The Orphan Drug Act and the Federal Government's Orphan Products Development Program

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DURING THE PAST DECADE, a number of independent groups in the executive and legislative branches of the Government and in the private sector examined the problem of orphan drugs and made recommendations for its amelioration.

Orphan drugs are drugs with demonstrated or potential effectiveness in the diagnosis, prophylaxis, or treatment of an uncommon disease that remain unavailable because of lack of commercial interest on the part of pharmaceutical manufacturers. These drugs have been termed "orphans" not only because they are not available to most physicians and their patients but also because the research required to permit marketing approval is not conducted, due to lack of financial incentives for manufacturers.

The pharmaceutical industry has, over the years, provided a considerable number of therapeutic and diagnostic agents as a public service for patients with rare diseases. In many cases, all or most of the research leading to development of these agents was conducted by investigators under Government or private grants. This, of course, does not lessen the contributions of drug companies in seeking marketing licenses, developing finished dosage forms, and distributing the products. In some cases, drug companies have performed a considerable amount of research themselves. Understandably, they cannot be expected to divert much of their resources away from the study of drugs for common diseases. Therefore, all groups that investigated the orphan drug problem concluded that special incentives were needed to stimulate research on and development of these drugs.

Such incentives are provided, to a considerable degree, by the Orphan Drug Act. The act was signed into law by the President on Jan. 4, 1983. An earlier version had been introduced in the Congress by former Representative Elizabeth Holtzman. The present act was passed largely through the efforts of Representative Henry A. Waxman, Chairman of the House Subcommittee on Health and the Environment.

Provisions of the Orphan Drug Act

The act defines an orphan drug as a drug or biologic intended for a disease or condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing the drug and making it available will be recovered from sales in the United States. Examples of rare diseases given in the act include Huntington's disease, amyotrophic lateral sclerosis, Tourette syndrome, and muscular dystrophy. Among these examples, the disorder with the highest prevalence is Tourette syndrome, with an estimated prevalence in the United States, for the full-blown syndrome, of 100,000 patients.

The Orphan Drug Act provides four incentives for drug companies:

1. A tax credit of 50 percent for the expenses of the clinical trials performed prior to marketing approval. This credit, together with the normal deduction for the remainder of the clinical expenses, amounts to about 73 cents' return per dollar spent. The tax credit is permitted only for clinical testing conducted in the United States unless there is an insufficient testing population in this country.

2. A 7-year exclusive marketing license for unpatentable drugs. During this period, the Food and Drug Administration (FDA) cannot approve another marketing application for the same drug for the same orphan use. The exclusivity applies only to the specific orphan indication. If another firm develops the same drug for a common-disease indication or for a different orphan indication, approval will also be granted to that firm. It should be noted that exclusivity continues only so long as the firm can supply the needs of the US. population with the orphan disease. Should a firm charge a high price unjustified by the costs of development, so that few patients can afford the drug, or, in the case of a complex biological, should a firm be unable to manufacture enough of the product, then approval will be granted to other manufacturers.

3. Protocol assistance. Under this provision, the FDA must provide, on request, written advice to a sponsor of an orphan drug on the studies (animal and clinical) needed for marketing approval.

4. Grants and contracts. The act permits the Congress to appropriate $4 million per year for grants or contracts to support clinical trials of orphan drugs. The act author-

izes such appropriations only for fiscal years 1983–85. The grants and contracts may be awarded to private entities or individuals.

The Orphan Drug Act requires the establishment, in the Department of Health and Human Services (HHS), of an Orphan Products Board comprising the Assistant Secretary for Health and representatives of the FDA, the National Institutes of Health, the Centers for Disease Control, and other Federal agencies that have activities relating to orphan drugs and orphan devices.

Such a board was established by the HHS Secretary before passage of the Orphan Drug Act. In addition to representatives of the agencies just named, it includes representatives of the Alcohol, Drug Abuse, and Mental Health Administration; the Health Care Financing Administration; the Veterans Administration; and the Department of Defense. The board evaluates the activities of the represented agencies with respect to orphan product research and development and ensures appropriate coordination among Federal agencies, manufacturers, and organizations representing patients with rare diseases. The board also seeks investigators to perform research, seeks sponsors to complete development of and distribute orphan drugs, and recognizes the efforts of public and private entities and individuals to promote the availability of orphan drugs. The seeking of sponsors is delegated to the FDA; the seeking of investigators is delegated to all of the grant- and contract-awarding agencies represented on the board. In addition, the board is a policy-making organization.

