



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

DEC 29 2003

Herbert G. Luther, Ph.D.  
ETHEX Corporation  
10888 Metro Court  
St. Louis, MO 63043-2413

Re: Docket No. 78N-0227/PRC2; DESI 11853

Dear Dr. Luther:

This letter responds to your petition for reconsideration (Petition) submitted on January 23, 2003. You request that the Food and Drug Administration (FDA) take the following actions: (1) reconsider the conclusions stated in the December 24, 2002, *Federal Register* notice (67 FR 78476) (2002 notice) announcing the resolution of issues concerning trimethobenzamide hydrochloride injection and capsules; (2) rescind the notice on the basis that it does not adequately address the data contained in Docket No. 78N-0227; and (3) rule that no final Agency action has been made on any or all of four matters listed in your Petition.<sup>1</sup> Alternatively, you request that FDA reconsider any substantive resolution of any or all of the four matters and render a decision based on the consideration of the data, information, analyses, and views previously submitted in the docket. For the reasons set forth below, we deny your Petition.

**I. BACKGROUND**

The 2002 notice (copy enclosed) sets forth in detail the relevant history of FDA's actions in the Drug Efficacy Study Implementation (DESI) proceeding concerning trimethobenzamide hydrochloride injection and capsules. We briefly summarize that history here.

On January 9, 1979, FDA published a notice in the *Federal Register* (44 FR 1017) (1979 notice) announcing that we were reclassifying trimethobenzamide hydrochloride injection and capsules to effective for certain indications (i.e., the treatment of postoperative nausea and vomiting and for nausea associated with gastroenteritis) and to lacking substantial evidence of effectiveness for their other (previously designated) less-than-effective indications. The 1979 notice stated that the marketing of trimethobenzamide hydrochloride injection and capsule products that were the subject of an approved or

<sup>1</sup> These matters are (1) the indications for which trimethobenzamide hydrochloride injection and capsule products are effective; (2) the historically labeled indications for which these products are not effective; (3) the dosage or dosages at which these products are effective for their indicated uses; and (4) whether these products are subject to the definition of "new drug" under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 321(p)).

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effective new drug application (NDA) could be continued provided that, on or before March 12, 1979, the holder of the application submitted a supplement for revised labeling and a supplement to provide other specified information. One of the marketing conditions for the capsule products was that capsules containing 100 milligrams (mg) or 250 mg be reformulated to 200 mg or 400 mg, respectively.

The 1979 notice proposed to issue an order under section 505(e) of the Act (21 U.S.C. 355(e)) withdrawing approval of the NDAs and all amendments and supplements to the NDAs providing for the indications determined by the Agency to lack substantial evidence of effectiveness (44 FR 2017 at 2020). In accordance with section 505 of the Act and 21 CFR Parts 310 and 314, in the 1979 notice we gave the applicants and all other persons who manufacture or distribute identical, related, or similar drug products (as defined in 21 CFR 310.6) an opportunity to (1) request a hearing to show why approval of the NDAs providing for the claims involved (i.e., those claims found to be lacking substantial evidence of effectiveness) should not be withdrawn and (2) raise, for administrative determination, all issues relating to the legal status of the named drug products and all identical, related, or similar drug products (44 FR 2017 at 2020).

Beecham Laboratories (Beecham), which held the NDAs for Tigan (trimethobenzamide hydrochloride) Injection and Capsules, was the only party to request a hearing. We did not issue a response to Beecham's request. On November 12, 1999, King Pharmaceuticals, Inc. (King) purchased the Tigan NDAs and subsequently entered into discussions with us on bringing the Tigan products into compliance with the 1979 notice.

In an agreement that became effective on August 16, 2001 (Agreement), FDA and King agreed to take several actions to resolve the matter of the compliance of Tigan products with the 1979 notice. Among other things, King agreed to withdraw the request for a hearing (originally submitted by Beecham) on matters related to the Tigan NDAs; King withdrew the request on August 24, 2001. On December 13, 2001, we approved King's supplemental NDA for 300-mg Tigan Capsules. Subsequently, King revised the labeling for Tigan Injection. In light of these events, on December 24, 2002, we issued the notice resolving all matters in the proceeding involving trimethobenzamide hydrochloride injection and capsules.

## **II. DISCUSSION**

You maintain that although only Beecham requested a hearing in response to the 1979 notice, other interested parties continued to be entitled to participate in any proceedings under 21 CFR 12.45 and are now entitled to a substantive response to the data and information submitted to Docket No. 78N-0227 (Petition at 3-4). You state that this includes companies that continued to market trimethobenzamide hydrochloride 250-mg capsule products as well as other firms, including ETHEX, which chose to begin marketing such products after publication of the 1979 notice.

