Policy Forum

Curing the Orphan Drug Act

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THE ORPHAN DRUG ACT OF 1983 (PUBLIC LAW 97-414) has been remarkably successful in inducing the drug industry to produce treatments for rare disorders. Along with this success has come accusations of abuse of the act, because certain products, designated as orphans, have yielded enormous profits to their manufacturers. To the extent that Congress sees an increase in the cost of medical care as deriving directly from the Orphan Drug Act, the future of the act is threatened. To amend the Orphan Drug Act so as to preserve the incentives for the development of true orphan drugs while eliminating the pseudo-orphans from its protection is the current policy dilemma.

The average drug takes 10 years and costs $125 million for research and development to reach the market (*1*). Clearly, incentives are needed to induce the development of unprofitable drugs. The Orphan Drug Act has these incentives as its goal. Its key provisions are a 50 percent tax credit for the clinical research and development costs incurred by a drug company that produces and markets an orphan drug, and a 7-year exclusive marketing period for that product. An orphan drug is defined in the original legislation as a treatment for which the research and development costs exceed the profit potential. The definition was broadened in 1985 to be a treatment for any condition affecting fewer than 200,000 persons in the United States.

By skillfully exploiting the exclusive marketing provisions of the act, a few drug companies have found a way around an impasse created by the failure of the U.S. Patent Office to provide timely patent protection for biomolecules. Although of shorter duration than a patent, the exclusivity afforded orphan drugs is easily secured and has allowed sales of a few bioproducts approaching $200 million per year (*2*). Reaction to sales of this magnitude has resulted in calls for modification or abolition of this legislation from the Inspector General's office of the Department of Health and Human Services (DHHS) (*3*), and the Senate Appropriations Committee (*4*), both of which are concerned with the costs to federal programs to pay for erythropoietin used to treat the anemia of end stage renal disease, as well as AZT and pentamidine used to treat AIDS patients. Representative Fortney H. Stark, (D–CA), who was chairman of the House Ways and Means Health Subcommittee, accused some producers of orphan drugs of making windfall profits on these sales and introduced legislation to amend the act (*5*).

On the surface, the Orphan Drug Act appears to be functioning well, with a significant increase in the number of products introduced to treat rare disorders since enactment. As of June 1990, 375 drugs or biologicals had received orphan status. In the 10 years just prior to enactment, only ten orphan products were developed by the drug industry.

Use of the act is relatively simple. The sponsor of a drug that is intended for the treatment of a rare disorder seeks orphan status designation by certifying to the Food and Drug Administration (FDA) that the product is for a rare condition within the meaning of the act, by providing a therapeutic rationale for the use of the agent in that condition and by providing supporting epidemiologic data. The FDA reviews the orphan drug submission and, if it concurs, grants orphan status designation to the sponsor of that product for that specific use. When the product receives new drug approval, the 7-year exclusive marketing provision begins. For the bulk of the approved orphan products this is all there is to the story. Drugs are manufactured and distributed, the manufacturers hopefully break even, and persons with rare disorders benefit from the availability of the new treatment. This is how the law was intended to work.

Unforeseen in the drafting of the Orphan Drug Act was the rapid emergence of the biotechnology industry and the inability of the U.S. Patent Office to keep up with the flood of applications resulting from this research. (Note, however, that the Patent Office now grants manufacturing and use patents for bioproducts, providing a way to secure patent protection for naturally occurring and genetically engineered drugs.) In particular, the patenting of bioproducts derived from the mammalian or human genome has proved to be difficult, time-consuming, and prone to legal challenge. Some compounds have taken 4 to 6 years to receive patent approval, others are locked in litigation because of patent infringement suits (*6*). Conversely, orphan status designation costs nothing outside of preparing the submission and has been granted within 30 days of filing (*7*). In the highly competitive world of bioengineering, this accessibility has been irresistible. Moreover, it is feasible to find an orphan designation for almost every bioproduct engineered from the genome. This is because of the spontaneous mutation rate that occurs at each genetic locus with a frequency of approximately 1 per 100,000 per generation (*8*). The protein product of the mutated gene will be deficient in a person who is homozygous for a mutation at that locus. This is, of course, an oversimplification because one would have to assume that such homozygous individuals would survive long enough to be identified and that detection methods are available for them. One would have to further assume that the condition would be recognized as a disease and that replacement of that product would be therapeutic. If these criteria are met, however, the powerful market protection of the Orphan Drug Act can be obtained for that bioproduct.

Another way to broaden the scope of the Orphan Drug Act to include pseudo-orphans is by dividing the FDA-approved indications for a given product to its smallest possible market. Of the currently designated orphan products, human growth hormone has received orphan status designation for 11 indications by four different sponsors. Thirty-four other orphan products have two or more indications, sponsors, or both. These represent only 10 percent of the 375 currently designated orphan products. If a company is confronted with a product that is either unpatentable, or moving slowly through the system, then finding an appropriate orphan indication allows sewing up the market and potentially enjoying the monopolistic profits until the patent becomes available. This market protection is seen as the major cause for blockbuster sales of certain orphan products. For example, both human growth hormone (hGH) and erythropoietin (Epo) have annual sales in the range of $200 million per year. Human growth hormone, originally approved for treatment of growth hormone deficiency, costs approximately $10,000 to $30,000 per patient per year; it now has a vast additional market for the treatment of burns and aging (*9*).

