DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 18 2013

David B. Clissold
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700 13th Street, N.W., Suite 1200
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Re: Docket Nos. FDA-2011-P-0869 and FDA-2013-P-0995

Dear Mr. Clissold:

This letter responds to your citizen petitions, Docket No. FDA-2011-P-0869 received December 2, 2011 (First Petition) and Docket No. FDA-2013-P-0995 received August 12, 2013 (Second Petition) (collectively, the Petitions). The Petitions ask that the Food and Drug Administration (FDA or the Agency) refuse to file any new drug application (NDA) submitted through the pathway described by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)(2)) seeking approval of a buprenorphine/naloxone drug product consisting of a polymer film for application to the oral mucosal membranes unless such 505(b)(2) application references NDA 22-410 for Suboxone (buprenorphine hydrochloride (HCl) and naloxone HCl) sublingual film and provides an appropriate patent certification to all patents listed for NDA 22-410. Your petitions also ask that we refuse to approve any application for a buprenorphine and naloxone drug product unless the applicant demonstrates that any genotoxic or potentially genotoxic impurities associated with naloxone are limited appropriately.

We have carefully considered the issues raised in the Petitions, the May 3, 2012, comment submitted to the docket by Foley & Lardner LLP on behalf of BioDelivery Sciences International, Inc. (BDSI) (First BDSI Comment), your June 13, 2013, letter submitted to the docket (Supplement), and the July 15, 2013, comment submitted to the docket by Foley & Lardner LLP on behalf of BDSI (Second BDSI Comment). For the reasons explained below, your petitions are granted in part and denied in part.

I. BACKGROUND

A. Suboxone

Suboxone (buprenorphine HCl and naloxone HCl) has been approved in two dosage forms: a sublingual film (NDA 22-410), and a sublingual tablet (NDA 20-733). These NDAs are held by Reckitt Benckiser Pharmaceuticals, Inc. (Reckitt).[1] Both products are indicated for the

[1] Reckitt also holds NDA 20-732 for Subutex, a sublingual tablet version of buprenorphine HCl that does not contain naloxone. Subutex is indicated for the treatment of opioid dependence and is preferred for induction (i.e., for beginning the process of opioid addiction treatment with buprenorphine HCl in a controlled setting).

maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support. Buprenorphine, a partial opioid agonist, is a Schedule III narcotic under the Controlled Substances Act. Naloxone is an opioid antagonist, and is present in Suboxone sublingual tablets and Suboxone sublingual film for the purpose of discouraging misuse by injection.[2]

1. NDA 20-733 (Sublingual Tablet)

NDA 20-733 for Suboxone sublingual tablets was approved on October 8, 2002. The effectiveness of Suboxone sublingual tablets was supported by data from two studies of a buprenorphine sublingual solution that used a dose (8 milligrams (mg) per day) that is roughly comparable to a dose of 12 mg per day of Suboxone sublingual tablets, as demonstrated by a comparative bioavailability study. One of these two studies involved 24 weeks of dosing, and the other involved 16 weeks of blinded treatment followed by an open-label, flexible dose extension, which provided long-term safety data. In addition, a single, four-week, placebo-controlled study was conducted using the Suboxone sublingual tablet to demonstrate that the dosing regimen was effective. These three studies, taken together, were sufficient to support approval of the Suboxone sublingual tablet for the maintenance treatment of opioid dependence.[3]

In a letter dated September 18, 2012, Reckitt notified FDA that Suboxone sublingual tablets, 2 mg/0.5 mg and 8 mg/2 mg, would be discontinued from marketing. Reckitt informed the Agency that it ceased distributing Suboxone sublingual tablets in March 2013, at which time FDA moved the product to the "Discontinued Drug Product List" section of FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book). The Agency subsequently determined that Suboxone sublingual tablets were not withdrawn from sale for reasons of safety or effectiveness.[4]

2. NDA 22-410 (Sublingual Film)

NDA 22-410 for Suboxone sublingual film, 2 mg and 8 mg, was approved on August 30, 2010. The data supporting approval of this application included pharmacokinetic studies evaluating bioavailability and dose proportionality, and data previously submitted in support of the NDAs for Suboxone sublingual tablets, NDA 20-733, and Subutex, NDA 20-732. A small, open-label safety study of Suboxone film and a small laboratory study comparing Suboxone film to a buprenorphine-only film were included. No new efficacy studies were required for this NDA.

B. BDSI NDA

On August 1, 2013, BDSI announced that it had submitted an NDA to FDA for a buprenorphine naloxone buccal film for the maintenance treatment of opioid dependence (Second Petition at 2).

