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May 3, 2012

Docket No. FDA-2011-P-0869

VIA FACSIMILE & FEDERAL EXPRESS

Division of Dockets Management
Food and Drug Administration, HFA-305
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Comments Regarding the Citizen Petition on SUBOXONE® Sublingual Film Docket No. FDA-2011-P-0869

The Citizen Petition is Without Merit With Respect to the Request to Refuse to File 505(b)(2) NDAs and Should be Denied

Dear Sir/Madam:

On behalf of our client, BioDelivery Sciences International, Inc., ("BDSI"), I am hereby transmitting comments regarding the above referenced Citizen Petition.

The Citizen Petition requests that FDA refuse to:

(1) file any 505(b)(2) NDA for a buprenorphine/naloxone oral mucosal film drug product unless the 505(b)(2) references NDA # 22-410, the NDA for SUBOXONE® Sublingual Film, and certifies to patents listed in FDA's Approved Drug Products List with Therapeutic Equivalence Evaluations (the FDA's Orange Book) with respect to NDA # 22-410, the NDA for SUBOXONE® Sublingual Film; and

(2) approve any application for a buprenorphine/naloxone drug product unless the applicant can demonstrate that any genotoxic or potentially genotoxic impurities associated with naloxone are limited appropriately.

As demonstrated below, the Petitioner's request that the Commissioner refuse to file a 505(b)(2) NDA for buprenorphine/naloxone oral mucosal film drug product unless the 505(b)(2)

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references NDA # 22-410, the NDA for SUBOXONE® Sublingual Film, is not supported by the law, regulations, science or logic and should be denied.

The basis for our position is set forth below.

I. FDA Regulations Are Explicit with Respect to Reasons for Refusing to File an Application

The FDA regulations at 21 CFR § 314.101 provide 9 reasons that FDA may refuse to file an Application and 2 reasons the FDA will refuse to file an Application. These reasons are set forth below.

> (d) FDA **may** refuse to file an application or may not consider an abbreviated new drug application to be received if any of the following applies:
>
> > (1) The application does not contain a completed application form.
> >
> > (2) The application is not submitted in the form required under 314.50 or 314.94.
> >
> > (3) The application or abbreviated application is incomplete because it does not on its face contain information required under section 505(b), section 505(j), or section 507 of the act and 314.50 or 314.94.
> >
> > (4) The applicant fails to submit a complete environmental assessment, which addresses each of the items specified in the applicable format under 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under 25.30 or 25.31 of this chapter.
> >
> > (5) The application or abbreviated application does not contain an accurate and complete English translation of each part of the application that is not in English.
> >
> > (6) The application does not contain a statement for each nonclinical laboratory study that it was conducted in compliance with the requirements set forth in part 58 of this chapter, or, for each study not conducted in compliance with part 58 of this chapter, a brief statement of the reason for the noncompliance.
> >
> > (7) The application does not contain a statement for each clinical study that it was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter, or, if the study was subject to but was not conducted in compliance with those regulations, the application does not contain a brief statement of the reason for the noncompliance.

(8) The drug product that is the subject of the submission is already covered by an approved application or abbreviated application and the applicant of the submission:

(i) Has an approved application or abbreviated application for the same drug product; or

(ii) Is merely a distributor and/or repackager of the already approved drug product

(9) The application is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act.

In addition, FDA regulations stipulate that FDA will refuse to file an application or will consider an abbreviated new drug application not to have been received if:

(e)(1) The drug product is subject to licensing by FDA under the Public Health Service Act (42 U.S.C. 201 *et seq.*) and subchapter F of this chapter.

(e)(2) In the case of a 505(b)(2) application or an abbreviated new drug application, the drug product contains the same active moiety as a drug that:

(i) Was approved after September 24, 1984, in an application under section 505(b) of the act, and

ii) Is entitled to a 5-year period of exclusivity under section 505(c)(3)(D)(ii) and (j)(4)(D)(ii) of the act and 314.108(b)(2), unless the 5-year exclusivity period has elapsed or unless 4 years of the 5-year period have elapsed and the application or abbreviated application contains a certification of patent invalidity or non-infringement described in 314.50(i)(1)(i)(A)(*4*) or 314.94(a)(12)(i)(A)(*4*).

The request in the Citizens Petition that FDA refuse to file any application for a buprenorphine/naloxone oral mucosal film drug product unless the application references the SUBOXONE® Sublingual Film product does not even purport to rely upon any of the grounds set forth in 21 CFR 314.101 as a basis for FDA to refuse to file an application. This request is clearly beyond the limits of the regulations and there is no legal basis to grant the Petitioner's request.

II. Choice of Reference Listed Drug

The Petitioner asserts that any 505(b)(2) application for a film dosage form for mucosal administration of a buprenorphine/naloxone drug product must identify the sublingual film formulation approved in NDA #22-410 as the reference listed drug ("RLD"), and not the sublingual tablet formulation approved in NDA #20-733. Both formulations are listed as RLDs in the FDA Orange Book. The Petitioner further argues that under FDA's draft Guidance for

Industry: Applications Covered by Section 505(b)(2) (October 2, 1999) ("the FDA Guidance"), if there is a listed drug that is a "pharmaceutical equivalent" of the drug proposed in the 505(b)(2) application, the drug should be identified as the RLD, and if there is no pharmaceutical equivalent, the 505(b)(2) application should identify the RLD that is the most similar to the drug for which approval is sought. The Petitioner also asserts that a 505(b)(2) application for a film formulation for mucosal administration must therefore identify the sublingual film formulation, not the sublingual tablet formulation, as the RLD.