Orphan Products Development Program

The Orphan Products Board. Since its inception in March 1982, the board has developed a number of procedures and policies; has examined potential obstacles to product availability; and has opened communications with the drug industry, rare disease organizations, and investigators involved in the study of rare diseases and of drugs for those conditions. The board has reviewed the issue of liability and whether it serves as a serious disincentive to firms to study and market drugs of little or no commercial value, and it has concluded that, in general, liability is not an obstacle.

Two public meetings have been held by the board to listen to and act on the concerns of clinical investigators and patients with rare diseases. A major interest of these individuals is the establishment of a national clearinghouse that would provide information to patients and physicians on rare diseases and on products under study or marketed for these conditions, and would maintain a registry of physicians who are studying and treating these diseases. The board is actively considering the desirability of a clearinghouse, its nature, and methods for its establishment.

The board has also met with two pharmaceutical industry organizations to determine how it and these entities can work together to help make orphan products available. (The organizations—the Pharmaceutical Manufacturers Association's Commission on Drugs for Rare Diseases and the Generic Pharmaceutical Industry Association's Institute for Orphan Drugs—were formed within the last 2 years to consider the merits of specific orphan drugs and seek sponsors for them.) Indeed, several agencies represented on the board, including the FDA, have been liaison members of the Commission on Drugs for Rare Diseases since its inception, and the FDA has worked closely with the Institute for Orphan Drugs.

The Board has monitored the progress toward availability of more than 30 orphan products. It has considered the types of research it will support under the appropriations provided by the Orphan Drug Act and has engaged in many other activities, including development of a policy that will permit, when it is in the public interest, the granting of an exclusive license to a firm to complete development of and market an orphan product that has been developed almost entirely with Government funds.

NIH and ADAMHA. Through their intramural and extramural programs, the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration have provided considerable support over the years for research on orphan drugs, although such support was not at the time thought of in "orphan" or "nonorphan" terms. The NIH, in order to underline its commitment to support of orphan product research, recently issued an announcement encouraging grant applications for clinical testing of orphan products. These applications will undergo the usual peer review process.

Centers for Disease Control. The CDC has for years distributed to physicians investigational orphan drugs and biologics. Approximately 30 such products have been distributed since 1965. CDC also collects data on adverse reactions to these drugs. Such data are useful when FDA finds a sponsor to take over the drugs' distribution.

Food and Drug Administration. The largest program in the Federal Government directed specifically to orphan products is that of the FDA. The FDA program, which has been in existence since May 1982, has a broader mandate than that encompassed by the Orphan Drug Act. The program's scope includes orphan medical devices, medical foods, and veterinary products as well as drugs for humans. In addition, the program is directed

not only to products for rare diseases but also to products for common diseases for which there is no commercial sponsor because the products are not patentable or the patents have expired or are about to expire. The program also addresses unlabeled uses for marketed drugs when such uses are for serious, uncommon diseases.

FDA identifies new products by means of (*a*) continuous review of the published medical literature and of investigational applications submitted to the FDA by drug companies and academicians, and (*b*) communications from professional organizations, voluntary disease associations, foreign and domestic drug companies, foreign regulatory agencies, and clinical investigators. Manufacturers who will complete development of compounds of interest, submit marketing applications, and distribute the products are sought through notices published in the Federal Register, direct approach to companies with expertise in the manufacture of certain types of products, or request to the Commission on Drugs for Rare Diseases or the Institute for Orphan Drugs.

