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# ORPHAN PRODUCTS: Origins, Progress, and Prospects*

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## INTRODUCTION

Products to treat diseases or conditions characterized by low prevalence, by special subsegment patient populations, or by lack of economic viability all fall within the category of "orphan products." This is the Federal legal definition of an orphan product where the term "product" refers to drugs and biologics and sometimes includes devices and medical foods for some limited purposes. The 1989 Report of the National Commission on Orphan Diseases includes a statement that captures the essence of "orphan" products and diseases or conditions:

> Between 10 million to 20 million Americans suffer from one of the approximately 5,000 known rare diseases. Most of these rare diseases are also orphan diseases: they have no parent organization, investigator, or agency dedicated to research on the prevention, diagnosis, or treatment of their victims. . . .

Although there is general agreement that the overall number of patients afflicted with rare diseases is very significant in total, the limited number of patients and hence the market for any one particular therapy, the geographic dispersion of patients for clinical trials and product distribution, the unavailability of third-party payments for treatment before drug approval, and

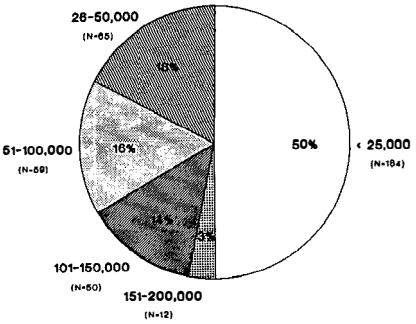


*Figure 1* Orphan designations by disease prevalence (1983–1990). Includes data as of May 1990.

the probability that the product will not be patentable, all diminish the motivation and incentives to pursue marketing approval as well as the potential profitability of a given orphan product. The orphan products program is the decision that society cannot "write off" these small groups of patients totaling 20 million or more in the United States.

The executive director of the National Organization for Rare Diseases (NORD), a patient-consumer oriented voluntary health association, has described how difficult it is to motivate sponsors to develop products to treat these diseases and conditions, even for some of the largest of the "orphan" populations. NORD must struggle to find sponsors for narcolepsy and multiple sclerosis drugs, even though the disorders affect almost 200,000 patients each (1). Figure 1 shows that of the 370 orphan product designations granted as of May, 1990, two thirds were for diseases and conditions with a prevalence of 50,000 patients or less, and 83 per cent fell below 100,000.

The Congressional Findings included as the preamble in the 1983 Orphan Drug Act (2) reflect and summarize all of these concerns as the inspiration for the Act by stating:

> The Congress finds that—
>
> (1) there are many diseases and conditions, such as Huntington's disease, myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome, and muscular dystrophy which affect such small numbers of individuals residing in the United States that the diseases and conditions are considered rare in the United States;
>
> (2) adequate drugs for many of such diseases and conditions have not been developed;
>
> (3) drugs for these diseases and conditions are commonly referred to as "orphan drugs";
>
> (4) because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss;
>
> (5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs; and
>
> (6) it is in the public interest to provide such changes and incentives for the development of orphan drugs.

In addition, the Orphan Drug Act approved and established as a matter of public policy that the Federal Government, and the Food and Drug Administration (FDA) in particular, could and should assist with and cooperate fully in the development of orphan products. The new law provided some new tools and incentives to help with the task.

## HISTORICAL CONTEXT



Although there has been interest for decades in problems of inadequate resources and incentives for orphan products, specific legislative provisions and attention is less than a decade old. Historically, FDA has often had to wrestle with how to stimulate sufficient interest in research to determine whether or not incidental findings from some clinical trials or the literature are viable avenues to effective or improved orphan treatments.

Perhaps the first organized attempt to deal with the problem of special patient needs and inadequate resources for development and distribution of orphan products (then referred to as "useful drugs of limited commercial value") was the voluntarily initiated DHEW (now HHS) Interagency Committee on Drugs of Limited Commercial Value. The Food and Drug Administration (FDA) which, for some time, had been dealing with these matters on an informal basis established and sponsored this Committee in 1974.

The Interagency Committee in its "Interim Report" of 1975 described the problems (principally those concerned with definition, the availability of governmental and industry support, and legal and insurance issues) and mentioned various potentially useful administrative mechanisms mainly based on economic incentives. Essentially, the report suggested that a more definitive study be undertaken.

