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THE ORPHAN DRUG ACT: PROVISIONS AND CONSIDERATIONS

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The United States Orphan Drug Act passed in 1983 provides four provisions to spur the development of medications for conditions that might otherwise have been abandoned. The Office of Orphan Drug Product Development was established to provide assistance in protocol development, and to administer a grants program. A tax credit incentive also was enacted but the most significant incentive has been the market exclusivity clause. Despite such measures, the act in the wake of technological and economic developments should continually be reexamined to enhance efficiency in development of orphan products, to ensure accessibility of these products to patients, and to minimize economic abuses by developers.

Key Words: Orphan Drug Act; Drug development; Rare diseases

INTRODUCTION

OVER 20 MILLION AMERICANS suffer from one of approximately 5000 orphan diseases, each affecting a relatively small number of people (1). The United States Orphan Drug Act (ODA) was initiated with the intent to promote the development of pharmaceuticals for orphan diseases—those diseases or conditions that have been classified as "rare," by defining the conditions and establishing attractive incentives for industry to develop medications for such designations (2). Its impetus was the lack of attention toward these diseases primarily due to the negative balance of development costs versus the fiscal gains once marketed. The notion of high profitability was not seriously considered, and the statutory language as had been written originally addressed an atmosphere and situation of limited profitability. Interest in such legislation was initiated by the rare disease patient community and spearheaded by a group now known as the National Organization of Rare Disorders (NORD). It was opposed by the Pharmaceutical Manufacturer's Association (PMA) because of the perceived intrusion by government into their private enterprise, and the fact that agreement might have suggested an admission to their lack of development of products for these so-called orphan diseases.

Since its passage in 1983 during the Reagan Administration, the Office of Orphan Products (OPD) of the United States Food and Drug Administration (FDA) has designated over 800 orphan products with over 170 of these receiving FDA marketing approval, benefitting more than eight million Americans. The act was originally designed for unprofitable or unpatentable medicines. In 1984 an amendment shifted the standard designation of orphan drug from profitability to prevalence and the requirement of unprofitability was dropped from the act. The overwhelming concentration of products have been for cancer and genetic diseases, ac-

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counting for approximately one-third of all designations with the greatest increase seen in infectious and neurological conditions (3). Orphan designations for AIDS have accounted for only approximately 12% of the designations, due primarily to the broad definition of AIDS by the Centers for Disease Control which in effect encompasses all HIV infected individuals with CD4+ T-lymphocyte cell counts below 200cells/mm (4). This has made the orphan drug program less of a possibility for development of AIDS-related treatment and diagnostic products.

Controversy has surrounded the act since its inception and subsequent enactment and enforcement, particularly regarding the alleged unfair reaping of profits by pharmaceutical companies. One specific concern has been the extraordinary prices charged for some of the products in relation to the costs for development of the drug. A number of orphan products have annual sales of less than $5 million, however, several products have reached $200 million which raises troubling questions for policy makers and the public, particularly as it negatively influences access or creates an excessive burden to out-of pocket payers. Another source of contention is the fact that private profits have been made on publically funded ventures (5). Furthermore, while there is rationale to protect property through market exclusivity, there is debate about the extent of limitation of those rights. Both too little or too much protection can impede production, and/or limit access.

ORPHAN DEFINED

The ODA specifically pertains to drugs that are intended to treat a rare disease or condition which can be defined in one of two ways:

1. A disease or condition affecting less than 200000 persons in the United States at the time of designation. If the prevalence increases above this ceiling during development the designation still holds (6), and
2. A disease or condition affecting more than 200000 people in the United States, if the sponsor can establish that costs of development would not be recovered from United States sales in seven years.

The major sources of evidence for prevalence figures are from peer-reviewed literature, texts, surveys, data from the Centers for Disease Control or the National Center for Health Statistics, and/or the testimony of experts based on personal or professional experience. The majority of orphan products have been for conditions for populations of less than 50000. Ninety percent of the designations are for populations less than 100000 (7).

As a consequence of these definitions, patient populations have the potential to be fragmented into subgroups in order to come under the 200000 ceiling (8). In the future, however, with advances in genetic technology and completion of the Human Genome Project, such fractioning may, in fact, turn out to be real subclassifications of heretofore defined single diseases or conditions. What to date have been classified as single disease entities may, in fact, be a heterogenous collection of disease processes, presenting with the same clinical manifestations. This has happened in oncology, and is happening in neurology, particularly for neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Lou Gehrig's disease). Truly, drugs will be developed and targeted for specific mechanisms affecting specific populations, and indeed the 200000 prevalence ceiling of the ODA may warrant reexamination. Moreover, with various disease processes and improvements in technology and treatment, morbidity should improve and the criterion for the number of individuals affected might be more appropriately based upon incidence rather than on prevalence.

