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Docket No. 2004P-0320/CP1

VIA FEDERAL EXPRESS

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Refrain from Approving Certain Applications Submitted Under Section 505(B)(2) of the FDCA that Reference Depokote (divalproex sodium delayed-release tablets)

Andrx Laboratories, Inc. Response to July 15, 2004 Citizen Petition Submitted on Behalf of Abbott Laboratories

On behalf of Andrx Laboratories, Inc. ("Andrx"), we submit this response to the above referenced citizen petition, submitted on behalf of Abbott Laboratories ("Abbott"). Abbott's July 15, 2004 Citizen Petition, FDA Docket No. 2004P-0320/CP1 requests that the FDA refrain from approving Andrx's Zalkote® sodium valproate delayed-release tablets because the approval would be arbitrary, capricious and contrary to the law. The product at issue is the subject of a new drug application ("NDA") filed under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") which was tentatively approved on May 10, 2004, pending expiration of a 30-month stay or favorable resolution of patent infringement litigation filed by Abbott in connection with its product Depakote® (divalproex sodium delayed-release tablets). Although the sodium valproate in Andrx's product and the divalproex sodium in Depakote are distinct chemical entities, both compounds are quickly metabolized in the body to the valproic ion, which is the pharmacologically active substance in both products.

In essence, Abbott's Citizen Petition contends that FDA may not lawfully approve Andrx's NDA under § 505(b)(2) of the Act without requiring Andrx to conduct and submit studies that independently establish the safety and effectiveness of the active ingredient sodium valproate. As a factual matter, Abbott also presumes that the Andrx NDA is identical to a previously denied abbreviated new drug application ("ANDA") submitted for the same product

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with Depakote as the reference listed drug. Finally, Abbott interprets FDA's consolidated response to several earlier citizen petitions concerning § 505(b)(2) applications as calling for FDA to conduct a "public process" to resolve various "scientific, legal, and policy issues" purportedly raised by Andrx's application before approving it or "similarly situated" applications. (Consolidated Petition Response in Docket Nos. 2001P-0323, 2002P-0447 and 2003P-0408 dated October 14, 2003 ("Consolidated Petition Response"). In this Consolidated Petition Response, FDA considers numerous issues relating to the approval of NDAs under § 505(b)(2) of the FDCA, including the issue of pharmaceutical dosage forms that contain different salts of previously approved products, (such as paroxetine mesylate where the previously approved product was paroxetine hydrochloride).

As the following discussion will demonstrate, Abbott's petition is wholly without merit and should be denied on legal, factual, and policy grounds. Upon review of the relevant statutes and regulations, and when Andrx's NDA and the Consolidated Petition Response relied upon by Abbott are considered in their entirety, it is clear that FDA and Andrx have acted in an appropriate manner consistent with current law and an overwhelming wealth of scientific data. In addition, to deny or delay approval of Andrx's NDA would be contrary to the clear purpose of the 1984 Hatch-Waxman amendments which is to make less expensive drug products available to the public more quickly.

Factual Background

Abbott is correct in its Citizen Petition that Andrx's NDA is significantly supported by data submitted in its previously-rejected ANDA for divalproex sodium. However, it is not true that the NDA is "simply a carbon copy" of the rejected ANDA as the petition repeatedly asserts. Andrx originally submitted the ANDA based upon a now rejected interpretation of the regulations. At the time that Andrx originally prepared and submitted its ANDA, Andrx believed that based upon a reasonable interpretation of the applicable regulations, it could file an ANDA for Depakote® because the first step in the manufacturing process for the Andrx product involved dissolving divalproex sodium in water and subsequently processing the dissolved divalproex sodium into an enteric coated tablet. After initial acceptance of the ANDA, the FDA conducted a more detailed review of Andrx's manufacturing process and determined that the original starting material in Zalkote® (divalproex sodium) was changed during manufacturing to sodium valproate. This was Andrx's intention in order to avoid extant patents on divalproex sodium currently owned by Abbott. Because FDA concluded that Andrx's active ingredient was different than that of the reference listed drug Depakote®, the ANDA was denied. At the time however, FDA suggested that the proposed product might be suitable for filing as a § 505(b)(2) NDA.