Neither ETHEX nor any other manufacturer of a trimethobenzamide hydrochloride capsule product is entitled to a substantive response to the data and other information

originally submitted by Beecham in 1979 to Docket No. 78N-0227. As you note, only Beecham requested a hearing in response to the 1979 notice. The failure of all other persons who were subject to the 1979 notice to request a hearing constituted a waiver of any contentions concerning the legal status of any drug product subject to the notice (§ 314.200(a)(2); 44 FR 2017 at 2020; 67 FR 78476 at 78478). Any trimethobenzamide hydrochloride injection or capsule product that was labeled for the indications determined to be lacking substantial evidence of effectiveness could not thereafter be lawfully marketed and was subject to appropriate regulatory action for removal from the market (44 FR 2017 at 2020). Moreover, FDA clearly stated that any new trimethobenzamide hydrochloride injection or capsule product marketed without an approved NDA, which includes the 250-mg product manufactured by ETHEX, would be subject to regulatory action at any time (*id.*).

Under § 314.200(g)(8), “[a] request for a hearing, and any subsequent grant or denial of a hearing, applies only to the drug products named in such documents.” Therefore, Beecham’s request for a hearing quite clearly did not apply to any other drug products that may also have been subject to the notice. Beecham was the only manufacturer to submit a request for hearing. When King, Beecham’s successor in interest, withdrew its request for a hearing on Tigan Injection and Capsules, there were no remaining requests for a hearing on this issue. Furthermore, once King withdrew the request for a hearing, FDA was under no legal or procedural obligation to address the merits of the data that Beecham had submitted in support of its hearing request.

Although FDA has the authority to take regulatory action against drug products for which no request for hearing has been submitted in response to a notice of opportunity for a hearing, it is generally our policy not to take action against such drug products while there is a pending hearing request regarding any drug product that is the subject of such notice. Therefore, while Beecham’s request for a hearing on Tigan Injection and Capsules was pending, we did not take regulatory action against manufacturers of other trimethobenzamide hydrochloride injection and capsule products. After King withdrew the request for a hearing on the Tigan products and we approved 300-mg Tigan Capsules, it was appropriate for us to notify the manufacturers of unapproved trimethobenzamide hydrochloride injection and capsule products that continued marketing of these products is unlawful and is subject to regulatory action (67 FR 78476 at 78478).

Under 21 CFR § 10.33(d), the Commissioner of Food and Drugs shall grant a petition for reconsideration in any proceeding if the Commissioner determines that all of the following apply:

- The petition demonstrates that relevant information or views contained in the administrative record were not previously or not adequately considered.
- The petitioner’s position is not frivolous and is being pursued in good faith.
- The petitioner has demonstrated sound public policy grounds supporting reconsideration.

- Reconsideration is not outweighed by public health or other public interests.

If one or more of the conditions is not met, the decision to grant a petition for reconsideration is discretionary.

You contend that § 10.33(d)(1) is met because (1) extensive data and information submitted in Docket No. 78N-0227 do not appear to have been considered and (2) the issues in the 1979 notice about the effective use and the regulatory status and approvability of 250-mg trimethobenzamide hydrochloride capsule products have not been resolved (Petition at 5). You argue that the 2002 notice erroneously suggests that 250-mg trimethobenzamide hydrochloride capsule products have been found to be unsafe or ineffective or to be lacking in general recognition of safety or effectiveness. In addition, you maintain that the 2002 notice is the functional equivalent of a rule and that FDA must comply with the rulemaking procedures set forth in the Administrative Procedure Act (APA) (5 U.S.C. 553), including issuance of a proposed rule, receipt and consideration of comments, and issuance of a final rule.

We disagree with each of these contentions. First, as stated above, in issuing the 2002 notice we were not required to consider the data submitted by Beecham in response to the 1979 notice because King, Beecham's successor in interest, had withdrawn the hearing request. Second, we have in fact resolved the issues in the 1979 notice concerning the 250-mg trimethobenzamide hydrochloride capsule products by noting King's withdrawal of its hearing request and by reiterating the statements in the 1979 notice that continued marketing of these products is unlawful and is subject to regulatory action. Third, the 2002 notice did not "erroneously suggest" that 250-mg capsule products were ineffective; the 1979 notice had already concluded that the products lacked substantial evidence of effectiveness and the 2002 notice effectively reaffirmed that conclusion.

Finally, the 2002 notice is not a rule and therefore is not subject to the requirements for rulemaking in 5 U.S.C. § 553. Rather, the 2002 notice constitutes an "order" under the APA. DESI matters are considered adjudications. An "adjudication" is defined in § 551(7) of the APA as the "agency process for the formulation of an order." Section 551(6) of the APA defines the term "order" as "a final disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency in a matter other than a rulemaking but including licensing." Furthermore, in *Weinberger v. Hyson, Westcott and Dunning, Inc.*, 412 U.S. 609 (1973), the Supreme Court specifically affirmed that the issuance of a declaratory order (such as the 2002 notice) falls under § 554 of the APA, relating to adjudications, and not under § 553.