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[2] Intravenous administration of buprenorphine/naloxone combinations may produce opioid withdrawal effects.

[3] The same studies supported approval of NDA 20-732 for Subutex, which was submitted concurrently.

[4] 78 FR 34108 (June 6, 2013).

C. Legal Framework

1. 505(b)(2) Applications

Section 505(b)(2) of the FD&C Act was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, Public Law 98-417 (the Hatch-Waxman Amendments). The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low-cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[5]

Section 505(b)(2) of the FD&C Act describes an application that contains full reports of investigations of safety and effectiveness, 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 or use (i.e., published literature or the Agency's finding of safety and/or effectiveness for one or more listed drugs). A 505(b)(2) applicant may rely on FDA's finding of safety and effectiveness for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication, conditions of use) in common with the listed drug(s). The 505(b)(2) application must include sufficient data to support any differences between the proposed drug and the listed drug(s) and demonstrate that the proposed drug product meets the statutory approval standard for safety and effectiveness. The 505(b)(2) pathway permits sponsors to rely on what is already known about a drug, thereby avoiding unnecessary duplication of human or animal studies and conserving resources.

A sponsor interested in submitting a 505(b)(2) application that relies upon FDA's finding of safety and/or effectiveness for one or more listed drugs[6] should determine which listed drug(s) is most appropriate for its development program, and must establish that such reliance is scientifically appropriate.[7] However, if there is a listed drug that is a "pharmaceutical equivalent"[8] to the proposed drug product, FDA advises that a sponsor should identify the

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[5] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-48.

[6] For example, in certain cases, a sponsor may rely on FDA's finding of safety and/or effectiveness for different listed drugs to support different aspects of its development program (e.g., where appropriate, reliance on oral and topical dosage forms containing the same active ingredient to support systemic and local toxicology, respectively).

[7] See FDA Response to Sanzo, Chasnow, Lawton, and Rakoczy (October 14, 2003) (Joint 505(b)(2) CP response) at 12. This joint response was previously assigned Docket Nos. 2001P-0323, 2002P-0047, and 2003P-0408, but as a result of FDA's transition to its new docketing system (Regulations.gov) these numbers were combined to Docket No. FDA-2003-P-0274.

[8] *Pharmaceutical equivalents* are drug products with:

> . . . 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 of modified release forms that require a reservoir or overage . . . 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 standards of identity, strength, quality and purity, including potency, and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

21 CFR 320.1(c).

pharmaceutically equivalent product as a listed drug relied upon and provide patent certifications for the patents listed for the pharmaceutically equivalent drug.[9] This approach is intended to prevent applicants from using the 505(b)(2) pathway to avoid patent protections that would have applied had the application been submitted under section 505(j).[10]

2. Patents and Exclusivity

A 505(b)(2) applicant is subject to applicable periods of marketing exclusivity granted to the listed drug relied upon and is required to submit an appropriate patent certification or statement for each patent that claims the listed drug or a method of using the drug for which the applicant is seeking approval and for which information is required to be filed under section 505(b)(1) or 505(c)(2) of the FD&C Act (see section 505(b)(2)(A)-(B) of the FD&C Act).

Section 505(b)(1) of the FD&C Act requires NDA applicants to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[11] FDA is required to publish the patent information provided by the NDA holder for drugs approved under 505(c) and does so in the Orange Book (section 505(b)(1), (c)(2), and (j)(7) of the FD&C Act, and 21 CFR 314.53(e)).

For each unexpired patent listed in the Orange Book for a listed drug it references, the 505(b)(2) applicant must submit either a paragraph III certification (delaying approval until the date on which such patent will expire), a paragraph IV certification (certifying that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted), or, with respect to a method of use patent, a statement that the patent does not claim a use for which the applicant is seeking approval (section 505(b)(2)(B) of the FD&C Act). The applicant is not required to certify to all patents "for every drug containing the same active ingredient that relied in part on the same underlying investigations on which the 505(b)(2) applicant seeks to rely."[12] Rather, the applicant's patent certification obligations are limited to those patents that claim the *specific listed drug* upon which the applicant has relied for FDA's finding of safety and effectiveness to support the approval of the NDA.

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[9] FDA draft guidance for industry *Applications Covered by Section 505(b)(2)*(October 1999) (Draft 505(b)(2) Guidance), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

[10] The Agency may refuse to file 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 FD&C Act (21 CFR 314.101(d)(9)).

