REVIEW ARTICLE

Accepted 7 July 2004
Revised 9 March 2004
Received 21 July 2003
Indian J. Pharm. Sci., 2004, 66(5): 587-594

Orphan Drugs

MEERA SUMANTH* AND S. PARASHER,
Al-Ameen College of Pharmacy, Hosur Road, Near Lal Bagh Main Gate, Bangalore-560027.

As per the United States Food and Drug Administration, orphan drugs are defined as drugs used in diseases or circumstances which occur so infrequently in USA, that there is no reasonable expectation that the cost of developing and making available, a drug for such disease or condition will be recovered from its sales in USA. In this article, the current state of orphan drugs in different countries and the benefits provided by the drug authorities/government of the country for the development of drugs for rare disease is discussed.

Orphan drugs have been defined in USA as those drugs intended to treat either a rare disease or a more common disease where the sponsor cannot make any profit[1]. As per the definition US FDA, orphan drugs are those drugs used in diseases or circumstances which occur so infrequently in USA, that there is no reasonable expectation that the cost of developing and making available, a drug for such disease or condition will be recovered from its sales in the USA (www.fda.gov) Further, rare disease or condition is any disease or condition which affects less than two hundred thousand persons in the United States or affects more than two hundred thousand persons in the United States, but, for which there is no reasonable expectation that the cost of developing and making available, a drug for such disease or condition will be recovered from its sales in US. About two decades ago or so, Alzheimer's or Parkinson's disease were labeled as rare diseases, which has become common now in geriatric patients and the pharmaceutical industries, with their R and D, have come out with newer drugs and better dosage forms for drug delivery. Thus, the orphan drug shift from its 'orphan drug' status to frequently used drugs with good market potential.

But, with the advances in science and technology, newer diseases, (some termed as rare disease) are reported and hence, we have USFDA designated orphan drug with t-IND (treatment Investigational New Drug) in some cases. This article reviews the basis for classification of orphan drugs, the discovery of orphan drugs, and attempts by pharmaceutical industries, academician (scientist) and practicing physician, with their respective perspectives, advantages and disadvantages in discovery and development of orphan drugs and some historical aspects.

*For correspondence
E-mail: meerasumanth@hotmail.com

CLASSIFICATION OF ORPHAN DRUGS

Earlier, based on the stage of development, orphan drugs were divided into four general categories[2] or eighteen separate detailed categories[3]. Amongst the various alternative classifications that are developed, Table 1 presents a classification consisting of five categories of orphan drugs based on their commercial potential and the availability of suitable treatment. The major difference between Type-I and Type-III orphan drugs is that the latter are used for diseases that already have at least some useful therapy available. A number of diseases have gone from the Type-I to Type-III categories over the previous few decades. These diseases include many rare bacterial diseases that can be treated by common antibiotics, plus Wilson's disease, which can now be treated with penicillamine, zinc and triethylenetetramine[4]. Type-I and III orphan drugs are generally most difficult ones to find sponsors, for the drugs are known to have activity but are not yet marketed. There is often a hope that a Type-I, II, or III drug will also be found useful for treating a common disease and become a profitable type-V drug Since

TABLE 1: CLASSIFICATION OF ORPHAN DRUGS

Categorization of the drug	Description of the drug	Anticipated profit for the new drug
Type I	Therapeutic orphan with no or little commercial potential	Poor to marginal
Type II	Therapeutic orphan with commercial potential	Good to excellent
Type III	Orphan drugs for rare disease that can be currently treated	Variable
Type IV	Unprofitable drug for a common Disease	Poor to marginal
Type V	Orphan drug used for both a rare & common disease	Variable

Classification of orphan drugs based on commercial potential and availability for marketing.

pharmaceutical companies consider both the stages of drug development as well as commercial and medical potential when describing or classifying orphan drugs, whereas, Practicing physicians think in terms of drug's availability for patient use, this classification is most appropriate of all the classifications for orphan drugs.