Not until March 1978, however, was a new Task Force convened, again voluntarily, composed of most of the original Committee members, other advisors within and outside the agency, representatives of the pharmaceutical industry and special consultants. By this time, additional interest in focusing on orphan products had been stimulated by several intervening developments:

1. In 1977, a chapter devoted to the problem of "drugs of little commercial value" in an Office of Technology Assessment (OTA) Report to the Congress indicated that the problem had existed for some time but had not received adequate attention, and that the needs of a number of groups would not be effectively met without a systematic study.
2. A 1977 report by the Commission for the Control of Huntington's Disease and Its Consequences to the Secretary of HEW recommended the immediate formation of a task force to propose solutions.
3. An appeal in 1977 by professional staff in the executive office of the White

House asked the Pharmaceutical Manufacturers Association to consider incentives in this area. In part, this request was motivated by the need to develop alternative therapies to meet the increasing problem of drug abuse in certain population groups.

4. A 1978 survey by the Pharmaceutical Manufacturers Association, in response to the White House request, inventoried what its member firms were doing with orphan product areas.
5. A general heightened Congressional interest in drug law reform legislation in the late 1970s and early 1980s included questions of providing orphan drugs either through federal production or industry persuasion.
6. Considerable interest, beginning in 1978, was expressed by the then Secretary of Health, Education, and Welfare in the form of inquiry to FDA on what was being done to alleviate the problem.

The conclusion of this Task Force effort was a report to the Secretary in June of 1979, which recommended what has now become the basic legislative and regulatory approach and provisions for orphan product development (3). In March of 1982, the Assistant Secretary for Health in the Department of Health and Human Services (HHS) established the Orphan Products Board to coordinate federal policy and efforts, one of the Task Force recommendations. And, in May, 1982, FDA established an Office of Orphan Products Development in the Office of the Commissioner.

## CONGRESSIONAL ACTION

The initial law in 1983 is the Orphan Drug Act (4). This amended the Federal Food, Drug and Cosmetic Act (FFDCA) by adding authority to "designate" appropriate drugs and biologics, provide protocol assistance to their sponsors and investigators, to grant a patentlike seven-year exclusivity for the designated product for the designated indication upon approval for marketing. Additionally, the Orphan Drug Act amended the Public Health Service Act to provide a statutory foundation for the Orphan Products Board to oversee the program within the US government, amended the US Internal Revenue Code to allow tax credits for qualified clinical testing expenses for certain drugs for rare diseases or conditions (5), and provided authority for the FDA Orphan Products Grants Program to make grants to defray costs of qualified clinical testing expenses incurred in connection with the development of drugs for rare diseases or conditions. This latter provision is the only one that applies to nondrug products, as well as drugs by specifically including medical devices and medical foods.

The Orphan Drug Act was amended in 1984 (6) to refine and simplify the "orphan" status designation by providing a clarification to the economic

viability analysis. Prior to this amendment, the law required a determination that "there was no reasonable expectation that the cost of developing and making the a drug available . . . will be recovered from sales. . . ." (7). This change added the following language:

> the term rare disease or condition means any disease or condition which
> (a) affects less than 200,000 persons in the U.S. or
> (b) affects more than 200,000 persons in the U.S. and for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from U.S. sales of such drug.

The law was amended again in 1985 (8) to delete the requirement that only designated orphan drugs for which a US Letter of Patent *may not be issued* qualified for marketing exclusivity. This amendment also clarified that antibiotics were eligible for orphan designation.

The Orphan Drug Act was further amended in 1988 (9) to establish a specific time period for the filing of an application for orphan designation. Originally, a designation request could be filed anytime prior to marketing approval but this change required that the designation request must be made prior to the submission of an application for marketing approval, i.e. New Drug Application (NDA) for drugs or Product License Application (PLA) for biologics.

## SPECIFIC ORPHAN DRUG PROVISIONS

### *Orphan Drug Designation*

To obtain "orphan designation" for a drug or biological product, a sponsor must submit an application to the Office of Orphan Products Development at FDA (10). Materials documenting and supporting the disease or condition prevalence, and scientific rationale must be included in the application. If the prevalence exceeds 200,000 patients in the United States, the sponsor must also show economic and financial data that would support a determination that sales revenues would not be adequate to repay the development and marketing expenses. A sponsor must file an application for designation prior to the submission of an application for marketing approval. *Interim Guidelines* for the content of designation requests are available from FDA. Eventually, formal regulations will be promulgated to supplant these *Guidelines*.

