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Wyeth

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VIA HAND DELIVERY
Dockets Management Branch
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Comments to Lachman Consultant Services, Inc. Suitability
Petition, Docket Number 03P-0159 (CP1)**

Ladies and Gentlemen:

Wyeth Pharmaceuticals ("Wyeth") submits these comments in response to the above-referenced Suitability Petition submitted pursuant to section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ("FDCA") by Lachman Consultant Services, Inc. on April 14, 2003. These comments highlight several important safety and efficacy concerns that are raised by the request of the Suitability Petition to allow an abbreviated new drug application ("ANDA") to be filed for an extended release tablet venlafaxine HCl product in reliance on Wyeth's new drug application ("NDA") for an extended release capsule formulation of venlafaxine HCl.

I. Background

A. Effexor[®] XR Capsules

Wyeth developed and markets Effexor[®] XR (venlafaxine HCl) Extended Release Capsules ("Effexor XR"), which was approved by FDA on October 20, 1997 pursuant to NDA 20-699. The active ingredient in Effexor XR is venlafaxine HCl, which metabolizes into O-desmethylvenlafaxine ("ODV") in the body. ODV is an active metabolite.

Effexor XR is indicated for treatment of major depressive disorder, generalized anxiety disorder, and social anxiety disorder. It is administered in a single dose with food either in the morning or the evening. Each capsule should

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be swallowed whole with fluid, or may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce.¹

B. The Suitability Petition

The Suitability Petition seeks FDA's approval to submit an ANDA for extended release tablets in reliance on Effexor XR capsules as the reference listed drug. The Suitability Petition does not contain any support for the change to an extended release tablet dosage form other than proposed labeling.

II. The Legal Standard

Section 505(j)(2)(A)(iii) of the FDCA states that all ANDAs must contain "information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the [reference listed drug]" unless a suitability petition has been approved by the FDA.² Section 505(j)(2)(C) governs FDA's approval of suitability petitions. That section states that FDA must deny a suitability petition (bearing the same active ingredient) if it finds that "investigations must be conducted to show the safety and effectiveness of the drug or any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug."³

FDA's regulations define the phrase "investigations must be conducted" to mean "that information [must be] derived from animal or clinical studies" demonstrating "that the drug product is safe or effective."⁴ FDA further illuminated the meaning of this phrase in the preamble to its proposed rule, where it noted that "[i]f preclinical or clinical data are needed to support safety, or if clinical data are needed to support the effectiveness of the requested change, then an ANDA is not appropriate for the proposed drug product, and FDA will not approve the petition."⁵

¹ See Effexor XR, Prescribing Information (Aug. 2003) (Attached at Tab 1).

² 21 U.S.C. § 355(j)(2)(A)(iii).

³ 21 U.S.C. § 355(j)(2)(C).

⁴ 21 C.F.R. § 314.93(e)(2).

⁵ 54 Fed. Reg. 28872, 28880 (July 10, 1989).

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In addition, FDA's regulations require that the Agency must deny a suitability petition if any of the proposed changes would "jeopardize the safe or effective use of the product so as to necessitate significant labeling changes to address the newly introduced safety or effectiveness problem" ⁶ As a result, a proposed change that presents "diminished safety or effectiveness" or would require "heightened labeled warnings" to ensure safe use of the product, must be denied. ⁷

III. Analysis

A dosage form change from venlafaxine HCl extended release capsules to venlafaxine HCl extended release tablets raises at least three potentially serious safety and efficacy concerns. First, venlafaxine HCl extended release tablet formulations may cause greater incidence, duration, and/or severity of nausea and vomiting in patients. Second, venlafaxine HCl extended release tablet formulations appear to be prone to significant intra-subject variation in bioavailability. Such variability could risk leaving certain patients under-medicated or not medicated. Third, for patients with difficulty swallowing tablets or capsules, Effexor XR can be administered by opening the capsule and sprinkling the contents over applesauce. Tablets, however, cannot be administered in this way.

These issues cannot be addressed by standard ANDA bioequivalence testing alone as per the current FDA guidance on bioequivalence testing. ⁸ As a result, FDA must give serious consideration to these issues before approving the Suitability Petition. At the very minimum, it would appear from the available data that FDA should require additional *in vitro* testing and/or more stringent bioequivalence testing as part of its review of the ANDA for any generic venlafaxine HCl extended release tablet relying on Effexor XR as the reference listed drug. If investigations must be conducted to show the safety and effectiveness of an extended release tablet formulation, FDA would be required to deny the Suitability Petition.

⁶ 21 C.F.R. § 314.93(e)(1)(iv).

