DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 21 2010

Mark S. Aikman, Pharm.D.
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1205 Culbreth Drive, Suite 200
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Re: Docket No. FDA-2009-P-0356

Dear Dr. Aikman:

This responds to your citizen petition dated July 24, 2009, submitted on behalf of Osmotica Pharmaceutical Corp. (Osmotica) regarding venlafaxine hydrochloride (HCl) extended-release tablets (Second Venlafaxine Petition).[1] In Osmotica's Second Venlafaxine Petition, you request that the Food and Drug Administration (FDA or the Agency) clarify the patent certification requirements for an abbreviated new drug application (ANDA) that relies upon a reference listed drug (RLD) approved through the pathway described by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(b)(2)). Specifically, you request that when an ANDA relies upon an RLD approved through the 505(b)(2) pathway (505(b)(2) application) and the 505(b)(2) application relied upon FDA's finding of safety and effectiveness for a listed drug, FDA require the ANDA applicant to provide an appropriate patent certification or statement to patents listed for the RLD (e.g., Osmotica's venlafaxine HCl extended-release tablets (NDA 22-104)) and for the listed drug upon which the RLD relied (e.g., Effexor XR (venlafaxine HCl) extended-release capsules (NDA 20-699)). You assert that if Sun Pharmaceutical Industries, Ltd's (Sun's) ANDA for venlafaxine HCl extended-release tablets did not contain such patent certification(s) or statement(s), the ANDA should not have been received by FDA because it was deficient on its face. Accordingly, you request that FDA require Sun to submit a new ANDA with appropriate patent certifications.

We have carefully reviewed your Second Venlafaxine Petition. For the reasons described in further detail in this response, your Second Venlafaxine Petition is denied.

## I. BACKGROUND

### A. Venlafaxine Products

On October 20, 1997, Wyeth Pharmaceuticals, Inc. (Wyeth) obtained approval for Effexor XR (venlafaxine HCl) 37.5-milligram (mg), 75-mg, 100-mg,[2] and 150-mg extended-release capsules (Effexor XR or Effexor XR extended-release capsules) for the treatment of major depressive

[1] Osmotica's First Venlafaxine Petition is described in section I.A of this response. FDA intends to issue a separate response to Osmotica's third citizen petition regarding venlafaxine HCl extended-release tablets, submitted on August 20, 2009 (see Docket No. FDA-2009-P-0403).

[2] The 100-mg strength of Effexor XR extended-release capsules has been discontinued from marketing.

disorder.[3] Effexor XR subsequently was approved for the treatment of generalized anxiety disorder in 1999, treatment of social anxiety disorder in 2003, and treatment of panic disorder in 2005.

On April 15, 2003, Lachman Consultant Services, Inc. (Lachman) submitted a suitability petition requesting permission to file an ANDA for a drug product, venlafaxine HCl extended-release tablets, 37.5 mg, 75 mg, and 150 mg, that differed from Effexor XR, the RLD, in dosage form (see section 505(j)(2)(C) of the Act and 21 CFR 314.93).[4] FDA determined that Lachman's request for a change in dosage form (from extended-release capsules to extended-release tablets) was a type of change authorized by section 505(j)(2)(C) of the Act, and granted Lachman's suitability petition on March 30, 2005 (March 2005 Suitability Petition Response).[5] The approval of the suitability petition permitted an ANDA to be submitted for venlafaxine HCl extended-release tablets, 37.5 mg, 75 mg, and 150 mg, that referred to the corresponding strengths of Effexor XR extended-release capsules as the basis for ANDA submission (see 21 CFR 314.94(a)(3)).

On December 12, 2006, Osmotica submitted a 505(b)(2) application (NDA 22-104) for venlafaxine HCl extended-release tablets, the drug product described in the approved suitability petition. The 505(b)(2) application relied for approval on FDA's finding of safety and effectiveness for Effexor XR extended-release capsules and was supported by comparative bioavailability data (see Second Venlafaxine Petition at 3). On May 20, 2008, Osmotica's 505(b)(2) application for 37.5-mg, 75-mg, 150-mg, and 225-mg venlafaxine HCl extended-release tablets was approved for treatment of major depressive disorder and social anxiety disorder. Osmotica did not seek approval of venlafaxine HCl extended-release tablets for the treatment of generalized anxiety disorder or panic disorder, indications for which unexpired marketing exclusivity and/or method-of-use patents are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for Effexor XR, the listed drug relied upon in support of Osmotica's 505(b)(2) application.

