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Petition for Reconsideration

Docket No. 78N-0227; DESI 11853

On behalf of ETHEX Corporation the undersigned submits this petition for reconsideration of the decision of the Director, Center for Drug Evaluation and Research (hereinafter, the "Center Director"), in Docket No. 78N-0227; DESI 11853, published at 67 Fed. Reg. 78476, December 24, 2002.

A. Decision Involved

In the above-referenced Federal Register notice, the Center Director states that ". . . FDA is issuing this notice in final resolution of all matters in this proceeding involving trimethobenzamide hydrochloride injection and capsules." The referenced "matters" are those raised initially in a Notice of Opportunity for Hearing published on January 9, 1979 at 44 Fed. Reg. 2017, and include the following:

1. The indications for which trimethobenzamide hydrochloride injection and capsule products are effective;

2. The historically labeled indications for which trimethobenzamide hydrochloride injection and capsule products are not effective;

3. The dosage(s) at which trimethobenzamide hydrochloride injection and capsule products are effective for their indicated uses;

4. Whether trimethobenzamide hydrochloride injection and capsule products are subject to the definition of "new drug" at 21 U.S.C. § 321(p).

B. Action Requested

The undersigned requests that the Commissioner reconsider the conclusions stated in the cited December 24, 2002 Federal Register notice, rescind the notice on the basis that it does not adequately address the data contained in the relevant Docket, and rule instead that no final agency decision has been made on any or all of the four matters listed in section A above.

In the alternative, the undersigned requests that the Commissioner reconsider any substantive "resolution" reached on any or all of the four matters listed in section A above and render a decision based on due consideration of the substantive data, information, analyses, and views submitted previously in this Docket.

C. Statement of Grounds

1. Factual and Procedural Background

Trimethobenzamide hydrochloride drug products have been marketed since prior to 1962 for the treatment and/or prevention of nausea and vomiting. Because new drug applications for trimethobenzamide hydrochloride injection and capsule products had been submitted by Roche Laboratories and had become effective prior to 1962, a review of the status of trimethobenzamide hydrochloride products was initiated as part of the DESI review implementing the efficacy provisions of the 1962 amendments to the Federal Food, Drug and Cosmetic Act ("FFDCA"). As part of that review, FDA published a Federal Register notice on February 24, 1971. 36 Fed. Reg. 3435. In that notice, FDA stated that the approved Roche products "are regarded as new drugs." FDA also announced its tentative conclusions that trimethobenzamide hydrochloride is "probably effective" for nausea and

vomiting due to radiation therapy or travel sickness and for emesis associated with operative procedures, labyrinthitis, or Meniere's syndrome; "lacking substantial evidence of effectiveness" for the treatment of nausea and vomiting due to infections, underlying disease processes or drug administration; and "possibly effective" for all other labeled indications. 36 Fed. Reg. 3435 (Feb. 24, 1971). All persons marketing trimethobenzamide hydrochloride drug products, including persons marketing such products without approval, were directed to remove from the labeling of those products the indications deemed to be lacking substantial evidence of effectiveness. In addition, all such persons were offered the opportunity to obtain and submit additional data supporting the use of the drug for the "probably effective" and "possibly effective" indications.

Based on review of the additional information submitted in response to the 1971 notice, FDA published a "Followup Notice and Opportunity for Hearing" in the Federal Register of January 9, 1979. 44 Fed. Reg. 2017. In that notice, FDA announced revised conclusions with respect to the drug, declaring trimethobenzamide hydrochloride drug products to be effective "[f]or the treatment of postoperative nausea and vomiting and for nausea associated with gastroenteritis" and lacking substantial evidence of effectiveness for all other labeled indications. FDA also announced its conclusion – based on data derived from an apparently poorly bioavailable capsule product – that the effective dose of an oral capsule dosage form of the drug would be 400 mg and not the previously marketed 100 and 250 mg strengths. FDA also reiterated its statement that "[s]uch drugs are regarded as new drugs." 44 Fed. Reg. at 2019.