⁷ See 54 Fed. Reg. at 28879.

⁸ See FDA: Guidance for Industry: *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations* (March 2003) [Hereinafter, Bioequivalence Guidance].

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A. **Extended Release Tablet Formulations of Venlafaxine HCl May Cause Greater Incidence, Severity, or Duration of Nausea and Vomiting.**

Venlafaxine has been associated with nausea and vomiting.⁹ Although the exact causes for this are unknown, there are at least two possibilities. In both cases, a tablet dosage form may be more prone to cause nausea and vomiting than is an Effexor XR capsule dosage form. As a result, in assessing the Suitability Petition, FDA must take the necessary steps to ensure that a tablet dosage form's safety profile will not differ from that of the Effexor XR capsules.

Venlafaxine HCl most likely causes nausea and vomiting through a centralized effect in the brain.¹⁰ This centralized effect is believed to be affected by the rate at which venlafaxine is absorbed into the blood stream. For example, clinical trials support a relationship between a given formulation's overall T_{max} and the incidence and severity of nausea and vomiting. In Wyeth protocol 0600B1-144-FR, Wyeth compared Effexor XR to an immediate release (IR) venlafaxine formulation and an IV formulation in healthy subjects. T_{max} for the three formulations was directly related to the severity and duration of nausea. The IV formulation (C_{max} of 66 +/- 17) had the fastest T_{max} at 0.5 +/- 0.1, and also led to the most frequent and severe nausea in patients. Similarly, Effexor XR (C_{max} of 36 +/- 15) had the slowest T_{max} at 5.8 +/- 1.6, and led to the least frequent and severe nausea. The IR formulation (C_{max} of 68 +/- 22) was in the middle in both T_{max} (2.8 +/- 0.8) and severity and duration of nausea.¹¹

Similarly, in protocol 0600B1-208-US, Wyeth compared Effexor XR capsules to an IR formulation in outpatients with major depressive disorder.

⁹ See Effexor (immediate release), Prescribing Information (Aug. 2003) (Attached at Tab 2); see also Entsuh R., Chitra R. A benefit-risk analysis of once-daily venlafaxine extended-release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. *Psychopharmacol. Bull.* 1997; 33:671-76 (Attached at Tab 3).

¹⁰ See McManis PG, Talley NJ. Nausea and vomiting associated with selective serotonin reuptake inhibitors: Incidence, mechanisms and management. *CNS Drugs.* 1997; 8:394-401, 395 (Attached at Tab 4).

¹¹ See Wyeth Pharmaceuticals, Supplemental New Drug Submission (S/NDS), Section 3.2.2.2.1, Venlafaxine Administration to Healthy Subjects (Submitted to the Canadian Health Protection Branch, December 1996) (Attached at Tab 5).

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Again, the IR formulation caused the greater severity and duration of nausea. It also caused the greater incidence and severity of vomiting.¹² These results support the existence of the relationship between a formulation's T_{max} and the incidence, severity, and duration of nausea and vomiting.

The tablet formulation contemplated by the Suitability Petition may exhibit a significantly different T_{max} as compared to Effexor XR capsules, thus leading to increased nausea and vomiting. Standard bioequivalence data submitted with an ANDA, however, are not adequate to address these potential safety issues. Standard bioequivalence methodology compares AUC and C_{max} , but does not take T_{max} into account.¹³ As a result, bioequivalence testing cannot ensure that an extended release tablet dosage form will not cause greater nausea and/or vomiting due to faster T_{max} values. It may be necessary, therefore, for FDA to require additional testing in order to be sure that a tablet formulation based on Effexor XR will not lead to unwarranted safety concerns.

It may also be possible that venlafaxine causes nausea and vomiting through a local serotonin effect in the upper gastrointestinal (GI) tract. The capsule formulation of Effexor XR may help it avoid this possible "local" effect. Dry-filled, hard shell capsules, such as those used for Effexor XR, contain packed spheroids of active ingredient within a gel casing. Because of their multi-particulate nature, the spheroids disperse more readily, and are less likely to have a highly localized effect in the upper GI tract. This strengthens the extended release profile of Effexor XR, and reduces the potential for a local effect in the upper GI tract.

As a result, in order to ensure that a tablet formulation has the same safety profile as Effexor XR capsules, FDA should consider requiring additional *in vitro* testing. Even then, there is a risk that the extended release tablet formulations will behave differently than Effexor XR capsules and lead to increased adverse events such as nausea and vomiting. Extended release tablets dissolve in a different way than capsules do. For example, a tablet may get "hung up" in the

¹² See Wyeth Pharmaceuticals, S/NDS Section 3.2.2.2.2, Venlafaxine Administration to Depressed Patients (Submitted to the Canadian Health Protection Branch, December 1996) (Attached at Tab 6).