On May 30, 2008, Osmotica submitted a citizen petition (First Venlafaxine Petition) requesting that FDA refrain from approving any pending ANDA for venlafaxine HCl extended-release tablets that identifies Wyeth's Effexor XR (NDA 20-699) as the RLD and was submitted based upon an approved suitability petition for the change in dosage form. Instead, Osmotica requested that FDA require any pending ANDA applicant (specifically Sun) seeking approval for venlafaxine HCl extended-release tablets to identify Osmotica's approved NDA 22-104 as the RLD and, in accordance with section 505(j)(2)(D)(i) of the Act, submit a new ANDA for the product. On November 25, 2008, we granted the First Venlafaxine Petition and required Sun or

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[3] Strengths of venlafaxine HCl are expressed as the base equivalent throughout this response.

[4] See Docket No. 2003P-0159/CP. Docket number 2003P-0159 was changed to FDA-2003-P-0351 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[5] See FDA-2003-P-0351-0001. On April 29, 2005, Wyeth submitted a petition for reconsideration of the March 30, 2005, decision on Lachman's suitability petition, and a petition to stay approval of Lachman's suitability petition pending a decision on the petition for reconsideration. On May 14, 2009, Wyeth withdrew its petitions for reconsideration and stay based upon FDA's November 25, 2008, petition response to Osmotica's First Venlafaxine Petition explaining that the intervening approval of an NDA for the product described by the suitability petition precludes an ANDA applicant from referring to the suitability petition and listed drug described therein as its basis for submission.

any other applicant seeking approval of an ANDA for venlafaxine HCl extended-release tablets to submit a new ANDA that identified the corresponding strengths of Osmotica's pharmaceutically equivalent drug product as its RLD. Such an ANDA would be required to contain data and information required by section 505(j) of the Act for approval (including, but not limited to, a demonstration of bioequivalence to the RLD, Osmotica's venlafaxine HCl extended-release tablets, and a patent certification or statement for each patent listed in the Orange Book for the RLD).[6]

### B. Abbreviated Approval Pathways Available Under the Act

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created sections 505(b)(2) and 505(j) of the Act. 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.[7] Section 505(j) of the Act established an abbreviated approval pathway for a drug product that is the same as a previously approved drug (the RLD)[8] with respect to active ingredient, dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics. An ANDA applicant also must demonstrate that its proposed product is bioequivalent to the RLD. An applicant that meets the requirements under section 505(j) for approval may reference the Agency's finding of safety and effectiveness for the RLD and need not repeat the extensive nonclinical and clinical investigations required for approval of a stand-alone NDA submitted under section 505(b)(1) of the Act.

Section 505(j)(2)(C) of the 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 Act and § 314.93(e)(1)(i)). After approval of a drug product that is a pharmaceutical equivalent to the drug described in the suitability petition, the suitability petition and listed drug described therein may no longer be used as the basis for ANDA submission by applicants with pending ANDAs or by prospective ANDA applicants.[9] Accordingly, applicants with pending ANDAs (and prospective ANDA applicants) would be required to identify the pharmaceutically equivalent drug product as their RLD and meet other applicable statutory requirements for ANDA approval.

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[6] See Docket No. FDA-2008-P-0329.

[7] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[8] As defined at 21 CFR 314.3(b), *reference listed drug* means "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application."

[9] We note, however, that it is the Agency's practice not to rescind approval of the suitability petition under these circumstances.

An applicant seeking approval for a drug product that differs from a listed drug in route of administration, dosage form, strength, or active ingredient, as described above, has the option of (1) requesting permission, through a suitability petition, to submit an ANDA (petitioned ANDA) or (2) submitting a 505(b)(2) application. Submission of an application under section 505(b) would be required if investigations were necessary to evaluate the safety and effectiveness of the changed product; however, the 505(b)(2) pathway also may be used to seek approval for changes to an approved product that do not require additional investigations.[10]

Section 505(b)(2) of the 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 a listed drug).[11] 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. To the extent that the listed drug and the drug proposed in the 505(b)(2) application differ, the 505(b)(2) application must include sufficient data to demonstrate that the proposed drug meets the statutory approval standard for safety and effectiveness.