What the Petitioner fails to note, however, is that FDA has itself noted, "where there is no listed drug that is a pharmaceutical equivalent to the drug product proposed in the 505(b)(2) application, neither the statute, regulation nor the draft Guidance directly addresses how to identify the listed drug or drugs on which a 505(b)(2) applicant is to rely (See FDA letter of Nov. 30, 2004 responding to a Citizen Petition, Docket No. 2004P-0386/CPl& RCl, filed on behalf of Abbott). Accordingly, there is no statutory or regulatory mandate that any such 505(b)(2) application must list the most similar drug or that a 505(b)(2) application for a film dosage form for mucosal administration of a buprenorphine/naloxone drug product must list the sublingual film formulation simply because the Petitioner asserts it is the most similar.

The FDA's response to the Abbott Citizen Petition agrees that in order "to avoid unnecessary duplication of research or review" where there is no pharmaceutical equivalent, the 505(b)(2) application should choose the listed drug or drugs that are most similar to the drug for which approval is sought. There is no obvious basis upon which to conclude, however, that the sublingual film dosage form would be the most similar to the drug for which the Petitioner believes a 505(b)(2) application may be submitted or that the use of the sublingual film dosage form, rather than the sublingual tablet as the reference listed drug will "avoid unnecessary duplication of research or review." Both RLDs are sublingual dosage forms and both are at different dosage strengths than the proposed drug in a 505(b)(2) application that may be submitted in the future. BDSI's proposed buprenorphine/naloxone mucosal film product is different in product design, the amounts of component active ingredients, and the mucosal surface of application from both of the reference listed drugs (sublingual film and tablet).

In short, there is no factual or scientific basis upon which to conclude that the BDSI product would be more similar to one RLD than the other, and there is no statutory or regulatory basis for the choice of the sublingual film formulation in NDA #22-410 as the RLD.

Significantly, in the Summary Basis for Approval of the product, FDA expressly stated that "There were no efficacy data submitted in support of the SUBOXONE® Sublingual Film application, and none were needed in support of the approval." FDA's summary of the review of SUBOXONE® Sublingual Film NDA # 22-410 noted that in addition to non-clinical and clinical safety information, the basis for FDA's approval rested on demonstration of the relative bioavailability of the SUBOXONE® Sublingual Film Product to the Sublingual Tablet Product.

BDSI intends to follow FDA's Guidance for the Industry, Applications Covered by Section 505(b)(2), October 1999 and identify in its application:

- Those portions of the application that rely on information the applicant does not own or to which the applicant does not have a right of reference (for example, for reproductive toxicity studies).

- Any and all listed drugs by established name, proprietary name (if any), dosage form, strength, route of administration, name of the listed drug's sponsor, and the Application.

- Those investigations relied on for approval: those without which the application cannot be approved (i.e., animal and human safety tests as well as clinical investigations of effectiveness).

It is highly significant to note that BDSI does not need to, nor does it intend to, rely on any studies contained in the SUBOXONE® Sublingual Film NDA # 22-410. As discussed during several meetings with the Division of Anesthesia and Analgesia Products, to support its application, BDSI is being required to submit its own non-clinical and clinical safety information similar to the information contained in the SUBOXONE® Sublingual Film NDA.

BDSI is conducting independent studies to demonstrate the relative bioavailability and safety of its proposed product and is not relying on FDA's review of any studies contained in the SUBOXONE® Sublingual Film NDA # 22-410. The application which contains investigations upon which BDSI will be relying are contained in the SUBOXONE® Sublingual Tablet NDA. BDSI does not need to, nor does it intend to, rely on any studies contained in the SUBOXONE® Sublingual Film NDA # 22-410. There are no studies in NDA #22-410 without which any application filed by BDSI could not be approved. Indeed, the BDSI 505(b)(2) application could be submitted and approved even NDA #22-410 had never been submitted or approved. Relying upon the sublingual film form as the RLD is not necessary "to avoid unnecessary duplication of research or review" (as stated by FDA in its response to the Abbott Citizen Petition), and there is simply no reason in the law, regulations, science or logic why BDSI would need to reference the sublingual film formulation approved in NDA #22-410.

III. Conclusion

The FD&C Act and FDA regulations clearly delineate the reasons for refusing to file an application. If none of the reasons for refusing to file the NDA set forth in 21 CFR §314.101(d) or (e) apply, then there is no basis for the Agency to refuse to file the application. Presuming that an NDA applicant, such as BDSI, were to submit an NDA for a buprenorphine/naloxone mucosal film drug product and the NDA on its face contained all information required under section 505(b)(2) of the FD&C Act and 21 CFR § 314.50, then the NDA must be filed by FDA.

Further, as noted above, there is no reason in the law, regulations, science or logic why BDSI would need to list the sublingual film formulation approved in NDA # 22-410 as the RLD.

In summary, the Petitioner's request that FDA to refuse to file any 505(b)(2) NDA for a buprenorphine/naloxone oral mucosal film drug product unless the 505(b)(2) references NDA # 22-410, the NDA for SUBOXONE® Sublingual Film is without merit and should be denied.

IV. Verification

I certify that, to my best knowledge and belief:

(a) I have not intentionally delayed submission of this document or its contents; and

(b) the information upon which I have based the action requested herein first became known to me on or about February 2, 2012. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: BioDelivery Sciences International, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of these comments to the above referenced Citizen Petition.

Respectfully submitted,

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