[11] Section 505(c)(2) of the FD&C Act imposes an additional patent submission requirement on holders of approved NDAs when those NDA holders subsequently obtain new patent information that could not have been submitted with the NDA.

[12] FDA Response to Abbott Laboratories and Laboratoires Fournier, Docket No. FDA-2004-P-0089 (previously Docket No. 2004-P-0386) (November 30, 2004) (Fenofibrate CP response) at 6.

A 505(b)(2) applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder for the listed drug and each patent owner with notice of its patent certification, including a description of the legal and factual basis for its assertion that the patent is invalid or will not be infringed (section 505(b)(3) of the FD&C Act). Should the NDA holder or patent owner initiate a patent infringement action against the 505(b)(2) applicant within 45 days of receiving the required notice, approval of the 505(b)(2) application generally will be stayed for 30 months from the date of receipt of the notice, unless a court orders otherwise (section 505(c)(3)(C) of the FD&C Act). This process may permit resolution of patent infringement issues before the product described in the 505(b)(2) application is approved and marketed.

Under section 505(c)(3)(E)(iii) of the FD&C Act and 21 CFR 314.108(b)(4), approval of a new drug application for a drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application qualifies for a three-year period of exclusivity. During this three-year period, the Agency will not make effective the approval of a 505(b)(2) application for the conditions of approval of the application covered by the exclusivity.

3. Impurities

Applications for new drugs submitted through the 505(b)(2) pathway must include information regarding chemistry, manufacturing, and controls, including specifications necessary to ensure purity of the product, among other things.[13] In 2008, the Agency issued a draft guidance concerning genotoxic and carcinogenic impurities in drug substances and products.[14] This document provides recommendations regarding the safety qualification of impurities with known or suspected genotoxic potential, including a maximum daily exposure target of 1.5 micrograms (μg) for genotoxic impurities.[15]

II. ANALYSIS

A. Selection of Listed Drug Relied Upon in a 505(b)(2) Application

The Petitions request that the Agency refuse to file any 505(b)(2) NDA that does not rely on NDA 22-410 (Suboxone sublingual film) and make appropriate certifications with respect to all patents listed for NDA 22-410 (First Petition at 1; Second Petition at 1-2). Specifically, the First Petition asserts that a 505(b)(2) applicant with "'a small, bioerodible polymer film for application to the mucosal membranes'" must identify NDA 22-410 as the listed drug because

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[13] 21 CFR 314.50(d)(1).

[14] FDA draft guidance for industry *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*, December 2008, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/default.htm. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

[15] This general threshold approach would not be appropriate for certain impurities for which adequate data exist to derive substance-specific risk assessments or for which structural alerts suggest particularly high genotoxic and carcinogenic potential.

there would be only one difference, route of administration, between this listed drug and the proposed product, compared with two differences, route of administration and dosage form, if NDA 20-733 was relied upon (First Petition at 6, quoting "BEMA® Technology" on the BDSI website (http://www.bdsi.com/BEMA_Technology.aspx)). In support of your contentions, you cite the Agency's 2004 citizen petition response to Abbott Laboratories and Laboratoires Fournier regarding fenofibrate (the Fenofibrate CP response) (First Petition at 4).

In its May 3, 2012, comment, BDSI contends that your First Petition should be denied.[16] First, BDSI asserts that the relevant regulations only provide for limited circumstances in which the Agency may refuse to file an application, and that the scenario here falls outside those addressed in the regulations (First BDSI Comment at 3). Second, BDSI asserts that there is no statutory or regulatory requirement that a 505(b)(2) application list the most similar drug (*Id.* at 4). According to BDSI, even if there were a requirement that the most similar drug be listed, that requirement would not bar a 505(b)(2) application listing NDA 22-410 here. BDSI states that the proposed film product differs from both Suboxone NDAs, 20-733 and 22-410, with regard to dosage strength, product design, concentration of active ingredients, and the mucosal surface of application, and hence, "there is no factual or scientific basis upon which to conclude that the BDSI product would be more similar to one [Suboxone product] than the other" (*Id.*).