¹³ See Bioequivalence Guidance.

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GI tract in a way that a capsule would not.¹⁴ Any tablet that gets “hung up” in the GI tract may release large amounts of drug that could enhance a highly localized effect. If this local effect actually does contribute to nausea and vomiting, the incidence of these adverse events could increase, possibly leading to poor compliance.

The potential for this local reaction exists even for an extended release tablet formulation that is bioequivalent to Effexor XR. Any local serotonin reaction in the upper GI tract would occur *before* the active ingredient enters the bloodstream. Bioequivalence measures compare bioavailability of a drug’s active ingredient *in the blood*. Bioequivalence testing thus cannot fully measure whether quantities of the active ingredient are causing a highly localized effect in the upper GI tract.

Not all extended release venlafaxine HCl tablet formulations will necessarily cause greater severity and duration of nausea or vomiting.¹⁵ Nonetheless, in its consideration of the Suitability Petition and any subsequent ANDA, FDA must ensure that an extended release venlafaxine HCl tablet formulation with Effexor XR as the reference listed drug will not cause greater severity and duration of nausea and vomiting in patients. Among other things, increased nausea and vomiting can lead to serious compliance concerns for patients who have been taking Effexor XR and are therefore less accustomed to the side effects.

Because bioequivalence testing might not ensure a similar safety profile, FDA should at the very least consider requiring additional preclinical testing that

¹⁴ A similar problem led to the market withdrawal of Osmosin in Europe after it was found that the dosage form of indomethacin caused drug hang-up on the gut wall, leading to deaths. See M. N. G. Dukes, Two Decades of Drug-induced Disasters, in *Iatrogenic Diseases*, (P. F. D’Arcy & J. P. Griffin, eds. 1986) (Attached at Tab 7).

¹⁵ For example, in protocol 0600D1-159-EU, Wyeth tested a 75 mg slow release carbopol tablet formulation of venlafaxine HCl, which demonstrated somewhat increased frequency, but reduced severity, of nausea than Effexor XR. This tablet formulation, however, was not bioequivalent to Effexor XR. See Wyeth Pharmaceuticals, Report of Clinical Study, Protocol 0600D1-159-EU (Feb. 1, 2001), Supportive Tables ST9-1 and ST9-2 (showing adverse event frequency and severity) (Attached at Tab 8).

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would be sufficient to demonstrate that a venlafaxine HCl extended release tablet based on Effexor XR does not cause heightened levels of nausea and vomiting. If such preclinical testing is not sufficient to rule out potential safety and efficacy concerns, further investigations would be required to support a change to an extended release tablet dosage form. Alternatively, these safety concerns may necessitate significant labeling changes. In either case, FDA would be required to deny the Suitability Petition.

B. Venlafaxine HCl Extended Release Tablet Formulations Can Exhibit Significant Intra-Subject Variation in Bioavailability.

Extended release tablet formulations of venlafaxine HCl may be prone to large intra-subject bioavailability variation. Wyeth has observed this intra-subject variability in clinical pharmacokinetic trials with candidate tablet formulations. For example, in protocol 0600D1-159-EU, Wyeth compared Effexor XR capsules with a carbopol formulation tablet, as well as short-lag, long-lag, and wax matrix extended release tablet formulations using 19 healthy volunteers in a cross-over design.¹⁶ All 19 patients received therapeutically sufficient amounts of venlafaxine and ODV when administered Effexor XR capsules. The tablet formulations, however, exhibited significant incidences of low bioavailability or no bioavailability. For example, 6 of 19 subjects had very low venlafaxine and ODV plasma concentrations after administration of the long-lag tablet formulation. Certain subjects administered the short-lag and wax matrix formulations experienced similar low bioavailability results.¹⁷

Wyeth found similar results in some of its additional clinical pharmacokinetic trials involving developmental formulations of modified release tablets. These results are summarized in Table 1, below:

¹⁶ These tablet formulations were not bioequivalent to the reference Effexor XR formulation.

¹⁷ See Wyeth Pharmaceuticals, Report of Clinical Study, Protocol 0600D1-159-EU (Feb. 1, 2001), Supportive Table ST8-3 (showing AUC Ratio for all four tablet formulations) (Attached at Tab 9). Low bioavailability was defined as < 40% of the AUC for the reference formulation.