You assert that § 10.33(d)(2) is met because there is legitimate confusion as to the significance of the 2002 notice. To the contrary, FDA does not believe that there should be any confusion as to the significance of the 2002 notice. That notice clearly set forth the history of the issues involving trimethobenzamide hydrochloride capsule products and described the approval of the 250 mg capsule and the subsequent withdrawal of the sole request for a hearing under the 1979 notice. Finally, the 2002 notice reaffirmed that

continued marketing of unapproved trimethobenzamide hydrochloride capsule products is unlawful and subject to regulatory action (67 FR 78476 at 78478).

In arguing that § 10.33(d)(3) is met because there are sound public policy grounds for reconsideration, you maintain that there should not be an “abrupt shift” from the 250-mg trimethobenzamide hydrochloride capsules to a 300-mg dosage without consideration of the data that Beecham presented in support of its hearing request (Petition at 7). As stated above, FDA concluded in 1979—24 years ago—that the 250-mg capsule product lacked substantial evidence of effectiveness for the indications specified in the 1979 notice. Contrary to your claim, the approval of King’s 300-mg Tigan Capsules supports rather than undermines that conclusion. Consequently, preventing the withdrawal of the 250-mg trimethobenzamide hydrochloride capsule products from the market does not constitute a sound public policy ground for reconsidering the 2002 notice.

You argue that § 10.33(d)(4) is met because the benefits of reconsidering the conclusions in the 2002 notice are not outweighed by public health or other public interests (Petition at 7). You contend that (1) numerous companies have marketed 250-mg trimethobenzamide hydrochloride capsule products without FDA interference for over 40 years; (2) these products have been safely and effectively used by innumerable patients over those years; and (3) there is no apparent public health need to remove these products from the market, particularly prior to following appropriate procedures. You claim that the fact that FDA published the 2002 notice more than 12 months after the approval of 300-mg Tigan Capsules supports your position. Finally, you state that there is no provision in the Agreement between King and FDA that precludes the Agency from concluding the matters in the 1979 notice in a manner consistent with your request for reconsideration.

We believe that any speculative benefits from reconsideration of the conclusions in the 2002 notice are outweighed by the significance of the review and approval of 300-mg Tigan Capsules and by the need for adherence to the established procedures of the DESI program. As explained above, we have followed the appropriate statutory and regulatory procedures in issuing the 1979 notice and resolving all pending issues with respect to trimethobenzamide hydrochloride injection and capsules. The fact that 250-mg trimethobenzamide hydrochloride capsule products have been marketed even after the issuance of the 1979 notice is irrelevant, particularly given the fact that there is now an approved 300-mg trimethobenzamide hydrochloride capsule product (Tigan). Moreover, the fact that we did not issue the 2002 notice concurrent with the approval of the supplemental NDA for 300-mg Tigan Capsules provides no support for the continued marketing of 250-mg trimethobenzamide hydrochloride capsule products. Our actions with respect to King’s Tigan capsule products, as addressed in the Agreement, necessarily took into account the pending request for hearing submitted by Beecham.

As stated above, FDA had the authority to remove the 250-mg trimethobenzamide hydrochloride capsule products (other than the Tigan product) from the market in 1979 after the manufacturers of those products failed to submit a request for a hearing. Any company, including ETHEX, knew or should have known that if it began producing a

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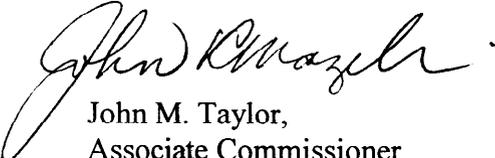
250-mg trimethobenzamide hydrochloride capsule product after issuance of the 1979 notice without first obtaining FDA approval, it was marketing an unapproved new drug product that was subject to regulatory action at any time. We find no compelling reason to conclude that the public interest would be served in this instance by disregarding the established procedures for appealing Agency determinations in DESI proceedings.

Consequently, we conclude that you have not met the requirements for granting reconsideration under § 10.33(d).

### III. CONCLUSION

For the reasons stated above, we deny your request that we rescind the 2002 notice announcing the resolution of issues concerning trimethobenzamide hydrochloride injection and capsules. In addition, we deny your alternative request that we reconsider our conclusions on the matters that you have specified, review the data submitted in response to the 1979 notice, and issue revised conclusions.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "John M. Taylor".

John M. Taylor,  
Associate Commissioner  
for Regulatory Affairs

Enclosure