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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: Docket No. FDA-2011-P-0869

To Whom It May Concern:

By letter dated May 3, 2012, Foley and Lardner LLP, on behalf of their client BioDelivery Sciences International, Inc. ("BDSI") submitted a comment (the "BDSI comment") to the above-referenced docket. The BDSI comment was filed in response to a Citizen Petition requesting 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; and

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.[1]

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1 BDSI comment at 1.

I. FDA has the legal authority to grant the requests in the Citizen Petition

The BDSI comment first claims (in Section I) that there is no legal basis for FDA refusing to file a 505(b)(2) application that does not reference NDA # 22-410 (SUBOXONE®), which is the NDA for the sublingual film formulation of this product. The BDSI comment cites 21 C.F.R. § 314.101 for that assertion.[2] That assertion is incorrect.

Section 505(b)(2)(A) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") requires a 505(b)(2) applicant to submit a certification for each patent for the listed drug. Likewise, 21 C.F.R. § 314.50(i) also requires the 505(b)(2) application to contain all appropriate patent certifications for the listed drug ("LD").[3] In fact, FDA regulations explicitly state that, among other requirements, a 505(b)(2) application must contain:

> Any patent certification or statement required under section 505(b)(2) of the act with respect to any relevant patents that claim the listed drug or that claim any other drugs on which investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug.[4]

Thus, a 505(b)(2) application that lacked an accurate patent certification would not "on its face" contain the information required under section 505(b) of the FDC Act, or the information required under 21 C.F.R. § 314.50. Accordingly, a 505(b)(2) NDA that contained incorrect patent certifications would not, "on its face contain information required under section 505(b) . . . of the act and 314.50 . . ." and would thus satisfy the conditions for refusal to file under 21 C.F.R. § 314.101(d)(3). FDA has ample legal authority to 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 that does not reference the appropriate LD. As will be shown below, the appropriate LD in this case is NDA # 22-410.

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2 Id. at 2-3.

3 21 C.F.R. § 314.50(i).

4 Id. § 314.54(a)(1)(vi).

II. A 505(b)(2) NDA for a buprenorphine/naloxone drug product consisting of a polymer film for application to the oral mucosal membranes must reference NDA # 22-410

The BDSI comment appropriately recognizes that "neither the statute, regulation, nor the draft Guidance directly addresses how to identify" the appropriate LD in the present case.[5] However, the BDSI comment goes on to argue that FDA should ignore the precedent established in FDA's response to an earlier Citizen Petition addressing precisely the issue at hand.[6] Of course, FDA is not free to ignore previously established precedent, and the BDSI comment presents no legal, factual, or scientific basis for making such an extraordinary request in this case.

FDA has already ruled that if a 505(b)(2) NDA is filed that relies on FDA's previous finding of safety and efficacy, and there is no pharmaceutical equivalent product, then the 505(b)(2) applicant must reference and 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.[7]

As FDA observed, this approach "ensures that patent certification obligations for 505(b)(2) applications and for ANDAs are parallel."[8]

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5 BDSI comment at 4, quoting FDA, Petition Response, Docket No. FDA-2004-P-0386 (Nov. 2004).

6 See FDA, Petition Response, Docket No. FDA-2004-P-0386 (Nov. 2004).

7 Id. (emphasis added).

8 Id.

The avoidance of unnecessary duplication of research is only one of the goals of this FDA policy. The BDSI comment ignores the other goal, namely, preventing 505(b)(2) applicants from circumventing validly listed patents.

> [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."[9]

Whatever the other differences or similarities may be, a ***film*** is not a ***tablet***. "A small, bioerodible polymer ***film*** for application to the mucosal membranes (inner lining of cheek)" must therefore identify the ***film*** product (NDA #22-410) as the appropriate LD. The BDSI comment never addresses this fundamental point. BDSI is obviously seeking to circumvent the patents listed for the sublingual film product, and FDA should not permit them to do so.

Importantly, FDA has provided ample information on which to conduct an analysis of the appropriate LD in cases such as this. As noted above, FDA has stated that the LD must be "a pharmaceutical equivalent or the most similar alternative to the product for which approval is sought."[10] As we explained in the original Citizen Petition, FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book), provides the definition of "pharmaceutical equivalent," and so the analysis must begin there.

