

Hints on Preparing Successful Orphan Drug Designation Requests

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I. INTRODUCTION

The Orphan Drug Act (ODA),¹ was originally enacted in 1983 to amend the Federal Food, Drug, and Cosmetic Act (FDCA)² and the Internal Revenue Code.³ The ODA and its later amendments of 1984,⁴ 1985,⁵ and 1988,⁶ provide incentives and aid to research and development (R&D) firms in the discovery, development, approval, and commercialization of orphan products. These products include pharmaceuticals and biologicals that otherwise might not be researched and brought to the market because of the rarity of the disorder they treat and/or the low return on investment.

The ODA represented a social policy initiative that combined government support with private R&D. At the time no other nation had a comparable statute in force, pending, or under consideration. Only recently have other nations passed similar legislation emulating the American scientific and commercial experience. Nevertheless, while many of the early concerns over the possible abuses and negative impact of the ODA were unwarranted, some criticisms have proven legitimate (e.g. large profits by a few firms).

The Office of Orphan Products Development (OOPD) was instituted at the Food and Drug Administration (FDA) in 1982, several months prior to passage of the ODA, as an early response to the imminent legislation. This unit has several tasks, including awarding orphan drug designations based on acceptable confidential requests made under the regulatory provisions.⁷ These award designations are decided solely by the OOPD staff, but the Office occasionally will request opinions from the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER), especially when dealing with issues such as the appropriateness of the requested indication or the scientific rationale described by the sponsor.⁸ The OOPD, however, does not play a role in the actual assessment of human drug applications submitted for rare disorders, although it attends meetings between orphan sponsors and the reviewing divisions.

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¹ Pub. L. No. 97-414, 96 Stat. 2049 (1983).

² Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended 21 U.S.C. §§ 301-393 (1988).

³ 26 U.S.C. § 28 et seq.

⁴ Pub. L. No. 98-551, 98 Stat. 2815 (1984).

⁵ Pub. L. No. 99-91, 99 Stat. 387 (1985).

⁶ Pub. L. No. 100-290, 102 Stat. 90 (1988).

⁷ 21 C.F.R. § 316.20 -.21 (1995). The contents of a request cannot be publicly released under the Freedom of Information Act regulations (21 C.F.R. § 20) before the underlying marketing application is approved by the FDA. See 21 C.F.R. § 316.52(f), 314.430. Even then the released designation request will be expurgated of trade secrets.

⁸ Letter from John V. Kelsey, Deputy Dir., OOPD, FDA to Paul V. Buday, Dir., Reg. Affairs, Porton Int'l (July 27, 1995).

II. ORPHAN DRUG DESIGNATIONS

The orphan drug designation permits developers to accrue certain benefits from the ODA. The incentives to develop orphan drugs under the provisions of the Act include:

- financial support or subsidies (tax credits for clinically testing and developing orphan drugs);⁹
- preclinical and clinical protocol design assistance from the FDA;
- marketing benefits to sponsors of drugs (especially off patent or unpatentable that promise to benefit a select group of relatively few patients (less than 200,000 patients or under 0.08% of the U.S. population) who are afflicted by specified rare diseases or disorders, or those that will help a larger group of patients, but the ability of the sponsors to pay for the R&D to bring the drugs to the U.S. market is nonexistent;¹⁰
- possible fast track review priority from CDER¹¹ for new drug applications (NDAs);
- the waiver, wholly or in part, of NDA or product license application (PLA) review user fees¹² in circumscribed instances where the ordinarily imposed fee would be a

⁹ These benefits expired in late 1994, but revival is being sought for a permanent tax credit status through the companion bills S. 1568 and H.R. 2994. 58 F-D-C REP. ("The Pink Sheet"), Mar. 4, 1996, at T&G 14.

¹⁰ The principal marketing benefit offered to the first human orphan drug application for a specified rare disease is market exclusivity for seven years from the date of approval. This exclusivity bars competing firms from marketing the same drug for the same rare disease, unless the first firm waives its temporary, legal monopoly or if the pioneer firm is unable to assure distribution of sufficient supplies of its product to meet medical needs. This latter contingency is difficult to prove; no sponsor has yet lost exclusivity for failure to provide sufficient quantities of its drug. Letter from John V. Kelsey, *supra* note 8. Supercession of the 200,000 prevalence threshold does not revoke a designation nor bar the market exclusivity once rendered. Market exclusivity is irretrievable once lost. 21 C.F.R. § 316.36(b).