In response to the 1979 Federal Register notice, a request for hearing was filed on behalf of Beecham, Inc. on January 30, 1979. In addition, data and information were submitted by Beecham to this Docket in support of that request on at least two occasions: March 5, 1979 and April 17, 1980. These submissions included data and information supporting the historically labeled indication for trimethobenzamide hydrochloride for the "control of nausea and vomiting" without limitation as to etiology, including clinical data from investigations conducted in various conditions other than those included within the agency's efficacy conclusion, and investigations conducted with the historically marketed 250 mg strength of the oral trimethobenzamide hydrochloride capsule product. Although no separate requests for hearing were filed by other parties, other interested parties

continued to be entitled to participate in any proceedings pursuant to 21 C.F.R. § 12.45, and are entitled to a substantive response to the data and information submitted to the Docket. This includes firms such as ETHEX Corporation, which was not even in existence at the time the 1979 notice was issued.

Throughout the ensuing 22+ years, numerous parties continued to manufacture and distribute trimethobenzamide hydrochloride 250 mg capsule products, including a number of firms who continued to market the drug based on the general recognition of its safety and effectiveness and on the apparently still unresolved status of the drug under the DESI review. Other firms, including ETHEX Corporation, chose to begin competing in the market for this product during this period, based on these same considerations.

During this extended period of time, FDA appears to have recognized that the conclusion stated in its 1979 notice about the proper dosage strength of a trimethobenzamide hydrochloride capsule product was erroneous. Rather than announce this revised conclusion publicly, however, and thereby encourage the submission of NDAs for 250 mg capsule products, FDA negotiated a private agreement with Beecham's successor (King Pharmaceuticals), which resulted in King obtaining approval of a 300 mg capsule product and withdrawing the relevant request for a hearing (while continuing to manufacture and market its 250 mg capsule product).

After the revised version of the King product was approved, and then only after another 12 months had passed, FDA addressed publicly the error it had made in its 1979 notice. 67 Fed. Reg. 78476 (Dec. 24, 2002). In that notice, however, FDA acknowledges the subsequent actions taken by it and King, but fails to correct the erroneous conclusions of its 1979 notice. Rather, FDA simply announced that, by virtue of its acceptance of the King product, and King's withdrawal of its request for a hearing, the proceedings on the 1979 notice are concluded without any analysis of the data and information submitted to the Docket in response to the 1979 notice which showed that the conclusions stated in that notice were wrong.

2. The Regulatory Grounds For Reconsideration Are Met

Pursuant to 21 C.F.R. § 10.33(d), the Commissioner shall reconsider a matter upon request if the four criteria discussed below are met.

a. Relevant Information or Views Were Not Previously or Adequately Considered

As outlined above, extensive data and information submitted to the Docket in response to the 1979 notice were not addressed by FDA in the December 24, 2002 notice and, indeed, do not appear to have been considered. Despite approval of a 300 mg trimethobenzamide hydrochloride capsule product in 2001, the issues addressed in the 1979 notice about the effective use and the regulatory status and approvability of 250 mg capsule products remain outstanding and have not been resolved. Therefore, it appears that the statement in the 2002 notice that "FDA is issuing this notice in final resolution of all matters in this proceeding involving trimethobenzamide hydrochloride injection and capsules" overstates the substantive significance of the notice and erroneously suggests that 250 mg trimethobenzamide hydrochloride capsule products have been found to be unsafe or ineffective or to be lacking in general recognition thereof. Any such finding would have to be made in light of the data and information timely submitted to this Docket but which were not addressed at all by the agency in the 2002 notice.

Indeed, because the 2002 notice purports to be a statement of general applicability and future effect designed to implement and prescribe law, the notice is the functional equivalent of a rule. *See* 5 U.S.C. § 551(4). As the agency noted, "several different manufacturers" are affected if the far reaching statements in the notice are regarded as final, binding conclusions of fact and law. 67 Fed. Reg. at 78478. Accordingly, the rationale underlying the Administrative Procedure Act rulemaking process, and the procedural safeguards attendant thereto, apply with equal force here. In order to issue a rule, the agency must complete a three-step process – issuance of a notice of proposed rulemaking, receipt and consideration of comments on the proposed rule, and issuance of a final rule incorporating a statement of basis and purpose. *See* 5 U.S.C. § 553. Though the 2002 notice has the impact of a rule, the agency has not considered information submitted to the Docket on a timely basis and has not explained the basis for its conclusions in light of that information. If the agency intends to apply these conclusions to all persons, including manufacturers and distributors

that were not even in existence at the time of the 1979 notice, the agency must not side-step or short-circuit these critical procedural safeguards.

