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VIA HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
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RESPONSE TO COMMENTS

Refrain from Approving Certain Applications Referencing Depakote®

Docket No. 2004P-0320/CP1

Abbott Laboratories (Abbott) submits the following comments under 21 CFR 10.30 in support of the above-referenced petition and in opposition to comments lodged by Andrx Laboratories, Inc. (Andrx) dated October 29, 2004 (the Andrx Comments).¹

Andrx concedes the three essential points in the petition: that Andrx's product contains as its primary ingredient sodium valproate, which is chemically different from Depakote® (divalproex sodium delayed-release tablets); that this difference exists solely as a means of avoiding Abbott's intellectual property rights and offers no clinical benefit to patients; and that Andrx's 505(b)(2) application is essentially a repeat of its tried-and-failed 505(j) application, bolstered by some published literature. Taken together, these concessions place Andrx's application squarely within FDA's concern that such applications raise significant public policy and public health issues. See FDA Dockets 2001P-0323, 2002P-0447, and 2003P-0408, PDN at 33-34 ("Marketplace Confusion and Incentives for Development") (hereafter the Consolidated Petition Response).

¹ On January 11, 2005, the Food and Drug Administration (FDA) issued an interim response to the petition, stating that it has been unable to reach a decision due to competing demands on the agency's resources.

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With the benefit of the Andrx Comments, the outcome of this proceeding is straightforward. FDA must defer final approval of Andrx's 505(b)(2) application pending completion of a public process to consider whether a 505(b)(2) application is appropriate where the only change from the listed drug is a structural change to the active ingredient, and where the only reason for the change is to avoid an innovator's patent. Consolidated Petition Response at 33-34. Thereafter, depending on the outcome of that proceeding, it may be necessary to continue to stay final approval of the application until the expiration of Abbott's intellectual property rights (in January 2008).

I. THE ZALKOTE® NDA CONTAINS THE SAME FUNDAMENTAL FLAWS AS THE ZALKOTE® ANDA

Andrx asserts that the active ingredient in its proposed product, Zalkote® (sodium valproate delayed-release tablets), is a "distinct chemical entit[y]" from the active ingredient in Depakote® (divalproex sodium delayed release tablets). Andrx Comments at 1.² This difference was significant enough for Andrx's product to be denied approval under the abbreviated new drug application (ANDA) process. *Id.* at 2; *see* 21 USC 355(j)(2)(A)(ii).

As a result, Andrx was required to submit a new drug application (NDA) for Zalkote®. Unlike the ANDA process, which allows for approval based on a showing of "sameness" and bioequivalence (21 USC 355(j)(2)(A)), the NDA process requires an independent demonstration of safety and effectiveness. Whether the NDA is submitted under 505(b)(1) or 505(b)(2) of the Food, Drug, and Cosmetic Act (the FDCA), the evidentiary standards are identical. An NDA must include "full reports of investigations," and must satisfy the "substantial evidence" standard for each labeled indication. 21 USC 355(b)(1), (b)(2), and (d). "Substantial evidence" consists of at least one "adequate and well-controlled clinical investigation" plus "confirmatory evidence." 21 USC 355(d).

The Andrx Comments show that Zalkote® is no more approvable under 505(b), (c), and (d) than it was under 505(j). Andrx concedes that the NDA is simply a literature-enhanced repeat of its failed ANDA. Andrx Comments at 2, 3, and 6. The Zalkote® NDA contains "the bioequivalence study originally conducted by Andrx to support its ANDA," along with "literature references" to *in vivo* studies of

² In pending litigation against Andrx, Abbott contends that Andrx's product contains some divalproex sodium. *Abbott Labs v. Andrx Corp.*, Case No. 03-60867 (S.D. Fla.) (Highsmith, J.).

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sodium valproate and other valproate products. *Id.* at 2, 3. The literature, according to Andrx, provides "additional support for its application." *Id.* at 6. "Taken together with the data from Andrx's bioequivalence study," Andrx claims it has met the standard for approval of an NDA. *Id.*

Not so. By all appearances, Andrx is still seeking to reference the Depakote® labeling, including the use of Depakote® in the prophylaxis of migraine headaches and the treatment of manic episodes associated with bipolar disorder. The agency, however, has already determined that Zalkote® and Depakote® contain different active ingredients for purposes of the FDCA – so much so that Zalkote® was determined to be ineligible for approval under the ANDA process. Put another way, Andrx would need to provide the agency some additional data – either preclinical or clinical – that could support the labeling of Zalkote® for the same uses as Depakote®.³

The purported active ingredient in Zalkote®, sodium valproate, has not been shown to be safe and effective for the migraine headache and bipolar disorder indications. Only divalproex sodium has been approved for those uses. As a matter of law, a purported showing of bioequivalence between Zalkote® and Depakote® does not meet the evidentiary standard for an NDA. 21 USC 355(d) (requiring "substantial evidence" consisting of at least one "clinical investigation"); *see* 21 CFR 314.108(a) (stating that a bioavailability study is not a "clinical investigation"). Based on what little may be gleaned from the comments, it is unlikely that the literature offered by Andrx establishes that sodium valproate is safe and effective for the treatment of migraine headache and bipolar disorder. Again, under the NDA standard, any such showing must be based on "full reports of investigations" providing "substantial evidence" for each proposed use.⁴

³ In our opening petition, we showed that Andrx would have a viable path to market if it referenced Depacon® rather than Depakote®. Depacon® contains sodium valproate as its active ingredient, and Andrx could pursue a 505(j) suitability petition for a change in dosage form – from Depacon's injectable format to delayed-release tablets. Andrx, however, has refused that option; it does not want to be limited to the Depacon® label. Instead, Andrx wants the Depakote® label, albeit without doing the clinical work needed to support the Depakote® labeling.