Andrx accordingly prepared an NDA for its product and submitted its application to FDA under § 505(b)(2). Included in Andrx's 505(b)(2) application was the bioequivalence study originally conducted by Andrx to support its ANDA, which compared the Andrx product to Depakote® and showed that both products produced an equivalent rate and extent of absorption of the pharmacologically active substance, *i.e.*, valproic ion. However, this was not the only

information submitted to support the 505(b)(2) application. In addition to other data and information required to be contained in an application, Andrx's 505(b)(2) NDA also contained the results and a detailed analysis of a literature search that provided many literature references that related to *in vivo* studies conducted using sodium valproate and other valproate products such as valproic acid and divalproex sodium.¹ Andrx's NDA also references the marketing of other "valproate" products such as Depekene®, Depakote® and Depacon®² in the United States and to the marketing of various valproate products outside the United States. Although specific products outside the United States are not mentioned, a reference to Martindale, The Extra Pharmacopeia, 31st ed., is provided as supplying information on the various non U.S. valproate products.³ Our research has indicated some of these non U.S. products are sodium valproate products.⁴

The literature reference to the various "valproate" products in the NDA are important because, the "pharmacologically active substance" in all the valproate products is identical. More specifically, as explained in the introduction to the NDA and in § 8.1 and 8.3 of the NDA, valproic acid, sodium valproate and divalproex sodium all convert to the valproate ion in the body. It is this ion that is measured in *in vivo* bioequivalence studies and used to determine and provide the pharmacological activity.

The relationship between the known valproate products is as follows:

- Valproic acid, such as the Depakene® product which has been sold in the United States since 1978, comprises a valproate ion and a hydrogen ion. When the valproic acid product is administered to a patient the valproic acid molecule dissociates into the valproate ion and the hydrogen ion.
- Sodium valproate such as the Depacon® product and the Ergenyl® and Orfiril® products (both non U.S. sodium valproate products) that have been sold since the mid 1970's comprise a valproate ion and a sodium ion. When the sodium

¹ This information is contained in Vols. 29-33 of Andrx's NDA. The literature search and analysis (or at least portions thereof) contain confidential commercial and trade secret information which only disclosable portions are releasable under FOIA. While Andrx is referring to its NDA for FDA's reference, it is not waiving any rights with respect to disclosure of such information under FOIA.

² See Vol. 29, Table 8.1.

³ See Sec. 8.4.3 of Vol. 29.

⁴ See Rote Liste from 1974, entry No. 15 003B for Ergenyl® tablets and an IV solution containing sodium valproate sold by Labaz; and Rote Liste from 1976, entry No. 14004B for Ergenyl® coated tablet, tablets and an IV solution containing sodium valproate sold by Labaz and entry No. 14 011B for Orfiril® for coated tablets containing sodium valproate sold by Desitin Pharmaceuticals, GmbH.

valproate product is administered to a patient, the sodium valproate disassociates into the valproic ion and the sodium ion.

- Divalproex sodium such as the Depakote® product comprises an oligimer (small polymer) that consists of four to six repeating units. Each repeating unit is a combination of a molecule of valproic acid and a molecule of sodium valproate. When a divalproex sodium product is administered to a patient, the divalproex sodium molecule disassociates into two valproic ions, a sodium ion and a hydrogen ion, for each repeating unit present.

Support for this mechanism is provided in the label for Depakene®, Depakote® and Depacon® as well as other numerous literature references provided in Andrx's NDA. Thus, the only difference between the Andrx product and Depakote® is some additional sodium ions (actually 0.5 moles more sodium). However, this difference is irrelevant from a pharmacological perspective since the additional sodium ions have no pharmacological activity.

Finally, Abbott fails to note that Depakote® was originally approved in 1983 and has enjoyed over 20 years without competition. Abbott's attempts to delay generic competition for Depakote® have a long history. As early as 1986, Abbott petitioned the Agency for a stay of approval of any ANDA's referencing Depakote. *See Abbott Laboratories v. Young*, 691 F. Supp. 462, 465 fn.2 (D.D.C. 1988).⁵ In *Abbott Laboratories*, Abbott sued the Agency for denying its request for ten year New Chemical Exclusivity, even though Abbott had already gained approval for Depakene (valproic acid). *Id.* Ultimately, Abbott lost the case and the Court granted only two years of market exclusivity for the product, until September 24, 1986. *Id.* at 473. Although Abbott's marketing exclusivity expired nearly eighteen years ago, Abbott still enjoys a monopoly on this product. Abbott should not be permitted to delay competition any longer.

