

# ORPHAN DRUG DEVELOPMENT

## Position Paper

of the

## AMERICAN COLLEGE OF PHYSICIANS

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Ensuring the development and availability of medically important but commercially unprofitable drugs (known colloquially as orphan drugs) is a problem with which the pharmaceutical industry, the federal government, and the physician community have wrestled for years. There is agreement as to the problem: drugs for rare diseases and other drugs with potentially high therapeutic value but low economic value to the manufacturer are not being developed and marketed sufficiently. Full agreement has not been reached, however, as to the solution.

### POSITION

The American College of Physicians calls on the pharmaceutical industry, the federal government, and the nation's physicians to fulfill their individual responsibilities and to cooperate in the joint venture of stimulating orphan drug development:

1. The pharmaceutical industry, which as a profit-making operation may be prevented from developing large numbers of commercially unprofitable drugs, should continue its attempts to fulfill its social responsibility to sponsor orphan drug development.
2. Although the primary role of the federal government in drug development is to ensure the safety and effectiveness of marketed drug products, additional responsibilities may need to be fulfilled when incentives for private sector initiative are insufficient:
  - to provide a regulatory climate conducive to private sector drug research and development, or
  - to provide economic incentives and alleviate market disincentives for orphan drug development, or
  - to develop orphan drugs.
3. Physicians need to recognize their responsibility to participate in the basic and applied research necessary for development of orphan drugs, especially new uses for marketed drugs.

### INTRODUCTION

The process of drug development can be divided into three stages: pre-clinical, clinical, and post-marketing. A Notice of Claimed Investiga-

tional Exemption for a New Drug (IND) application must be filed with and approved by the Food and Drug Administration (FDA) before clinical investigation can begin. Under special circumstances, a drug sponsor can submit an abbreviated IND or a "treatment IND," which provides for use of the investigational drug to treat patients who have no satisfactory alternative therapy for their disease. While clinical research is being conducted under the IND, the sponsor is required to report at least annually to the FDA. FDA approval must be obtained for every protocol that is submitted by the sponsor.

Phase I of the clinical investigation entails initial administration of the drug to human subjects (usually, normal volunteers) to determine pharmacokinetics and tolerance; less than 20 subjects are usually required. Phase II encompasses initial short-term administration of the drug to patients under carefully controlled conditions. The object of this phase is to determine effectiveness and to screen for toxic reactions that might be common enough to be detected in a small sample population (usually 50 to 200 patients recruited from three to 10 centers). Phase III requires more extensive drug administration to patients under conditions more nearly approximating those of routine clinical practice. The main objective is to document safety and effectiveness. This phase usually involves multi-center collaborative studies requiring a total of 200 to 2000 patients. When Phase III of the clinical investigation is completed, the developer must prepare a New Drug Application (NDA) and submit it to the FDA for review.

The NDA usually requests permission to market the new drug for the indication(s) supported by the clinical trials. The FDA may make approval of the NDA conditional on the marketer's agreement to complete further investigations after the drug is marketed; these would constitute Phase IV or post-marketing studies. For example, the FDA may make approval of an NDA for a new antiarrhythmic drug to be marketed as an agent to treat ventricular arrhythmias conditional on the developer's evaluation of the drug's efficacy in treating patients with atrial arrhythmias or investigation of the consequences of the drug's negative inotropic actions in patients with compensated congestive heart failure.

Attention has long been focused on the length and cost of the drug approval process, particularly in attempting to assess the impact of regulatory requirements on developmental costs. The pharmaceutical industry asserts that development of a chemical entity to a marketable drug product takes from five and one-half to 11 1/2 years and costs more than \$50,000,000 (including overhead and other fixed costs). The majority of that time and expense (as much as \$30,000,000 in two and one-half to seven years, according to industry estimates) occurs in the exploratory, pre-clinical research stage necessary for a drug sponsor to ascertain that clinical research (under an IND) is likely to lead to marketing of a product.

Orphan drugs include those that cannot be marketed profitably. The pharmaceutical industry defines "a drug of limited commercial value" as one "with total annual drugstore and hospital sales less than \$5,000,000." There are three major classes of orphan drugs. The first, and largest, includes those for which the number of patients requiring

treatment with the drug is small. Marketing experts in the pharmaceutical industry generally contend that a minimum of 100,000 paying patients are needed if a product is to gross \$5,000,000 annually. Diseases with less than 100,000 patients in this country and without adequate drug therapy include cystic fibrosis, Tourette's syndrome, Prader-Willi syndrome, myoclonus, Wilson's disease, and Huntington's chorea, which together affect approximately 160,000 Americans. The second class includes drugs for which the number of patients requiring treatment with the drug is large, but the patients generally reside in impoverished, thirdworld countries (e.g., Iamprene for leprosy). Drugs for which the number of patients requiring their use is large, but the drug itself is not patentable (e.g., acecainide for ventricular arrhythmias; acecainide, the N-acetylated metabolite of procainamide, is not patentable because the Patent Office has declared that metabolites do not meet the requirement of "non-obviousness") comprise the third class.