To date, market exclusivity has statutorily expired for some 26 different orphan designated drugs for 29 disorders. See OOPD's *List of Orphan Products Designations and Approvals Through December 1995*, as updated by January/February 1996 addenda.

¹¹ Many orphan drugs have been classified as 1A. FOOD & DRUG ADMIN., PRESS OFFICE, ORPHAN PRODUCT DEVELOPMENT POLICIES 2 (May 8, 1989) (FDA Talk Paper T89-30). CDER's drug chemical type classification and priority review policy describes designated orphan drugs as Type V, in addition to therapeutic potential: Type P (priority) or Type S (standard) review. CTR. FOR DRUG EVALUATION & RESEARCH, FDA, STAFF MANUAL GUIDE # 4820.3 (1992). See also Marlene E. Haffner, *Applications of the Orphan Drug Act to Special Patient Populations*, 28 DRUG INFO. J. 495-503 (1994). The average approval time for pharmaceutical orphans historically is shorter than non-orphan approval times by a couple of months. ORPHAN PRODUCT DEVELOPMENT POLICIES, *supra*. Priority A-track orphans gain approval seven months earlier than non-priority orphans. *Id.* The faster approval times for orphan versus non-orphan drugs probably is explained by the rarity of the target disorders, the inherent impossibility in recruiting and testing large patient groups, and the smaller amount of data available to the FDA for review and analysis. *Id.*; OFFICE OF TECHNOLOGY ASSESSMENT, U.S. CONGRESS, PHARMACEUTICAL R&D: COSTS, RISKS AND REWARDS 71 (1993) (No. OTA-H-522). The FDA's desire to highlight orphan drugs with important therapeutic gain also must play a role.

If a designated orphan-drug has exclusivity and has been approved for a given use, competing versions of the same product generally are not accepted by the reviewing divisions until shortly before the end of the exclusivity period. If, however, the sponsor of a second drug application claims that the product is different from the one under exclusivity protection (as defined by 21 C.F.R. § 316.3(b)(12), (13)), the division commonly will accept the application for review and make a difference determination. Letter from John V. Kelsey, *supra* note 8. If no chemical or clinical differences can be discerned, the review ceases and does not begin again until the exclusivity period ends.

¹² There are no direct user fees for designations under the provisions of the Prescription Drug User Fee Act. Pub. L. No. 102-571, 106 Stat. 4491 (1992). Neither is there any formal refusal to file determination under 21 C.F.R. § 314.101.

material obstacle to development of an innovative product necessary to protect the public health;¹³

- the transferability, with FDA consent, of the designation as intellectual property;¹⁴ and
- submission of only abbreviated environmental assessments¹⁵ for orphan drug NDAs and PLAs.¹⁶

Orphan drug designation, however, does not preclude other sponsors from obtaining a designation for the same drug for the same disease. The FDA's cumulative *List of Orphan Products Designations & Approvals*,¹⁷ codified quarterly and updated monthly for intervening periods, contains several examples of this redundancy, for the ODA is designed to spur competition. If a sponsor holding a designation elects to abandon it, the designation is deleted from the cumulative list, but no specific public notice is made.¹⁸

III. DESIGNATION REQUEST REQUIREMENTS

There are five eligibility criteria that a drug must possess to qualify for orphan drug designation.¹⁹

- The finished product must be a pharmaceutical, biological, or antibiotic new drug. Medical devices, medical foods, veterinary drugs, and other FDA-regulated products are not eligible for orphan designation or market exclusivity.²⁰ The drug ordinarily must be prescription legend and subject either to NDA approval under sections 505(b) and 507 (antibiotic certification) of the FDCA,²¹ or licensure as a biological under section 351 of the Public Health Service Act.²²

While several competitors can receive orphan designations for the same therapeutic indication for the same drug, only the first to receive NDA or PLA approval gets the seven-year exclusive right to sell the drug (unless other rules apply). Therefore, requests should stress the contrasts in chemical structure, medical potential, and real benefit between the drug offered for approval and competitors' drugs.

- The drug must have a sponsor who is testing or will test the product for a rare disease or disorder.

