

(3) A description of the rare disease or condition for which the drug is being or will be investigated, the proposed indication or indications for use of the drug, and the reasons why such therapy is needed.

(4) A description of the drug and a discussion of the scientific rationale for the use of the drug for the rare disease or condition, including all data from nonclinical laboratory studies, clinical investigations, and other relevant data that are available to the sponsor, whether positive, negative, or inconclusive. Copies of pertinent unpublished and published papers are also required.

(5) Where the sponsor of a drug that is otherwise the same drug as an already-approved orphan drug seeks orphan-drug designation for the subsequent drug for the same rare disease or condition, an explanation of why the proposed variation may be clinically superior to the first drug.

(6) Where a drug is under development for only a subset of persons with a particular disease or condition, a demonstration that the subset is medically plausible.

(7) A summary of the regulatory status and marketing history of the drug in the United States and in foreign countries, e.g., IND and marketing application status and dispositions, what uses are under investigation and in what countries; for what indication is the drug approved in foreign countries; what adverse regulatory actions have been taken against the drug in any country.

(8) Documentation, with appended authoritative references, to demonstrate that:

(i) The disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year as specified in § 316.21(b), or

(ii) For a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of re-

search and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in § 316.21(c).

(9) A statement as to whether the sponsor submitting the request is the real party in interest of the development and the intended or actual production and sales of the product.

(c) Any of the information previously provided by the sponsor to FDA under subpart B of this part may be referenced by specific page or location if it duplicates information required elsewhere in this section.

§ 316.21 Verification of orphan-drug status.

(a) So that FDA can determine whether a drug qualifies for orphan-drug designation under section 526(a) of the act, the sponsor shall include in its request to FDA for orphan-drug designation under § 316.20 either:

(1) Documentation as described in paragraph (b) of this section that the number of people affected by the disease or condition for which the drug product is indicated is fewer than 200,000 persons; or

(2) Documentation as described in paragraph (c) of this section that demonstrates that there is no reasonable expectation that the sales of the drug will be sufficient to offset the costs of developing the drug for the U.S. market and the costs of making the drug available in the United States.

(b) For the purpose of documenting that the number of people affected by the disease or condition for which the drug product is indicated is less than 200,000 persons, "prevalence" is defined as the number of persons in the United States who have been diagnosed as having the disease or condition at the time of the submission of the request for orphan-drug designation. To document the number of persons in the United States who have the disease or condition for which the drug is to be indicated, the sponsor shall submit to FDA evidence showing:

(1) The estimated prevalence of the disease or condition for which the drug is being developed, together with a list of the sources (including dates of information provided and literature citations) for the estimate;

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(2) Upon request by FDA, the estimated prevalence of any other disease or condition for which the drug has already been approved or for which the drug is currently being developed, together with an explanation of the bases of these estimates; and

(3) The estimated number of people to whom the drug will be administered annually if the drug is a vaccine or is a drug intended for diagnosis or prevention of a rare disease or condition, together with an explanation of the bases of these estimates (including dates of information provided and literature citations).

(c) When submitting documentation that there is no reasonable expectation that costs of research and development of the drug for the disease or condition can be recovered by sales of the drug in the United States, the sponsor shall submit to FDA:

(1) Data on all costs that the sponsor has incurred in the course of developing the drug for the U.S. market. These costs shall include, but are not limited to, nonclinical laboratory studies, clinical studies, dosage form development, record and report maintenance, meetings with FDA, determination of patentability, preparation of designation request, IND/marketing application preparation, distribution of the drug under a "treatment" protocol, licensing costs, liability insurance, and overhead and depreciation. Furthermore, the sponsor shall demonstrate the reasonableness of the cost data. For example, if the sponsor has incurred costs for clinical investigations, the sponsor shall provide information on the number of investigations, the years in which they took place, and on the scope, duration, and number of patients that were involved in each investigation.

(2) If the drug was developed wholly or in part outside the United States, in addition to the documentation listed in paragraph (c)(1) of this section:

(i) Data on and justification for all costs that the sponsor has incurred outside of the United States in the course of developing the drug for the U.S. market. The justification, in addition to demonstrating the reasonableness of the cost data, must also explain the method that was used to determine

which portion of the foreign development costs should be applied to the U.S. market, and what percent these costs are of total worldwide development costs. Any data submitted to foreign government authorities to support drug pricing determinations must be included with this information.

