketing company. In this way, profitable orphan drugs would no longer be government funded while unprofitable orphan drugs would maintain their incentives.

Also at the beginning of the 1990s, senators Metzenbaum and Kassebaum had planned the introduction of legislation which would redefine what constitutes an orphan drug [12]. With current advances in medical technology, which forecast an era of personalized medicine, and the aging of the population which leads to new rare diseases, the time seems just for a redefinition of "orphan drug" and "rare disease". This endeavour would permit controls on the number of indications per disease, create more homogeneous distribution of investments among rare diseases and restrict the therapeutic market of orphan drugs. These changes could be implemented through a more active role of the FDA. Alternatively, the European Union's European Medicines Agency could be used as an example. Free trade agreements could be used to establish an International Orphan Drug Office with Canada and other industrialized countries. This would provide Canada with an active role in orphan drug policy and stimulate healthcare collaboration between neighbouring countries. Benefits would include reduced application fees for manufactures, reduced product prices with increased market size and clinical trials would benefit from greater patient pools [2]. In fact, such an agency is already in early infancy with current sharing of orphan drug information between the FDA and the Australian Therapeutic Goods Administration [2]. The U.S. and European drug regulatory agencies have also adopted a single form which may be submitted to both agencies during orphan drug application [20]. Finally, an International Orphan Drug Office could develop standards which would assist courts in the litigation of cases related to orphan drugs. Controversial products, such as Humatrope, a growth hormone that differs from Protropin by only one amino acid, could thus be addressed as standards would assist in clarifying what constitutes a "different" or "same" drug. Such an agency would also clarify whether the federal government or the court hold jurisdiction under specific cases. In addition, the issues of using orphan drug approval to recycle products or extend patent life of previously launched non-orphan drugs would also be addressed.

5. Conclusion

The Orphan Drug Act is recognized as one of the most successful legislation actions of the United States in recent history [1]. Prior to its enactment, only ten products which treat rare diseases were approved in the United States [2]. The ODA significantly increased the annual flow of new clinical trials, spurred innovation in novel drug technologies as well as in personalized drugs and lead to the identification of numerous new disease types [8]. The multitude of orphan products now available and the consistent growth in the number of orphan designations demonstrates the ability of the ODA in stimulating research into rare diseases. Nonetheless, the ODA has numerous issues which permit specific orphan drugs, under relatively uncommon instances, to become highly profitable and/or treat patient populations in excess of 200 000. The issues surrounding orphan drugs will likely amplify as these essential and emotionally compelling pharmaceutical products occupy a greater place in healthcare budgets and within pharmaceutical product portfolios. A quarter of a century after its enactment, the time is now right for reform of the ODA. However, ODA reform should proceed cautiously in order to prevent the hindrance of investment and research into rare diseases. Current orphan drug incentives should be maintained in order to benefit patients, the United States economy and the pharmaceutical industry. Suggested reforms could include the establishment of price regulation for all pharmaceuticals, subsidy paybacks for manufacturers with profitable orphan drugs as well as the establishment of an International Orphan Drug Office endowed with regulatory powers.

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