DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(16), 2369-2382 (1990)

EFFECTS OF THE ORPHAN DRUG ACT : AN INDUSTRIAL PERSPECTIVE

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ABSTRACT

The recommendations of the Interagency Task Force on "Significant Drugs of Limited Commercial Value" had a major role in the passage of the Orphan Drug Act of 1983. This act was designed to create incentives for the industry to develop orphan drugs, in order to make these drugs available to those who need them. This paper discusses the incentives built into the Act, reports on the results of a mail survey to 100 pharmaceutical manufacturers, and generates recommendations for increasing the effectiveness of the 1983 Orphan Drug Act. The majority of the respondents felt that the delays in orphan drug development reflect the lack of specific FDA guidelines and/or clinical data on safety and efficacy. Industry feels that a ten year marketing exclusivity and increased federal grants for clinical research would accelerate development and marketing of orphan drugs.

BACKGROUND

There has been progressively increasing government regulation of the drug development process ever since the first federal law regulating medical therapy was passed in 1902. Such regulations permit introduction of those drugs which have a favorable risk-to-benefit ratio. To market a new drug entity, the 1962 Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act require documentation of the safety and effectiveness of the drug to the satisfaction of the Food and Drug Administration (FDA).

The pharmaceutical industry spent $ 6.5 billion in R & D in 1988, $ 7.3 billion in 1989, and this year it is projected to increase to $ 8.2 billion (1,2). A good 84% of these R & D dollars is allocated to the development of new products.

A pharmaceutical company typically examines about 30,000 compounds in the laboratory in order to come up with a viable new drug entity (3). In 1990 the pre-tax cost of the entire R & D process of a new drug entity is estimated to exceed $ 200 million compared to $ 129 million of 1988 (4). The PMA survey reported that in 1989 FDA approved 23 new drug entities which took an average time of 10 years for development (1,5).

According to the survey report of the National Commission on Orphan Diseases, the developmental cost expended in 1989 for products in the treatment of rare disease totalled $ 54.6 million (6). An orphan drug is defined as one that is used in diagnosis or treatment of a disease in such low incidence that its costs must be paid from a source other than the income from its sales, hence making it to be of little commercial value (7).

Orphan Drug Legislation

To provide an incentive for the development of new drug products for the treatment of rare diseases, the then President Ronald Reagan signed the Rep. Henry Waxman (R-Calif.) sponsored Orphan Drug Bill in 1983, three years after it was introduced in Congress. The Act authorizes FDA to set the upper limit of the incidence of a disease (currently 200,000 patient threshold) for the orphan status. The existing law offers the following privileges to the orphan drug sponsor (8).

(a) A tax credit of 63% of the cost of clinical studies

(b) A 7 year period of exclusive use (from NDA approval date)

(c) A federal grant support for clinical research ($ 70,000 maximum).

These privileges were incorporated into the Orphan Drug Act to serve as incentives for furthering orphan drug development and to provide hope to those who suffer from rare diseases that sincere efforts are made to find solutions to their medical problems. But since the passage of the Act, incidence of rare diseases (whose population is too small to be considered a profitable market) has rapidly increased a large number of patients suffer while waiting for their orphan drugs (9). An estimated 5000 rare diseases affect 20 million Americans and as of September 1989 more than 300 drugs have been designated the orphan status by the FDA (10). Of these 300 drugs, thirty-six have received marketing approval, 40 are pending before the FDA for review, and 133 are in the clinical trial phase as orphan drugs (6). Since some of the drugs are being investigated for more than one

disease, these 133 drugs have a potential to treat 93 rare disorders (6). This paper compiles opinions of manufacturers to assess the strengths and weakness of the Act and possible changes that may be required.

OBJECTIVES

The specific objectives of this study were two-fold:

(i) To solicit opinions of pharmaceutical manufacturers concerning the effectiveness of specific provisions of the Orphan Drug Act in stimulating research on diseases of rare incidence.