Both ANDA and 505(b)(2) applicants are subject to applicable periods of marketing exclusivity granted to the listed drug relied upon and are 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 Act (see section 505(b)(2)(A)-(B) and 505(j)(2)(A)(vii)-(viii) of the Act). However, only the holder of an application submitted under section 505(b) can, and is required to, file with FDA information on each patent claiming the drug or method of using the drug for listing in the Orange Book (see section 505(b)(1) and 505(c)(2) of the Act).

### C. Patent Listing and Patent Certification Requirements

Section 505(b)(1) of the Act requires the applicant for an NDA to "file with the application 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" (see also 21 CFR 314.53 and section 505(c)(2) of the Act). This requirement applies to both stand-alone NDAs and 505(b)(2) applications. Upon approval of an application under section 505(c) of the Act, FDA publishes the patent information provided by the drug product's application holder in the Orange Book.

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[10] See the draft guidance for industry on *Applications Covered by Section 505(b)(2)* (October 1999) (noting, with reference to the 1992 Final Rule, that "an applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration pursuant to a suitability petition under Section 505(j)(2)(C) of the Act").

[11] A 505(b)(2) application differs from a stand-alone NDA in which the full reports of investigations of safety and effectiveness were conducted by or for the applicant or for which the applicant has a right of reference.

An ANDA applicant must provide a patent certification or statement described in section 505(j)(2)(A)(vii)-(viii) of the Act for each patent that claims the RLD or a method of using the RLD 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 Act. For each unexpired patent listed in the Orange Book, the ANDA 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 ANDA is submitted), or, with respect to a method of use patent, a statement that the patent does not claim a use for which the ANDA applicant is seeking approval (section 505(j)(2)(A)(viii) of the Act).

## II. ANALYSIS

### A. Patent Certification Requirements for an ANDA that Relies Upon an RLD Approved Through the 505(b)(2) Pathway

Osmotica maintains that an ANDA applicant must provide a patent certification or statement to patents that relate to "earlier-approved, underlying NDAs" in specified circumstances to comply with section 505(j)(2)(A)(vii)-(viii) and (B) of the Act. Specifically, Osmotica states that "Sun cannot comply with the patent certification requirements of the Act without including in an ANDA for Venlafaxine HCl Extended-Release Tablets certifications to all Orange Book-listed patents that apply to Effexor XR Capsules" (Second Venlafaxine Petition at 5). Although Osmotica acknowledges that FDA has never explicitly required an ANDA applicant to provide a patent certification or statement to patents listed in the Orange Book for a listed drug relied upon by an RLD approved through the 505(b)(2) pathway, Osmotica asserts that such a requirement would be analogous to FDA policy in other scenarios and requests that FDA "announce and apply to Sun" a similar policy (Second Venlafaxine Petition at 5).

*FDA Response:*

We disagree with Osmotica's assertion that an ANDA must contain a patent certification or statement with respect to patent(s) listed in the Orange Book for a listed drug relied upon by an RLD approved through the 505(b)(2) pathway. There is no statutory or regulatory requirement for an ANDA applicant to submit a patent certification or statement with respect to any patent other than a patent required to be filed by the application holder of the RLD under section 505(b)(1) or 505(c)(2) of the Act and listed in the Orange Book.[12]

As discussed in section I.C of this response, a 505(b)(2) applicant must file patent information on any patent which claims the drug or a method of using the 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" (section 505(b)(1) of the Act; see also section 505(c)(2) of the Act and 21 CFR 314.53). We interpret "drug" in section 505(b)(1) and 505(c)(2) of the Act to mean the drug product (see ANDA Regulations; Patent and Exclusivity

[12] If, in the opinion of the ANDA applicant and to the best of the ANDA applicant's knowledge, information on a patent should have been submitted by the application holder of the RLD for listing in the Orange Book but was not, the appropriate certification is a paragraph I certification. See section 505(j)(2)(A)(vii)(I) of the Act and 21 CFR 314.94(a)(12)(i)(*1*)(permitting an ANDA applicant to certify, with respect to the RLD, that "the patent information has not been submitted to FDA").