¹³ See Letter from Mary Jo Veverka, Deputy Comm'r, Management & Sys., FDA, to industry, attachment G, Interim Guidance Document for Waivers of and Reductions in User Fees. User Fee Correspondence 2, at 18, 23, 33 (July 16, 1993). See also OFFICE OF THE CHIEF MEDIATOR & OMBUDSMAN, FDA, PRESCRIPTION DRUG USER FEE ACT OF 1992. WAIVERS AND REDUCTIONS (Small Business Exception Report No. 2, July 16, 1993 through April 28, 1995) (May 1995). Such waivers, however, are not automatic for orphan drugs; they involve making a separate request to the Commissioner or the Chief Mediator/Ombudsman. See 21 C.F.R. § 5.20(h); 59 Fed. Reg. 14,549 (Mar. 29, 1994).

¹⁴ 21 C.F.R. § 316.27.

¹⁵ 21 C.F.R. § 25.31 a(b)(3).

¹⁶ Current regulations require environmental assessments to be submitted with virtually all NDAs and PLAs. As part of the FDA reform measures, however, many of the expensive environmental assessments required of applicants may be eliminated. See 11 U.S. REG. REP. 7 (1995).

¹⁷ As of February 1996, approximately 405 different designated drugs are listed for the prophylaxis or therapy of approximately 474 different rare diseases or disorders.

¹⁸ Letter from John V. Kelsey, *supra* note 8.

¹⁹ M. MATHIEU, NEW DRUG DEVELOPMENT: A REGULATORY OVERVIEW 261-72 (3d. ed. 1994); 21 U.S.C. §§ 360bb, 360cc.

²⁰ See 21 C.F.R. § 316.1(b).

²¹ 21 U.S.C. §§ 355(b), 357.

²² 42 U.S.C. § 262 (1988).

- The disease to be treated, prevented, or diagnosed by the drug must afflict less than 200,000 people in the United States at the time of submission or, if the disorder afflicts more than 200,000 patients, there must be no reasonable expectation for developers to recover R&D and commercialization costs from the product's sales receipts in the United States.
- The finished product must not have been approved previously in the United States under an NDA or PLA for the specific rare disorder. In other words, it must *not* have been the subject of a marketing application submitted prior to filing a designation request for a specific orphan disease. This requirement, established by the Orphan Drug Amendments of 1988, was designed to reward true prospective developers of orphan drugs and to deny benefits of the designations to those who would attempt to enhance the status and profitability of their product after an application appears approvable. Contrariwise, a drug with an approved NDA for a non-orphan indication can become an orphan-designated drug for a unique or rare disease, provided no human drug application has been approved specifically for that rare disease. While the request for orphan status of a given drug must be made prior to NDA/PLA submission, the designation does not have to issue prior to the application's submission. The sponsor should make certain that the NDA's/PLA's therapeutic indications or labeling claims match that of the designation to ensure market exclusivity.
- The application must have a scientific rationale or underlying basis for its usefulness in the disorder. The FDA has stated, "[a] plausible hypothesis backed by some experimental evidence would be sufficient for orphan drug designation."²³

Patents play no role in the designation awards. The ODA and current regulations apply whether the drug product is patented or not.²⁴ Two or more orphan sponsors may receive FDA approval for a given orphan medication if the approvals are for different indications and do not overlap patent limitations.²⁵ Off-label abuses of approved orphan drugs may occur, but any infractions in using the approved orphan for more than its approved use are rare.

It has been suggested that it is easier and cheaper to get a designation than to receive a grant of patent.²⁶ Orphan designation grants, however, are open to litigation, like patents.

The content of designation requests needs to be substantive; they are no longer the two to three page documents that were acceptable early in the 1980s under the less demanding *Interim Guidelines*²⁷ that were released by the OOPD prior to the imposition of the regulations. Originally, the OOPD had promised to respond to an original petition within sixty days of its receipt, but with the promulgation of the orphan drug

²³ *The FDA's Orphan Drug Development Program*, 4 U.S. REG. REP. 1-6 (1987).

²⁴ J.J. McDonnell & N. Milosavljevic, *Exclusivity Through Orphan Drug Designation and Patent Rights*, presentation at the Accelerated New Drug (NDAs) Regulations Conference, sponsored by The Institute for International Research, San Francisco, CA (Mar. 9, 1992).

²⁵ OFFICE OF TECHNOLOGY ASSESSMENT, *supra* note 11.

²⁶ Bruce F. Mackler & Gary E. Gamerman, *Submission of Orphan Product Designation Applications: Obtaining Useful Designations for Difficult Populations*, presentation at BioEast '95, FDA Regulatory Workshop, Washington, D.C. (Jan. 11, 1995).