Through these mechanisms, during the period May 1982 through December 1983, company sponsors were found for 24 unmarketed products and 4 new uses of marketed products. One of the sponsored products—hematin, for hepatic porphyria—was approved for marketing in July 1983, several others are under review, and marketing applications are scheduled to be submitted for the remainder in 1984 and 1985, depending upon the

Examples of sponsor commitments for orphan products

Drug	*Sponsor*	*Intended use*	*Date of commitment*
Trien (triethylene tetramine dihydrochloride)	Merck Sharp and Dohme	Wilson's disease	October 1982
NP-59 (6-beta-19-iodonorcholesterol)	Mallinckrodt	Adrenal cortical imaging	June 1982 (presentation to PMA commission[1])
Hematin	Abbott	Hepatic porphyria	May 1982 (licensed July 1983)
Amiodarone	Ives	Cardiac arrhythmias	October 1982
Indium^{111} Oxine	Amersham	Platelet imaging	December 1982
Methacholine Cl	Roche	Diagnosis of occult bronchial asthma	March 1982
Pimozide	McNeil	Tourette syndrome	November 1982
Bacitracin	A. L. Laboratories	Pseudomembranous enterocolitis	August 1982
Hydroxy-ethyl starch	American Critical Care	White blood cell harvesting	August 1982
L-5 hydroxy-tryptophan	Bolar	Postanoxic myoclonus	June 1982
Vitamin E	Roche	Neuromuscular disorders secondary to cholestatic disease in vitamin E deficient patients	October 1982
Pentamidine	Zenith	*P. carinii* pneumonia	November 1982
Carnitine	McGaw	Carnitine deficiency	July 1982
Ethanolamine oleate	Glaxo	Bleeding esophageal varices	December 1982
Deprenyl	(2)	Certain patients with Parkinson's disease	January 1983
I^{131}-M-iodobenzyl-guanidine (I^{131}-MIBG)	Mallinckrodt	Adrenal medullary imaging agent	March 1983
Monooctanoin	Ascot	Cholesterol gallstone dissolution	July 1983
Citric acid, gluconic acid, magnesium hydroxycarbonate, magnesium acid citrate, calcium carbonate solution	Guardian Chemical	Dissolution of urinary tract calculi and prevention and treatment of encrusted indwelling urinary tract catheters	November 1983

[1] Pharmaceutical Manufacturers Association's Commission on Drugs for Rare Diseases.

[2] Confidential.

amount of research to be completed. Examples of products for which commitments have been made by sponsors are presented in the table.

FDA also administers certain portions of the Orphan Drug Act previously described, namely, advice on studies needed for marketing approval and the designation, when appropriate, of drugs as "orphans" so that tax credits can be claimed by sponsors and an exclusive marketing license obtained for nonpatentable drugs. In September 1983, FDA issued guidelines for sponsors, describing the information to be submitted in order to obtain orphan drug designation and protocol assistance. Regulations are expected to be issued in 1984.

FDA has received an appropriation from the Congress to support orphan products research. This appropriation is separate from that provided by the Orphan Drug Act. In fall 1983, FDA made 12 awards for clinical study of unmarketed orphan drugs and of new uses for marketed products.

Summary

Through the combined efforts of agencies and organizations in the public and private sector, drugs have been made available that would not have been at hand without a specific focus on the orphan drug issue. It is anticipated that these cooperative efforts will continue beyond the first enthusiastic burst engendered by the inception of new and interesting activities.

The Population Attributable Risk of Hypertension from Heavy Alcohol Consumption

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Synopsis

The association between alcohol consumption and hypertension was studied in 11,899 men aged 40–55 years. The prevalence of hypertension among heavy drinkers was significantly higher than among those who did not drink heavily. Heavy drinking was defined as consumption of five or more drinks daily or four or more drinks daily. A total of 136 persons fulfilled the five drinks or more per day definition and 230, the four drinks daily definition.

The population-attributable risk of hypertension contributed by heavy drinking, depending on the diagnostic criteria used to define each endpoint, varied from 3 to 12 percent. There is reason to suspect that the contribution of alcohol to hypertension in the general population may be somewhat higher at the present time than in the late 1950s when the study was conducted.

Moderation of alcohol consumption, in addition to weight reduction and salt restriction, is another important nonpharmacological means to control hypertension.

THE ASSOCIATION BETWEEN EXCESSIVE alcohol consumption and hypertension, first suggested at the turn of the century (*1*), has been found in several clinical and epidemiologic studies (*2–13*). While some studies have shown a linear relationship, others indicate a U-shaped or threshold response. The association is independent of [illegible] ment, adiposity, social class, and physicial fitness. Former heavy drinking is not associated with high blood pressure; current consumption of alcohol seems to be the essential factor.

It has been suggested that 10–20 percent of essential hypertension in the United States and Australia (*5–14*) [illegible]