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BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
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CITIZEN PETITION

On behalf of Abbott Laboratories ("Abbott"), this citizen petition is submitted under section 505 of the Food, Drug, and Cosmetic Act ("FDCA"), 21 CFR 10.30, and other provisions of law.

This petition requests that the Commissioner of Food and Drugs (the "Commissioner") refrain from approving certain applications submitted under section 505(b)(2) of the FDCA that reference Depakote® (divalproex sodium delayed-release tablets), but which contain a different active ingredient than that contained in Depakote®. The approval of any such application, where the sponsor relies on the prior approval of Depakote® to establish the safety and effectiveness of the proposed product, would be arbitrary, capricious, and contrary to law. The Food and Drug Administration ("FDA") recently granted tentative approval to one such application, submitted by Andrx Laboratories ("Andrx"), which appears to lack the data necessary to support approval under section 505(c) of the FDCA.

The Andrx 505(b)(2) application also raises unresolved procedural and policy issues regarding the appropriate scope of section 505(b)(2). In its landmark citizen petition response regarding the scope of section 505(b)(2), FDA called into question the appropriateness of using section 505(b)(2) "to obtain approval of drug products for which the *only* difference from the listed drug is in the form of the active ingredient, such as a change in salt." FDA Consolidated Petition Response, Docket Nos. 2001P-0323, 2002P-0447, and 2003P-0408 (Oct. 14, 2003) at 34 (emphasis in original) ("Consolidated Petition Response"). The agency concluded that such applications "may have undesirable policy and public health consequences." *Id.* Accordingly, FDA stated that it "is considering whether to begin

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a public process” and would reserve the issue “for further review” to determine whether “there is some narrow subset of applications that should be exempted from the scope of section 505(b)(2) in the future.” *Id.*

The Andrx 505(b)(2) application falls squarely within FDA’s stated concerns; the only proposed difference from the reference drug is in the active ingredient. *See id.* The agency, however, has yet to initiate the public process outlined in its Consolidated Petition Response. FDA has not indicated how it intends to resolve the public policy and public health issues presented by the Andrx 505(b)(2) application. Therefore, Abbott respectfully requests that the Commissioner withhold final action on the Andrx application, and any similarly situated applications, pending resolution of the scientific, legal, and policy issues associated with such applications.

ACTIONS REQUESTED

Abbott respectfully requests that the Commissioner: (1) Refrain from granting final approval to the Andrx 505(b)(2) application and any similarly situated applications; and (2) initiate the public process previously announced by FDA, to seek input from interested persons, including industry and consumer groups, on the use of section 505(b)(2) to obtain approval of drug products for which the *only* proposed difference from the reference drug is the active ingredient.

STATEMENT OF GROUNDS

I. BACKGROUND

Depakote® Delayed-Release Tablets (“Depakote®”) contain the active ingredient divalproex sodium. FDA first approved Depakote® in 1983 for the treatment of absence epilepsy. In the mid-1990s, after review of extensive clinical data, FDA approved Depakote® for use in the treatment of complex partial seizures and the manic phases of bipolar disorder, and in the prophylaxis of migraine headaches. Depakote® is marketed in 125, 250, and 500 mg strengths.

In December 1999, Andrx submitted to FDA an abbreviated new drug application (“ANDA”) that referenced Depakote®.^{1/} Andrx’s ANDA, however,

^{1/} An ANDA is approved by FDA under section 505(j) of the FDCA, which permits applicants to rely exclusively on the clinical investigations conducted on a previously approved “listed” drug. *See* 21 USC 355(j). Among other things, an ANDA applicant must demonstrate that the active ingredient in its proposed product is “the same as that of the listed drug.” *Id.* at 355(j)(2)(A)(ii).

