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To: Tan Nguyen, John J. McCormick, OOPD,

From: Elizabeth Dickinson, OCC

RE: Orphan Designation for Lyotropic's Colloidal Dantrolene for Malignant Hyperthermia

Date: April 25, 2006

Lyotropic Therapeutics (Lyotropic) seeks orphan designation for its colloidal dantrolene formulation for the treatment of malignant hyperthermia. A lyophilized dantrolene drug product was approved for this use in 1979, and is currently being marketed. Lyotropic's product contains the same active moiety as the approved product, and would be seeking approval for the same indication. OOPD has informed Lyotropic that, because a dantrolene product has already been approved for this orphan indication, they will not be eligible for designation for dantrolene for the treatment of malignant hyperthermia unless they can provide a plausible hypothesis that colloidal dantrolene may be clinically superior to the approved lyophilized dantrolene product. Lyotropic does not believe that it must provide such evidence of possible clinical superiority to the approved dantrolene product, to be eligible for orphan designation for its product. Lyotropic also asserts that there is adequate evidence that colloidal dantrolene would be clinically superior to the approved product.

I have reviewed OOPD's position and the arguments made by Lyotropic, and have concluded that OOPD's position that colloidal dantrolene is not eligible for orphan designation for the treatment of malignant hyperthermia is legally supportable.

Background

Lyotropic submitted on October 22, 2003, a request for orphan drug designation of a new formulation of dantrolene called "colloidal dantrolene" (Ryanodex) for treatment of malignant hyperthermia. A lyophilized preparation containing the same active moiety, dantrolene, was approved in 1979 for the same use and is currently marketed by Procter & Gamble Pharmaceuticals (Proctor & Gamble) in the United States under the trade name Dantrium Intravenous (Dantrium). Proctor & Gamble did not seek orphan designation for the use of dantrolene to treat malignant hyperthermia, and thus did not receive orphan exclusivity for Dantrium.

Lyotropic argues in an August 10, 2005, letter that, although Dantrium is approved to treat malignant hyperthermia, because it was not previously designated and approved as an orphan drug to treat malignant hyperthermia, Lyotropic's colloidal dantrolene is eligible for orphan designation without any showing of a plausible hypothesis that colloidal dantrolene would be clinically superior to Dantrium for that orphan indication.

This issue is similar to one presented in 2001-2003 with respect to Merck's request for orphan designation for alendronate to treat Paget's disease, although in the case of alendronate, the

original approved alendronate product for Paget's disease was a Merck product as well. In addition Sandoz sought orphan designation in 1992 for a new formulation of its cyclosporine drug, Sandimmune, for prevention of organ transplant rejection. The original approved Sandimmune product was not a designated orphan drug, although organ transplant rejection was an orphan indication. In the alendronate and cyclosporine matters, OOPD took the position that it would designate the proposed drug only if the sponsor could demonstrate that the new formulation could be clinically superior to the already approved product and thus, under 21 CFR 316.3(b)(13), was not the same drug as the previously approved orphan drug.

This approach also has been applied to the dantrolene designation request. Because the drug dantrolene has been previously approved for the malignant hyperthermia orphan indication, Lyotropic may not receive orphan designation for its drug without establishing a plausible hypothesis that the new colloidal dantrolene drug product could be clinically superior to the Proctor & Gamble's dantrolene product, Dantrium, which is already approved for malignant hyperthermia. Under this standard, dantrolene, like alendronate and cyclosporine, is not eligible for orphan designation for malignant hyperthermia.

Statutory and Regulatory Provisions Governing Orphan Designation

Section 526(a)(1) of the Federal, Food, Drug, and Cosmetic Act provides

> The manufacturer or the sponsor of a drug may request the Secretary to designate the drug for a rare disease or condition. A request for designation of a drug shall be made before the submission of an application under section 505(b) for the drug, or the submission of an application for licensing of the drug product under section 351 of the Public Health Service Act.

This statutory provision is implemented in FDA regulations addressing orphan designations which provide that

> (a) A sponsor that submits a request for orphan-drug designation of a drug for a specified rare disease or condition shall submit each request in the form and containing the information required in paragraph (b) of this section. A sponsor may request orphan-drug designation of a previously unapproved drug, or of a new orphan indication for an already marketed drug. In addition, a sponsor of a drug that is otherwise the same drug as an already approved orphan drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug.
> ...

and

> (b)(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

21 CFR 316.20 (emphases added).

Lyotropic's Position

It is Lyotropic's view that, even though dantrolene has already been approved for malignant hyperthermia, dantrolene may nevertheless receive orphan designation for that same indication without any additional evidence of plausible clinical superiority. Lyotropic argues that such demonstration of possible clinical superiority is only necessary under 21 CFR 316.20(a) and (b)(5), when the drug at issue is otherwise the same drug as an already approved drug that received both orphan designation and orphan exclusivity. Specifically, Lyotropic interprets "already approved orphan drug" in these regulatory provisions to mean an approved drug that was given orphan drug designation and exclusivity.