(ii) Data that show which foreign development costs were recovered through cost recovery procedures that are allowed during drug development in some foreign countries. For example, if the sponsor charged patients for the drug during clinical investigations, the revenues collected by the sponsor must be reported to FDA.

(3) In cases where the drug has already been approved for marketing for any indication or in cases where the drug is currently under investigation for one or more other indications (in addition to the indication for which orphan-drug designation is being sought), a clear explanation of and justification for the method that is used to apportion the development costs among the various indications.

(4) A statement of and justification for any development costs that the sponsor expects to incur after the submission of the designation request. In cases where the extent of these future development costs are not clear, the sponsor should request FDA's advice and assistance in estimating the scope of nonclinical laboratory studies and clinical investigations and other data that are needed to support marketing approval. Based on these recommendations, a cost estimate should be prepared.

(5) A statement of and justification for production and marketing costs that the sponsor has incurred in the past and expects to incur during the first 7 years that the drug is marketed.

(6) An estimate of and justification for the expected revenues from sales of the drug in the United States during its first 7 years of marketing. The justification should assume that the total market for the drug is equal to the prevalence of the disease or condition that the drug will be used to treat. The justification should include:

(i) An estimate of the expected market share of the drug in each of the

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first 7 years that it is marketed, together with an explanation of the basis for that estimate;

(ii) A projection of and justification for the price at which the drug will be sold; and

(iii) Comparisons with sales of similarly situated drugs, where available.

(7) The name of each country where the drug has already been approved for marketing for any indication, the dates of approval, the indication for which the drug is approved, and the annual sales and number of prescriptions in each country since the first approval date.

(8) A report of an independent certified public accountant in accordance with Statement on Standards for Attestation established by the American Institute of Certified Public Accountants on agreed upon procedures performed with respect to the data estimates and justifications submitted pursuant to this section. Cost data shall be determined in accordance with generally accepted accounting principles.

(d) A sponsor that is requesting orphan-drug designation for a drug designed to treat a disease or condition that affects 200,000 or more persons shall, at FDA's request, allow FDA or FDA-designated personnel to examine at reasonable times and in a reasonable manner all relevant financial records and sales data of the sponsor and manufacturer.

§ 316.22 Permanent-resident agent for foreign sponsor.

Every foreign sponsor that seeks orphan-drug designation shall name a permanent resident of the United States as the sponsor's agent upon whom service of all processes, notices, orders, decisions, requirements, and other communications may be made on behalf of the sponsor. Notifications of changes in such agents or changes of address of agents should preferably be provided in advance, but not later than 60 days after the effective date of such changes. The permanent-resident agent may be an individual, firm, or domestic corporation and may represent any number of sponsors. The name of the permanent-resident agent shall be provided to: Office of Orphan Products De-

velopment (HF-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

§ 316.23 Timing of requests for orphan-drug designation; designation of already approved drugs.

(a) A sponsor may request orphan-drug designation at any time in the drug development process prior to the submission of a marketing application for the drug product for the orphan indication.

(b) A sponsor may request orphan-drug designation of an already approved drug product for an unapproved use without regard to whether the prior marketing approval was for an orphan-drug indication.

§ 316.24 Granting orphan-drug designation.

(a) FDA will grant the request for orphan-drug designation if none of the reasons described in § 316.25 for requiring or permitting refusal to grant such a request applies.

(b) When a request for orphan-drug designation is granted, FDA will notify the sponsor in writing and will publicize the orphan-drug designation in accordance with § 316.28.

§ 316.25 Refusal to grant orphan-drug designation.

(a) FDA will refuse to grant a request for orphan-drug designation if any of the following reasons apply:

(1) The drug is not intended for a rare disease or condition because:

(i) There is insufficient evidence to support the estimate that the drug is intended for treatment of a disease or condition in fewer than 200,000 people in the United States, or that the drug is intended for use in prevention or in diagnosis in fewer than 200,000 people annually in the United States; or

(ii) Where the drug is intended for prevention, diagnosis, or treatment of a disease or condition affecting 200,000 or more people in the United States, the sponsor has failed to demonstrate that there is no reasonable expectation that development and production costs will be recovered from sales of the drug for the orphan indication in the United States. A sponsor's failure to comply with § 316.21 shall constitute a failure