I. Abbott's Interpretation of the Data Required by Section 505(b)(2) Has No Basis In Law, and Even If Correct, Would be Satisfied by Andrx's NDA.

A. Under Section 505(b)(2) of The FDCA Andrx is Not Required, as Abbott Alleges, To Submit "Additional Data" For Approval

Abbott's Citizen Petition insists that the Agency must "refrain from approving the Andrx 505(b)(2) application" and states that "[t]he application fails to meet the requirements of § 505(b)(2), as interpreted by the agency." Citizen Petition at 4. Specifically, Abbott presumes as a factual matter, that Andrx's NDA, "is simply a carbon copy of its NDA – no more and no less."

⁵ Abbott also fails to inform the Agency that it obtained approval for the Depakote® product in essentially the same manner that it is seeking to prevent Andrx from using. Specifically, Abbott obtained approval for the Depakote® product without conducting any safety and efficacy studies for divalproex sodium but rather by referring the Agency to the safety and efficacy studies for valproic acid that were filed with the Depakene® product. *Abbott Labs.*, 693 F. Supp. at 464.

Petition at 5. Abbott goes on to argue that, approval of the NDA must be unlawful because § 505(b)(2) “must be supported by data different from *and in addition to* any data that FDA is permitted to review under § 505(j),” and that “at minimum, Andrx must support its change to the reference drug with data beyond that required for an ANDA.” That position is flatly incorrect on both legal and factual grounds.

Puzzlingly, Abbott’s discussion of the “requirements” of § 505(b)(2) does not begin by citing the language of the statute itself, which instead is described by selective quotations of the FDCA from the Consolidated Petition Response. In fact, nothing in the language of § 505(b)(2), the FDA regulations, or the Consolidated Petition Response either constrain FDA’s judgment that the data submitted with an NDA are adequate for approval under that section, or otherwise support Abbott’s legal argument. Section 505(b)(2) itself simply provides that FDA may approve an NDA “for which the [safety and efficacy] investigations described in [section 505(b)(1)] . . . and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted[.]” *See* 21 U.S.C. § 355(b)(2); FDCA 505(b)(2). Whether or not the particular data at issue adequately demonstrate that the product is safe and effective is a matter for FDA to determine using the same standards that apply to all NDAs under § 505(b) of the Act.

Abbott also cites no support for its position in FDA’s regulations. This is not surprising given that the regulations do not support Abbott’s view. Regarding the necessary information to be provided in a 505(b)(2) application, § 314.54 merely states that:

[t]his [505(b)(2)] application need contain only that information needed to support the modification(s) of the listed drug. 21 C.F.R. § 314.54.

Nevertheless, Abbott argues that “Andrx must – as a matter of science and law – submit additional data to support its change to the reference listed drug” and that “at a minimum . . . Andrx must support its change to the reference listed drug with data beyond that required for an ANDA.” Citizen Petition at 6. Yet as noted above, there is no basis whatsoever for this assertion in either the statutes or regulations applicable to 505(b)(2) NDAs.

Even Abbott’s selective quotations from the Consolidated Petition Response undercut its argument. Contrary to Abbott’s argument, that document plainly states, “[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* (citations omitted)” Citizen Petition at 5, citing the Consolidated Petition Response at 14. This statement, like the statute and regulations, make it clear that there is no quantitative hurdle that must be surpassed to meet the 505(b)(2) requirements, but rather the application must be supported by additional data, *as appropriate* and necessary.

B. *Even If Abbott's Legal Interpretation Were Correct, Abbott's Citizen Petition Is Factually Incorrect, In That Andrx Did Submit "Additional Data" To Support Its 505(b)(2) NDA, As Appropriate and Reasonable As Determined By FDA*

Abbott states in its Citizen Petition that, "Andrx does not appear to have submitted any additional data to support a fundamental change to the active ingredient in the reference drug, Depakote®." Citizen Petition at 5. As noted above, this statement is simply factually incorrect since Andrx's 505(b)(2) NDA also contained the results of a literature search and significant analyses that provided many literature references that identified *in vivo* studies conducted using sodium valproate and other valproate products such as valproic acid and divalproex sodium. This public literature is one of the types of data that is contemplated as being part of a 505(b)(2) submission, since these studies were not conducted by Andrx, but nevertheless provide additional support for its application. Taken together with the data from Andrx's bioequivalence study demonstrating that the Andrx product and Depakote produce an equivalent rate and extent of absorption of the valproic ion, those data amply support FDA's conclusion that the statutory standards for approval were satisfied by Andrx's NDA. Abbott's total misperception of Andrx's application alone, should be the basis on which Abbott's Citizen Petition should be denied.