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described a product that, according to the company, did not contain divalproex sodium. *See* Tab 1, Notice of Certification of Invalidity or Noninfringement of a Patent (received Mar. 6, 2000) at 2.^{2/} Rather, Andrx stated that its product contained “sodium valproate” in a delayed-release tablet dosage form. Valproate sodium is a salt form of valproic acid; it is distinct from divalproex sodium, the active ingredient in Depakote®.^{3/}

On January 24, 2001, FDA notified Andrx that the agency was suspending further review of Andrx’s application because the proposed product did not meet the statutory requirements for an ANDA. *See* Tab 2 at 2. After further argument by Andrx, the agency rejected the ANDA on the ground that Andrx’s product contains a different active ingredient than that in the reference drug, Depakote®. Specifically, the agency stated:

[T]he ANDA cannot be approved under Section 505(j) of the Act because the active ingredient in the proposed product, i.e., valproate sodium, as determined by [the Office of Generic Drugs (“OGD”)] during the ANDA review is not the same as the active ingredient in the RLD, i.e., divalproex sodium.

Tab 2, Exhibit B, Letter from Gary J. Buehler to Andrx (July 18, 2002).^{4/}

Shortly thereafter, Andrx contacted FDA to inquire about submitting another application for the same product rejected under section 505(j). *See* Tab 2, Exhibit C, Letter from Andrx to Russell G. Katz, M.D. (Aug. 29, 2002). Importantly,

^{2/} Much of the information concerning Andrx’s applications and communications with FDA is based on documents released in patent infringement litigation brought by Abbott against Andrx. *See* Tab 2, Joint Status Report and Motion to Extend Stay, *Abbott Labs. v. Andrx Corp.*, Case No. 00-7823-CIV-HIGHSMITH/GARBER (S.D. Fla. Oct. 8, 2002) (unsealed Dec. 4, 2003). The Joint Status Report and each of the exhibits, including those marked “CONFIDENTIAL,” were unsealed by the court and are now available as public documents.

^{3/} Andrx states that its product contains a different active ingredient than divalproex sodium. The basis for Abbott’s patent litigation is that the Andrx product contains some divalproex sodium.

^{4/} Valproate sodium, which Andrx claims is the active ingredient in its product, is the active ingredient in Abbott’s product, Depacon® (valproate sodium) Injection. Depacon® is not available in a tablet dosage form. Also, Depacon® is approved for use only in treating absence epilepsy and complex partial seizures; Depakote®, by contrast, also is approved for use in treating bipolar disorder and in preventing migraine headaches.

Andrx suggested that it would seek to submit an application under section 505(b)(2) with the same substantive data as that submitted in its erstwhile ANDA. *See id.* When Andrx provided Abbott with written notification of the filing of its 505(b)(2) application, the company used the same patent notification form that it used in support of its ANDA. *Compare* Tab 3, Notice of Certification of Invalidity or Noninfringement of a Patent (received Mar. 27, 2003) *with* Tab 1. Andrx even neglected to revise the title of its second patent notification. The second notification cites 21 CFR 314.94 and 314.95, which apply to ANDAs; it should have cited 21 CFR 314.50 and 314.52, which apply to 505(b)(2) applications.^{5/} Andrx essentially repackaged its rejected ANDA into a substantively identical 505(b)(2) submission.

On January 14, 2004, Andrx announced that FDA had issued an “approvable letter” for Andrx’s 505(b)(2) application. Tab 4, Andrx Press Release. Andrx further stated that the company intends to “compete in the same market as the Depakote® family of brand products” and will market its product for the same approved uses as Depakote®, *i.e.*, “for the treatment of manic episodes associated with bipolar disorder, various seizure disorders and prophylaxis of migraine headaches.” *Id.*

Finally, on May 10, 2004, Andrx announced that FDA had issued a tentative approval of its 505(b)(2) application. *See* Tab 5, Andrx Press Release. The press release confirms that the Andrx product will have the same dosage form (delayed-release tablets) and same strengths as Depakote®, and will be used for the same indications (mania, epilepsy, and migraine headaches). *See id.*

II. ARGUMENT

As explained below, the agency must refrain from approving the Andrx 505(b)(2) application. The application fails to meet the requirements of section 505(b)(2), as interpreted by the agency. It also raises the precise public policy and public health considerations identified by FDA in its Consolidated Petition Response. In all, the Andrx 505(b)(2) application is contrary to the agency’s carefully structured legal and policy framework.