In a supplement dated June 13, 2013, you responded to BDSI's comment by asserting that FDA has the legal authority necessary to refuse to file an application that does not reference NDA 22-410 (Supplement at 2). You also reiterated your position that the Fenofibrate CP response requires a 505(b)(2) applicant to list the most similar drug, noting the Agency's dual goals of avoiding unnecessary duplication of research and preventing circumvention of patents (Supplement at 3-4). Your supplement compares the anticipated BDSI product, to the extent information about that product is publicly available, to Suboxone sublingual tablets and Suboxone sublingual film and concludes that the anticipated BDSI product is more similar to Suboxone sublingual film (Supplement at 5-8). Your supplement states that "FDA should not let would-be competitors to the Suboxone sublingual film circumvent Orange Book patent protections by allowing the use of an inappropriate RLD . . . purely to circumvent patent certification and a potential patent infringement lawsuit" (Supplement at 8).

In its July 15, 2013, comment, BDSI reiterates its position that it is not required to reference NDA 22-410 and that it will meet its regulatory obligations by referencing NDA 20-733 (Second BDSI Comment at 1-3). BDSI states that your allegations are without merit (*Id.* at 4).

Your second petition, received by FDA on August 12, 2013, was submitted pursuant to Section 505(q) of the FD&C Act after BDSI announced that it had submitted an NDA to FDA for a buprenorphine/naloxone product (Second Petition at 1-2). The Second Petition requests the same actions as the First Petition (Second Petition at 1, footnote 1).

[16] The Second Petition had not been filed at the time of BDSI's comments.

FDA Response

We agree that FDA has sufficient legal authority to refuse to file a 505(b)(2) application that does not on its face contain required information (see 21 CFR 314.101(d)(3)).[17] We do not agree, however, that we should refuse to file any 505(b)(2) application for a buprenorphine/naloxone drug product consisting of a polymer film for application to the oral mucosal membranes that does not cite NDA 22-410 as a listed drug relied upon.

FDA previously has explained:

> When there is no listed drug that is a pharmaceutical equivalent to the drug product proposed in the 505(b)(2) application, neither the statute, the regulations, nor the Draft Guidance [on 505(b)(2) applications] directly addresses how to identify the listed drug or drugs on which a 505(b)(2) applicant is to rely. However, because, under 21 CFR 314.54(a), a 505(b)(2) applicant seeking approval for a change to a listed drug need only supply information sufficient to support the change proposed, it follows that the more similar a proposed drug is to the listed drug cited, the smaller the quantity of data that will be needed to support the proposed change. Accordingly, to avoid unnecessary duplication of research and review, when a section 505(b)(2) application has been submitted and no pharmaceutically equivalent drug product has previously been approved, the 505(b)(2) applicant should choose the listed drug or drugs that are most similar to the drug for which approval is sought.[18]

The Fenofibrate CP response describes a suggested approach intended to enhance the efficiency of a prospective 505(b)(2) applicant's development program. An applicant choosing to rely on FDA's finding of safety and/or effectiveness for a listed drug very similar to the proposed product submitted in the 505(b)(2) application would generally need to submit less additional data to support the differences between the proposed product and the listed drug for approval of the 505(b)(2) application. However, as stated in the Fenofibrate CP response, this suggested approach does not reflect a statutory or regulatory requirement. Further, the determination of which listed drug is "most similar" to a proposed product may be difficult (except in cases in which a pharmaceutical equivalent previously has been approved) and dependent on the sponsor's approach to its development program. Accordingly, a sponsor interested in submitting a 505(b)(2) application that relies upon FDA's finding of safety and/or effectiveness for one or more listed drugs should determine which listed drug(s) is most appropriate for its development program. If there is a listed drug that is a "pharmaceutical equivalent" to the proposed drug product, the applicant should identify the pharmaceutically equivalent product as a listed drug relied upon and provide patent certifications for the patents listed for the pharmaceutically equivalent drug.[19]

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[17] We note, however, that an applicant's failure to identify a listed drug or identification of a listed drug that does not provide adequate support for its proposed product generally would not be a basis for refusal to file. Rather, this would be a review issue that could preclude approval if the application were not amended to cite reliance on an appropriate listed drug or provide the necessary data.

[18] Fenofibrate CP response at 9.

[19] Draft 505(b)(2) Guidance at 8.

This approach is consistent with the statement that you referenced from footnote 13 of the Fenofibrate CP response:

> [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 Act and 21 CFR 314.93 seeking to change to a tablet dosage form.