The designation of a drug or biologic is based upon the information submitted by the sponsor. That is, each sponsor requesting designation of the same drug for the same indication must submit its own data in support of its separate designation request. Orphan designation does not alter the standard legal and regulatory requirements for marketing approval. Specifically, the safety and efficacy of a product must be established through the conduct of adequate and well-controlled studies.

Only drugs and biologics can be given "designated" orphan status; devices and medical foods are not eligible. However, the Report of the National Commission on Orphan Diseases recommended that Congress amend the Orphan Drug Act to provide incentives for the development of orphan medical devices and medical foods (11).

### *Protocol Assistance*

Formal protocol assistance is available from FDA via written recommendations when requested by an orphan product sponsor (12). *Interim Guidelines* for use by sponsors in requesting protocol assistance have been published and are available from FDA. These *Guidelines,* too, will eventually be superseded by formal regulations. Information submitted with a protocol assistance request should include summaries and copies of any cited references, and the request should be specific and state the issue posed exactly, e.g. adequacy of available data to support an NDA or PLA. Also, where additional clinical studies are contemplated, copies of the proposed investigation protocols should be included in the request.

The formal review of a request for protocol assistance is the direct responsibility of the Center for Drug Evaluation and Research (CDER) or the Center for Biologic Evaluation and Research (CBER), depending on which Center is responsible for review of the application. The Office of Orphan Products Development (OPD) determines whether a request as submitted meets the legal requirements for designation. This, in part, involves a determination "whether there is reason to believe the sponsor's drug is a drug for a disease or condition that is rare in the United States." Once OPD determines that the proposed product is for a disease or condition that is rare in the U.S. and the application for assistance is complete, the request is forwarded to the responsible reviewing division for formal review and direct response.

A sponsor need not have obtained orphan drug designation to receive protocol assistance. OPD monitors the review process within the respective CDER/CBER reviewing division and, where possible, assists in resolving specific issues that may arise during the review process. The protocol assistance provided under the Act does not waive the necessity for the submission of an Investigational New Drug Application (IND) by sponsors planning to conduct clinical trials with the product.

## OPEN PROTOCOLS

The Orphan Drug Act facilitates the use of open protocols to permit patients to use orphan drugs for treatment purposes while the drugs are being investigated in clinical trials (13). This provision was considered an especially important advance because many orphan products never had had their human clinical trials completed nor obtained FDA marketing approval. The goal of

this provision was to make an orphan product involved in or eligible for clinical trials available for treatment of patients concurrent with clinical trials. As the committee report accompanying the original bill in the Congress put it:

> The . . . mechanism is particularly important for orphan drugs. Often there aren't alternative therapies to the drug being tested; and the testing period is lengthy. In some cases, clinical trials are not actively being conducted. . . . [This provision] would require FDA to encourage the sponsor of a designated drug to assume responsibility for adding to the tests individuals who need the drug for treatment. Under this procedure, often called 'open protocols', a physician would make a request for the drug directly to the sponsor and the sponsor would have FDA's prior approval to add new individuals at the sponsor's discretion. . . . [The law will] require FDA to notify the public of the designation of a drug. . . . One reason for this notice is to advise the appropriate health professionals and voluntary disease organizations of the testing . . . on the drug. This notice, plus the broader and more efficient distribution possible through open protocols, will increase the availability of orphan drugs during the lengthy testing period (14).



## *Incentives of the Orphan Drug Act*

The Orphan Drug Act includes various incentives that have stimulated a considerable amount of interest in the development of orphan drug and biological products. These incentives include, among others, tax credits for human clinical research undertaken by a sponsor to generate required data necessary for approval, as well as the granting of exclusive marketing rights for seven years for a designated drug or biological product, for the condition for which designation and approval are obtained.

A seven-year period of exclusive marketing to the first sponsor that obtains marketing approval for a designated orphan drug or biological product is a key incentive designed to motivate research and development of these products. The exclusivity period begins on the date that the designated orphan product marketing application is approved and applies only to the designated and approved indication.

A second application for the same drug for a different use could be approved for the same or any other sponsor. FDA may not approve second sponsor's application for an already approved product and indication for seven years. However, this orphan exclusivity may be inapplicable if the holder of the first approved application cannot assure the availability of sufficient quantities of the drug to meet the needs of the affected patients.