^{5/} Abbott filed a second patent infringement suit in the Southern District of Florida based on the Andrx 505(b)(2) application. The previous lawsuit involving the ANDA was dismissed. *See Abbott Labs. v. Andrx Corp.*, Case No. 03-60867 (S.D. Fla. filed May 2003). The filing of this second lawsuit triggered a stay on FDA’s authority to grant final approval to Andrx’s 505(b)(2) application. *See* 21 USC 355(c)(3)(C).

A. The Andrx 505(b)(2) Application Cannot be Approved on the Basis of a Prior Finding of Safety and Effectiveness for Depakote®

Section 505(b)(2) of the FDCA permits the filing of a new drug application (“NDA”) where the sponsor does not have a right of reference to all of the studies needed to support approval. *See* 21 USC 355(b)(2). As interpreted by FDA, section 505(b)(2) provides an alternative to section 505(j), where new studies are needed to support a proposed change to a listed drug product. *See* Consolidated Petition Response at 9. In FDA’s words:

(1) if a proposed modification may be approved without additional studies, the drug may be reviewed in a 505(j) application that relies *entirely* on the Agency’s finding of safety and effectiveness for the listed drug; and (2) if the proposed modification will require additional data for approval, the drug may be reviewed in a 505(b)(2) application that relies *in part* on the Agency’s finding of safety and effectiveness for the listed drug.

Id. (emphasis in original). In the latter case, under section 505(b)(2), “[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* (citation omitted).” *Id.* at 14 (emphasis added). Were no additional data necessary, the product could be reviewed and approved under section 505(j).

This distinction between section 505(b)(2) and 505(j) – as drawn by the agency – points out a fundamental flaw in the Andrx 505(b)(2) application. By all appearances, Andrx’s 505(b)(2) application is simply a carbon copy of its ANDA – no more and no less. Andrx does not appear to have submitted any additional data to support a fundamental change to the active ingredient in the reference drug, Depakote®. That is, the Andrx product purports to use the valproate sodium salt of valproic acid, which is distinct from the form of the active ingredient (divalproex sodium) contained in Depakote®. The agency determined that this departure from the reference drug rendered the Andrx application unreviewable under section 505(j). Yet, by all appearances, Andrx simply resubmitted its ANDA as a 505(b)(2) application. Such an approach is fundamentally at odds with the statutory framework presented in the Consolidated Petition Response.

Andrx must – as a matter of science and law – submit additional data to support its change to the reference drug. As FDA stated in its Consolidated Petition Response, the precise quantity and quality of data needed to support the change “will vary from case to case.” *Id.* at 14. What is clear, however, is that a 505(b)(2) application must be supported by data different from and *in addition to* any data that FDA is permitted to review under section 505(j).^{6/} At a minimum, and to remain consistent with FDA’s interpretation of the law, Andrx must support its change to the reference drug with data beyond that required for an ANDA.

This conclusion is confirmed by the express provisions in section 505(j) regarding authorized changes to listed drug products. Under section 505(j)(2)(C), a sponsor may seek to submit an ANDA for a pharmaceutical alternative product, including a product with a different strength or dosage form from that of the reference drug. *See* 21 USC 355(j)(2)(C). Permission may be granted if FDA determines that no clinical investigations would be needed to demonstrate the safety and effectiveness of the product. *See* 21 CFR 314.93(e). The one change that is not permitted, however, is a change to the active ingredient in a single ingredient drug product. *See* 21 USC 355(j)(2)(A)(ii). This statutory prohibition reflects a fundamental determination: A change to the active ingredient will always require reference to additional clinical data that cannot be reviewed under section 505(j), but which are essential to the safety and effectiveness of the product.