Provisions; Final Rule, 59 FR 50338 at 50346 (October 3, 1994)). Thus, if one or more patents listed in the Orange Book for a listed drug upon which the 505(b)(2) application relied for approval (e.g., Effexor XR extended-release capsules) also claim the drug product approved in the 505(b)(2) application (e.g., Osmotica's venlafaxine HCl extended-release tablets) or a method of using the drug product, then the 505(b)(2) applicant is required by statute to file information on such patents for listing in the Orange Book.[13] To the extent that the drug product approved in a 505(b)(2) application differs from the listed drug relied upon, the 505(b)(2) applicant would not be expected to list patents for the listed drug that do not claim the new drug product approved through the 505(b)(2) pathway. For example, Wyeth has listed "method of use" patents that claim one or more indications for which Effexor XR is approved. These method-of-use patents are listed below after the associated indication:

(1) Treatment of Major Depressive Disorder (U.S. Patent Nos. 6,403,120 ('120 patent) and 6,419,958 ('958 patent));
(2) Treatment of Social Anxiety Disorder ('120 patent, '958 patent);
(3) Treatment of Generalized Anxiety Disorder ('120 patent, '958 patent, U.S. Patent Nos. 5,916,923 ('923 patent) and 6,444,708 ('708 patent)); and
(4) Treatment of Panic Disorder (U.S. Patent No. 6,310,101 ('101 patent)).

Osmotica did not seek approval of its venlafaxine HCl extended-release tablets for the treatment of generalized anxiety disorder or panic disorder. Accordingly, Osmotica listed the following method-of-use patents (assigned to Wyeth) for its product:

(1) Treatment of Major Depressive Disorder ('120 patent, '958 patent); and
(2) Treatment of Social Anxiety Disorder ('120 patent, '958 patent).

Thus, an ANDA applicant that identifies Osmotica's venlafaxine HCl extended-release tablets as its RLD would be required to submit an appropriate patent certification or statement to the patents listed by Osmotica as claiming the drug product or a method of using the drug product (i.e., Osmotica's venlafaxine HCl extended-release tablets or its approved methods of use). Notice of a paragraph IV certification must be sent to both the application holder for the RLD and each patent owner (see section 505(j)(2)(B)(iii) of the Act and 21 CFR 314.95(a)).

Osmotica, however, proposes that an ANDA applicant should be required to submit a patent certification or statement for method-of-use patents *other* than those listed by Osmotica for the RLD. Such patents claim methods of using Effexor XR that have *not* been approved for Osmotica's venlafaxine HCl extended-release tablets *and, therefore, for which an ANDA applicant citing Osmotica's product as its RLD could not receive approval.* In addition, Osmotica proposes that an ANDA applicant seeking approval for a duplicate of Osmotica's product should be required to submit a patent certification to a drug substance and/or drug product patent listed for Effexor XR (U.S. Patent No. 6,310,101 (the '101 patent)), even though Osmotica already has effectively verified (by virtue of its filing of patent information for venlafaxine HCl extended-release tablets that omits the '101 patent) that the '101 patent does not claim its venlafaxine HCl extended-release tablets and a claim of infringement of the '101 patent could *not* reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug approved in Osmotica's 505(b)(2) application.

[13] For example, such patents may include patents for which the 505(b)(2) applicant obtained a license from the patent owner to avoid a claim of patent infringement.

There is no basis in the Hatch-Waxman statutory scheme and our implementing regulations for requiring an ANDA applicant seeking approval of a "duplicate" of the RLD to provide a patent certification or statement with respect to any patents other than those filed by the NDA holder for the RLD for listing in the Orange Book.[14] Indeed, FDA would not formally receive an ANDA that contained a paragraph III certification, paragraph IV certification, or 505(j)(2)(A)(viii) statement with respect to a patent that did not claim the RLD or a method of using the RLD. The Act provides an incentive — a period of 180-day exclusivity — for ANDA applicants to challenge patents listed for the RLD that may be invalid, unenforceable, or not infringed by the drug product described in the ANDA. The risks that 180-day exclusivity is designed to reward would not be realized by an ANDA applicant's paragraph IV certification to a patent listed for a drug product other than the RLD and for which a claim of infringement could not reasonably be asserted, in the judgment of the NDA holder for the RLD, against the ANDA applicant.

There are many ANDAs that have relied upon an RLD approved through the 505(b)(2) pathway. Such ANDA applicants have not been required to provide a patent certification or statement with respect to the patent(s) listed in the Orange Book for the listed drug(s) relied upon by the 505(b)(2) applicant in addition to the patents listed for the RLD approved through the 505(b)(2) pathway. For example, Schwarz Pharma's NDA 21-726 for Niravam (alprazolam) orally-disintegrating tablets is a 505(b)(2) application that relied on FDA's finding of safety and effectiveness for Pharmacia and Upjohn's NDA 18-276 for Xanax (alprazolam) tablets. An applicant that submitted an ANDA for alprazolam orally-disintegrating tablets and identified Niravam as its RLD appropriately provided patent certifications only to the patents listed for Niravam. To receive approval, the ANDA applicant was neither required nor permitted to provide a patent certification to the patent that was listed for Xanax at the time the applicant submitted its ANDA.

