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FDA Proposes Changes to Orphan Drug Regulations

On October 19, 2011, the Food and Drug Administration ("FDA") published a proposed rule in the *Federal Register* that would amend the 1992 Orphan Drug Regulations issued to implement the Orphan Drug Act (the "Proposed Rule"). Comments to the Proposed Rule should be submitted no later than January 17, 2012. This *Client Alert* summarizes these proposed changes and discusses the potential impact of the Proposed Rule on the drug, biological product, and biotechnology industry.

The amendments proposed are "intended to assist sponsors who are seeking and who have obtained orphan drug designation of their drugs, as well as FDA in administering the orphan drug program." The Proposed Rule addresses specific issues for amendment, each of which is described in more detail in this *Client Alert.*

I. Summary and Analysis of Proposed Amendments

A. Demonstration of an "Orphan Subset" of a Disease or Condition

In seeking orphan drug designation for a subset of persons with a particular disease or condition, the regulations currently require a sponsor to "demonstrat[e] that the subset is medically plausible." Citing confusion arising from the use of the term "medically plausible," FDA proposes to remove the term "medically plausible"[1] and instead provide a description of how an appropriate subset could be identified for the purpose of orphan-drug designation ("orphan subset"). The revised § 316.20(b)(6) would require the request for designation to contain, "Where a drug is under development for only a subset of persons with a particular disease or condition that otherwise affects 200,000 or more people, a demonstration that, due to one or more properties of the drug, the remaining persons with such disease or condition would not be appropriate candidates for the drug."

The FDA states in the Proposed Rule that the process for identifying an orphan subset remains the same as has been used by FDA for identifying a medically plausible subset under the regulations currently in effect. For a subset of persons with a non-rare disease or condition to be considered an orphan subset for the purpose of orphan-drug designation, the subset cannot be arbitrarily chosen simply to reduce the prevalence numbers to qualify a drug to treat that population as an orphan drug. The FDA suggests that one way for a sponsor to demonstrate that the proposed subset rests on a non-arbitrary foundation is to show that there is a reasonable scientific or medical rationale for limiting the investigation and potential use of the drug to only the subset of interest. The FDA explains that when a sponsor has established that the selected population constitutes a non-arbitrary subset, e.g., by describing the scientific or medical basis for limiting the potential use of the drug to that population and demonstrating that such scientific or medical basis is reasonable, the target population is an acceptable orphan subset of persons with the particular disease or condition for the drug of interest. In addition, the FDA suggests that other inherent properties of a drug, such as its pharmacologic or biopharmaceutical characteristics, may provide a reasonable basis upon which to identify a subset of patients to whom it would be appropriate to limit treatment and who thus would qualify as an orphan subset of a non-rare disease or condition. Likewise, characteristics of the drug that have been demonstrated through previous clinical experiences may be used to identify an appropriate orphan subset.

Finally, FDA recommends that the following practical questions be asked when assessing whether a subset of a non-rare disease or condition is an appropriate orphan subset:

- Is the intended subset artificially restricted in any way with respect to the use of the drug to treat the disease or condition?
- Given that the drug may potentially benefit this particular subset of persons, is there a reasonable scientific or medical basis for believing that the drug would also potentially benefit the remaining population with the non-rare disease or condition, or a larger subset of that population? If not, why not?

B. Eligibility for Orphan Drug Designation of a Drug That Was Previously Approved

FDA states that in the absence of a clinical superiority hypothesis, FDA will not grant orphan designation to a drug that is otherwise the same as a drug that is already approved for the same orphan use. This rule would apply regardless of the orphan designation status of the approved drug. It would apply in cases where the approved drug was never designated as an orphan drug, and in cases where the seven-year exclusivity period for the approved drug has expired. FDA believes that if the same drug has already been approved for the orphan disease or condition, with or without orphan exclusivity, designation would be inappropriate because it would not provide an incentive for researchers to develop promising drugs for rare diseases or conditions that would not otherwise be developed and approved. FDA also expresses concern that permitting orphan-drug designation of a drug that is already approved for the orphan indication could permit inappropriate "evergreening" of exclusive approval periods, such as obtaining a five-year new chemical entity exclusivity for a drug product and then, once the five-year exclusivity was about to expire, seeking orphan-drug designation and exclusive approval for a drug that is the same as the drug (e.g., in a new dosage form) and for the same indication.