For these reasons, the Commissioner should reconsider the conclusion stated in the 2002 notice, rescind the notice on the basis that it does not adequately address the data contained in the relevant Docket, and rule instead that no final agency decision has been made on any or all of the four matters listed in section A above. In the alternative, the Commissioner should reconsider any conclusions that may have been reached on the issues identified in section A above and, based on a review of the data and information submitted to the Docket in timely response to the 1979 notice, issue revised conclusions properly reflective of those data and of the subsequent findings, separately made in the context of the King application, to the effect that the conclusions of the 1979 notice were erroneous in significant respects, particularly with respect to the effective dosage of trimethobenzamide hydrochloride capsule products.

b. This Petition Is Not Frivolous and Is Being Pursued in Good Faith

As described above, there is legitimate confusion as to the significance of the 2002 notice given that the notice purports to conclude the proceedings on the 1979 notice without considering the data and information timely submitted in response thereto or correcting the apparent errors that were made in the 1979 notice itself. This petition seeks reconsideration of the "conclusions" stated in the 2002 notice so that those conclusions can be either recognized as lacking an adequate foundation or can be corrected to reflect the facts as they appear based on subsequent events.

250 mg trimethobenzamide hydrochloride capsule products have been marketed by many firms, both with and without approval, for over 40 years. The status of these products continues to be of legitimate concern because of this long history of safe and effective use. Indeed, the fact that 300 mg strength capsule products (differing in strength by only 20%) are now recognized as safe and effective serves to underscore the fact that the historically marketed 250 mg capsules are also safe and effective and generally recognized as such. Certainly, before a final determination is made with respect to the status of 250 mg capsule products, there should be an analysis and a clear conclusion reached as to whether there is indeed any

safety or efficacy problem which precludes continued reliance on the general recognition of the safety or efficacy of those drugs.

c. There Are Sound Public Policy Grounds For Reconsideration

Reconsideration and clarification of the "conclusions" reached in the 2002 notice, if any, will benefit both manufacturers and consumers of trimethobenzamide hydrochloride capsule products. 250 mg capsule products have been the standard and accepted dosage for this drug for over 40 years. There should not be an abrupt shift from this dosage to another (by virtue of a de facto "ban" on 250 mg products) without due consideration of the information which supports this dosage and which was timely submitted to the agency for review. This is particularly so when subsequent events, i.e., the approval of the 300 mg King product, show that the original basis for the agency's position that a 400 mg dosage was required was erroneous and that, indeed, there is no reason to believe that 250 mg products are not also efficacious.

d. The Benefits of Reconsideration Are Not Outweighed by Public Health or Other Public Interests

There do not appear to be countervailing interests that outweigh the benefits of reconsidering the matters presented here. 250 mg trimethobenzamide hydrochloride products have been marketed by numerous firms without interference from the FDA for over 40 years. They have been safely and effectively used by innumerable patients over those years and there is no apparent public health need to take action to remove any such products from the market, particularly prior to following appropriate procedures. This view is underscored by the fact that the 2002 notice itself was published over 12 months after the approval of the 300 mg King product. Moreover, although we understand that there was a private agreement reached between FDA and King which called for FDA to issue a notice concluding the matters raised by the 1979 notice, there is no provision in that agreement which precludes FDA from concluding those matters in a proper and considered manner consistent with the instant request for reconsideration.

3. Conclusion

For the foregoing reasons, the undersigned requests that the Commissioner reconsider the conclusion stated in the 2002 notice, rescind the notice on the basis that it does not adequately address the data contained in the relevant Docket, and rule instead that no final agency decision has been made on any or all of the four matters listed in section A above.

In the alternative, the undersigned requests that the Commissioner reconsider any conclusions that may have been reached on the issues identified in section A above and, based on a review of the data and information submitted to the Docket in timely response to the 1979 notice, issue revised conclusions properly reflective of those data and of the subsequent findings, separately made in the context of the King application, to the effect that the conclusions of the 1979 notice were erroneous in significant respects, particularly with respect to the effective dosage of trimethobenzamide hydrochloride capsule products.

Respectfully submitted,

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