²⁷ These early guidelines were never published in the Federal Register and are to be distinguished from the informal recommendations for promulgating orphan drugs that were later promulgated. *See* 21 C.F.R. § 316.10, .12, .14.

regulations in 1992, its time frame became less public.²⁸ The OOPD's policy, however, is that it will try to respond within sixty days of receipt of an initial request, but if consultations are required or if difficulties arise in recycling questions to and receiving answers from the sponsor, the determination may take longer.

IV. PREPARATION AND APPROVAL OF A DESIGNATION REQUEST

The regulations²⁹ prescribe the information that a sponsor is required to submit to the OOPD so that the Office can assess whether a drug deserves an orphan designation. The submission must be made in duplicate and stand on its own merits (although cross references to active investigational new drug applications are permitted). This section provides common sense suggestions how sponsors can ease and improve the preparation and expedite approval of a request.

A. Request for Orphan Drug Designation

Sponsors must submit a statement requesting orphan drug designation for a specified rare disease or condition.³⁰ Sponsors occasionally delay submitting an orphan drug designation request until just before submission of the premised human drug approval application. This tactic helps keep the matter secret until the last moment, and permits the data and information being filed with the application also to be used in the designation request. Amendments to designations are allowed, but only prior to designation allowance.

Procedurally, the OOPD will not permit a sponsor to use a single orphan drug designation request for more than one rare disease, although cross-referencing from one request of a sponsor to another by the same sponsor is permitted. It is probably best, however, to submit stand-alone (internally complete) requests. The OOPD does not allow use of a competitor's data to support a sponsor's designation request for the same drug for the same rare disease without permission.

B. Sponsor Information

Sponsors must provide the following information: name/address of the sponsor; name of the sponsor's primary representative and/or resident agent (title, address, telephone number); generic name and trademark, if available, of the drug or drug product; and name/address of the source of the drug if it is not manufactured by the sponsor.³¹ Self-evident responses are indicated. The OOPD welcomes foreign designation applicants, but such applicants must appoint an U.S. resident as an OOPD contact for receipt of notices and other regulatory communications.³²

C. Orphan Disease Background Information

Sponsors must provide a description of the rare disease for which the drug is to be

²⁸ See 57 Fed. Reg. 62,080 (Dec. 29, 1992) (comment 40).

²⁹ Prior to issuance of the orphan drug regulations, the FDA released interim guidelines describing the information sought when applying for a designation. Since the promulgation of these rules, it has not prepared any additional written guidances.

³⁰ 21 C.F.R. § 316.20(b)(1).

³¹ *Id.* § 316.20(b)(2).

³² See *id.* § 316.22.

or will be investigated; the proposed indication(s); and the reasons why such therapy is needed.³³ A rare disease may have several perspectives and, although the drug in question may be intended to affect only one attribute or sequela of the disease, the OOPD prefers to receive a complete discussion of the disorder. The role of the intended orphan drug in the over-all management of a multifaceted orphan disease must be addressed.

D. Orphan Drug Background Information

Sponsors must provide a description of the drug and a discussion of the scientific rationale for its use in the rare disorder, including all data from nonclinical laboratory studies, clinical investigations, and other relevant positive, contrary, or inconclusive data. Copies of pertinent unpublished and published papers are required.³⁴ If the drug in question is pharmacologically or structurally related to other drugs employed for the same use, the sponsor briefly must explain how the applied for agent is different. This is especially necessary when a designation is sought for a recombinant DNA drug or when a closely related nonrecombinant drug has been abandoned after marketing. A thorough description of the designated drug's safety and potential/actual adverse effects must be provided. Tabular data or summaries from an imminent human market application can be used. Any information in a language other than English must be translated.

E. Clinical Distinction of Identical Drugs

Where the sponsor seeks orphan drug designation for the same rare disorder as a drug that is the same and already an approved drug, an explanation is required as to why the proposed drug may be clinically superior to the first drug.³⁵ Without some basis for believing that there is a meaningful clinical distinction between two chemically identical drugs, the FDA must refuse to approve a human drug application for the second of two identical orphan agents for seven years if the first already has obtained market approval for the identical rare disorder. This denial takes the form of a refusal to file determination.³⁶ Contrariwise, the agency can extend orphan drug designation status and exclusivity to new versions of an already marketed drug if the follow-up drug can be shown by clinical studies to be superior to the chemically identical marketed product.³⁷ If only bioequivalence data are available to show a difference, then the second drug is not sufficiently different from its cousin to warrant orphan status and exclusivity.