To make this change, FDA would delete the word "orphan" in the phrase "approved orphan drug"[2] to clarify that these provisions would be applicable to a drug that is otherwise the same drug as any previously approved drug for the same orphan disease or condition, regardless of whether such drug was designated as an orphan drug. FDA also proposes similar revisions to § 316.25(a)(3).

These changes would eliminate, as FDA puts it, any future "gaming of the system" by stacking exclusive approval periods, and make it much more difficult for a company to persuade FDA or a court that the Orphan Drug Act permits multiple companies from obtaining orphan exclusivity sequentially.[3]

C. Eligibility for Multiple Orphan-Drug Exclusive Approvals

The Proposed Rule would allow FDA to award multiple orphan-drug exclusivities to subsets of a larger orphan drug population, provided that FDA is able to approve each drug for an indication or use that is limited to the specific subset of persons with the rare disease or condition.[4] The FDA reasons that after approval of the drug for one or more subsets of the orphan disease or condition, a subsequent sponsor may, without submitting a plausible hypothesis of clinical superiority, seek designation of the drug for the subset(s) of the orphan disease or condition for which the drug has not yet been approved. FDA may designate the drug for use in the remaining subset(s) without requiring a postulation of clinical superiority. To obtain such a designation, however, the sponsor must demonstrate that, at the time of its designation request, the entire population with the orphan disease or condition, not just the remaining subset(s) of the population, is under the prevalence limit, unless the sponsor can demonstrate that the remaining subset(s) is an orphan subset in accordance with § 316.20(b)(6).

The FDA also states that the proposed regulation would be applicable only in situations where the underlying disease or condition for which the drug was designated is an orphan disease or condition at the time designation is requested.

D. Demonstration of Clinical Superiority

The Proposed Rule clarifies that, in some cases, a sponsor who has obtained designation of its drug on the basis of a hypothesis that the drug will be clinically superior will be unable, upon submission of the marketing application, to demonstrate that the drug is clinically superior to the previously approved drug. The Proposed Rule would add the following new language to § 316.34(c): "If a drug is otherwise the same drug as a previously approved drug, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to substantiate, at the time of marketing approval, the hypothesis of clinical superiority over the previously approved drug that formed the basis for designation."

The Proposed Rule also clarifies that to be considered clinically superior based on a "major contribution to patient care," a drug must provide safety or effectiveness comparable to the approved drug. As a result, a sponsor seeking an orphan drug designation by arguing that the drug makes a major contribution to patient care must now address whether the change renders the drug less safe or less effective than the approved drug.

What is conspicuously absent from the Proposed Rule is any discussion about the level of evidence required to demonstrate safety or effectiveness for clinical superiority. FDA's flexibility in reviewing clinical superiority has been a recent topic of discussion in the industry. On October 11, 2011, the National Organization for Rare Disorders ("NORD") released a landmark study calling for FDA to acknowledge the flexibility in FDA's review of potential treatments for patients with rare diseases.[5] The NORD study is the first study of its kind ever conducted and the first time that there has been a systematic examination of the basis for approval for any category of drug products extending over such a long period of time. NORD states that the study demonstrates a decades-long pattern of flexibility in FDA review of orphan drugs.

E. Drug Names

Requests for orphan designation must include the generic and trade name, if any, of the drug. For some products, however, neither a generic nor trade name may be available. FDA would revise § 316.20(b)(2) so that, if neither such name is available, requests for designation would be required to include a chemical name or a meaningful descriptive name (i.e., one that would be meaningful to the public if published).

F. Required Drug Description and Scientific Rationale in Orphan-Drug Requests

FDA states in the Proposed Rule that many sponsors omit important information in a request for orphan drug designation, such as the identity of the active moiety or principal molecular structural features. Without such information, FDA states that it cannot determine whether the drug is the same as one already approved and so cannot render a decision on the request. The FDA also notes that some sponsors include only theories in their designation requests, unsupported by data, as to why the drug may be used in a particular disease or condition, which does not constitute an adequate scientific rationale for the use of the drug for the rare disease or condition. Other sponsors, by contrast, include all available data about a drug, rather than just the data pertinent to FDA's review.

FDA would revise § 316.20(b)(4) to include additional data in a request for designation. Specifically, FDA would add the identity of the active moiety or principal molecular structural features of the drug; the physical and chemical properties of the drug; a discussion of the scientific rationale behind the medically plausible basis for the drug, which discussion should include reference to in vitro data, preclinical efficacy data of the drug from studies conducted in a relevant animal model for the human disease or condition, and clinical data from use of the drug in the rare disease or condition; and copies of pertinent published and unpublished papers. FDA notes, however, that animal toxicology studies are generally not relevant to a request for orphan-drug designation.