⁴ Full reports" must provide detailed information on study design, conduct, and analysis to allow "critical evaluation" of the study. 21 CFR 314.126(a). Abstracts, reviews, anecdotal reports and discussions of studies lacking adequate controls are unacceptable. *See id.* Even the detailed

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The problem, as drawn to light by Andrx, is that a 505(b)(2) NDA – for a product that failed to meet the ANDA requirements – must include data to support the proposed change to the listed drug. In this case, the change is to the active ingredient itself. As explained in the Consolidated Petition Response, "[t]he safety and effectiveness of any differences between the listed drug and the drug proposed in the 505(b)(2) application *must be supported by additional data, including clinical or animal data, as appropriate (§ 314.54).*" Consolidated Petition Response at 14 (emphasis added).⁵ There is little indication in the Andrx Comments that its literature review can support such a material change, let alone satisfy the "substantial evidence" and "full reports" standards for an NDA.⁶

II. THE ZALKOTE® NDA FALLS FOUR-SQUARE WITHIN THE PUBLIC POLICY ISSUE RAISED BY FDA IN THE CONSOLIDATED PETITION RESPONSE

As discussed above, Andrx admits that it is using section 505(b)(2) solely to evade Abbott's patents on Depakote®. Andrx Comments at 2. This is precisely the issue identified in the "Marketplace Confusion and Incentives for Development" section of the Consolidated Petition Response. As the agency stated:

FDA is particularly interested in examining the use of 505(b)(2) applications to obtain approval of drug products for which the *only* difference from the listed drug is in the form of the active ingredient,

summaries prepared by FDA review teams following approval of an NDA do not to constitute "full reports of investigations" for purposes of section 505(b)(1). 21 CFR 314.430(e)(2).

⁵ Andrx claims that we omitted the "as appropriate" language from the opening petition. Andrx Comments at 5. In fact, we quoted the language in full on page 5 of the petition. According to Andrx, the "as appropriate" language signals that there is no minimum data requirement for a 505(b)(2) application beyond what may be submitted under 505(j). Abbott believes, in contrast, that the "as appropriate" language speaks to the type of data needed to support a change to a listed drug (*i.e.*, preclinical and/or clinical data), and not whether such data is needed at all. Abbott's interpretation tracks the language of 21 CFR 314.54. Were Andrx's view accepted, it would eliminate any real distinction between sections 505(b)(2) and 505(j).

⁶ The agency's reference to 21 CFR 314.54, quoted in the text, bears note. Section 314.54 speaks specifically to changes to a listed drug for which "*investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the change.*" 21 CFR 314.54(a) (emphasis added). The regulation plainly contemplates the submission of *investigations* (preclinical or clinical) to support changes to an approved drug product that would not be permitted under section 505(j).

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such as a change in salt. There are products that have the same dosage form, route of administration, strength, conditions of use, and labeling as the listed drug. The only reason these products may not be reviewed and approved in ANDAs submitted under section 505(j) is that they contain a different active ingredient from the listed drug.

Id. at 34 (emphasis in original). Such products, according to the agency, offer no incremental benefit over existing products and, as such “may have undesirable policy and public health consequences.” *Id.*

Zalkote® falls right in the heartland of this critical policy issue. Andrx’s use of section 505(b)(2), if allowed, would upset the careful balance achieved under Hatch-Waxman. The agency had its finger precisely on this issue in its October 2003 petition response. It should not let go, nor should it be swayed by Andrx’s suspect promise of lower drug prices. Rather, the agency should move ahead with the public process outlined in the Consolidated Petition Response and stay final approval of suspect 505(b)(2) applications, such as this one, until the policy issues have been fully considered.

III. CONCLUSION

The Zalkote® NDA is no more compelling than the failed Zalkote® ANDA. The NDA appears to lack "full reports of investigations" providing "substantial evidence" of the efficacy of the product for each proposed use.

The Andrx Comments solidify the policy concerns raised at the conclusion of the October 2003 Consolidated Petition Response. Andrx admits that it is using section 505(b)(2) solely to evade Abbott's patent rights on Depakote. Indeed, Andrx insists that any apparent differences between Zalkote® and Depakote® should be considered "irrelevant" from a clinical perspective. Andrx Comments at 4. As FDA recognized, careful consideration must be given to such applications, and a public review is needed before the 505(b)(2) doorway is opened to accommodate such applications.

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Respectfully submitted,

A handwritten signature in black ink, appearing to read "D.M. Fox", written in a cursive style.

David M. Fox
Hogan & Hartson L.L.P.

cc: Neal B. Parker
Senior Counsel
Abbott Laboratories