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BY HAND DELIVERY

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

To Whom It May Concern:

Hyman, Phelps & McNamara, P.C. submits this petition pursuant to the Federal Food, Drug, and Cosmetic Act ("FDCA"), and in accordance with 21 C.F.R. §§ 10.20 and 10.30 to request that the Food and Drug Administration ("FDA") refuse to file any 505(b)(2) new drug application ("NDA") for a buprenorphine/naloxone drug product consisting of a polymer film for application to the oral mucosal membranes unless such NDA references the NDA for SUBOXONE® the sublingual film formulation of this product, and to reaffirm that any such 505(b)(2) NDA will be subject to the impurity limits for naloxone established by FDA in response to a 2009 citizen petition (FDA-2009-P-0325).

A. Action Requested

The undersigned requests that FDA:

1. Refuse to file any 505(b)(2) NDA for a buprenorphine/naloxone drug product consisting of a polymer film for application to the oral mucosal membranes unless such 505(b)(2) NDA references NDA # 22-410 (SUBOXONE®), which is the NDA for the sublingual film formulation of this product, and makes the appropriate certifications with respect to all patents listed for NDA #22-410.

FDA-2011-P-0869

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2. Refuse to 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.

B. Statement of Grounds

Currently, two formulations of oral buprenorphine/naloxone drug products are approved for marketing. The sublingual tablet formulation of buprenorphine/naloxone is approved in NDA # 20-733, whereas the sublingual film formulation is approved in NDA # 22-410. Recently, we have become aware that a company is developing a film dosage form for mucosal administration of buprenorhine/naloxone. According to information released by that company, the product "consists of a small, bioerodible polymer film" and the route of administration is "to the mucosal membranes (inner lining of cheek)."[1] The company recently stated that it expects "to initiate the pivotal bioequivalence trial in December of this year with results expected during the first quarter of 2012" and that it "could be in a position to submit a New Drug Application (NDA) . . . in the second half of 2012."[2] As explained below, any 505(b)(2) NDA for such a product should be required to identify the sublingual film formulation in NDA # 22-410 (SUBOXONE®) as the listed drug.[3] In addition, the applicant must be able to demonstrate that any genotoxic or potentially genotoxic impurities associated with naloxone are limited appropriately.

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1 http://www.bdsi.com/BEMA_Technology.aspx

2 http://markets.financialcontent.com/ir/?Module=MediaViewer&GUID=19389121&Ticker=BDSI

3 We note that the rationale discussed below would also prevent an ANDA suitability petition for such a product. To our knowledge, no company has filed a suitability petition for this product.

1. The 505(b)(2) NDA must reference NDA # 22-410 (SUBOXONE®), and certify with respect to all patents listed for NDA #22-410

a. Statutory and Regulatory Background

FDCA § 505(b)(1) permits the submission of an NDA that contains full reports of investigations of safety and effectiveness (1) that are conducted by or for the applicant, and/or (2) for which the applicant has obtained a right of reference. FDCA § 505(b)(2) permits the submission of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference. Section 505(b)(2) NDAs, therefore, enable the NDA applicant to rely, in part, on FDA's previous findings of safety and efficacy for an approved drug product (and/or published literature) in support of its application for the marketing of a new drug. If a 505(b)(2) applicant is relying on FDA's previous findings of safety and efficacy for an approved drug product, the applicant must identify the drug application forming the basis for FDA's conclusions. 21 C.F.R. § 314.54(a)(1)(iii). The previously approved product is called the "listed drug" ("LD"). Modifications to that LD, including a new route of administration or dosage form, can be approved in a 505(b)(2) application that need "contain only that information needed to support the modification(s) of the listed drug." Id. § 314.54(a). FDA may then approve the new product candidate for all or some of the label indications for which the LD has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Federal law provides for a period of three years of exclusivity following approval of a new drug that contains a previously approved active moiety, the approval of which was required to be supported by one or more clinical trials conducted by or for the applicant (e.g., a new dosage form, route of administration or combination, or for a new use), during which FDA cannot grant effective approval of an abbreviated new drug application (ANDA) or 505(b)(2) NDA for the LD's protected conditions of use.[4] To the extent that the 505(b)(2) NDA applicant is relying on FDA's previous findings for an already approved product, the applicant is required to certify to any patents listed for that LD in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (commonly

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[4] NDA #22-410 has been awarded three years of exclusivity through August 30, 2013 under this provision of law.

known as the Orange Book). Specifically, the applicant must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product.

Regarding the LD that a 505(b)(2) applicant must select, FDA has stated: "If there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug." FDA Draft Guidance for Industry: Applications Covered by Section 505(b)(2) (October 1999). If there is no pharmaceutical equivalent, then FDA has stated that a 505(b)(2) NDA should reference the LD that is most similar to the drug for which approval is sought. FDA, Petition Response, Docket No. FDA-2004-P-0386 (November 30, 2004). In that case, FDA found that the 505(b)(2) applicant's choice of LD was appropriate since the only difference between the two products was "strength," whereas another product differed in both "strength and dosage form." Id.