(ii) To generate recommendations for increasing the effectiveness of the Orphan Drug Act of 1983.

METHODOLOGY

The sample for this survey was randomly selected from the population derived from the Membership Directory of the Regulatory Affairs Professionals Society (RAPS). It was presumed that these RAPS members disseminate, cultivate and interpret information relating to regulatory activities and hence qualify to respond to this survey. Survey kits were mailed to 100 members of RAPS who are responsible for "OTC and prescription" drugs.

The survey kit (a questionnaire and a cover letter) consisted of two different sets of questions. One set of questions made specific reference to provisions of the Act that were intended to stimulate the development and marketing of orphan drugs. The manufacturers were asked to express their opinions on the effectiveness of tax credit, market exclusivity and federal grant provisions of the Act in stimulating development and marketing of orphan drugs.

The second set of questions was designed to generate recommendations for actions that would increase the effectiveness of the 1983 Orphan Drug Act. The manufacturers were asked to provide their opinions on: (a) the amount of clinical data to establish safety and efficacy of the product, (b) length of time taken by the FDA to review the application prior to granting marketing approval, (c) amount of toxicity data required from animal studies, (d) regulatory guidelines provided by the FDA for conducting clinical studies, (e) issuance of marketing approval by the FDA for an orphan drug whose clinical studies have been conducted in another industrialized country, and (f) granting approval to two companies that have independently researched on it to market the same orphan drug (11).

RESULTS

The survey was closed for tabulation with 58 usable responses — a 58% completion rate. The maximum sampling error for percentages based on 58 responses was ±4% at the 95% confidence level. Of these 58 manufacturers, 31 (53.4%) have been involved in the research, development, and marketing of orphan drugs while the remaining 27 (46.6%) have not developed any orphan drugs since 1960.

I. PROVISIONS OF THE ACT

Tax Credit: Twenty-five manufacturers (43.1%) felt that the current tax credit for 63% of the cost of clinical research is a good incentive for development of orphan drugs. But among those who felt otherwise, 27 (81.8%) thought that the manufacturers should be entitled to receive a tax credit for 75% of the clinical research expenses. The literature

indicates that the industry feels that an increase to cover research costs is necessary (12).

Market Exclusivity: The current system establishes a de facto exclusivity arrangement for orphan drugs for a 7-year period from the date of approval for marketing. Such exclusivity period is very important to the majority (62.1%) of the manufacturers because it is related to the extent to which developmental costs can be recovered. Thirty manufacturers (51.7%) felt that the exclusivity period should be revised to a minimum of 10 years. The congressionally appointed National Commission on Orphan Diseases also recommended that the period of exclusivity should be increased (13). But Capitol Hill counters such a recommendation and has expressed serious concern that the exclusivity provision may create monopoly for products with significantly larger market potential than was intended by the Act (14,15).

Federal Grant: The Orphan Drug Act authorizes the sponsor to receive financial support to cover a portion of the expenses incurred in clinical testing. The survey results show that the range ($20,000 to $70,000) of federal grant to support clinical research lacked popular support among the manufacturers. Fifty manufacturers (86.2%) felt that the range for such funding should start at $100,000.

II. RECOMMENDATIONS

According to the survey, various factors contribute to the lack of development of orphan drugs. These include product liability, lack of efficacy data, lack of safety data, and application review time. The major reason cited by those manufacturers who have developed orphan drugs was the length of application review time by the FDA. On the other

hand, manufacturers who have not developed orphan drugs cited, lack of effective data and lack of safety data as the major stumbling blocks to be obstacles in the development of orphan drugs (Table I).