Lyotropic also asserts that colloidal dantrolene is clinically superior to the approved Dantrium product. OOPD has addressed the merits of the clinically superiority claim in its review of the Lyotropic designation request, and does not find Lyotropic's arguments persuasive.

Analysis

The outcome in this case is governed by 21 CFR 316.20(a) and (b). The regulation at 21 CFR 316.20(a) states that a sponsor may request orphan designation of

> (1) a previously unapproved drug, or
> (2) of a new orphan indication for an already marketed drug.

Dantrolene for malignant hyperthermia does not fall into either of these categories. In the orphan drug context, dantrolene is not a previously unapproved drug. Under the regulatory scheme implementing the orphan drug provisions of the statute, the word "drug" in the context of small molecule drugs like dantrolene means "active moiety." 21 CFR 316.3(b); see also Baker-Norton Pharm. v. FDA, 132 F.Supp. 2d 30 (D.D.C. 2001)(FDA's definition of drug as "active moiety" in the orphan drug provisions is reasonable). Colloidal dantrolene, therefore, is not a previously unapproved drug because the active moiety, dantrolene, already has been approved for malignant hyperthermia. Lyotropic also does not propose a new orphan indication for an already marketed drug. The malignant hyperthermia indication for which Lyotropic would seek designation is already an approved orphan indication for dantrolene.

The regulations also directly address the designation process for a drug that is otherwise the same drug as an already approved orphan drug. This is the category into which dantrolene for malignant hyperthermia falls because, as noted above, it is the same drug as an already approved orphan drug, Dantrium. The regulation at 21 CFR 316.20(a) provides that

> a sponsor of a drug that is otherwise the same drug as an already approved orphan drug may seek orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug.

In addition, 21 CFR 316.20(b)(5) states that

> 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, [the sponsor must submit] an explanation of why the proposed variation may be clinically superior to the first drug.

Both of these provisions of 21 CFR 316.20 use the term "already approved orphan drug." A drug need not go though the designation process to be an approved orphan drug, that is a drug for an orphan indication. FDA's regulations at 21 CFR 316.3(b) define "orphan drug" as "a drug intended for use in a rare disease or condition as defined in section 526 of the act." An indication may be an orphan indication, even without designation. For example, the orphan drug grants program does not require designation of a drug for the indication to be considered an orphan. See http://www.fda.gov/orphan/grants/faq.htm. The Federal Food, Drug, and Cosmetic Act describes a rare disease or condition (an "orphan" in the parlance adopted by the regulations at 21 CFR 316.3(b)) as including any disease or condition which affects less than 200,000 persons in the United States. Section 526(a)(2). Under this definition, malignant hyperthermia is an orphan indication.

The regulations also set out the grounds on which the agency may deny orphan designation. These provisions at 21 CFR 316.25 do not precisely track the eligibility requirements for designation described at 21 CFR 316.20, and in that lack of consistency there is some vulnerability to FDA's denial of exclusivity in this case. As described above, the regulations at 21 CFR 316.20 state that to be eligible for designation, the drug must not be an already approved orphan drug. The regulation at 21 CFR.316.24 (Granting Orphan Drug Designation) states that "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." The regulation at 21 CFR 316.25 in turn states that

> "FDA will refuse to grant a request for orphan drug designation if any of the following reasons apply: ...[a] drug that is otherwise the same drug as one that already has orphan drug exclusive approval for the same rare disease or condition and the sponsor has not submitted a medically plausible hypothesis for the possible clinical superiority of the subsequent drug."

This suggests that designation will be denied only if the same drug currently has orphan exclusivity for the same orphan indication. This is a narrower grounds for denying exclusivity than denial based on previous approval of the drug for the same orphan indication (with or without existing exclusivity). If designation could be denied only if the same drug has exclusivity for the indication, dantrolene would qualify for designation, as the drug has never received orphan exclusivity for malignant hyperthermia. However, because the regulations are internally inconsistent (e.g., in the description at 21 CFR 314.20 of what drugs qualify for designation and in the description at 21 CFR 314.24 and 314.25 of the grounds for denying designation), there is sufficient ambiguity to permit the agency to interpret and apply the statute

and regulations as it believes is reasonable.[1] OOPD has determined that, because the orphan drug provisions of the Act are intended to provide necessary incentives to develop drugs for rare diseases where such drugs would not otherwise be developed, it is reasonable to interpret the regulations not to compel a grant of orphan designation to a drug that has already been approved for the orphan indication. By requiring that designation will be granted only if the sponsor submits evidence that the drug product may be clinically superior to the existing drug in treating the orphan indication, orphan exclusivity acts as an incentive to improve the treatment of rare diseases and conditions and increase the therapeutic options for patents.