> Pharmaceutical Equivalents. Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of

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9 FDA, Draft Guidance for Industry and FDA Staff, Applications Covered by Section 505(b)(2) (Oct. 1999) at n.13, *available at* http://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf (emphasis added).

10 FDA, Petition Response, Docket No. FDA-2004-P-0386 (Nov. 2004).

> administration and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules).
> Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.[11]

The first sentence of this definition identifies four key factors that must be compared in order to determine whether two drugs are pharmaceutical equivalents, or in this case, which LD is "most similar" to the product for which approval is sought. Examining each of those key factors in turn:

- **Active ingredient(s):** Suboxone film and tablets both contain identical active ingredients (buprenorphine hydrochloride and naloxone hydrochloride). The BDSI product apparently contains the bases of buprenorphine and naloxone. Therefore, this factor does not help determine which LD is most similar to BDSI's product.

- **Dosage form:** CDER's Data Standards Manual provides definitions of "dosage form."[12] The definition of "film" is "A thin layer or coating."[13] A tablet is defined as "A solid dosage form containing medicinal substances with or without suitable diluents."[14] BDSI's product is undoubtedly a film, and the "most similar" LD is the Suboxone film dosage form.

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11 See Preface, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (Apr. 2013); see also 21 C.F.R. § 320.1(c).

12. FDA, CDER, Data Standards Manual (monographs), *available at* http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071666.htm.

13 Id.

14 Id.

- **Route of administration:** The route of administration for both Suboxone products is sublingual. It is not yet clear how FDA will describe the route of administration of BDSI's product (e.g., "to the mucosal membranes (inner lining of cheek)"). In any case, the comparison of route of administration to the LDs will not help determine which LD is most similar to BDSI's product since both LDs are administered sublingually.

- **Strength or concentration:** Two strengths of the Suboxone tablet product were marketed: a 2mg/0.5 mg tablet and a 8 mg/2 mg tablet (buprenorphine hydrochloride/ naloxone hydrochloride, content expressed in terms of free base). In contrast, four strengths of the film product are marketed: 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, and 12 mg/3 mg (buprenorphine hydrochloride/ naloxone hydrochloride, content expressed in terms of free base). BDSI has apparently not yet announced the strength of the buprenorphine/naloxone product for which it intends to seek approval. However, BDSI is currently enrolling patients into a clinical trial with the following strengths: 3.5/0.6 mg and 5.25/0.9 mg (buprenorphine/naloxone).[15] Thus, the strength of the BDSI product in the NDA is likely "most similar" to the strength of a Suboxone film product (i.e., 4 mg/ 1 mg).

In sum, two of the four factors (active ingredients and route of administration) do not help determine which LD is most similar to BDSI's product. For one of the four factors (strength), it seems likely that the "most similar" LD will be the Suboxone film product. Finally, the dosage form factor clearly identifies the film product as the appropriate LD in this case.[16]

To understand the fundamental similarities between Suboxone Sublingual film and the BDSI Bunavail(BNX) film and their fundamental differences from a tablet, it is important to compare the marketed Suboxone sublingual products to BDSI's BEMA

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[15] BDSI, Clinical Trial, An Open Label Study to Assess the Safety and Tolerability of BEMA® Buprenorphine NX In Opioid Dependent Subjects, *available at* http://clinicaltrials.gov/ct2/show/NCT01666119?term=BEMA&rank=1.

[16] It should be noted that the BDSI comment states: "Both RLDs are sublingual dosage forms." BDSI comment at 4. Of course, this is incorrect since there is no such thing as a sublingual dosage form. As explained above, sublingual refers to the route of administration. The relevant dosage forms here are tablet and film and since BDSI's product is a film dosage form, the appropriate LD is the Suboxone film product.