DISCOVERY OF ORPHAN DRUGS

Most of the drugs have multiple indications in either the same therapeutic area or in different/several therapeutic areas and one or more of the indications may be for a rare disease. Discovery of orphan drugs is similar to that of non-orphan drugs i.e., preclinical evaluations and clinical trials. Preclinical activities leading to discovery of orphan drugs include chemical synthesis targeted to find a drug for the treatment of a rare diseases, biological testing of compounds/molecules in an animal model of a rare disease with the aim of finding a new activity, serendipitously found biological activities in animal studies that suggest a potential clinical usefulness of the molecule/compound in treating a rare disease and a new theory proposed to suggest that the lead molecule has activity for a rare disease[5]. Clinical activities leading to discovery of orphan drugs include serendipitously found clinical activity in human patients with a rare disease or clinical testing conducted in patients with a rare disease, and a theory suggesting a new clinical activity against a rare disease in a known drug. In some instances, a novel chemical was originally synthesized with the hope of its intended clinical use in treatment of a rare disease. Most common mode of discovery of orphan drug is by serendipitously found clinical activity in patients with a specific rare disease. These patients often have a co-existent rare disease along with the disease for which he is being treated and during the course of treatment; it is found to have activity for the rare disease with which the patient is suffering. In some other cases, the physicians managing their patients with a rare disease have a personal belief or theory that the drug might be helpful for the treatment of a rare disease and they test the drug and thus some of the drugs for rare diseases or novel indications for humans were found[6].

Academic investigator's perspective in discovery and development of orphan drug:

An academic chemist or a government laboratory chemist may synthesize compounds targeted towards a rare disease, as a result of scientific and social environment existing at the work place of the academician. Sometimes, he/she may collaborate with other agencies for biological testing of synthesized molecule. An academician, who gets grants or financial support for his/her research activities and encouragement from managers and superiors, may develop a drug targeted towards a rare disease. Also, there may be a perceived medical need for such research. There are certain advantages to academicians for developing drugs for rare diseases. They get public recognition and can publish papers in national and international journals. They may get grants for new developments which may further their careers to newer heights. They may get a chance to participate in preclinical and clinical studies and might also, be able to treat patients more effectively. The only disadvantage is that the clinical practice may take a backseat as physicians devote most of their time to academic research.

Pharmaceutical companies' perspective in development of orphan drug:

Companies are encouraged for R and D work for discovery of drugs intended for the treatment of rare diseases by providing the incentive in term of intellectual property and marketing exclusivity. (www.fda.gov) President Ronald Reagan, in 1983 established Orphan Products Board under the Orphan Drugs Act of Department of Health and Human

Services, for the development of drugs (including biologicals) and devices (including diagnostic products) for rare diseases or conditions. The Board is comprised of the Assistant Secretary for Health of the Department of Health and Human Services and representatives, selected by the Secretary, of the Food and Drug Administration, the National Institute of Health, the Centers for Disease Control and, any other Federal department or agency which the Secretary determines has activities relating to drugs and devices for rare diseases or conditions. The function of the Board is to promote the development of drugs and devices for rare diseases or conditions and the coordination among Federal, other public, and private agencies in carrying out their respective functions relating to the development of such articles for such diseases or conditions.

In USA, granting orphan drug status may enable the sponsor to obtain 50% tax credit on the cost of clinical trials undertaken in USA, seven years of marketing exclusivity following the Marketing Authorization, written recommendations provided by the Food and Drug Administration concerning clinical and preclinical studies to be completed in order to register the new drug, and fast track procedure for the Food and Drug Administration to evaluate registration files.

The availability of orphan drugs to patients before being granted a Marketing Authorization is possible. In some cases of compassionate use, a t-IND may be obtained under specific condition such as when the drug is intended for the treatment of a serious or life threatening disease, when no alternative drug or treatment is available, and thirdly, the product is in the process of clinical trials and in an active phase of Marketing Authorization application.