These provisions permit the approval of other products that may provide valuable alternatives or additions to the treatment of a rare disease or condition, and the granting of a separate exclusivity period, if appropriate.

## *Research Grants*

The original Act provided authority for FDA to make grants to assist in "defraying the costs of qualified clinical testing expenses incurred in connection with the development of drugs for rare diseases and conditions." Eligibil-

ity for such grants has been extended to both clinical and/or preclinical studies, and to medical devices and medical foods that offer no reasonable expectation of development without such assistance. FDA has limited grants to clinical studies.

No funds have been appropriated under the Orphan Drug Act. However, the FDA, through OPD, uses its grants authority to fund and support clinical studies to develop orphan products. The Request for Applications (RFA) announcing the availability of funds is published usually in the *Federal Register* in October or November of each year. Interested parties have a period of time specified in the notice (usually 60–90 days from the date of publication of the RFA) to submit research grant applications.

FDA has disbursed more than $20 million in orphan product research grants since 1983. Currently, $7.5 million is expended annually to support over 65 studies, which are in various stages of progress, to clinically evaluate the safety and effectiveness of drugs, medical devices, and medical foods.

The FDA will consider awarding grants to support clinical studies for determining whether the products are safe and effective for premarket approval under the FFDCA, or the Public Health Service Act. These clinical studies may be designed to assist in the approval of unapproved products or of unapproved new uses for already marketed products. Applications should be for one discrete clinical trial. The applicant must provide supporting evidence that the product to be investigated is available to applicants in the form needed for the clinical trial. The typical study funded may involve up to several dozen subjects, and will be designed to provide substantial evidence of the product's safety and effectiveness. All applications must show documentation of a completed review and approval of human subject protection by an institutional review board (IRB). This IRB review must include information on the characteristics of the subjects, the sources of research materials, recruitment plans, and consent procedures, any potential risks procedures for protecting against or minimizing potential risks, and potential benefits to the subjects.

Applications by respondents to FDA's annual grants program announcement are carefully reviewed to determine the expertise required by those who will conduct field reviews and ranking of proposals. The nature of grants proposals submitted to FDA frequently involve highly complex and specialized medical, pharmaceutical, and/or bioengineering processes. FDA makes a special effort to ensure that field reviewers who are knowledgeable in the clinical, scientific, and/or technical focus of the proposal are selected. Reviewers are chosen based on many factors including: recent clinical research completed in the field; history of publication in appropriate medical journals; absence of real or apparent conflict of interest; balance between research expertise and clinical background; educational achievement; affiliation with an institution.

## GENERAL ORPHAN PRODUCTS PROGRAM

As explained above, the Orphan Drug Act pertains primarily to drug and biologic products. However, FDA, through OPD, is concerned with orphan products development at large. Under the OPD Grants Program, medical foods and devices may be included. In addition to providing grants and financial incentives where applicable and to the extent available for the development of orphan products, the FDA program is concerned with the identification and the facilitation of the development of all orphan products.

The identification of orphan products is accomplished through various mechanisms including, among others: letters or referrals from academia, the pharmaceutical industry and its respective association, i.e. The Pharmaceutical Manufacturers Association (PMA) and Generic Pharmaceutical Industry Association (GPIA), as well as a constant and continuous review of the literature.

Facilitation of the development of products, once identified, is accomplished through a variety of approaches. One is a direct request to manufacturers with particular expertise in the type of product of interest. Another approach is a request in the *Federal Register* through a notice that may outline the required material necessary for an NDA, and identify available data that could be used in support of a marketing application. The additional research and development required by a sponsor in these cases depends, of course, on the amount and adequacy of existing data available to satisfy safety and effectiveness requirements established by law.

The OPD devotes significant effort to learning about products that have been identified throughout the world as demonstrating promise for the diagnosis or treatment of rare diseases or conditions. To locate such products, the Office interacts with the medical community, professional organizations, academia, pharmaceutical and device manufacturers, Congress, domestic and foreign governments, and the public; surveys current literature in medical and other scientific journals that report research on new products or new uses of marketed products for serious diseases; interacts with the HHS Orphan Products Board, the National Institutes of Health, the National Organization for Rare Diseases, the Pharmaceutical Manufacturers Association's Commission on Drugs for Rare Diseases, the Generic Pharmaceutical Industry Association, and professional societies such as the American Academy of Pediatrics.