Limited Clinical Data and Product Liability : One common outcome of an examination of the power of a statistical investigation is the discovery that the investigation is too small or that the scientific tools are too insensitive for a study of feasible size to give us the assurance we desire. Lack of adequate number of subjects/observations from clinical trials of rare diseases, which are of low incidence, result in poor power of the statistical investigation. Therefore the potential for damages incurred from the use of approved orphan drugs on the basis of limited clinical data for safety and efficacy is high. The Orphan Products Board discusses broad policy issues relating to the mission, problems, causes and cares of those who suffer from rare diseases. In 1984, the Orphan Products Board in its comment on the issue of damages incurred from the use of approved orphan drugs said that there was no evidence at that time that product liability coverage would be a disincentive to develop orphan drugs (7). However, the Board said that the liability coverage issue can be opened for discussion if situation warranted in the future.

From the results of this survey it is evident that 24 manufacturers viewed product liability as one of the obstacles in developing orphan drugs. Seventeen of the 58 manufacturers surveyed felt that the Department of Health and Human Services should not be responsible for damages that may be incurred from the use of approved orphan drugs. This

TABLE I

Obstacles In Development Of Orphan Drugs

Factors	Percent of Drug Manufacturers Who	
	Have Developed Orphan Drugs* (n=31)	Have Not Developed Orphan Drugs* (n=27)
Product liability	32.3% (n=10)	51.9% (n=14)
Lack of efficacy data	32.3% (n=10)	51.9% (n=14)
Lack of safety data	32.3% (n=10)	51.9% (n=14)
Application Review Time	45.2% (n=14)	29.6% (n= 8)

* The percent does not add to 100 as multiple responses are possible.

comes as a surprise especially in light of a recent ruling by the U.S. Supreme Court on product liability (concerning the drug DES) where all manufacturers of the product are held potentially liable for damages in proportion to the share they had of the national market. That is, a company can be held liable, in proportion to its market share, even if the plaintiff could not have taken its drug (16).

Application Review Time : According to the FDA, the sponsor has the privilege to obtain written recommendations from the FDA prior to or during the pre-clinical and/or clinical investigations. Conformance to such recommendations can be presumed to shorten the FDA review time. Yet, an average of 32.5 months was taken in 1989 by the FDA to review the applications for new molecular entities (5). The PMA has expressed concern to such prolonged review time and has recommended that a maximum time limit (say 6 months) should be set for review (5). The National Commission on Orphan Diseases concluded that allocation of additional resources for FDA review could put orphan drug for 1A 'fast track'

approval similar to the NCE representing significant therapeutic advances (13). In response to the questions in this survey, the manufacturers have made several recommendations that could significantly reduce the FDA review time (Table II).

The FDA is valued by the public for its integrity in assuring safe and effective drugs. Such consciousness has further strengthened the desire of the FDA to trade off time for safety (17). But prompt patient access to new products (or products already in the European market) has started to put pressure on FDA for faster approvals of new drugs. A recent example is the influence of the AIDS activists in their access to experimental drugs. Gerald F. Meyer, Deputy Director of the Center for the Drug Evaluation and Review said that the approval process could be faster if the manufacturers submitted well organized applications (17).

This survey finds the majority (47 out of 58) of the manufacturers suggesting that the FDA should provide much more specific guidelines for clinical and pre-clinical studies so that conformance to such recommendations may help reduce the time required by the FDA to review the application.

The respondents of this study prefer relaxation of data requirements for clinical and animal toxicity studies. Such relaxation might enable more orphan drug products to be marketed over a short period of time. But the FDA appears to be acting cautiously in not granting approval to products after Phase I, because very frequently most of them are dropped during Phase II (17). On the contrary, if orphan drugs are brought to the patients quickly, the manufacturers

TABLE II

Recommendations For Reducing FDA Review Time

Recommendation	Percent of Drug Manufacturers Who	
	Have Developed Orphan Drugs* (n=31)	Have Not Developed Orphan Drugs* (n=27)
FDA provide specific guidelines for studies	71% (n=22)	92.6% (n=25)
Relax present requirement of data	66.7% (n=20)	70.4% (n=19)
Reduce data gathering in animal toxicity studies	46.7% (n=14)	37% (n=10)
Market exclusivity to two independent sponsors	93.5% (n=29)	55.6% (n=15)

* The percent does not add to 100 as multiple responses are possible.

could get increased data through the physicians' cooperation in providing feedback on the drug's adverse effects while the patient would have access to the orphan drugs (7). The respondents of this study prefer to have the provision that would enable exclusivity to the two sponsors (who have researched independently) for the marketing of the drug.