Once the 505(b)(2) applicant has identified the appropriate LD, the 505(b)(2) application must contain a "patent certification or statement as required under section 505(b)(2) of the [FDCA] with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug." 21 CFR 314.54(a)(1)(vi). If there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application, the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug. FDA Draft Guidance for Industry: Applications Covered by Section 505(b)(2) (October 1999). FDA has repeatedly refused to permit a 505(b)(2) applicant to "use the 505(b)(2) process to end-run patent protections that would have applied had an ANDA been permitted." Id. As FDA observed:

> [I]f a tablet and a capsule are approved for the same moiety with patents listed for the tablet and none listed for the capsule, an ANDA applicant seeking approval for a tablet should cite the approved tablet as the reference listed drug. It should not circumvent the patents on the tablet by citing the capsule as the reference listed drug and filing a suitability petition under section 505(j)(2)(C) of the [FDCA] and 21 CFR 314.93 seeking to change to a tablet dosage form."

Id. at note 13.

If there is no pharmaceutical equivalent, then the 505(b)(2) applicant should certify to patents listed for the most similar alternative. As FDA explained:

> [I]f all the information relied on by FDA for approval (excluding information submitted in the 505(b)(2) application itself) is contained in a single previously approved application and that application is a pharmaceutical equivalent or the most similar alternative to the product for which approval is sought, the 505(b)(2) applicant should certify only to the patents for that application. This is the case even when another application also contains some or all of the same information.

FDA, Petition Response, Docket No. FDA-2004-P-0386 (November 30, 2004) (emphasis added). As FDA observed, this approach "ensures that patent certification obligations for 505(b)(2) applications and for ANDAs are parallel."[5] Id. Such an approach is a guiding principle in ensuring that the parallel structure and logic of the patent certification provisions in sections 505(b)(2) and 505(j) in the Hatch-Waxman amendments are interpreted faithfully.

b. The Appropriate LD in This Case is the Sublingual Film Product

According to FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book), "[d]rug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules)."[6] Thus, the highlighted characteristics

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5 In fact, FDA may reject an applicant's LD choice if the Agency determines that another (or an additional), drug product is more appropriate (i.e., more similar). See, FDA, Petition Response, Docket No. FDA-2008-P-0329 (Nov. 25, 2008).

6 See also 21 C.F.R. § 320.1(c). *Pharmaceutical equivalents* means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, *i.e.* , the same salt or ester of the same therapeutic moiety, or, in the case

must be examined by a 505(b)(2) applicant and FDA in order to determine which alternative is the appropriate LD (i.e., the most similar alternative to the product for which approval is sought).

As mentioned above, two formulations of oral buprenorphine/naloxone drug products are approved for marketing: a sublingual ***tablet*** formulation is approved in NDA # 20-733 and a sublingual ***film*** formulation is approved in NDA # 22-410. A 505(b)(2) applicant seeking to market "a small, bioerodible polymer ***film*** for application to the mucosal membranes (inner lining of cheek)"[7] must therefore identify NDA #22-410 as the appropriate LD. If permitted to rely on the tablet NDA, there would be two differences between the products (i.e., route of administration and dosage form). Reliance on the film NDA, in contrast, results in products that are different only in the route of administration.[8] It follows then that the 505(b)(2) applicant should be required to submit the appropriate certifications for all patents listed for NDA # 22-410.

2. Impurities Associated with Naloxone Must be Limited

FDA has already stated that ANDA and 505(b)(2) applications containing naloxone are required to comply with a limit of 0.01% on 7,8-didehydronaloxone in naloxone. FDA, Petition Response, Docket No. FDA-2009-P-0325 (Oct. 8, 2009). Further, any naloxone impurity with the α,β-unsaturated ketone (ABUK) moiety is subject to the same 0.01% limit, unless the applicant can demonstrate that the impurity is nongenotoxic. Id. Finally, the sum of ABUK impurities, including 7,8-didehydronaloxone, should not exceed 1.5

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of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

7 http://www.bdsi.com/BEMA_Technology.aspx

8 See Orange Book at Appendix C (uniform terms for dosage form, and uniform terms for route of administration).

µg/day. Id. Accordingly, we ask FDA to re-affirm that any product referencing NDA # 22-410 (SUBOXONE®) will be subject to these same requirements.

C. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

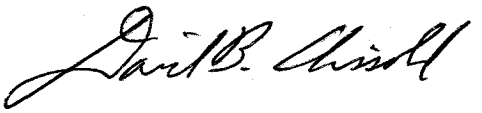
D. Economic Impact Statement

Petitioner will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

E. 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 which are unfavorable to the petition.

Sincerely,



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