The orphan products program is concerned with and directed at public health needs and problems beyond the borders of the United States. While a given disease or condition may be rampant in some developing nation or area of the world, if its prevalence fits the orphan definition, or if it is clear that sales of the product "in the United States" would be insufficient to stimulate is development and distribution, then the orphan program provisions are available to its sponsor. One of the objectives of the program is to stimulate the

medical and pharmaceutical community in the United States to develop products to meet the needs of populations elsewhere.

## DETERMINING PROBLEMS OF AVAILABILITY OF PROMISING PRODUCTS

OPD also functions as a type of ombudsman on orphan products for sponsors and patients. Upon notification that progress has been retarded on development of a product needed for a rare disease, OPD staff attempts to help the sponsor to determine what studies need to be evaluated or completed, the sponsorship to be obtained, or specialists to be consulted. The FDA premarket review process is established partly on the assumption that sponsors will continue to pursue drugs that are attractive in their potential for return on investment. With orphan products, however, reliance on the economic potential as the primary motivation for the sponsor to seek a timely completion of the review process is questionable. Therefore, the OPD staff continually interacts to assist sponsors who may have abandoned promising products due to a misunderstanding or perceived impasse in obtaining approval from FDA review divisions.

Frequently, formidable obstacles exist to discourage development of products for rare diseases. Lack of funds for research and development, unavailability of product in a clinically useful form, nonpatentability of product, high production or distribution costs, high costs or technical difficulties in manufacturing, lack of incentives for research by commercial sponsors, and liability concerns are examples of problems that OPD staff attempt to help sponsors to overcome.

## PROMOTING RESEARCH AND DEVELOPMENT OF ORPHAN PRODUCTS

The OPD seeks commercial sponsors of research and commercial development through informal contacts with manufacturers, through formal publication of notices in the *Federal Register,* or through the mechanisms established by the Pharmaceutical Manufacturers Association and the Generic Pharmaceutical Industry Association. This is accomplished by: (*a*) Meeting with investigators who have therapeutic concepts in need of development assistance; (*b*) Working with product sponsors, when identified, to assist in communications with reviewers in FDA to expedite a scientifically sound evaluation and review of the product; (*c*) Monitoring progress of studies funded under the FDA Orphan Product Grants program and expediting resolution of problems or required alterations of clinical protocols in order to obtain required data for New Drug Application or Premarket Approval for a medical

device; (*d*) Advising and/or assisting investigators, sponsors, or manufacturers in identifying sources and obtaining grants or other funding for needed research.

## ADDITIONAL AND UPDATED INFORMATION

Patient/practitioner needs, as well as the purpose of the orphan products program, are poorly served if patients and practitioners who could and should be utilizing or benefitting from the program do not have access to timely information. If a potentially safer, more effective, or alternative treatment for an orphan disease is being tested, OPD attempts to circulate that information to both patients and practitioners who may be affected and to encourage or solicit the establishment of open protocols for those trials. This is especially important where no effective treatment exists for a given condition. Contacts for clinical investigations, sponsor contacts for treatment sources, and exchange of literature references are all part of the OPD general program activities.

At least annually, FDA publishes a cumulative list of designated drugs with quarterly revisions or updates for those who need or want to keep abreast of orphan product advances and developments. FDA also sponsors and supports the National Information Center on Orphan Drugs and Rare Diseases (NICODARD), an informational service focused on health care practitioners. NICODARD provides information by telephone (1-800-456-3505) on designated orphan products and federally funded grant research on rare diseases and conditions. This information includes sources of products being used in clinical trials, names of investigators, and related data. When known or available, NICODARD supplies other information or provides resource referrals to nongovernmental entities.

Another informational resource is the National Organization on Rare Diseases, which focuses on patients and their families, and voluntary disease organizations (1-800-999-NORD).

## RESULTS

Has all this attention and effort done any good? As of June, 1990, there were 49 approved indications for designated products, 370 designations, with the submissions and activity on a definite upward trend. The patient populations for the rare diseases and conditions affected by the already approved orphan products total approximately 1.8 million, and for all designated products, the total is near 18 million potential patient-benefactors.