### RATIONALE

The issue is largely an economic one: how to define public and private sector responsibility to stimulate and sustain development and marketing of therapeutically valuable products with low profitability. The crux of the issue confronting the pharmaceutical industry is the extent of its social responsibility to develop orphan drugs. Some policy makers argue that the industry has an obligation to return to society some of its profits -- earned from illness -- in the form of orphan drugs. The industry, on the other hand, contends that its financial responsibility to its stockholders forbids it from taking deliberate losses. Its public responsibility is fulfilled, it maintains, by activities such as those of the Pharmaceutical Manufacturers Association Commission on Drugs for Rare Diseases. This commission was founded in 1981 to collect and distribute basic research leads for drugs for rare diseases. By the end of 1982, the commission had received 16 proposals and inquiries, had found sponsors for clinical trials for three drug products -- L-5-hydroxytryptophan for myoclonus, trien for Wilson's disease, and hematin for porphyria -- and reported that interest has been stimulated for development of a number of other products.

The American College of Physicians applauds the work of this commission and the recognition by industry of a social responsibility for the development of orphan drugs that its establishment signifies. The College appreciates also that the pharmaceutical industry has developed and marketed 40 orphan drugs in the past decade, with more than half of that 40 being developed by seven manufacturers. The College believes, however, that the industry needs to do more to fulfill this social responsibility and that, through its own efforts or because of government action, it should be able to do so without loss of significant amounts of money.

In recent years, profits on drugs often have exceeded the estimates made by the sponsoring company's marketing department. Dopamine (Intropin), used for treatment of cardiogenic shock, is a classic example. Considered by the industry to be of limited profitability before its approval in 1974, it had sales of \$15,000,000 in 1978 and over \$21,000,000 in 1980. Other examples include valproic acid (Depakene),

for treatment of epilepsy; naloxone (Narcan), for reversal of opiate action, and sodium nitroprusside (Nipride), for treatment of hypertension. These had sales of \$5,000,000 to \$10,000,000 in 1979. Also grossing over \$5,000,000 in 1980 were two former orphans: bromocriptine (Parlodel), used for temporary relief of amenorrhea and galactorrhea, and mitomycin (Mutamycin), used for treatment of hypercalcemia in patients with metastatic carcinoma. Some other drugs for which industry claims it would lose significant amounts of money might prove to be at least marginally profitable if developed and marketed. The American College of Physicians calls on the pharmaceutical industry to re-examine its techniques for making marketing estimates in an effort to determine if some orphan drugs might turn out to be profitable after all. The College believes that decisions to develop drugs should be based on an appropriate mix of scientific and marketing considerations and should include considerations of the medical need for a product in addition to marketing data on the existing use of similar products.

The pharmaceutical industry needs also to reassess its research and development processes and their application to orphan drug development. Some drugs are not determined to be probably unprofitable and thus "orphan" until considerable exploratory research has been conducted. Possibly, the additional research required to prove such a drug's safety and efficacy could be conducted at substantially less cost than that required for an entity for which the exploratory research stage is less extensive. Reassessment of industry's research and development processes is warranted not only because of the industry's commitment to develop orphan drugs, but also because the industry is facing competition from foreign drug producers, which have much lower fixed costs and other overhead expenses. There is real fear that, without re-examination of its procedures, the American pharmaceutical industry may find itself in a difficult position to compete successfully with foreign drug manufacturers. Some in industry already have seen the need to develop more efficient methods of designing potential new drugs and are examining molecular modeling approaches that may allow drugs to be designed on a computer to fit a certain receptor. The College suggests that industry, in making this reassessment, consider increased use of well-qualified academic researchers to supplement in-house research.

Although the pharmaceutical industry, because of its technical expertise and capability, bears the brunt of responsibility for orphan drug development, the American College of Physicians does not believe that this social responsibility should be fulfilled at substantial financial loss. Thus, the College also believes that when orphan drugs cannot be developed without significant financial loss and when the pharmaceutical industry has attempted to revise its processes to decrease that loss, the burden of responsibility shifts, in part, to the federal government.