C. *FDA's Consolidated Petition Response Is Entirely Consistent With Andrx's 505(b)(2) Application*

FDA's Consolidated Petition Response makes it clear, after reviewing the history of paper NDA's and the legislative history of 505(b)(2), that applications filed under 505(b)(2) should be reviewed on a case by case basis so FDA can determine to what extent additional studies, if any, are necessary to support the changes referenced in the application. It also makes clear that § 505(b)(2) did not eliminate the old paper NDA's which were NDA's filed based solely upon literature references that establish the safety and efficacy of a drug product. FDA's Consolidated Petition Response was clear in its refusal to limit the scope of the 505(b)(2) application process. Language cited by the petitioner is akin to dicta without any particular regulatory authority. While FDA may raise issues it may consider or discuss in the future, these are not current policy or regulations. Therefore, it is respectfully submitted that FDA determined the Andrx NDA was properly filed, reviewed, and met all necessary and appropriate standards for approval. Andrx's NDA contained more than sufficient literature references and significant analyses of such data to support the safety and efficacy of sodium valproate and Andrx's own *in vivo* bioequivalence study comparing the Andrx sodium valproate product to Depakote®, (which in fact met statistical criteria for bioequivalence).

D. *Abbott's Argument That Andrx Must Resubmit Its Proposed Product Under The ANDA Suitability Petition Process Is Without Merit*

Abbott argues that Andrx must resubmit its application as an ANDA under the suitability petition process, citing the approved valproate sodium product Depakon® Injection as the reference listed drug. This position is without merit. Aside from the wasted resources, both from the perspective of the Agency and Andrx, and even assuming this was a viable mechanism

through which Andrx could have submitted its proposed product, there is nothing in the FDCA or FDA's regulations that would have compelled Andrx to submit its application through this route. Andrx has properly submitted its application through the 505(b)(2) process, FDA has already determined that its application met all necessary and appropriate standards for approval, and in fact, has granted tentative approval.

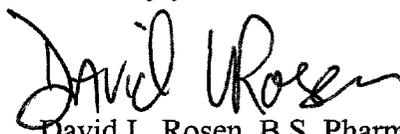
II. Abbott's Policy Concerns Are Not Legally Relevant and Policy Arguments Support The Approval of Andrx's Application

Given that Abbott's legal concerns are without merit, it is not surprising that Abbott attempts to bolster its argument by raising policy concerns. However, Abbott's policy concerns are not legally relevant and in any event are incorrect. Since Andrx's NDA meets the applicable statutory and regulatory requirements, policy arguments are not relevant. Nevertheless, contrary to Abbott's concerns, public policy supports the approval of Andrx's 505(b)(2) application, foremost the significant public need to get lower priced drug products into the hands of American consumers. *See e.g., Mead Johnson Pharmaceutical Group v. Bowen*, 838 F.2d. 1332 (D.C. Cir. 1988). Andrx has shown that its Zalkote product delivers the same quantities of valproate ion as the same strength divalproex sodium tablets (Depakote) and studies demonstrate that the two products are bioequivalent in terms of valproate. Andrx thus intends to offer Zalkote as a lower priced bioequivalent, alternative in the valproate marketplace.

Furthermore, Abbott's concerns of confusion in the marketplace are overstated and based on pure speculation. Andrx's labeling is clear and will not lead to confusion in the marketplace. As noted above, although Zalkote will not be AB rated to Depakote, Zalkote delivers the same quantities of valproate ion as Depakote and will offer a lower priced alternative to physicians to offer to their patients.

Given these facts, both law and public policy support the approval of Andrx's NDA for Zalkote. Abbott's unmerited attempt is merely one of a host of brand companies efforts to thwart generic competition and should therefore be denied.

Sincerely yours,



David L. Rosen, B.S. Pharm., J.D.

cc: Hershel Sparks, Esq.
Andrx Corporation