A list of the approved orphan products with a brief description of the indications and prevalence is set out as Table 1. Twenty-one of the indications

**Table 1** Approved designated Orphan Products January 1982 to May 1990

| Generic (Trade) name | Indication | Sponsor | FDA Approval date | Designation date | Prevalence |
|---|---|---|---|---|---|
| Alpha-1-proteinase inhibitor | Replacement therapy in the alpha-1-proteinase inhibitor congenital deficiency state | Cutter Labs | 12/02/87 | 12/07/84 | 30,000 |
| Antithrombin III human (Antithrombin) | For the treatment of patients with hereditary antithrombin III deficiency in connection with surgical or obstetrical procedures or those suffering from thromboembolism | Kabi Vitrum Incorporated | 12/13/89 | 02/08/85 | 2,500 |
| Benzoate and phenylacetate (Ucephan) | Adjunctive therapy in the prevention and treatment of hyperammonemia in patients with urea cycle enzymopathy (uce) due to carbamylphosphate synthetase, ornithine, transcarbamylase, or arginosuccinate synthetase deficiency | Kendall-McGaw | 12/23/87 | 01/21/86 | 100 |
| Botulinum toxin type A (Oculinum) | Treatment of blepharospasm | Oculinum Inc. | 12/29/89 | 03/22/84 | 1,500 |
| Botulinum toxin type A (Oculinum) | Treatment of strabismus | Oculinum Inc. | 12/29/89 | 03/22/84 | 14,700 |
| Calcitonin-human (Cibacalcin) | Treatment of symptomatic Paget's disease of bone (osteitis deformans) | Ciba-Geigy | 10/31/86 | 01/20/87 | 160,000 |
| Chenodiol (Chenix) | For patients with radiolucent stones in well opacifying gallbladders, in whom elective surgery would be undertaken except for the presence of increased surgical risk due to systemic disease or age | Reid-Rowell | 07/28/83 | 09/21/84 | 150,000 |

| | | | | | |
|---|---|---|---|---|---|
| Clofazimine (Lamprene) | Treatment of lepromatous leprosy, including dapsone-resistant lepromatous leprosy and lepromatous leprosy complicated by erythema nodosum leprosum | Ciba-Geigy | 12/15/86 | 06/11/84 | 4,000 |
| Cromolyn sodium (Gastrocom) | Treatment of mastocytosis | Fisons | 12/22/89 | 03/08/84 | 1,000 |
| Cromolyn sodium 4% opthalmic solution (Opticrom) | Treatment of vernal keratoconjunctivitis (vkc) | Fisons | 10/03/84 | 07/24/85 | 15,850 |
| Cytomegalovirus immune globulin (human) | Prevention or attenuation of primary cytomegalovirus disease in immunosuppressed recipients of organ transplants | Massachusetts Public Health Biologic Labs | 04/17/90 | 08/03/87 | 2,000 |
| Digoxin immune fab (ovine) (Digibind) | Treatment of potentially life-threatening digitalis intoxication in patients who are refractory to management by conventional therapy | Burroughs Wellcome | 03/21/86 | 11/01/84 | 4,000 |
| Epoetin alfa (Epogen) | Treatment of anemia associated with end-stage renal disease (ESRD) | Amgen | 06/01/89 | 04/10/86 | 78,000 |
| Ethanolamine oleate (Ethamolin) | Treatment of bleeding esophageal varices | Glaxo | 12/12/88 | 03/22/84 | 17,300 |
| Etidronate disodium (Didronel) | Treatment of hypercalcemia of a malignancy inadequately managed by dietary modification and/or oral hydration | Norwich Eaton | 04/21/87 | 03/21/86 | 71,000 |
| Ganciclovir sodium (Cytovene) | Treatment of cytomegalovirus (CMV) retinitis in immunocompromised patients with acquired immunodeficiency syndrome (AIDS) | Syntex (USA) | 06/23/89 | 10/31/85 | 20,000 |
| Gonadorelin acetate (Lutrepulse) | Induction of ovulation in women with hypothalamic amenorrhea due to a deficiency or absence in the quantity or pulse pattern of endogenous gnrh secretion | R. W. Johnson Research Institute | 10/10/89 | 04/22/87 | 29,000 |