The first such responsibility of the federal government is to provide a regulatory climate conducive to private sector drug research and development. It is essential that the government fulfill its mandate to ensure the safety and efficacy of drugs, but the regulations required for that mandate should not be applied in a way that places unnecessary burdens on orphan drug development.

Some members of industry and some federal policy makers have proposed that existing regulations need to be revised because they place undue, costly burdens on the development process. The American College of Physicians disagrees. It is not necessary to relax our country's standards of drug approval; what is needed is continued recognition by FDA that it should be flexible in the application of drug approval regulations on orphan drug development.

For example, some policy makers have argued that the FDA should approve all orphan drugs for marketing on the basis of one adequate and well-controlled clinical trial if the drug were proved effective in that trial (the FDA presently requires two trials usually, although it is not precluded by law from requiring only one trial). The American College of Physicians disagrees, believing that the question of one, two, or more trials is one that is best left to the FDA on a case-by-case basis. The College notes with approval that the FDA has marketed drugs after only one clinical study (e.g., timolol for treatment of post myocardial infarction patients) and recommends continued flexibility regarding this standard.

Legislators also have suggested that the FDA exempt from drug approval requirements orphan drugs intended solely for the treatment of patients for whom alternative therapeutic agents do not exist. As mentioned above, the FDA has the authority to provide the "treatment IND" exception for these and other drugs. The College believes it appropriate for FDA to continue to use this exception as it deems appropriate. The FDA is examining development of a systematic approach to handling treatment INDs, publicizing their use, and detailing the drugs for which this process is available. The American College of Physicians encourages systematic use of the treatment IND because it makes drugs available to patients who need them at an earlier stage of development. The College recognizes, however, that the treatment IND is not an acceptable substitute for research leading to an NDA and thus also encourages the sponsors of treatment INDs to complete the systematic research required to gain NDA approval.

Legislative proposals also have called for a change in FDA proof of efficacy standards from "substantial" to "sufficient" for orphan drugs. Assistant Secretary for Health Edward N. Brandt, Jr., MD, has testified that a change in standards for orphan drugs "might encumber them with scientific, ethical, and political controversy, clearly an unintended and undesirable result."

The American College of Physicians agrees and opposes such a change in the proof of efficacy standards also because of the possibility that if the standards are relaxed for orphan drugs, there may be pressure to relax the standards for all drugs; it is difficult to stipulate precisely what is and what is not an orphan drug.

By and large, the American College of Physicians finds that existing law affords FDA ample scope to provide a regulatory climate conducive to private sector drug research and development.

Nevertheless, there may be occasions when such provision of a regulatory climate may not be sufficient to overcome industry's probable significant financial loss from orphan drug development and marketing, and then the federal government may have an additional role -- to provide economic incentives and alleviate market disincentives.

Significant financial loss can occur when the developmental costs are greater than the profits of a product. Developmental costs -- and some suggestions on how industry can lower them -- have been reviewed above. It is possible that the federal government can decrease the portion of the development time required for proof of safety and efficacy of orphan drugs without reducing the requirements for that proof. The College commends FDA to study reductions in the numbers of patients required for clinical research trials on orphan drugs. Since the total number of patients requiring an orphan drug is often limited, the number available for testing that drug may be far fewer than for other drugs. Consequently, it may be acceptable that Phase I studies be conducted on 10 or less patients, Phase II studies on 20 to 30 patients, and Phase III studies include 50 or so patients treated under a fixed protocol, making comparisons based on blinded cross-over designs rather than concurrent treatment groups.

Another aspect of this problem is to examine ways in which profitability can be increased. Many in industry contend that the lack of a sufficient period of exclusive marketing is a cause for some drugs, including orphan drugs, to not earn back their developmental costs. The patent term, which provides for exclusive marketing and runs for a total of 17 years, including pre-marketing developmental time, could be extended either by tolling the patent during the regulatory period or by providing a period of marketing exclusivity to begin on the date of approval for marketing and not tied rigidly to a patent term. This second approach could be provided for non-patentable drugs as well as for patentable ones and would do the most to encourage development of drugs that are "orphan" for reasons for unpatentability. The American College of Physicians urges Congress to continue to study these approaches. Additionally, it may be necessary also for the federal government to provide economic incentives for industry development of orphan drugs.