In sum, Andrx cannot ignore those requirements of section 505(j) that it cannot meet, yet gain approval of the same product, with the same application and data, under section 505(b)(2). To find otherwise would be to elevate form over substance and negate the important statutory and scientific distinctions drawn by the agency between sections 505(b)(2) and 505(j).

B. Andrx Must Resubmit its Proposed Product under the ANDA Suitability Petition Process

As explained above, the Andrx 505(b)(2) application plainly conflicts with the regulatory framework outlined by the agency in its Consolidated Petition Response. There is, however, a regulatory pathway readily available to Andrx that is consistent with FDA’s regulatory construction of section 505(b)(2).

^{6/} In addition to *in vivo* bioequivalence studies, FDA has long held that it may also review the results of “limited confirmatory testing” under section 505(j). *See* 57 FR 17950, 17958 (Apr. 28, 1992); 54 FR 28872, 28880 (July 10, 1989).

The agency has determined that the active ingredient in Andrx's proposed product is valproate sodium. *See* Tab 2, Exhibit B. Valproate sodium is the active ingredient in the approved drug product known as Depacon® Injection. Andrx could avoid the conflict identified above by referencing Depacon® and submitting data sufficient to support a change from an injectable dosage form to a delayed-release tablet dosage form. That is, Andrx could apply under the "suitability petition" process for a change from an injectable to a tablet dosage form. *See* 21 USC 355(j)(2)(C); 21 CFR 314.93. The "suitability petition" process allows an applicant to pursue an ANDA, despite a difference in dosage form, if it can demonstrate that no additional investigations are needed to demonstrate the safety and effectiveness of the proposed product. *See id.* If the petition were granted, Andrx could proceed under section 505(j) to gain approval of a pharmaceutical alternative to Depacon®. *See* 21 CFR 314.93(c). If the petition were denied, Andrx could proceed under section 505(b)(2), and would use the 505(b)(2) process to submit whatever additional clinical and other data FDA determined is needed to assure the safety and effectiveness of the tablet dosage form.

This approach not only resolves the conflict, it is consistent with FDA's interpretation of the regulatory role of section 505(b)(2). As the agency explained in the Consolidated Petition Response:

Thus, Congress created a new type of application, a 505(b)(2) application to fill specific gaps left by the other approval pathways: a 505(b)(2) application can be used for approval of those changes that are not so significant that they require a stand alone NDA, but that are significant enough that they may require additional safety or effectiveness data (and, therefore, are not eligible for approval under section 505(j)).

Consolidated Petition Response at 16. Moreover, the suitability petition process would provide the opportunity for the agency and all interested persons to consider whether the change proposed by Andrx, from an injectable to a tablet dosage form, requires the submission of data under section 505(b)(2).

Andrx circumvented this process by referencing Depakote® rather than Depacon® and styling its application as an ANDA with a different form of the active ingredient. When FDA determined that this was improper, Andrx sought to remedy the problem by simply resubmitting its application under section 505(b)(2). Andrx, however, never addressed the fundamental issue, namely, that a change in the active ingredient from that of the listed drug requires an additional showing of

safety and effectiveness. Very clearly, Andrx must reference Depacon® and proceed under the suitability petition process, or Andrx must invest in its own clinical development program.

As FDA made clear in the Consolidated Petition Response, “[t]he linchpin of FDA’s interpretation of 505(b)(2) is that a 505(b)(2) applicant may rely on the FDA’s findings of safety and effectiveness for a listed drug *only to the same extent an ANDA applicant may rely on such findings under section 505(j).*” Consolidated Petition Response at 14 (emphasis added). Having presented a product with a different active ingredient, Andrx failed to meet the threshold for review under section 505(j). That is, Andrx was told it could not rely on FDA’s prior findings of safety and effectiveness for Depakote®. In short, and to the extent Andrx continues to reference Depakote®, the “linchpin” has been pulled from Andrx’s 505(b)(2) application.