An ANDA is required to (and only can) contain a patent certification or statement with respect to each patent which claims the RLD or which claims a use for the RLD and for which patent information is required to be filed under section 505(b)(1) or 505(c)(2) of the Act (see section 505(j)(2)(A)(vii) of the Act).

### B. FDA's Requirements for Patent Certification in the Scenarios Described by Osmotica Reflect a Consistent Approach

#### *1. ANDAs Submitted Pursuant to an Approved Suitability Petition*

Osmotica states "[i]t is well settled that FDA will require that an ANDA that is submitted subsequent to another ANDA that was itself approved based on a suitability petition include certifications to any Orange Book-listed patents that apply to the original NDA upon which

[14] In the preamble to our 1994 final rule on patent and exclusivity provisions, we noted: "FDA, however, believes it would be prudent for [ANDA] 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" (see "Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, Part II; Final Rule" (59 FR 50338 at 50346; October 3, 1994). In addition, FDA's regulations do not permit the filing of patent information with respect to certain types of patents, including process patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates (see § 314.53).

approval of the suitability petition was based" (Second Venlafaxine Petition at 6). Osmotica asserts that "*[b]ut for the fact that Osmotica's Venlafaxine HCl Extended-Releast [sic] Tablets product was approved under a 505(b)(2) application*, instead of an ANDA submitted subsequent to an approved suitability petition, the situation here is essentially the same" (Second Venlafaxine Petition at 8) (emphasis added).

*FDA Response*

We disagree with Osmotica's contention that the patent certification scenario for a subsequent ANDA applicant referencing a petitioned ANDA is "essentially the same" as that of an ANDA applicant relying upon a 505(b)(2) application. There is a clear regulatory distinction between reliance on an RLD approved for safety and effectiveness under section 505(c) of the Act (i.e., a stand-alone NDA or a 505(b)(2) application) and reference to a petitioned ANDA designated as the RLD for bioequivalence testing.

As explained in section I.B of this response, a petitioned ANDA is an ANDA that differs from a listed drug in specified ways and for which approval would be warranted without additional clinical safety and/or effectiveness data (see section 505(j)(2)(C) of the Act). FDA requires an ANDA applicant that refers to a petitioned ANDA designated as the RLD for bioequivalence testing (i.e., the reference standard) to include an appropriate patent certification or statement for each patent listed in the Orange Book for the listed drug that served as the basis for the approved suitability petition (see Orange Book, 29th ed., at xxi; see also 21 CFR 314.94(a)(3)(i) ("For an abbreviated new drug application based on an approved petition under § 10.30 of this chapter or § 314.93, the reference listed drug must be the same as the listed drug approved in the petition"). This requirement reflects the fact that, unlike a 505(b)(2) applicant, an ANDA applicant is not required (or permitted) by statute to file patent information with FDA for listing in the Orange Book. Thus, a subsequent ANDA applicant that refers to a petitioned ANDA is required to submit an appropriate patent certification or statement for the listed drug identified in the suitability petition upon which the ANDA necessarily relies. In the absence of this patent certification requirement, a subsequent ANDA applicant could circumvent the patent certification process by submitting an ANDA that references another ANDA and for which no patents can be listed (see, e.g., the example regarding prednisolone sodium phosphate oral solution cited in the Second Venlafaxine Petition at 7 to 8).

2. *A 505(b)(2) Application Relying Upon a Listed Drug Approved Through the 505(b)(2) Pathway*

Osmotica states that "FDA has indicated that ... it would apply a policy that is analogous [to the scenario involving patent certification requirements for a subsequent ANDA submitted pursuant to an approved suitability petition] where one 505(b)(2) application relies on another 505(b)(2) application, which itself relied on previous findings of safety and effectiveness of an earlier approved NDA" (Second Venlafaxine Petition at 8 to 9). In this scenario, Osmotica contends the subsequent 505(b)(2) applicant would be required to certify to patents listed for the listed drug relied upon by the referenced 505(b)(2) application (Second Venlafaxine Petition at 8 to 9). In support of this contention, Osmotica cites FDA's response to an earlier citizen petition

regarding fenofibrate.[15] Osmotica maintains that "the only difference" between a subsequent 505(b)(2) applicant relying upon FDA's finding of safety and/or effectiveness for a 505(b)(2) application and an ANDA applicant citing reliance on an RLD approved through the 505(b)(2) pathway" is that the applicant "seeks approval under section 505(j) instead of section 505(b)" (Second Venlafaxine Petition at 9).