There is an additional ground on which to decline to designate Lyotropic's dantrolene product for malignant hyperthermia. The statute provides that a "request for designation of a drug shall be made before the submission of an application under section 505(b) for the drug... ." Section 526(a)(1). This statutory requirement is described in the regulations governing the timing of requests for orphan drug designation, which provide that "[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." 21 CFR 316.23(b)

The requirement that a request for designation be made before the submission of an application was added to the Orphan Drug Act in 1988. In late 1988, FDA published a notice in the Federal Register stating that FDA was changing its previous policy of permitting designation up to the time of application approval. The notice stated that "to be eligible for orphan drug designation under section 526 of the act, FDA must receive the sponsor's request for such designation prior to the submission of a marketing application for that drug for that rare disease or condition." 53 Fed. Reg. 47577 (Nov. 23, 1988).

The language of the statute, regulation and preamble is ambiguous in that it does not specify what "application" or "marketing application" is being referenced. Do these provisions require that designation be sought only before the sponsor now seeking designation of the drug submits its marketing application for that drug for that indication or do they require that the designation be requested before any sponsor submits its marketing application for the drug for that indication.[2] The use of the indefinite article in the statute and regulation (i.e., "request for designation of a drug shall be made before the submission of an application under section 505(b) for the drug") suggests that the reference is to any marketing application, not just the marketing application submitted by the sponsor seeking the designation. General policy considerations also support interpreting the provision to apply to any marketing application, even if it is not from the same sponsor, because once the drug for the orphan indication has been developed to the point of submission of an application, the incentives (grants, protocol incentives, tax benefits, the promise of exclusivity upon approval) are no longer necessary to spur a sponsor to develop the drug for

[1] OOPD is preparing a proposed rule to clarify these regulations and to provide that a drug that is otherwise the same drug as an already approved drug for the same rare disease or condition will not qualify for designation unless the sponsor has submitted a medically plausible hypothesis for the possible clinical superiority of the subsequent drug.

[2] In the case of Merck's alendronate and Sandoz' cyclosporine, the sponsor seeking designation had already submitted (and received approval for) an NDA for the drug for the orphan indication. In this matter, Proctor & Gamble, not Lyotropic, has already submitted an NDA for dantrolene for malignant hyperthermia.

the orphan indication; providing the same incentives to another sponsor who is seeking to develop the same drug[3] for the same indication would be duplicative.

There is one practical consideration that would weigh against interpreting 21 CFR 316.23(b) to apply to applications submitted by a party other than that seeking designation. A party seeking designation of a drug may not know when another sponsor's application has been submitted to FDA. FDA will only disclose the existence on an application (when it has not been otherwise disclosed) when the application is issued an approval, tentative approval, or approvable letter. 21 CFR 314.430(b). In this case, the applicant seeking designation would not know until approval of an application for the drug for the orphan indication that it could not submit a designation request for the drug.[4] Therefore it could be difficult for the agency to enforce the provision with respect to a party seeking designation for a drug after an application for the same drug for the same orphan use has been submitted, but before it is approved. Although this factor contributes to the ambiguity of the provision, it nevertheless is reasonable to interpret 21 CFR 316.23(b) to mean that a sponsor must request orphan designation of a drug (active moiety) before any application for that drug, for that orphan indication has been submitted to FDA.

Conclusion

There is substantial legal support for OOPD's position that the sponsor of a drug that is already approved for an orphan indication may not receive orphan designation for that drug for the orphan indication unless it can present a plausible hypothesis that the drug may be clinically superior to the first drug. Because dantrolene has already been approved for malignant hyperthermia, it will not be grated orphan designation unless Lyotropic can provide a plausible hypothesis that its colloidal dantrolene may be clinically superior to Proctor & Gamble's approved Dantrium product.

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[3] As described above, if the party seeking designation can establish a plausible hypothesis that its product is clinically superior to the orphan drug for which an application has already been submitted, then the drug for which designation is sought would not be the same drug as that for which the application was submitted.

[4] FDA interpreted an earlier version of the Orphan Drug Act to require only that FDA receive a request for designation of a drug "before the agency has approved a marketing application for that drug for that rare disease or condition." 51 Fed. Reg. 4505, 4506 (Feb. 5, 1986). This approach was abandoned in 1988, when the statute was amended to expressly provide that designation must be sought before a marketing application is submitted. 53 Fed. Reg. 47577 (Nov. 23, 1988).