**Table 1** (*continued*)

| Generic (Trade) name | Indication | Sponsor | FDA Approval date | Designation date | Prevalence |
|---|---|---|---|---|---|
| Hemin | Ameloriation of recurrent attacks of acute intermittent porphyria (AIP) temporarily related to the menstrual cycle in susceptible women and similar symptoms which occur in other patients with AIP, porphyria variegata and heredita coproporphyria | Abbott Labs | 07/20/83 | 03/16/84 | 100 |
| Ifosfamide (Ifex) | Treatment of testicular cancer | Bristol-Myers | 12/30/88 | 01/20/87 | 10,000 |
| Interferon alfa-2a (recombinant) (Roferon-A) | Treatment of AIDS-related Kaposi's sarcoma | Hoffmann-LaRoche | 11/21/88 | 12/14/87 | 10,000 |
| Interferon alfa-2b (recombinant) (Intron A) | Treatment of AIDS-related Kaposi's sarcoma | Schering | 11/21/88 | 06/24/87 | 10,000 |
| L-carnitine (Vitacarn) | Treatment of genetic carnitine deficiency | Kendall McGaw | 04/10/86 | 02/28/84 | 100 |
| L-carnitine (Carnitor) | Treatment of primary and secondary carnitine deficiency of genetic origin | Sigma Tau | 12/27/85 | 07/26/84 | 100 |
| Leucovorin (Leucovorin Calcium) | For rescue use after high dose methotrexate therapy in the treatment of osteosarcoma | Lederle Labs | 08/31/88 | 08/17/88 | 5,000 |
| Mefloquine HCl (Lariam) | Treatment of acute malaria due to plasmodium falciparum and plasmodium | Hoffmann LaRoche | 05/02/89 | 04/13/88 | 1,000 |
| Mefloquine HCl (Lariam) | Prophylaxis of plasmodium falciparum malaria which is resistant to other available drugs | Hoffmann LaRoche | 05/02/89 | 04/13/88 | 150,000 |
| Mesna (Mesnex) | For use as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis | Degussa Corp. | 12/30/88 | 11/14/85 | 40,000 |
| Metronidazole topical gel (Metrogel) | Treatment of acne rosacea | Curatek Pharmaceuticals | 11/22/88 | 10/22/87 | 136,000 |
| Mitoxantrone HCl (Novantrone) | Treatment of acute myelogenous leukemia (AML), also referred to as acute nonlymphocytic leukemia (ANLL) | Lederle Labs | 12/23/87 | 07/13/87 | 30,000 |

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|---|---|---|---|---|---|
| Monooctanoin (Moctanin) | Dissolution of cholesterol gallstones retained in the common bile duct | Ethitek | 10/31/85 | 05/30/84 | 4,500 |
| Naltrexone HCl (Trexan) | Blockade of the pharmacological effects of exogenously administered opioids as an adjunct to the maintenance of the opioid-free state in detoxified formerly opioid-dependent individuals | E. I. Du Pont de Nemours | 11/30/84 | 03/11/85 | 40,000 |
| Peg-Adenosine deaminase (Adagen) | Enzyme replacement therapy for ADA deficiency in patients with severe combined immunodeficiency (SCID) | Enzon | 03/21/90 | 05/29/84 | 40 |
| Pentamidine isethionate (Pentam 300) | Treatment of pneumocystis carinii pneumonia | Lyphomed | 10/16/84 | 02/28/84 | 3,000 |
| Pentamidine isethionate (Nebupent) | Prevention of pneumocystis carinii pneumonia in patients at high risk of developing this disease | Lyphomed | 06/15/89 | 01/12/88 | 17,000 |
| Pentastarch (Pentaspan) | Adjunct in leukapheresis to improve the harvesting and increase the yield of leukocytes by centrifugal means | Dupont Critical Care | 05/19/87 | 08/28/85 | 50,000 |
| Potassium citrate (Urocit-K) | Prevention of uric acid nephrolithiasis | Univ. of Texas Health Sciences | 08/30/85 | 11/01/84 | 184,000 |
| Potassium citrate (Urocit-K) | Prevention of calcium renal stones in patients with hypocitraturia | Univ. of Texas Health Sciences | 08/30/85 | 09/16/85 | 17,000 |
| Potassium citrate (Urocit-K) | Avoidance of the complication of calcium stone formation in patients with uric lithiasis | Univ of Texas Health Sciences | 08/30/85 | 11/01/84 | 17,000 |
| Rifampin (Rifadin IV) | Antituberculosis treatment where use of the oral form of the drug is not feasible | Merrell Dow Pharmaceuticals | 05/25/89 | 12/09/85 | 40,000 |
| Selegiline HCl (Deprenyl) | Adjuvant to levodopa and carbidopa treatment of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism | Somerset | 06/05/89 | 11/07/84 | 30,000 |
| Somatrem (Protropin) | Long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion | Genentech | 10/17/85 | 12/09/85 | 15,000 |