C. The Andrx 505(b)(2) Application Raises the Precise Policy Concerns Outlined by FDA in its Consolidated Petition Response

In its Consolidated Petition Response, FDA made clear that it has rarely applied section 505(b)(2) to products that differ from reference drugs only in the form of the active ingredient. *See* Consolidated Petition Response at 33. The agency then recited several policy reasons why approval of such products was not in the public interest. Consequently, the agency said that it “may wish to consider further whether there is some narrow subset of applications that should be exempted from the scope of section 505(b)(2) in the future.” *Id.* at 34. The agency then “reserv[ed] for further review” through a “public process” resolution of the public health and policy reasons it had identified. *Id.*

Andrx’s application raises the precise concerns identified by FDA in its Consolidated Petition Response. First, approval of Andrx’s product would not result in an innovative drug product with any new therapeutic benefits. Second, approval of the product would undermine incentives for the development of new active moieties. And third, approval of the product would contribute to the proliferation of pharmaceutical alternative products, with resulting confusion in the marketplace. The Andrx 505(b)(2) application was reviewed and tentatively approved without any resolution of the issues memorialized in the Consolidated Petition Response. The public process suggested by the agency likewise has not been initiated. *See* Consolidated Petition Response at 34.

1. *The Andrx product offers no new or different therapeutic effect and no improvement in safety or effectiveness*

Andrx's 505(b)(2) application will not result in bringing an improved product to market. The value of section 505(b)(2) is as a pathway for bringing to market innovative changes to already approved drug products. *See, e.g.*, Consolidated Petition Response at 15, 18-21. Indeed, the 505(b)(2) successes cited by FDA in the Consolidated Petition Response include novel treatments for exposure to radiological and chemical agents; products with specific labeling for pediatric patients; and novel combination products that bring real benefits to the public. *See id.* at 18-21. Andrx's proposed product does not provide any innovation in terms of safety or effectiveness.

2. *Approval of the Andrx product will undermine incentives for the development of new moieties*

Andrx cannot market a divalproex sodium product without infringing Abbott's patents.^{7/} Andrx therefore is attempting to use 505(b)(2) to gain approval of a valproate sodium product, albeit with indications that are identical to those approved for Depakote®. This strategy is designed solely to undermine Abbott's intellectual property rights and its investment in extensive clinical testing in support of new uses for Depakote®.

Andrx's strategy is clear. In its most recent notification to Abbott, Andrx described the manufacturing process for its proposed product:

The initial manufacturing step for Andrx' Proposed Product, utilizing divalproex sodium, is performed *outside the United States* and outside any United States territories subject to United States patent laws. This initial formulation step involves adding excess sodium hydroxide solution to divalproex sodium, thereby resulting in a high pH solution . . . which contains non-oligomeric, non-complexed sodium valproate. . . . The sodium valproate in pH-adjusted solution is then shipped into the United States where the sodium valproate pH-

^{7/} *See Abbott Labs. v. Torpharm, Inc.*, 300 F.3d 1367 (Fed. Cir. 2002) (upholding the validity of Abbott's patents). On March 15, 2004, the District Court for the Northern District of Illinois determined, after a trial on the merits, that TorPharm's proposed generic version of Depakote® infringed Abbott's patents. *See Abbott Labs. v. TorPharm, Inc.*, 309 F. Supp. 2d 1043 (N.D. Ill. Mar. 15, 2004).

adjusted solution is diluted with alcohol and sprayed onto anhydrous lactose to form a granulation.