In USA, the grants for clinical trials of orphan drugs may cover up to $ 2 00 000 of direct costs per year, for up to three years, depending on the stage of the clinical study. As a result, there were $ 67 million of orphan drugs research grants contributing to the research on approximately 265 substances for an estimated 180 rare diseases. The current budget for funding grant is estimated to be around $ 12 million[7]. The involvement of pharmaceutical companies in the orphan drug development is likely to increase as a result of new regulation schemes. The close collaboration between small biotechnology companies and multinational pharmaceutical companies is increasing. It is expected that a lot of orphan drugs will be discovered by biotechnology companies and be developed in partnership with multinational companies or contract organizations. It is also expected that the orphan drug status will encourage the birth of new small and medium-size companies requiring highly qualified personnel[8]. As a result of US Orphan Drugs Act, new therapies have been developed for specific rare diseases such as Gaucher diseases, cystic fibrosis, haemophilia, multiple sclerosis, leprosy, tourett syndrome, porphyriasis and many other ailments for which no treatments were available earlier. (www.fda.gov) The Pharmaceutical Industry is also seeking new ways to treat disease like cellular therapies, gene therapies that could have a lot of applications in the orphan drugs sector. Twenty years after the passage of the Orphan Drug Act, as we see today, it has exceeded its original expectations. During the decade before its appearance, 34 Orphan products went on the market, 10 of them developed by the pharmaceutical industry and other 24 by federally funded efforts. In the past two decades (till 2000), 229 orphan drugs that together treated 11 million patients, were marketed in USA[9]. In the past decade 17% of total drugs sold in USA constitute orphan drugs. From 1983 to 1992, only 3 drugs against tropical diseases (eflornithine, mefloquine and halofantrine) received orphan drug status in the USA whereas in 1998 the FDA gave marketing approval to 19 Orphan Drugs and products. Of the 1239 applications, the designated orphan drugs from 2003 to 1998 are listed in Table 2, some of which have got approval from USFDA for marketing them in USA. The orphan drugs approved by the U.S. Food and Drug Administration (FDA) for marketing in the U.S. in 2003 are (With date of approval for marketing in brackets): bortezomib for treatment of multiple myeloma (5/13/2003), botulism immune globulin for treatment of infant botulism (10/23/2003), alpha-galactosidase for treatment of Fabry disease (4/24/2003), iron(III)-hexacyanoferrate(II) for treatment of patients with known or suspected internal contamination with cesium or thallium (10/2/2003), laronidase for treatment of patients with mucopolysaccharidosis I (4/30/2003), miglustat for treatment of Gaucher disease (7/31/2003), pegvisomant for treatment of acromegaly (3/25/2003), porfimer for treatment of Barrett's esophagus (8/1/2003), ibavirin for treatment of chronic hepatitis C in pediatric patients (7/29/2003), somatropin (r-DNA) for treatment of short bowel syndrome (12/1/2003), and tositumomab for treatment of non-Hodgkin's B-cell lymphoma (6/27/2003).

The authors of the article have searched for information regarding the orphan drug policy and status of orphan drugs in India but there was no relevant documents indicating that there is a government policy to promote research and development of drugs for rare diseases. Japan and Australia are the other countries having regulatory bodies for

TABLE 2: LIST OF ORPHAN PRODUCTS DESIGNATED

Generic Name/ Trade Name (if present):	Date designated (DD)	Indication Designated	Sponsor and Address
(+/-)-7-[3-(4-acetyl-3-methoxy-2-prop ylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid	3/31/2003	Prevention of serious adverse events associated with vascular leak syndrome caused by Interleukin-2 therapy	BioMedicines, Inc.
2',3',5'-tri-o-acetyluridine	1/13/2003	Treatment of mitochondrial disease	Repligen Corporation
4,5-dibromorhodamine 123 *Theralux Irradiation Device*	4/10/2003	Treatment of chronic myelogenous leukemia	Celmed BioSciences Inc.
a-(3-aminophthalimido) *Actimid*	1/15/2003	Treatment of multiple myeloma	Celgene Corporation
a-Galactosidase A *Plant-Produced Human a-Glactosidase*	1/21/2003	Treatment of Fabry's disease	Large Scale Biology Corporation
(4S)-4-ethyl-4-hydroxy-3,14-dioxo-3, 4,12,14-tetrahydro-1-H-pyrano[3',4',6,7]-indolizino-[1,2-b]-quinoline-11-carbaldehyde O-(tert-butyl)-(E)- oxime *Gimatecan*	11/29/2002	Treatment malignant glioma	Sigma-Tau Research, Inc
(R)-N-[2-(6-chloro-5-methoxy-1H-indol-3-yl)propyl]acetamide	10/3/2001	Treatment of circadian rhythm sleep disorders in blind people with no light perception	Phase 2 Discovery, Inc.
2-chloroethyl-3-sarcosinamide-1-nitrosourea *Sarmustine*	11/15/2001	Treatment for malignant glioma	Pangene Corporation
2-chloroethyl-3-sarcosinamide-1-nitrosourea	8/3/2001	Treatment for malignant gliomas	Lawrence Panasci MD, McGill University
2-methoxyestradiol *Panzem*	7/10/2001	Treatment of multiple myeloma	EntreMed, Inc.
3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione *Revimid (proposed)*	9/20/2001	Treatment for multiple myeloma	Celegene Corporation
9-nitro-20-(S)-camptothecin *Camvirex*	5/15/2001	Treatment of pediatric HIV infection/AIDS	NovoMed Pharmaceuticals, Inc.
Acetylcysteine *Acetadote*	10/19/2001	For the intravenous treatment of moderate to severe acetaminophen overdose	Ligand
1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine hydrogen methanesulfonate	1/18/2000	Treatment of hormone refractory prostate carcinoma.	Cell Therapeutics, Inc.
3,5,3'-triiodothyroacetate	9/20/2000	Treatment of well-differentiated	Elliot Danforth, Jr., M.D.