PROVISIONS OF THE ODA

Drug development is an expensive endeavor with estimates ranging from $290 to $500 million to bring a drug to market. Products whose target population represents a potential for greater monetary gain with $100 mil-

lion in annual sales as a minimum are given priority, therefore, it follows that pharmaceutical firms in the United States give little attention to drugs whose sales potential is less than $20 million per year (9). The Orphan Drug Act was initiated to overcome this great economic disincentive through four general provisions: a grants program, protocol assistance, tax incentives, and market exclusivity. Grants, tax credits, and protocol assistance intend to reduce the research and development costs of a compound; exclusivity promotes successful market opportunities upon approval of the product.

Nonetheless, while provisions have been made to entice development of these drugs, sponsors are still required to follow the same rigorous development and review processes that apply to nonorphan status drugs. On average, review and approval times for orphan drugs may be shorter than nonorphans, but total development time is comparable due to the longer clinical development period which is directly related to the ability to identify and to enroll eligible patients into the investigational clinical protocol(s).

GRANTS AND PROTOCOL ASSISTANCE

An enticement of the ODA is grants awarded by the OPD to help defray the costs of testing products for rare diseases at the clinical stage. Each year requests for applications are published in the *Federal Register* that announce the availability of funds to support clinical trials to determine safety and efficacy parameters of products either to diagnose or to treat rare diseases. Funding is given primarily to academic researchers. To date, 350 clinical studies have been supported, totaling $100 million between 1983 and 1997; with 21 orphan products achieving marketing approval. It is interesting to note that 25% of the grants have gone to support alternative indications for approved drugs (10,11). While specific wording in the ODA does not address clinical trial design, certain designs are used and permitted as part of the New Drug Application (NDA). The most desirable study design is double-blind, parallel design, placebo controlled. For orphan populations these are not always possible and other designs are used: open-label, historical control, and crossover. Validated surrogate endpoints may be used as proxies to measure clinical efficacy. As an example of the development environment, approval for the treatment of genetically-caused carnitine deficiency was based upon 16 cases (12).

TAX CREDITS

Tax credits are another provision of the ODA. Sponsors of orphan products are given tax credits up to 50% of their clinical development costs for that drug generated within that year. This expired at the end of 1994 but was extended under provisions of the Small Business Provision Act of 1996 and a revision to the Internal Revenue Code was amended. In 1997 a permanent tax credit was enacted; a strong coalition headed by NORD, including patient advocacy groups, and pharmaceutical and biotechnology companies saw this through (13). Previously, sponsors were required to use the credits in the year when the clinical expenses were incurred. This amendment allows credits to be carried forward for a maximum of 15 years or backward for up to 3 years, and claimed when the tax liability arises; this is provided specifically for small developers, including both pharmaceutical companies and biotechnology firms.

MARKET EXCLUSIVITY

The most motivating provision of the ODA has been the market exclusivity clause, which provides seven years of marketing exclusivity from the time the FDA grants approval of the product. This provision provides the potential for a monopoly to be maintained, as well as to remove a substantial degree of uncertainty by the developers when making an investment decision about orphan drugs. Market exclusivity is not unique to the ODA, as it has become a tradition of government practice to protect intellectual property rights

in this manner, for example, patent protection and copyright law. The ODA exclusivity provision applies only to the orphan indication for that drug, and limits the capabilities of the FDA to approve another developers' version(s) of that drug for an identical indication.

Market exclusivity hinges on the definition of 'same' as defined by the by the FDA but does not distinguish between macro and simple molecules. Two or more drugs with orphan designation could be considered the 'same' drug if the primary structure or the principal mechanism of action are the same —even though some structural features of the compounds may be different (14); this does not deal with the active moiety. Differences also may be achieved through the drug's mode of delivery, or method of production and purification (15). The pivotal point of 'same' is the difference in efficacy and safety between products. If one product demonstrates clinical superiority over an already approved product for treatment of the same condition, an orphan FDA approval may be granted for the new drug. This is usually ascertained through head-to-head comparative clinical protocols. The burden of proof is the responsibility of the sponsor whose subsequent drug is seeking orphan status over its predecessor. Under the act, cost is not a criterion to establish differences.

During the first few years after enactment there was little progress in the area of orphan drug development, however; pharmaceutical companies realized that the exclusivity provision could be used to prevent competition while disputed patents were being litigated or finalized (16). Legislation has been drafted to address the consequences of this provision only to fail in Congress or to be vetoed by the President. In the early 1990s one amendment sought to limit the extent of exclusivity based on a target sales figure, intending to keep prices low in order for a producer to maintain its monopoly, or to promote competition by shortening the time frame for exclusivity, should the target sales figure be met prior to expiration of the seven years of market exclusivity. This was vetoed by President Bush.