Bunavail (BNX) Buprenorphine/Naloxone film product from a pharmaceutics perspective. Table 1 lists several pharmaceutics characteristics that are relevant to the present case, and compares the anticipated BDSI Bunavail(BNX) product to the Suboxone film and tablet on each of those characteristics. The expected excipient profile for Bunavail in Table 1 was

Table 1			
	BEMA Bunavail (BNX)	**Suboxone Sublingual Film**	**Suboxone Sublingual Tablet**
Dosage Form	***Film***	***Film***	Tablet
Route of Administration	Buccal	***Sublingual***	***Sublingual***
Mucoadhesive	***Yes***	***Yes***	No
Erodible Polymeric Matrix	***Yes***	***Yes***	No
High Surface Area to Weight Ratio	***Yes***	***Yes***	No
Polymeric Dosage Form	***Yes*** ***Hydroxypropyl cellulose, hydroxyethyl cellulose, polycarbophil, carboxy methyl cellulose, buffer, sweetener, flavor, color and ink***[17]	***Yes*** ***Polyethylene oxide, hydroxypropyl methylcellulose, sweetener, flavor, buffer, color and ink***	No Lactose, mannitol, cornstarch, povidone K30, buffer, color, magnesium stearate, sweetener and flavor
Buprenorphine/ Naloxone	***3.5/0.6 and 5.25/0.9 mgs***[18]	12/3, 8/2, ***4/1*** and 2/0.5 mgs	8/2 and 2/0.5 mgs

17 U.S. Patent No. 8,147,866, Example 3 (filed July 15, 2011) ("Preparation of Devices in Accordance with the Present Invention").

18 BDSI, Clinical Trial, An Open Label Study to Assess the Safety and Tolerability of BEMA® Buprenorphine NX In Opioid Dependent Subjects, *available at* http://clinicaltrials.gov/ct2/show/NCT01666119?term=BEMA&rank=1.

taken from an example in "the USPTO granted US Patent #8,147,866, (issued from US Patent Application No. 13/184,306)," which, according to BDSI, "will extend the exclusivity of the BEMA® drug delivery technology for BEMA® Buprenorphine and BNX in the United States from 2020 to 2027."[19]

Upon analysis of Table 1, it can be seen that the most similar dosage form to the BEMA Bunavail (BNX) film is definitively the Suboxone sublingual film product in NDA # 22-410. To further explain, BDSI's BEMA Bunavail (BNX) Buprenorphine/Naloxone product is a mucoadhesive high surface area to weight ratio polymeric dosage form that is orally delivered and applied to a mucosal surface (i.e., the inside of the cheek). Additionally, the excipient profile and associated functionality of the excipients are very different when compared to those of the Suboxone sublingual tablet, where traditional tableting excipients are used to create a non-polymeric low surface area to weight ratio dosage form with no mucoadhesivity that disintegrates and dissolutes to deliver its drug payload.

Conversely, the BEMA Bunavail (BNX) Buprenorphine/Naloxone film and the Suboxone sublingual film both mirror the form and function that one would expect when comparing a film to a film rather than a film to a tablet. In fact, for film dosage forms, it is mandated that these polymeric excipients be used to obtain not only the desired physical manipulability, but also the overall functionality to enable proper dosing and pharmacokinetic performance.

Importantly, 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 (Suboxone sublingual tablet) purely to circumvent patent certification and a potential patent infringement lawsuit. Allowing such circumvention is not consistent with the 1984 Hatch-Waxman Amendments.

Furthermore, BDSI has offered no substantive analysis showing how its proposed film product is in fact actually more similar to the Suboxone tablet than it is to Suboxone film. Plainly, BDSI seeks to have it both ways: marketing and characterizing its proposed film product to the investing public as poised to be the second film entrant in the market to

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19 BDSI, Form 10K, Fiscal Year Ending Dec. 31, 2012 at 16. We also note that if the actual excipient profile for Bunavail in Table 1 differs to some extent from this expected profile based on the example in BDSI's '866 patent it will not affect any of the points made in this submission.

compete against Suboxone film, while insupportably telling the FDA that somehow its film is really more similar to the Suboxone tablet. Thus, as BDSI would have it, Bunavail is most like Suboxone Film when BDSI seeks to raise money and is most like Suboxone tablets when BDSI seeks to avoid the legal requirement of certifying against Orange Book-listed patents. Such gamesmanship should not be countenanced by FDA.

III. 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 May 25, 2012 (filing of BDSI comment) through June 10, 2013 (BDSI press release announcing filing of NDA). 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: MonosolRx. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,

David B. Clissold

DBC/tee