Cont... TABLE 2: LIST OF ORPHAN PRODUCTS DESIGNATED

		papillary, follicular or combined papillary/follicular carcinomas of the thyroid gland.	University of Vermont
3-(3,5-Dimethyl-1H-2ylmethylene)-1, 3-dihydro-indol-2-one	3/23/2000	Treatment of von Hippel-Lindau disease.	Sugen, Inc.
Abetimus	7/28/2000	Treatment of lupus nephritis.	La Jolla Pharmaceutical Co.
111Indium pentetreotide	6/10/1999	Treatment of somatostatin receptor positive neuroendocrine tumors.	Louisiana State University Medical Center Foundation
166Ho-DOTMP	2/10/1999	Treatment of multiple myeloma.	NeoRx Corporation
506U78	9/2/1999	Treatment of chronic lymphocytic leukemia.	GlaxoSmithKline
6-hydroxymethylacylfulvene	4/6/1999	Treatment of histologically confirmed advanced or metastatic pancreatic cancer.	MGI Pharma, Inc.
6-hydroxymethylacylfulvene	7/27/1999	Treatment of renal cell carcinoma.	MGI Pharma, Inc.
6-hydroxymethylacylfulvene	7/6/1999	Treatment of ovarian cancer.	MGI Pharma, Inc.
1,5-(Butylimino)-1,5 dideoxy,D-glucitol	5/12/1998	Treatment of Fabry's disease.	Oxford GlycoSciences
1,5-(Butylimino)-1,5 dideoxy,D-glucito l	5/29/1998	Treatment of Gaucher disease.	Oxford GlycoSciences

orphan drugs development. Table 3 gives the scenario regarding orphan drugs in these two countries as compared to USA. In Japan, Orphan Drug Regulation under Ministry of Health and Welfare awards 10 years of marketing exclusivity to sponsor of 113 orphan drugs and 5 medical devices, whereas in Australia, 11 designated orphan drugs are under evaluation by Therapeutic Goods Administration for award of 5 years of marketing exclusivity.

INTERESTING HISTORICAL ASPECTS REGARDING ORPHAN DRUGS

Drugs that wouldn't die:

The phrase "drugs that wouldn't die" is taken from an article by Weintraub and Northington[7]. They described case histories of five unprofitable drugs that were taken off the market, but later were reintroduced as a result of pressure from physicians, patients and other health professionals. Each of these drugs is an orphan, either based on the small size of the disease population or because the drug is unprofitable and only benefits a small segment of patients with a common disease. The five drugs are tranylcypromine (parnate), an MAO inhibitor used for depressed patients; mecamylamine (inversine), a ganglionic blocking agent used as an antihypertensive and reintroduced for patients with autonomic hyperreflexia due to spinal cord injuries; methoxamine (vasoxyl), a nearly pure alpha receptor agonist that is used to avoid and reverse hypotension during anesthesia and for cardiopulmonary resuscitation; methotrimeprazine (levoprome), parenterally used as narcotic analgesic, which provides an alternative for patients in whom physical dependence, respiratory depression, and/or other adverse reactions would be a significant problem; and alphaprodine (nisentil), a short-acting narcotic analgesic that was particularly effective in the out patient management of certain pe-

diatric patients in dentistry.