*FDA Response*

FDA implementation of section 505(b)(2)(A)-(B) and 505(j)(2)(A)(vii)-(viii) of the Act reflects a consistent approach to patent certification requirements; differences are attributable to the distinct attributes of the 505(b)(2) and ANDA approval pathways. As we noted in the Fenofibrate Petition Response, "[j]ust as ANDAs need only certify to patents on the listed drugs they reference and on which they rely for approval (and not to patents on other products in the product lines that reference the same underlying investigations that supported the approval of the listed drug referenced), so too, are the 505(b)(2) applicant's patent certification obligations correlated to patents on the listed drug or drugs relied on for approval" (Fenofibrate Petition Response at 8).

Unlike an ANDA submitted for a "duplicate" of an approved drug product, a 505(b)(2) application may rely on the Agency's finding of safety and/or effectiveness (or published literature describing a listed drug) for more than one listed drug to support the safety and/or effectiveness of different aspects of the proposed drug product. If a 505(b)(2) applicant intends to rely upon more than one listed drug, the applicant is required to identify each listed drug in accordance with 21 CFR 314.54 and comply with applicable regulatory requirements (including, but not limited to, an appropriate patent certification or statement with respect to each listed drug relied upon) (see, e.g., Fenofibrate Petition Response at 3, note 2).

For example, a hypothetical 505(b)(2) applicant seeking approval of venlafaxine HCl extended-release tablets for the treatment of generalized anxiety disorder may rely upon Osmotica's NDA 22-104 to support the safety and effectiveness of venlafaxine HCl in an extended-release tablet dosage form and may rely upon Wyeth's NDA 20-699 for Effexor XR capsules to support use of an extended-release formulation of venlafaxine for the treatment of generalized anxiety disorder (an indication for which Osmotica's NDA 22-104 has not been approved). In this scenario, we would require the applicant to identify both NDA 20-699 and NDA 22-104 as listed drugs relied upon in support of its proposed 505(b)(2) application and to submit an appropriate patent certification or statement with respect to each patent listed for each listed drug relied upon.

Although we noted in the Fenofibrate Petition Response that a 505(b)(2) applicant seeking approval for a drug product that relies upon FDA's finding of safety and/or effectiveness for a drug product approved through the 505(b)(2) pathway "*should* certify to the patents of the 505(b)(2) NDA relied on, as well as to the patents of any underlying NDA on which that approved 505(b)(2) NDA relied for approval" (Fenofibrate Petition Response at 10, note 14)

[15] See November 30, 2004, response to Donald O. Beers and William F. Cavanaugh, Jr., re: Docket No. 2004P-0386/CP1 & RC1 at 10, note 14 (Fenofibrate Petition Response). Docket number 2004P-0386 was changed to FDA-2004-P-0089 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

(emphasis added), this was not the situation at issue in the Fenofibrate Petition.[16] We subsequently have *required* an appropriate patent certification or statement to an "underlying NDA" only if the subsequent 505(b)(2) applicant specifically relied for approval on the drug product approved in the underlying NDA, as indicated in the example above.[17] This requirement recognizes the statutory obligation for a 505(b)(2) applicant to list patents in accordance with section 505(b)(1) and 505(c)(2) of the Act given that the 505(b)(2) application may itself become a listed drug relied upon by a subsequent 505(b)(2) applicant (see section I.C of this response). In addition, our approach reflects FDA's experience since issuing the 2004 Fenofibrate Petition Response in consistently applying the statutory and regulatory patent certification requirements to 505(b)(2) applications that relied on the Agency's finding of safety and/or effectiveness for a drug approved through the 505(b)(2) pathway.