Although it is illegal to promote a drug for treatment of a condition for which the FDA has not approved it, there are no constraints on physicians' use of approved drugs. Once a drug is on the market, physicians may prescribe it for any condition that in their judgment appears indicated. By having market exclusivity for a limited indication, a product may enjoy a much wider market by this mechanism. Erythropoietin costs approximately $8000 per patient per year and is used to treat the anemia of end stage renal disease,

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but is effective for many other kinds of anemia. Aerosolized pentamidine costs approximately $1000 per patient per year and is used to treat and prevent a frequent pneumonia in patients with AIDS. These agents, AZT and pentamidine, were designated as orphan products when the AIDS epidemic was just beginning and few persons were known to be affected. Now the drugs have huge markets. Of 42 approved and marketed orphan products, all but six were designated for patient populations of fewer than 50,000 persons and only four have so far realized astronomical profits.

Why then the concern over revising the act to eliminate these Goliaths from the orphan drug arena? Members of House and Senate appropriations committees are viewing with justified alarm the continued acceleration in the cost of the Medicaid and Medicare programs. A recent report to the Health Care Finance Administration from the DHHS Inspector General's Office stated that the cost to Medicare for Epo alone would be $100 million this year and could grow to $255 million by next year (*3*). This cost was attributed to "lack of competition at the manufacturer's level" (*3*, p. 2). The report went on to suggest (*3*, p. 2): "[C]onsideration should be given to modifying the Orphan Drug Act to encourage competition by eliminating the 7-year market exclusivity provision." Furthermore, in a letter to Secretary Sullivan from five members of the Senate Appropriations Committee regarding the need for approval of a different means of administration of pentamidine to AIDS patients they said that "thus far, the administration has declined to express support for an amendment to the Orphan Drug Act to correct this situation. The position of the administration particularly concerns us as members of the Appropriations Subcommittee with responsibility for funding AIDS research and treatment programs . . . with appropriated funds difficult to provide and the demand for these funds growing, it would be unfortunate for the administration not to lend its support to efforts to allow this new and different therapy with its promise for cost savings onto the market without delay" (*4*).

The National Commission on Orphan Diseases was a congressionally chartered body that studied the problems of orphan diseases for 2 years. It concluded that, although the 7-year exclusive marketing period was by far the major incentive for orphan drug development, "the potential for abuse of the incentives in the Orphan Drug Act will threaten its future" (*10*). The report went on to recommend specific corrective legislation when abuses were documented and noted "that patent protection for naturally occurring biotechnology products should be strengthened" (*10*). This emphasis on patent protection was an early recognition by the commission of the pressure the Orphan Drug Act would incur if profits on orphan drugs soared.

An amendment to the Orphan Drug Act (HR4638) was passed by both houses of Congress, but "pocket vetoed" by President Bush in November 1990. The amendment recognized that true orphan drugs can be distinguished from "psuedo-orphans" by ascertaining the level of interest in their development by the drug industry. Human growth hormone has received 11 designated orphan indications involving four different drug companies. On the other hand, cysteamine, a drug used to treat nephropathic cystinosis, which affects about 200 persons in the United States, took more than 10 years to find one corporate sponsor. By applying to only those orphan drugs for which there is intense competition, the proposed amendment would have protected development of true orphan drugs, encouraged competition to lower the price of pseudo-orphans, and removed pressure to abolish the act in the name of cost containment.

As proposed, such an amendment would have permitted simultaneous licensing of the same orphan product for the same indication if (i) the second company requests orphan designation within 6 months of publication by the FDA of its action to designate the drug for the first company; (ii) the second company initiates human clinical trials not more than 12 months after the first company initiated clinical trials; and (iii) the second company submits an approvable new drug application to the FDA no more than 1 year after the first company submits its new drug application. These are rigorous hurdles that do not permit a "me too" approach. To have a product engaged in clinical trials within 1 year from the time the first company engages in clinical trials means that both companies have invested substantial resources in the same project. By permitting competition, market forces should result in lower prices. There is precedent for assuming that competition in drug marketing will lower prices. For example, when the Department of Agriculture made its patent for the production of penicillin available to any producer without charge, the cost of penicillin fell from $200 per million units to 60 cents per million units (*11*). In the case of hGH and Epo, the provisions of the amendment would permit other manufacturers to market their versions of the products. Regardless of whether prices come down or not, the resulting competition would then eliminate the accusation that the Orphan Drug Act is responsible for exorbitant drug costs due to a government-sanctioned monopoly.

The future of the Orphan Drug Act is unclear. A number of alternatives to last year's amendment were discussed before the President's veto. These included reconsideration of a sales cap, beyond which a windfall profit tax would be imposed. Another alternative called for determining whether an orphan drug was being used outside of its labeled indication. If the annual sales of a given orphan product greatly exceeded the projected market for the labeled indication, then recognition of this fact by the FDA could be used as a trigger to de-designate an orphan product, allowing competitors onto the market.

The policy dilemma clearly revolves around the need to protect the development of true orphan products while eliminating from consideration those products that are enjoying vast sales under the protection of an act designed to induce the development and marketing of drugs of little commercial value. This paradox may be a typical example of success in our capitalist system, but it is not one that the government, with its ever increasing concern for growing health care costs, can ignore. If we want to preserve the development of orphan products for persons with orphan diseases, then we must make sure that the Orphan Drug Act does not in itself appear to contribute to spiraling health care costs.

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