G. Real Party in Interest Requirement

FDA regulations at § 316.20(b)(9) currently require that requests for orphan-drug designations include 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. FDA proposes to remove this requirement altogether because it has proved to be of marginal utility, has caused confusion for sponsors, and has had the effect of discouraging agents of sponsors (e.g., a sponsor's lawyer) from submitting requests on the sponsor's behalf.

H. Timing of Request for Orphan-Drug Designation

To clarify the requirements regarding the timing of a designation request, FDA proposes to revise § 316.23(a) to indicate that a sponsor may request orphan-drug designation at any time in its drug development process prior to the time that sponsor submits a marketing application for the drug for the rare disease or condition. The revision is intended to clarify that a sponsor may not submit an orphan-drug designation request after it has submitted a marketing application for the drug for that use, and that submission by a sponsor of a marketing application for the drug for the orphan indication does not prevent another sponsor from submitting a request for orphan designation of the same drug for the same orphan use.

I. Responding to FDA Deficiency Letters

FDA regulations are currently silent on when sponsors must respond to a deficiency letter from FDA on an orphan-drug designation request. To address this issue, FDA is proposing to require that sponsors respond to a deficiency letter within one year after issuance of the letter, unless the sponsor requests in writing an extension of time to respond. Such a request would specify both the reason(s) for the requested extension and the length of time of the requested extension. FDA stated in the Proposed Rule that it will grant all reasonable requests for an extension.

In the event the sponsor fails to respond to the deficiency letter or to request an extension of time within a year, the Proposed Rule would allow FDA to consider the designation request voluntarily withdrawn at the conclusion of the one-year period. Should FDA deny a request for an extension of time, FDA may consider the designation request voluntarily withdrawn and will so notify the sponsor in writing.

FDA proposes to change the title of the section to "Deficiency letters and granting orphan-drug designation."

J. Publication of Orphan-Drug Designations

Section 316.28 requires that FDA publish a monthly updated list of designated drugs, in addition to placing on file at the FDA Division of Dockets Management an annual cumulative list of all designated drugs. FDA currently makes available a cumulative list of all designated drugs to date and a cumulative list of designated drugs in the current year on its website. These lists are updated monthly. The Orphan Drug Act requires that notice respecting designation of a drug be made available to the public (§ 526(c) of the FD&C Act). FDA proposes to revise § 316.28 to reflect FDA's existing publication practices.

Holders of orphan-drug designations are required by § 316.30 to submit an annual progress report on their designated drugs. The FDA states in the Proposed Rule that a number of holders of orphan-drug designations have failed to submit annual reports as required for the designated drug, and some have terminated their orphan-drug development program without notifying FDA. Although the failure of a sponsor to submit an annual report does not necessarily signal that the sponsor has ceased development of the orphan drug, this information could nevertheless prove useful to patients, medical practitioners, and the drug development community. The FDA is actively seeking public comment on whether it would be useful to make public, information about whether the sponsor of a designated drug has submitted annual reports as required under § 316.30. The Proposed Rule indicates that FDA does not contemplate disclosing the contents of the annual report, only whether such annual report has been submitted.

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1. 21 C.F.R. § 316.20(b)(6).
2. As the term "approved orphan drug" is used in 21 C.F.R. §§ 316.3(b)(3), 316.20(a), and 316.20(b)(5).
3. Octapharma USA, Inc., Response to CSL Berhing Petition FDA 2011-P-0213, September 23, 2011 (claiming that because CSL's orphan exclusivity had expired at the time Wilate was approved, Wilate could have been approved and awarded orphan drug exclusivity even if it had not been clinically superior).
4. The Proposed Rule sets forth new language that would be added to § 316.31: "Orphan-drug exclusive approval protects only the approved indication or use of a designated drug. If such approved indication or use is limited to a particular subset of persons with a rare disease or condition, FDA may later approve the drug for use in one or more additional subsets and, if the sponsor who obtains approval in the additional subset(s) has orphan-drug designation for the drug, FDA will recognize a new orphan-drug exclusive approval for the use in the new subset(s) of persons with the rare disease or condition from the date of approval of the drug for use in the new subset(s)."
5. NORD, Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs, October 11, 2012, available at www.rarediseases.org/docs/policy/NORDstudyofFDAapprovaloforphandrugs.pdf

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