CONCLUSION

From the results of this study, it is evident that there is a strong desire among the respondents to strengthen the current incentives of the Orphan Drug Act. Based on the results of this study, the following conclusions are drawn and relevant follow-up studies are recommended:

1: It has been observed that a consensus to raise the 63% tax credit limit of the Orphan Drug Act persists in the minds of the respondents. It would be interesting to study the cost-benefit aspect of the products enjoying

the tax credit privilege. The objective of such a study should center on the concerns of the Congress, namely, that while the spending on research has been very limited, the companies save billions of dollars in tax revenue and add the tax credit dollars to research spending (12).

2: Because of its limited commercial value the development of orphan drugs is not an attractive proposition. The provisions of the federal grant support in the Orphan Drug Act serves as an incentive to make it attractive. The respondents of this study concur with such intention, but have expressed the need to increase the funding amount. The current $ 20,000 to $ 70,000 funding range does not have the flexibility to even adjust for inflation. It is therefore suggested that a feasibility study should be undertaken by the PMA and the FDA to develop a working formula that would automatically adjust for inflation and adjust for increase in cost in conducting R & D. The findings of such a study could help in developing a plan that would substantiate the recommendations for increase in funding made by Senator Orrin Hatch (R-Utah) and the National Commission on Orphan Diseases (13,15).

3: One of the attractive provisions of the Orphan Drug Act is the exclusivity of marketing the product for 7 years. In exploring the reasons behind rising health care costs, the pricing structure of drug products was criticized by the legislators. Senator Robert Kennedy (D-Mass.) had put together, but eventually withdrew, a legislation that would have permitted removal of exclusivity benefits for

products with unusually high price vis-a-vis their cost (18,19). Yet the respondents of this survey have expressed that the exclusivity period be increased to at least 10 years. Therefore a future study should be done to develop and validate an individualized arrangement to guarantee justifiable period by which the sponsor will have reasonable opportunity to recoup (or significantly recoup) the developmental costs. The cooperation of the PMA and the FDA in looking at the pros and cons of such an approach to the problem could provide response to the concerns of Capitol Hill.

4: Given the importance of new drug therapy, the length of time taken for FDA review must be shortened. But quality of review should not be sacrificed for the sake of promptness. The FDA needs to increase its resources so that it can help the sponsors with extended guidelines in developing protocols for the tests. A detailed protocol developed jointly by the FDA and the sponsor for an individualized orphan drug would inevitably provide sound research and shorten the time for the FDA to review the application for marketing approval. The outcome would be availability of new drugs at a much faster pace. Such a follow-up action would be an extension of the plan of the FDA Orphan Products Office that has planned to develop a "compilation of materials to help sponsors" for regulatory conformance in winning FDA approval (20).

5: A rare disease with an incidence of less than 200,000 greatly limits the ability of a single sponsor to obtain volunteers for clinical trials in the numbers that they would need for sound statistical analysis. In such

instances the provisions of marketing exclusivity should be provided to two independent sponsors as has been suggested by the respondents of this study. Such a provision would permit prompt establishment of sufficient data that would help establish the safety and effectiveness of the potential drug. A similar viewpoint has been found in literature (17).

ACKNOWLEDGEMENTS

The author would like to thank Dipan K. Ray (graduate student) for his help in the collection of data, and Professors Robert Sause and Parshotam Madan for their help in preparing this manuscript.

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