**Table 1** (*continued*)

| Generic (Trade) name | Indication | Sponsor | FDA Approval date | Designation date | Prevalence |
|---|---|---|---|---|---|
| Somatropin (Humatrope) | Long-term treatment of children who have growth failure due to inadequate secretion of normal endogenous growth hormone | Eli Lilly | 03/08/87 | 06/12/86 | 10,000 |
| Teriparatide (Parathar) | Diagnostic agent to assist in establishing the diagnosis in patients presenting with clinical and laboratory evidence of hypocalcemia due to either hypoparathyroidism or pseudohypoparathroidism | Rorer Pharmaceuticals | 12/23/87 | 01/09/87 | 5,000 |
| Tiopronin (Thiola) | Prevention of cystine nephrolithiasis in patients with homozygous cystinuria | Charles Y. C. Pak M.D. | 08/11/88 | 01/17/86 | 33,700 |
| Tranexamic acid cyclokapron | Treatment of patients with congenital coagulopathies who are undergoing surgical procedures e.g. dental extractions | Kabi Vitrum | 12/30/86 | 10/29/85 | 20,000 |
| Trientine HCl (Cuprid) | Treatment of patients with Wilson's disease who are intolerant, or inadequately responsive to penicillamine | Merck Sharp and Dohme | 11/08/85 | 12/24/84 | 700 |
| Urofollitropin (Metrodin) | Induction of ovulation in patients with polycystic ovarian disease who have an elevated LH/FSH ratio and who have failed to respond to adequate clomiphene citrate therapy | Serono Labs | 09/18/86 | 11/25/87 | 118,000 |
| Zidovudine (Retrovir) | Treatment of acquired immunodeficiency syndrome (AIDS) | Burroughs Wellcome | 03/19/87 | 07/17/85 | 10,000 |
| Zidovudine (Retrovir) | Treatment of AIDS-related complex (ARC) | Burroughs Wellcome | 03/19/87 | 05/12/87 | 100,000 |

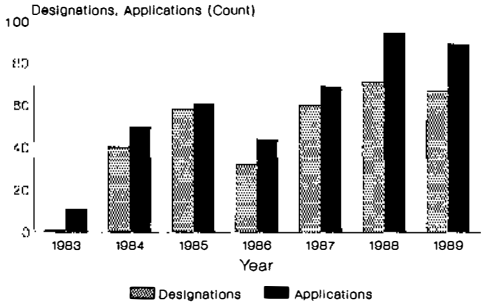


*Figure 2* Orphan drug applications and designations, by year (1983–1990).

are for patient populations of 10,000 or less, and 39 are for 50,000 or less. While it will be obvious that zidovudine (AZT) for AIDS, for example, shows a prevalence number of 10,000 that is far lower than the number of patients that would be estimated today, the Act specifically requires that the determination of eligibility for orphan status be "made on the basis of the facts and circumstances as of the date" the request for designation is made (15). About 25% of the designation requests received have been found to exceed the maximum allowable prevalence for orphan products (200,000) specified in the statutory standard. Designations and requests for designations are increasing (Figure 2). Projecting the 1990 rate on the experience so far suggests a banner year for designations. Diseases and conditions on the lower levels of the prevalence scale consistently account for the bulk of the orphan product designations each year (Figure 3).

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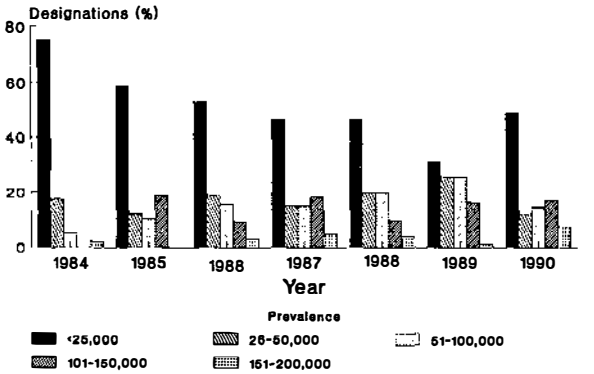


*Figure 3* Designations by prevalence and year. 1990 percentages based on data to May.

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