Drugs killed by publicity:

Some of the potential useful drugs get killed by over publicity. An example of such a drug is thalidomide, which was initially used indiscriminately and injudiciously. The drug had teratogenic effect, which led to serious adverse effects in large population, particularly children and this was fol-

TABLE 3: SCENARIO OF ORPHAN DRUGS IN VARIOUS COUNTRIES

Legal	U.S.A Orphan Drug Act	Japan Notice Of DG	Australia Orphan Drug
Framework	(1983) Orphan Drug Regulation (1993)	PAB (1985) Orphan Drug Regulation (1993)	Policy set up in 1997
Administrations	Food and Drug Administration (FDA/Office of Orphan Drug	Ministry of Health and Welfare Development (MWH) Drugs fund for ADR Relief and Research Promotion	Therapeutic Goods Administration (TGA)
Beneficiaries	Sponsor and investigator	Sponsor	Sponsor
Orphan drugs Status	Prevalence: 0, 75 Per thousand	Prevalence: 0, 4 Per thousand	Prevalence: 0, 1 Per thousand
Marketing Exclusivity	7 years	10 years	5 years
R&D incentives	50%, clinical trials conducted in the U.S.A.	6% of any kind of studies,limited to 10% of the company's taxes	R&D is not supported by grants or tax incentives
Fundings	Phase I, II, III under $100 000 per year by donations during three years. Phase II, III under $200 000 per year by donations during two years	Under 50% of R&D, 3% of the companie's incomes distributed to raise funds.	Fee waiver and possible market exclusivity for small companies
Files reexamination	No	Yes	A 12 months review is to be done in January 1999
Number of designated orphan drugs	890	113+5 medical devices	15 applications, of which 11 are under evaluation for orphan designation.
Number of orphan drugs marketing authorizations	173	36+2 medical devices	0
Number of companies involved in orphan drugs providing (which have already launched one orphan drug or more)	92 (including institutes and universities)	28	
Number of patients eligible to existing treatments	6,5 millions		
Number of eligible patients	20 millions		

Comparison of orphan drug scenario in USA, Japan, and Australia.

lowed by large number of court cases for teratogenicity. Decision of non scientific juries against manufacturers and emotional decision making against the company, enormous liability settlements made it unprofitable and unwise to continue marketing of this drug. Now, thalidomide is being launched in the market but for a new indication, and it is in the process of clinical trials in the US.

Pediatric Drug Development and the Orphan Drug Act Incentives:

The Office of Orphan Products Development (OOPD) of the Food and Drug Administration (FDA) has long recognized pediatric patients as "therapeutic orphans" due to the lack of adequate pediatric dosing information among drugs that are on the market. OOPD encourages drug sponsors to give attention to the multiple economic incentive provisions of the Orphan Drug Act including tax credits for clinical research and waiver of Prescription Drug User Fee Act (PDUFA) application fee, and to obtain orphan-drug designation of a drug or biological product intended for pediatric use. The designated orphan drug or biological product is entitled to seven years of orphan-drug marketing exclusivity upon its approval for pediatric use. In the pediatric population, growth and developmental changes can influence the way drugs are absorbed, distributed, metabolized, and excreted, which are vastly differently from the adult. Based on these unique pharmacokinetic properties, OOPD has determined that pediatric patients constitute a medically plausible subset of patient population. Therefore, a sponsor of a new drug or biological product may seek orphan-drug designation for treatment of a disease or condition in the relevant pediatric subset of patient population.

USES AND ABUSES OF ORPHAN DRUG ACT 1983:

In the late 1970s, some pharmaceutical companies decided against manufacturing and marketing of some drugs, e.g. pimozide for Tourette syndrome, penicillamine for Wilson's disease, 5-hydroxytryptophan for myoclonus, gamma-hydroxybutyrate for narcolepsy, sodium valproate for certain forms of epilepsy, and cysteamine to treat children with cystinosis, when they proved more costly than their meager sales projections warranted. The desperate need of these and such other drugs to be manufactured and marketed in USA lead to emergence of Orphan Drug Act 1983. The Orphan Drug Act was needed not only to provide financial incentives to companies, but also to allow drug makers more leeway in designing studies to prove that a drug candidate is safe and effective. The standard set of human clinical trials can take years and involve thousands of patients at multiple sites. The entire patient population with a rare disease, on the other hand, may be smaller than the number of subjects in most ordinary trials, so testing cannot follow the usual protocols. Only 12 children in the U.S. suffered from adenosine deaminase (ADA) deficiency, a cause of severe combined immunodeficiency disease (SCID), for example, when a company was developing a drug for it. Similarly, sacrosidase, for a congenital enzyme disorder (sucrase-isomaltase deficiency), was approved on the basis of two trials that had a grand total of 41 patients.