Tab 3 at 3 (emphasis in original). Thus, Andrx's proposed product begins with divalproex sodium, Abbott's patented active ingredient. The divalproex sodium is intentionally altered overseas, outside the reach of United States patent laws, and then brought into the country to be granulated. Clearly, Andrx is trying to evade the scope of Abbott's intellectual property, rather than to bring an innovative product to market.

The agency already has determined that Andrx's proposed product does not meet the statutory requirements for approval of a generic divalproex sodium product.^{8/} Approval of this same product (*i.e.*, valproate sodium delayed-release tablets) under 505(b)(2), based on a reference to Depakote® and based on the same substantive information that was rejected under 505(j), would disrupt the careful balance between innovator and generic rights under the Hatch-Waxman Act. See Consolidated Petition Response at 2. The agency's determination under section 505(j) should protect Abbott's investment in Depakote® until the expiration of its valid patents, when Andrx may then seek approval of a therapeutically equivalent divalproex sodium product.

3. *The Andrx product will lead to confusion in the marketplace*

The agency acknowledged when it rejected Andrx's ANDA that "a drug product containing valproate sodium will not be rated therapeutically equivalent to a drug product containing divalproex sodium, since they will not contain the same active ingredient." Tab 2, Exhibit B. In its Consolidated Petition Response, the agency recognized that the approval of such products under section 505(b)(2) may lead to inappropriate marketplace substitution and confusion, and adverse impacts on patient care. See Consolidated Petition Response at 33-34.

The Andrx product cannot be represented as "therapeutically equivalent" to Depakote® because Andrx states it does not contain the same active ingredient; at the same time, it cannot readily be distinguished. Andrx seeks to exacerbate this confusion by introducing its product in the same market as Depakote®. See Tab 4 (stating that the company intends to "compete in the same

^{8/} As explained above, Andrx's product purports to contain valproate sodium and should be submitted for approval based on a direct reference to Depacon®.

market as the Depakote® family of brand products” and will market the product “for the treatment of manic episodes associated with bipolar disorder, various seizure disorders and prophylaxis of migraine headaches.”).

The company’s intent is further clarified in its correspondence with FDA. In one letter to the agency, Andrx asked whether the labeling of its proposed product would “contain the statement that the product is bioequivalent to Depakote?” Tab 2, Exhibit C. Including such a statement in the Andrx labeling would encourage inappropriate substitution and confusion. Andrx would be able, through advertising and promotion, to market its product as one that may be used in place of Depakote®, despite the fact that the product was denied approval under the agency’s generic drug program and will not receive an “AB” therapeutic equivalence rating.

III. CONCLUSION

Final approval of the Andrx 505(b)(2) application, based on FDA’s prior finding of safety and effectiveness for Depakote®, would stand in direct conflict with the agency’s interpretation of section 505(b)(2) in the Consolidated Petition Response. Andrx must either re-cast its product as a pharmaceutical alternative to Depacon®, or invest in a clinical development program to support the approval of valproate sodium for each of the uses it seeks under its 505(b)(2) application.

Moreover, by Andrx’s own admission, the alleged differences between the active ingredient in its product and that in Depakote® offer no therapeutic benefit to the patient, but are merely an attempt to evade the scope of Abbott’s intellectual property. It therefore raises precisely the policy concerns outlined by FDA in its Consolidated Petition Response. Final approval of Andrx’s application will not bring to market any product with a new therapeutic benefit, will undermine incentives for the development of new active moieties, and will lead to confusion in the marketplace, all to the detriment of the public health.

Abbott therefore requests that FDA refrain from approving the Andrx 505(b)(2) application, and instead promptly initiate the public process described in the Consolidated Petition Response.

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ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusions under 21 CFR 25.30 and 25.31.

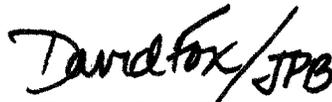
ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner of Food and Drugs.

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully submitted,

Handwritten signature of David M. Fox in black ink, with the initials 'JPB' written below the name.

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cc: Neal B. Parker
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