As a preliminary matter, we note that this footnote discusses the requirements for an ANDA, an application that seeks approval for a duplicate of a reference listed drug and a petitioned ANDA.[20] FDA has explained that "a suitability petition will not be granted for a product for which a pharmaceutical equivalent has been approved, as the suitability petition process is intended for a proposed "drug product which is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug" (§ 314.93(b)). In such a case, the ANDA applicant should refer to the approved pharmaceutical equivalent designated by the Agency as the RLD as its basis for ANDA submission."[21] A 505(b)(2) applicant also should identify the pharmaceutically equivalent product as a listed drug relied upon and provide patent certifications for the patents listed for the pharmaceutically equivalent drug.[22] As FDA previously has stated, this "provision[] ensure[s] that the 505(b)(2) applicant does not use the 505(b)(2) process to end-run patent protections that would have applied had an ANDA been permitted."[23] However, in contrast to an ANDA, a 505(b)(2) application may describe a drug with substantial differences from a listed drug, and except where a pharmaceutical equivalent already has been approved, the 505(b)(2) applicant should determine which listed drug(s) is most appropriate for its development program. FDA has routinely advised prospective 505(b)(2) applicants that if the applicant intends to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, the applicant must establish that reliance on the listed drug(s) is scientifically appropriate and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s).[24]

The Hatch-Waxman Amendments are directed to facilitating the availability of drug products that meet the statutory requirements for approval while protecting innovator intellectual property

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[20] Section 505(j)(2)(C) of the FD&C Act provides that an applicant may submit a suitability petition to FDA requesting permission to file an ANDA that differs from a listed drug in route of administration, dosage form, or strength, or that has one different active ingredient in a combination drug product. A suitability petition is submitted to the public docket, and third parties may submit comments and information regarding the changes proposed in the petition (see 21 CFR 10.20, 10.30, and 314.93). FDA will grant a suitability petition unless it determines that the safety and effectiveness of the proposed change from the listed drug cannot be adequately evaluated without data from investigations that exceed what may be required for an ANDA (see section 505(j)(2)(A), (C) of the FD&C Act and § 314.93(e)(1)(i)).

[21] See FDA Response to Osmotica Pharmaceutical Corp., Docket No. FDA-2008-P-0329 (Nov. 25, 2008) at 4.

[22] Draft 505(b)(2) Guidance at 8.

[23] Fenofibrate CP response at 9.

[24] Joint 505(b)(2) CP response at 12.

rights and allowing for an early resolution of any patent infringement litigation. It has been FDA's longstanding position that "[p]atent certification obligations ... are linked to identification of the listed drug or drugs on which the application relies and are limited to the patents submitted and published for the listed drug or drugs identified."[25] Regarding your concerns regarding potential circumvention of patents listed for NDA 22-410, we have noted that 505(b)(2) and ANDA applicants may be subject to potential litigation based on infringement of a patent that is not listed in the Orange Book (see, e.g., "Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, Part II; Final Rule" (59 FR 50338 at 50346; October 3, 1994) ("FDA, however, believes it would be prudent for applicants to conduct patent searches if possible. A patent search could reveal the existence of an unlisted, but valid, patent and thus prevent an unnecessary expenditure of resources by applicants and FDA on a product that might not be marketable")). A 505(b)(2) applicant that selects a listed drug that avoids patent(s) listed in the Orange Book would not have the opportunity for early resolution of any questions of patent infringement. It would thus risk an unnecessary expenditure of resources on a product that might be subject to patent infringement litigation after approval and, if the patent holder is successful in that litigation, could be enjoined from marketing until patent expiry.

B. Genotoxic Impurities

Your petitions also ask that the Agency refuse to approve any application for a buprenorphine/naloxone drug product unless the applicant can demonstrate that genotoxic impurities associated with naloxone are limited appropriately (First Petition at 2; Second Petition at 2). Elsewhere, your petitions express this request more narrowly, referencing the specific limit, 0.01%, on the amount of 7,8-didehydronaloxone in naloxone discussed in the above-referenced response letter and asking us to affirm that any product referencing NDA 22-410 "will be subject to these same requirements" (First Petition at 7; Second Petition at 12). Your petitions reference FDA's October 2009 Response to Reckitt Benckiser Pharmaceuticals Inc., Docket No. FDA-2009-P-0325 (October 8, 2009) ("Reckitt CP response"), in support of this request.

FDA Response:

As discussed above and in our 2009 Reckitt CP response, our 2008 draft guidance provides recommendations regarding the safety qualification of impurities, including a maximum daily exposure target of 1.5 µg/day for genotoxic impurities.[26] Reckitt's 2009 petition identified 7,8-didehydronaloxone as an impurity associated with naloxone that is believed to be genotoxic and stated that FDA required 7,8-didehydronaloxone to be limited to no more than 0.01% in the naloxone drug substance during the Agency's review of the NDA for Suboxone sublingual tablets (NDA 20-733). Our 2009 Reckitt CP response states that "we agree [the 0.01% limit on 7,8-didehydronaloxone] should be applied to all applicants seeking approval of ANDAs or, as

[25] Fenofibrate CP response at 7-8.