F. Subset Justification

For orphan drugs being studied for only a subset (sub-population) of individuals with a particular disease, an explanation (defense) that the subset is medically plausible is necessary.³⁸ This requirement exists to prevent an applicant from unduly restricting

³³ *Id.* § 316.21(b)(3).

³⁴ *Id.* § 316.21(b)(4).

³⁵ *Id.* § 316.20(a).

³⁶ *Id.* § 314.101(d)(8).

³⁷ 57 Fed. Reg. at 62,081 (comment 45). Levitt and Kelsey give succinct, helpful guidance on this subject of chemical sameness and clinical superiority. Joseph A. Levitt & John V. Kelsey, *The Orphan Drug Regulations and Related Issues*, 48 FOOD & DRUG L.J. 525 (1994).

³⁸ 21 C.F.R. § 316.20(b)(6).

the cited orphan disease prevalence or unnecessarily subdividing its characteristics into artificial and medically implausible subsets, thus creating unreasonable market niches that allow the applicant to reach the prevalence threshold.³⁹ Applicants must be prepared to explain why the population identified should be limited to the one aspect (subset) selected by the sponsor for designation and to supply information (or to answer questions) on other disorders that might be benefited from the drug. The agency has announced⁴⁰ that it will grant orphan status to approved or investigational drugs for non-orphan (common) diseases when such drugs may be useful in the treatment of a rare disease and are being so studied.

G. Historical Data

Sponsors must provide a summary of the regulatory status/marketing history of the drug in the United States and in foreign countries (enumeration of investigational new drug and marketing application status and dispositions; what uses are under investigation and where; the indications, if any, for which the drug is approved in foreign countries; and what adverse regulatory actions have been taken against the drug in foreign countries).⁴¹ If a drug has been approved for U.S. marketing for any indication or if a drug is currently being tested for one or more uses, the sponsor needs to explain or justify the method used to apportion the development costs among the several indications.

The sponsor also must render a statement/justification of the R&D costs expected to be incurred after submission of the designation request, a statement/justification for manufacturing and marketing costs already incurred and expected during the seven year commercial exclusivity period, and an estimate/justification of expected sales revenues in the United States during the exclusivity period. This justification must include an estimate of expected annual market share for the exclusivity period, an estimate of the price at which the drug will be sold, and a sales comparison with similar drugs.

Finally, the applicant must supply the names of all nations where the drug has been approved for marketing for any use, with the dates of approval, the indication, and the annual sales/number of prescriptions filled by each country since the drug first was approved. This information should be accompanied by a report from an independent certified public accountant attesting that the estimates were developed by professional standards using accepted accounting principles.

H. Disease Prevalence and Justification for Orphan Status

Documentation, with appended authoritative references, must be provided to show that:

- The disease for which the drug candidate is intended affects less than 200,000 patients in the United States or, if a vaccine, diagnostic, or prophylactic drug, the number of persons in the United States to be administered the agent are less than 200,000 per year (disease prevalence/incidence alone is unacceptable).⁴²

³⁹ Marlene E. Haffner, *Orphan Products 10 Ten Years Later and Then Some*, 49 FOOD & DRUG L.J. 593 (1994).

⁴⁰ See 57 Fed. Reg. at 62,082 (comment 56).

⁴¹ 21 C.F.R. § 316.21(b)(7).

⁴² *Id.* § 316.20(b)(8)(i).

- For drugs intended to treat more than 200,000 patients, or for a vaccine, diagnostic, or preventative drug to be given to more than 200,000 people per year, evidence that there is no reasonable expectation that R&D costs can be recovered by sales in the United States.⁴³

The sponsor should answer either the first part or the second part of this documentation requirement, depending on the disease prevalence. If the application is based on the first part, 21 C.F.R. section 316.21 requires that the estimated prevalence or number of U.S. residents who have the rare disease for which the drug is indicated at the time of the request be supported by submission of documentation (published/ unpublished). The currency of such information also should be provided.

The FDA expects a dedicated search for information on the prevalence of diagnosed symptomatic patients, realizing such data often are difficult to procure. The sponsor can use such documentation as:

- reference to like drugs previously granted orphan status on the basis of the rarity of the underlying disease;
- National Ambulatory Medical Care Survey (NAMCS) statistics for a given disease using the current edition of the *International Classification of Diseases*, developed/conducted by the Ambulatory Care Statistics Branch of the Division of Health Care Statistics of the National Center for Health Statistics at the Centers for Disease Control and Prevention;
- information of the incidence of a rare disease provided by the relevant national foundation, such as the Cystic Fibrosis Foundation or National Spasmodic Torticollis Association;
- authoritative medical experts' estimates (including opinion letters and/or interviews where epidemiological data do not exist) or projections based on regional reports of disease prevalence and extrapolations made to the current U.S. population.⁴⁴
- estimates from proprietary medical or market research firms, such as the Physician Drug and Diagnosis Audit or other medical audit services; and
- current published medical literature, information from electronic databases (such as Medline or Dirline), or the services of the National Library of Medicine.