Despite these legislative attempts, there are various ways that competitors can weaken a product's market exclusivity without violating the act:

1. One or more versions of the same drug may be developed and approved for other indications, and then made available to be prescribed via "off-label" use. This should have a greater impact with recent legislation expanding marketing practices directed at alternative (unapproved) uses of a medication,
2. Under the 1992 Orphan Drug regulations (17), a subsequent version of the same drug for the same indication demonstrating 'clinical superiority' as stated previously, may be approved and prescribed. Nonetheless, this makes efficient development paramount because the one to market first is able to block other competitors for exclusivity until comparisons of clinical efficacy can be determined with the burden for proof placed on developers, and
3. Different drugs may be approved for an already approved orphan indication prior to the expiration of the seven-year market exclusivity period. Release is granted immediately upon expiration of the predecessor's exclusivity period. Therefore, while an orphan approval appears to limit competition, it does not necessarily preclude it.

While the ODA has promoted the development of products aimed at lower prevalence disease groups, accessibility to some of these medications still is limited. Orphan products may be extremely expensive. Insurance may provide coverage but patients still may face considerable copayments or deductibles which may be financially devastating to these individuals. It is unlikely that the insurance picture will change unless some attention is paid to the pronounced costs of some of these products or some other arrangements are enacted, for example tax-

credits. These third-party arrangements coupled with the rising drug prices certainly have exacerbated the social and economic impact of the ODA.

CONSIDERATIONS

Improvement in the accessability to orphan drugs might be achieved through revisions of the ODA and also through changes in third-party coverage arrangements and/or legislation governing the drug approval process in the United States, as well as the movement toward global harmonization of drug development. Accessibility may be enhanced by improvement in the drug approval process in toto. Through the FDA Modernization Act passed in November 1997, streamlining procedures should decrease development time lines and thereby costs for orphan drugs. This includes increased access to experimental therapies for serious or life-threatening conditions, medical product approval, expanding consumer access to information on unapproved or "off-label" drug uses, and reauthorization of the Prescription Drug User Fee Act (18). What also would be advantageous to improve the current cost and accessability environment is greater utilization of non-United States based clinical trial data as part of the New Drug Application dossier which has been allowed since 1987.

In conjunction with the former, costs to develop drugs for rare diseases in some instances may be greater due to the difficulty in recruiting adequate numbers of patients into clinical trials for statements about safety and efficacy. This is due to low numbers within any one country. Recruitment of patients from geographically diverse areas is necessary, that is, multinational recruitment for a single clinical trial. As countries pull down their colloquial barriers, as is being achieved in Europe, albeit slowly and as we move toward harmonization in the development and approval of drugs and devices worldwide, development costs have the opportunity to be reduced. Additionally, global patient networks, accomplished by NORD and its constituent member organizations, make possible the easier identification and subsequent enrollment of patients into protocols, and research grants could be awarded to those products targeted against the high priority diseases. This approach might result in appropriations for additional grants and better target research and development.

CONCLUSIONS

Before the ODA few treatments for orphan conditions were developed, albeit serendipitous indications did, in fact, occur, but with the passage of this landmark legislation that has changed. Manufacturers and sponsors have become familiar with the provisions of the ODA, and now are better acquainted with rare diseases and treatments thereof. In fact, some corporations have devoted themselves entirely to this type of work, if not to one disease. The act has been successful as evidenced by the number of products approved for marketing. Despite controversies since its inception, the program remains intact and has promoted the development of treatments and diagnostics for orphan drugs, and has proven successful in compensating for the high stakes of development in this arena.

One also should realize that coincident with the ODA three other factors have provided significant influence for development in this area:

1. Advances in science and technology undoubtedly have expanded opportunities and will continue to do so,
2. The return on investment in the industry sought for profits 2% to 3% higher than other industries, allowing for more riskier projects with the hopes of creating a novel or blockbuster compound, and
3. The 1984 Drug Competition and Patent Term Restoration Act has provided additional patent protection and market exclusivity for certain drug types.

The act as it stands now should be reexamined to address issues of efficiency and equity, while still maintaining the incentives for

developers. We need to move from exclusive economic incentive provisions to the advantage of developers to more public policy issues of equity. Abuses of the law must be prevented and could be through a sales cap or similar measures. The provisions of the act could be reduced via redefining "orphan" drug, and reexamining the market exclusivity clause and grants program, and eliminating the other general provisions that have had influence on the development of orphan products.

It also has served as a template for similar initiatives in other countries and should be used to develop a comprehensive international policy to minimize waste and duplication of efforts among developers, public and private organizations, regulators, and participants. The anticipated results would be a reduction in development time and a reduction in cost with improved accessibility for the treatment and diagnosis of rare diseases.

The ODA and its founders should be applauded despite concern for manipulation of the act's language amidst advances in development technologies, concerns in disease group fractioning, and subsequent "off-label" uses. Its initial goal achieved, the goal now is to move forward on a global level in hopes that costs can be reduced and accessibility increased for orphan products and the patient populations they serve.

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