[26] FDA draft guidance for Industry *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*, December 2008, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (Draft Genotoxic Impurities Guidance). This draft guidance, when finalized, will represent FDA's current thinking on this topic.

appropriate, 505(b)(2) applications that reference Suboxone."[27] We further stated that the α,β-unsaturated ketone (ABUK) moiety is the structural alert in 7,8-didehydronaloxone that suggests it is potentially genotoxic, and it would be appropriate to restrict the sum of all ABUK impurities, including 7,8-didehydronaloxone, to not more than 1.5 µg/day if technically feasible.

As indicated in our 2009 Reckitt CP response, the 0.01% limit of 7,8-didehydronaloxone could be adequate to meet the maximum daily exposure target of 1.5 µg/day for genotoxic impurities for a drug product with a similar dosing regimen as Suboxone. However, neither the 0.01% nor the 1.5 µg /day limits is considered to be absolute by the Agency. As noted in the 2008 guidance, we emphasize the need for flexibility, stating that "[i]n some cases, acceptance criteria higher than the recommended thresholds can be supported in the presence of a potential pharmacological benefit to patients."[28] Our approach to impurities control takes into account the totality of the circumstances, including safety concerns, manufacturing capabilities, clinical experience with the product, and other factors.

The circumstances the Agency would consider when applying the 1.5 µg/day target exposure limit to ABUK impurities, including 7,8-didehydronaloxone, in the context of reviewing a new application for a buprenorphine/naloxone product, include the range of daily doses at which the proposed drug product is expected to be administered and the amount of naloxone present in the product. Without knowing the daily dose of the proposed drug product or the concentration of naloxone in the proposed drug product, we cannot affirm that we would apply any specific numerical limit to genotoxic impurities in naloxone in reviewing such an application.

This result is consistent with our Reckitt CP response, which reflects an assumption that a 505(b)(2) application for a proposed product that relies upon Suboxone would seek approval for a dosing regimen similar to that of Suboxone. Unlike proposed generic drugs submitted in an ANDA, a proposed drug submitted in a 505(b)(2) application may differ from the listed drug relied upon in several respects (hence the inclusion of the phrase "as appropriate" in the Reckitt CP response at 8).

Furthermore, we cannot exclude the possibility that a future applicant will submit data showing that one or more ABUK impurities are not, in fact, genotoxic or will otherwise demonstrate that a different approach is appropriate. Alternative thresholds will be considered on a case-by-case basis. We anticipate, however, that for any application seeking approval of a drug product containing naloxone, in the absence of new toxicological data, we would limit exposure to total ABUK impurities, including 7,8-didehydronaloxone, to the 1.5 µg per day target, consistent with our 2008 draft guidance.

We grant your request that we affirm that FDA would not approve an application for a buprenorphine/naloxone drug product unless genotoxic or potentially genotoxic impurities associated with naloxone are limited appropriately. However, to the extent you ask us to commit to the application of a specific numerical limit to such impurities, we deny that request for the reasons explained above.

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[27] 2009 Reckitt CP Response at 8.

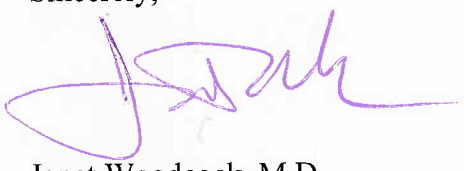
[28] Draft Genotoxic Impurities Guidance at 12.

III. Conclusion

For the reasons discussed above, your petitions are granted in part and denied in part. First, FDA does not agree that the Agency should refuse to file any 505(b)(2) application for a buprenorphine/naloxone drug product consisting of a polymer film for application to the oral mucosal membranes that does not cite NDA 22-410 as a listed drug relied upon. In the absence of a pharmaceutically equivalent product, a 505(b)(2) applicant is not required to select a listed drug that is the "most similar" (in your view) to the proposed product as long as reliance on the listed drug is scientifically justified.

Second, we will require applicants seeking approval of a buprenorphine/naloxone drug product to demonstrate that any genotoxic or potentially genotoxic impurities associated with naloxone are appropriately limited. However, given the possibility of new toxicological data, we will not necessarily impose the specific numerical limit you request on any application referencing NDA 22-410.

Sincerely,



Janet Woodcock, M.D.
Director
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