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Table 1

Protocol	Reference Formulation	Test Formulation	Frequency of Low Relative Bioavailability	Observed Relative Bioavailability (AUC_{Reference}/AUC_{Test}) in the Low Bioavailability Subjects
0600D1-159-EU ¹⁸	Effexor XR	Carbopol Short-Lag Long-Lag Wax Matrix	0/19 5/19 6/19 5/19	-- 0%, 0%, 0%, 0%, 0% 5 = 0%, 1 = 18% 0%, 19%, 20%, 23%, 30%
0600D1-161-EU ¹⁹	Effexor XR	Short Lag 1.5 Short Lag 3.0 Wax Matrix	3/20 3/20 4/20	13%, 23%, 34% 0%, 5%, 36% 19%, 24%, 30%, 33%

Alternate explanations have been posited for this marked intra-subject variability seen with extended release tablet formulations. In particular, there is a risk that the tablets are dissolving in such a manner that portions are getting “hung up” and not properly absorbed, as discussed further in Section III.A above. Alternatively, tablets may be passing too quickly through the digestive system with inadequate time for full release/absorption of venlafaxine, or the low bioavailability may represent individual tablet failure to release the full dose of venlafaxine. In any event, the data are clear from the work Wyeth has done on

¹⁸ See Tab 9.

¹⁹ See Wyeth Pharmaceuticals, Report of Clinical Study, Protocol 0600D1-161-EU (Apr. 22, 2003), Supportive Table ST8-3 (showing AUC ratios for all studied formulations) (Attached at Tab 10).

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extended release tablet formulations that there is a strong risk of large intra-subject pharmacokinetic variation.²⁰

Any ANDA for a generic venlafaxine HCl extended release tablet formulation with Effexor XR as the reference listed drug must show bioequivalence to Effexor XR in its ANDA.²¹ Bioequivalence, however, is not guaranteed to identify intra-subject variability in individual subjects. FDA generally employs an average bioavailability standard for ANDAs. Intra-subject variability, however, involves single individuals who do not receive enough of the active ingredient, or none at all, from one treatment to the next. A bioequivalence study of a sufficient power could mask some individual variances, which might be dismissed as single outlier values.²² Similarly, a study that is too small could contain insufficient numbers of subjects to give rise to the intra-subject variability that would be evident in a larger study.

The consequences for patients of such a failure to identify significant intra-subject variability could be clinically significant. Effexor XR is indicated for treatment of major depressive disorder. Low bioavailability tablet formulations therefore pose serious safety risks. For example, a patient who is switched from Effexor XR capsules to a low bioavailability extended release tablet formulation could suffer severe adverse reactions associated with sudden discontinuation. These risks of drug discontinuation are identified in the Effexor XR approved labeling, and include agitation, anorexia, anxiety, confusion, impaired coordination, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, seizures, sensory disturbances, somnolence, sweating, tremor,

²⁰ See Table 1, *supra*.

²¹ See 21 U.S.C. § 355(j)(2)(A)(iv).

²² FDA typically does not set maximum limits on the number of subjects in a bioequivalence study.

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vertigo, and vomiting.²³ Of even greater concern, left untreated, patients suffering from major depressive disorder are at risk of suicide or suicide ideation.²⁴

In order to address this important potential issue, FDA should require that any bioequivalence study for a tablet formulation be able to evaluate the frequency of low bioavailability. At the very least, FDA should require a single dose, repeated measure study (e.g. a four-period cross-over design), capable of assuring consistency in performance between individual dosage units. The Agency should then review the bioequivalence data submitted in any ANDA for an extended release tablet formulation for inappropriate intra-subject variability. If FDA determines that it cannot impose such additional bioequivalence requirements, or if such requirements would be insufficient to ensure that the tablet formulation would not exhibit inappropriate intra-subject variability, the Agency should deny the Suitability Petition on the ground that the change to a tablet formulation could present safety or effectiveness issues.²⁵

²³ See Tab 1. Because generic drugs subject to a suitability petition cannot be AB rated, there is a reduced risk of a classic “switch” by pharmacists from Effexor XR to a generic tablet. There is a real risk, however, that managed care organizations may mandate that plan physicians prescribe the generic tablet.

²⁴ See *id.*

²⁵ There also appears to be dosage form dependent variation in venlafaxine bioavailability among different age groups. For example, the dose correction factor for adolescents in Effexor XR is lower than that for Effexor IR (as compared to adults). Similarly, with Effexor XR capsules, the extent of absorption from the gastrointestinal tract is lower in children and adolescents than it is in adults. A tablet formulation may not match the bioavailability profile of Effexor XR in these respects. This could cause potentially dangerous results for children and adolescents if doctors choose to prescribe the tablet formulation in these populations.