Indeed, rare diseases and orphan drugs have been boons to applied pharmaceutical research. It stimulated tremendous growth of biotech industry. A recent study by the Tufts Center for the Study of Drug Development found that from 1983 to 1992 the biotech industry secured 19 percent of all orphan drug approvals; 76 percent of such approvals went to pharmaceutical companies. By 2001 biotech's share had grown to 41 percent. Of the 10 best-selling biotech drugs worldwide in 2001, five were originally approved as orphan drugs, and three more were approved for orphan indications in addition to their original use. The orphan indication afforded their developers seven years of marketing exclusivity. Indeed, the biggest moneymaking orphan products helped to launch some of the major players in the biotech industry, including Amgen and Genentech.

One can make money on orphan drugs. In 1988 Lars-Uno Larsson, a former Bristol-Myers Squibb executive, founded Swedish Orphan International in Stockholm. According to him, the Orphan Drug Act made it possible to earn modest but sufficient returns on drugs for rare diseases. Now with affiliates around the world, Swedish Orphan has developed a number of products and inspired others to establish similar companies. According to John Bullion, a former venture capitalist and now the CEO of Orphan Medical, a Minnesota-based company with half a dozen approved orphan products, you can make very good money with a $10-million product, (orphan drug product) but you need several of them.

People with rare diseases are usually treated by a handful of doctors who have experience in the disease and often join patient education or advocacy groups to share information and to lobby for more research on their disorder. This combination makes finding patients to participate in clinical trials and to buy the drugs relatively easy and cost-effective. According to a recent industry analysis, it costs about one fourth as much to develop a drug for a rare disease as one for high blood pressure, and annual marketing costs are one seventh as high.

But some of the abuses of the Orphan Drug Act are glaring. Initially, when they were first introduced, Amgen's epoetin alfa, Genentech's human growth hormone (hGH) and GlaxoSmithKline's AZT were approved for rare disorders (anemia in end-stage kidney failure, hGH deficiency and AIDS, respectively). Subsequently, these products earned billions when physicians began to prescribe 1. Epoetin alfa for restoring red blood cells in people suffering from bone marrow suppression as a result of taking AIDS drugs or cancer chemotherapy, and reducing the need for transfusions in surgery. 2. hGH for many short-statured children and 3. When the AIDS epidemic ballooned. Some critics suggest that orphan drugs that make profits no longer need help and should forfeit the act's benefits. The European Union recently enacted a law that would strip orphan status from a drug that becomes "extraordinarily profitable" after five years. It is too early to tell whether Europe's law will prevent drug companies from abusing orphan drug designation; national health plans that exert controls on drug prices will also make the law's effects hard to assess.

Sometimes, orphan drugs are so costly, that many patients, who need to buy them, go bankrupt. One such example is Cerezyme of Genzyme. The drug—an enzyme-replacement therapy for Gaucher disease, is the world's most expensive medicine. Still, most companies that produce orphan drugs have formal or informal programs for providing drugs free to indigent patients, but they hardly ever make public the number of patients they accommodate or what such patients must do to qualify. In the end, the high cost of orphan drugs probably has to be addressed as part of the bigger problem of high drug costs in general. The FDA itself is in no position to insist that costs come down for orphan drugs or any others. It has no authority over pricing[9].

In conclusion, orphan drugs are those drugs used to treat rare diseases and the development and marketing of orphan drugs is assisted by the governments of USA, Japan, and Australia in form of grants, marketing exclusivity, thus helping the patients with rare diseases get drug treatment. But, some of the orphan drugs are Rich Orphans earning tremendous profits for the company.

REFERENCES

1. Spiker, B., In; Schelnberg, H and Walshe, J.M., Eds, Orphan Diseases and Orphan Drugs, Manchester University Press, Manchester, 1986, 119.
2. Spiker, B., **Trends Pharmacol. Sci.,** 1985, 6, 185.
3. Waxman, H.A., In; Schelnberg, H and Walshe, J.M., Eds, Orphan Diseases and Orphan Drugs, Manchester University Press, Manchester, 1986, 135.
4. Asbury, C., In; Orphan drugs, Lexington Books, Health and Co., Lexington, MA, 1985, 121.
5. Seharf, S.F., **Amer. J. Law Med.,** 1985, 10, 491.
6. Weintraub, M. and Northington, E.R., **J. Amer. Med. Assoc.,** 1986, 255, 2327.
7. Sheffield, I. J. and Batagol, R., **Med. J. Aust.,** 1985, 143-49.
8. Stubbins, J.F., In; Orphan Drugs, Lexington Books, Health and co., Lexington, MA, 1985, 281.
9. Maeder, T., **Sci. Amer.,** 2003, 288, 80.