On special request, the FDA can require an applicant to furnish the bases for the estimated prevalence of any other disease for which the drug has been approved or is being developed. The FDA has stated that such requests ordinarily will not be required, but the agency will reserve them for special circumstances. If the drug is a vaccine, a diagnostic or preventative of a rare disorder, the estimated number of people to whom the drug will be administered annually must be provided with an explanation for the bases of the estimates, the currency of the data, and literature citations. The OOPD independently verifies these estimates, but recognizes that prevalence data are hard to pin point, especially for very rare disorders.⁴⁵

⁴³ *Id.* §§ 316.20(b)(8)(ii), 316.21(c).

⁴⁴ If medical opinions are proffered, OOPD requires estimates from three experts and the bases for their projections. John V. Kelsey, How the Office of Orphan Products Development Handles/Reviews/Assesses Orphan Drug Designation Requests, presentation at the Regulatory Affairs Professionals Society's 19th Annual Conference/Exhibition, Session Rx 2-58 Advanced, Getting Orphan Drug Product Designation Requests Approved: Increasing the Odds, Washington, D.C. (Sept. 19, 1995).

⁴⁵ See Haffner, *supra* note 39, at 595.

If the application is based on the second part of the requirement, the petitioner must submit data on all R&D costs incurred for the U.S. market (such as preclinical, clinical, and pharmaceutical development; meetings with FDA; legal and other costs associated with determination of patentability; investigational new drug/market application preparation; licensing; liability insurance; overhead; and depreciation), and a basis for the reasonableness of the costs.

If the new drug was developed partially or entirely outside of the United States, the sponsor also must submit data and justifications for all non-U.S. development costs, explaining the method used to determine what percentage of the foreign development costs are applicable to the U.S. market, and what percentage these costs are of the total worldwide development costs. Any data submitted to foreign licensing authorities to support drug pricing must be included in the submission. The sponsor also needs to provide data showing which foreign development costs were recovered (such as overseas revenues collected).

The cost accounting and other administrative research required for obtaining designations for drugs exceeding the 200,000 U.S. resident threshold are tedious, and may discourage overseas orphan drug development expenditures and sale. One commentator on the early legislation was concerned that tax credits could be used to develop orphan medications for diseases prevalent overseas but rarely existent in the United States, allowing a developer to base the tax credit for developing new drugs on a small domestic market, while relying on large overseas markets for sales revenue.⁴⁶

I. Sponsor Status as Developer/Manufacturer

A statement as to whether the signatory sponsor is the actual R&D developer and intended manufacturer and seller of the orphan product must be submitted by the sponsor.⁴⁷ This information is requested so that the FDA can identify the intended sponsor at the time of the request to ensure compliance with the ODA and regulations, and to allay the OOPD's concern that the requesting designatee might have some motive other than developing an orphan drug. Such revelation does not prohibit the later assignment of the orphan drug status to another party,⁴⁸ but the OOPD must be so informed by the new assignee and former assignor, and must assent to the transfer of title.

V. CONCLUSION

Orphan drug designations are valuable commercial property, vital to the goals of the ODA. For sponsors to succeed in gaining designation awards, considerable library and in-house research and documentation, as well as clear, expositive, and enthusiastic replies and answers to the information sought by the FDA are needed. Orphan drug designation applicants can be denied the status for a variety of reasons. The OOPD gives applicants ninety days to respond to its request for more information lest the petition as submitted be withdrawn by the agency. Careful attention to the designation request regulations, early and open discussion with the OOPD's staff as to their review needs, a full understanding of the rare disease, a complete and timely awareness of

⁴⁶ Donna Brown Grossman, *The Orphan Drug Act: Adoption or Foster Care?*, 39 FOOD DRUG COSM. L.J. 128 (1984).

⁴⁷ 21 C.F.R. § 316.20(b)(9).

⁴⁸ *Id.* § 316.27.

competitive products, and a well-organized, polished designation request will increase an anticipatory sponsor's odds of procuring the official and prestigious orphan drug status in a timely manner.