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C. A Tablet Formulation Would Require Changes in the Dosage and Administration Portion of the Labeling that Could Prove Dangerous for Some Patients and Would be Impermissible Under the FDCA.

1. A Tablet Formulation Cannot be Administered with Applesauce.

In accordance with the approved labeling, Effexor XR capsules may be administered by opening the capsule and sprinkling the contents over applesauce. This is an important property of Effexor XR because some patients may be unable to swallow a capsule or a tablet. An extended release tablet formulation of venlafaxine HCl, however, cannot be administered with applesauce without compromising the tablet's extended release properties. This poses serious potential safety and efficacy concerns for patients.

Unlike a capsule, in order to sprinkle a tablet into applesauce, patients must crush the tablet into a powder. Crushing the tablet, however, will likely hamper the extended release properties of the tablet. Indeed, Attachment B to the Suitability Petition provides proposed labeling for a venlafaxine HCl extended release tablet formulation with Effexor XR as the reference listed drug. This labeling omits any reference to administration with applesauce and specifically warns patients that "each tablet should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water."²⁶

Even with the proposed labeling submitted with the Suitability Petition, this difference between the capsule and the tablet could pose significant safety and efficacy risks for some patients. Upon approval of a tablet formulation based on Effexor XR as the reference listed drug, some managed care organizations may replace Effexor XR in their formularies with the generic tablet. Patients accustomed to taking Effexor XR with applesauce may find that they are unable to take the drug, thus reducing the drug's overall efficacy. Of even greater concern, some of these patients may decide to crush the tablets and take them with applesauce without realizing that doing so damages the drug's extended

²⁶ See Suitability Petition, Attachment B, Dose and Administration.

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release properties.²⁷ This could result in dose-dumping, leading to potentially serious adverse events.²⁸

This “newly introduced safety or efficacy problem” potentially jeopardizes the safe and effective use of venlafaxine HCl extended release formulations “so as to necessitate significant labeling changes.” In addition to omitting language relating to administration with applesauce, such a venlafaxine HCl extended release tablet formulation based on Effexor XR should carry an affirmative warning instructing patients not to crush the tablet. Pursuant to 21 C.F.R. § 314.93(e)(1)(iv), this need for a new warning is grounds for FDA to deny the Suitability Petition.

2. A Tablet Formulation Would Violate the “Same Labeling” Provisions of the FDCA.

Both the omission of language relating to administration with applesauce and the inclusion of an affirmative warning against crushing the tablet to administer it with applesauce violate the same labeling requirements of section 505(j) of the FDCA. Section 505(j)(4)(G) states that a generic drug must bear the same labeling as its reference listed drug with only a few exceptions.²⁹ These exceptions include “changes required because of differences approved under a [suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers.”³⁰

Section 314.94(a)(8)(iv) of FDA’s regulations describes the types of labeling changes that may be required by differences approved under a suitability petition. Such differences may include “differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an

²⁷ Pharmacists dispensing the drug to patients presumably would have no way of knowing if a given patient plans to administer it with applesauce. They would therefore be unable to warn these patients against doing so with a new tablet formulation.

²⁸ Dose-dumping is a rapid release of a dose from a modified release formulation, which closely resembles the release pattern of an immediate release formulation.

²⁹ See 21 U.S.C. § 355(j)(4)(G).

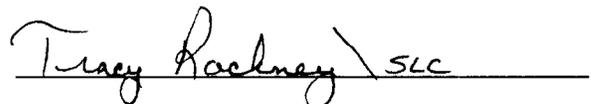
³⁰ *Id.*

indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.”³¹ None of these permitted differences encompasses the significant changes in dosage and administration required by the impossibility of administering a tablet formulation sprinkled over applesauce. As a result, failure to include the applesauce language in the labeling of a venlafaxine HCl extended release tablet with Effexor XR as the reference listed drug would violate section 505(j)(4)(G) of the FDCA.

IV. Conclusion

The changes in dosage form proposed by the Suitability Petition raise serious potential safety and efficacy concerns. Because many of these concerns cannot be addressed through bioequivalence testing, FDA must give serious attention to them as part of its consideration of the Suitability Petition. At the very least, FDA should require additional preclinical testing in order to address these issues. If “investigations” must be conducted to show the safety and effectiveness of the proposed tablet dosage form of extended release venlafaxine HCl, FDA must deny the Suitability Petition.

Respectfully Submitted,



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³¹ 21 U.S.C. § 314.94(a)(8)(iv).

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Attachments