### C. An ANDA That Identifies Osmotica's NDA 22-104 as its RLD and Contains an Appropriate Patent Certification or Statement for Each Patent Listed for the Corresponding Strengths of Osmotica's NDA 22-104 Is Eligible for Receipt

Osmotica asserts that "Sun should not be able to circumvent its statutory obligation to certify to all *relevant* patents (i.e., all patents that cover Wyeth's Effexor XR Capsules), just because Osmotica's product is the RLD for purposes of demonstrating bioequivalence" (Second Venlafaxine Petition at 9). Osmotica further states that FDA should not have received Sun's ANDA in accordance with 21 CFR 314.101 if the ANDA did not include a patent certification or statement for each patent listed for Effexor XR extended-release capsules in addition to each patent listed for Osmotica's venlafaxine HCl extended-release tablets. Osmotica contends that such an ANDA would be "deficient on its face" and that "[t]he opportunity to correct the deficiency by amending the application has passed once FDA deems that the application has been received" (Second Venlafaxine Petition at 12).

*FDA Response:*

Osmotica's assertion that Sun has circumvented its statutory obligation to certify to all relevant patents is without merit. The Agency's regulations at 21 CFR 314.94(a)(12)(i), implementing section 505(j)(2)(A)(vii) of the Act, require that an ANDA contain a certification with respect to each patent that "claims the reference listed drug or that claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the act and for which information

[16] The Fenofibrate Petition Response addressed whether a 505(b)(2) applicant must certify to patents on all later-approved products that were approved based, in part, on some or all of the same underlying investigations as the listed drug relied upon.

[17] We note, however, that reliance on a listed drug pursuant to section 505(b)(2) of the Act generally assumes that the drug the applicant is referencing is one for which it is not the application holder and for which it would not have a right of reference. Accordingly, a 505(b)(2) applicant that cross-references relevant studies in its own previous 505(b)(2) application (i.e., that were conducted by or for the applicant or to which the applicant has obtained a right of reference or use), would not be a 505(b)(2) applicant as to its previous 505(b)(2) application. However, the applicant may be relying, in part, for approval of its current 505(b)(2) application upon the Agency's finding of safety and/or effectiveness for the drug product identified in its previous 505(b)(2) application, to which it does not have a right of reference. In this scenario, the 505(b)(2) applicant cannot use its intervening 505(b)(2) application to circumvent its patent certification obligations to the original listed drug, if it continues to rely upon the original listed drug for approval of its current 505(b)(2) application.

is required to be filed under section 505(b) and (c) of the act and [21 CFR] 314.53" (see § 314.94(a)(12)(i); see also § 314.94(a)(12)(iii)). As explained in section II.A of this response, Osmotica's product is the listed drug approved for safety and effectiveness under section 505(c) of the Act upon which an ANDA for venlafaxine HCl extended-release tablets currently must rely.[18] An ANDA applicant that identifies Osmotica's NDA 22-104 as the RLD and submits an appropriate patent certification or statement for each patent listed in the Orange Book for the corresponding strengths of Osmotica's venlafaxine HCl extended-release tablets has satisfied the statutory obligation and the ANDA would be eligible for receipt under § 314.101. (Indeed, FDA would not formally receive an ANDA that contained a paragraph III certification, paragraph IV certification, or 505(j)(2)(A)(viii) statement with respect to a patent that did not claim the RLD or a method of using the RLD.) Thus, Osmotica's request that FDA require Sun to submit a new ANDA with appropriate patent certifications is groundless.

Finally, Osmotica fails to provide any support for its assertion that a patent owner's rights are being prejudiced by FDA's implementation of the patent certification requirements in section 505(j)(2)(A)(vii)-(viii) of the Act (see Second Venlafaxine Petition at 12 to 13). If a patent owner "believes that an applicant has failed to submit required patent information," the remedy for such an omission would be a request for correction of patent information under § 314.53(f) (21 CFR 314.53(f)).

## III. CONCLUSION

For the reasons described in detail in this response, your Second Venlafaxine Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[18] We previously have explained that the scientific justification for requiring a change in RLD for an ANDA submitted based upon an approved suitability petition to a subsequently approved NDA for the drug product described in the suitability petition reflected the need to ensure that the ANDA met applicable bioequivalence requirements with respect to the pharmaceutically equivalent RLD so that it could be determined to be therapeutically equivalent (see generally First Venlafaxine Petition Response). An ANDA that identifies Osmotica's 505(b)(2) application for venlafaxine HCl extended-release tablets as its RLD is referencing the Agency's finding of safety and effectiveness for this drug product; the ANDA must include data and information required under section 505(j) of the Act and FDA's regulations to obtain approval and a rating as therapeutically equivalent to Osmotica's product.