The American College of Physicians notes with approval the formation and activities of the FDA Orphan Drug Task Force and the Health and Human Services interdepartmental Orphan Products Board. The task force will coordinate FDA activities relating to orphan products (including biologics and devices as well as drugs). Headed by Director for Orphan Products Development Marion J. Finkel, MD, and Acting Associate Commissioner for Health Affairs Stuart L. Nightingale, MD, FACP, the task force has taken as one of its first assignments the compilation of a list of orphan drugs. This task force has written to foreign regulatory agencies, foreign manufacturers, US medical and other health care schools, and health care professional associations requesting assistance in identifying orphan products, offering research and developmental support, and asking for cooperative clinical trials. On 25 October 1982, Dr. Finkel announced FDA's intent to fund orphan drug clinical research for products that are not marketed or for drugs that are already marketed but not fully tested for an additional, rare

disease indication. The American College of Physicians believes that direct funding for controlled clinical trials is an excellent method of providing economic incentives for orphan drug development.

The Orphan Products Board, chaired by Dr. Brandt, will, like the FDA Task Force, extend its scope to orphan biologics, medical devices, and diagnostic products as well as drugs. Composed of representatives from within HHS (e.g., FDA, the National Institutes of Health, the Health Care Financing Administration, and the Centers for Disease Control) and from other government offices (e.g., the Department of Defense and the Veterans Administration), the Board will, according to Dr. Brandt,

set policy in this area by facilitating the research, development, and application of designated orphan drugs and products. (It) will work actively with the PMA Commission on Drugs for Rare Diseases in identifying and assigning priorities to products that need development or other assistance to secure marketing approval. It will identify needs and foster action within the government to expedite the development and approval of orphan products.

The prime solution offered by this board is one of coordination -- it promises an attempt to coordinate private and public sector activities in orphan drug development. Both it and the FDA Task Force also promise a very broad scope, extending beyond drugs for rare diseases (a common but limited definition of orphan drugs) to all classes of orphan drugs (as well as other orphan products). The American College of Physicians is heartened by these developments and believes that they will be able to enable the federal government to fulfill its responsibility to provide economic incentives and to alleviate market disincentives, when appropriate, for private sector development of orphan drugs.

Even after providing economic incentives and alleviating market disincentives, there may be cases -- when the development costs are so great or the number of patients requiring the drug so few -- when the industry cannot develop and market an orphan drug. The American College of Physicians calls on the federal government to examine whether, in these cases, it has a role to develop orphan drugs. The College, in recognition that at least 35 orphan drugs have been developed through government programs (including the National Cancer Institute's Cancer Chemotherapy Program), encourages the government to maintain its activity in orphan drug development.

There is one type of therapeutic orphan in addition to those already discussed -- an approved drug for which new therapeutic uses are found (e.g., the use of phenytoin for cardiac arrhythmias) -- on which the burden of research and development falls not only on the pharmaceutical industry and the federal government, but also on physicians. After completion of the Phase IV studies agreed upon when the NDA was approved, the manufacturer has no legal obligation to conduct further research on a product. Even though unanticipated uses may be found for a new drug, the FDA cannot mandate additional investigations. Physicians often find themselves using a drug for an unmarketed,

unadvertised, unlabeled, and so-called "unapproved" indication. In fact, the medical literature is replete with reports of relatively uncontrolled studies of new uses for approved drugs. And despite the fact that most of these reports conclude with a call for follow-up controlled, clinical trials, very rarely do these uncontrolled studies lead to further research using controlled studies.

The American College of Physicians urges physicians to recognize their part of the responsibility for developing orphan drugs and recommends that physicians file an IND with FDA when conducting research on a drug for unlabeled uses so that FDA and ultimately the public can benefit from the research. Unless an IND is filed, the information gained by the research does not necessarily lead to FDA approval of the additional indications for using the drug. Failure to comply with the IND process is a primary reason for a drug being used commonly for therapy before it is approved for that use.

One reason drug manufacturers do not sponsor controlled trials for new uses for previously approved drugs is that by the time the new use is discovered, the drug is no longer on patent, and the manufacturer cannot be assured that it will reap the financial rewards of its research. Manufacturers prefer to sponsor research on new, patentable products. One solution to this problem is for practicing physicians to reduce the developmental costs by partaking in the research--by filing an IND when conducting research on a drug for unlabeled uses.

### CONCLUSION

It is gratifying that the problem of orphan drug development and its causes are being recognized, and that attempts are being made to solve them by all the involved parties. New legislation signed by the President on 4 January 1983 includes a number of provisions designed to address many of the issues raised in this paper. The American College of Physicians supports these efforts and encourages their continuation and expansion. In addition, the College will continue to monitor the progress of the HHS Orphan Products Board and the effectiveness of the orphan drug development incentives contained in the Orphan Drug Act.