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September 28, 2007

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Re: Docket No. 2007D-0168: May 31, 2007 (72FR 30386-30388) –  
“Draft Guidance on Venlafaxine Hydrochloride”**

Dear: Sir/Madam:

Wyeth Pharmaceuticals is submitting the following comments on the FDA “Draft Guidance on Venlafaxine Hydrochloride,” which describes product-specific bioequivalence recommendations for generic venlafaxine hydrochloride extended release capsules.

Wyeth is one of the largest research-based pharmaceutical and healthcare products companies and is a leading developer, manufacturer and marketer of prescription drugs, biopharmaceuticals, vaccines, and over the counter medications.

Wyeth appreciates the opportunity to comment on the above-mentioned draft guidance, and is recommending the following changes to ensure that the test program outlined in the guidance will provide a valid assessment of bioequivalence between a proposed generic drug product and the reference listed drug, Effexor XR (venlafaxine hydrochloride extended release capsules).

The draft guidance recommends that generic applicants should perform two single-dose studies under fed conditions with 150 mg administered orally. However to ensure that the pharmacokinetics of a proposed generic drug product are not altered by a patient’s dietary habits, Wyeth recommends that a bioequivalence study under fed vs. fasted conditions should also be performed. In addition, a bioequivalence study under multiple dose (i.e., steady-state) conditions is also recommended to ensure that the peak/trough variability of the generic modified release product is minimized in order to meet the pharmacokinetic requirements of a once-per-day dosing interval.

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With regards to the proposed dissolution test method, to adequately demonstrate comparability between a proposed generic and the reference product, testing should be performed in additional media beyond what is specified in the draft guidance.

Our justifications supporting these recommendations are attached. We are submitting the enclosed comments in duplicate. Again, Wyeth appreciates the opportunity to comment on the above-mentioned draft guidance, and trusts that the Agency will take these comments into consideration.

Sincerely,

A handwritten signature in black ink that reads "Roy J. Baranello". The signature is written in a cursive style with a large initial "R" and a distinct "J" at the end.

Roy J. Baranello  
Assistant Vice President  
Global Regulatory Policy & Operations



## **INTRODUCTION**

Venlafaxine, a potent serotonin-norepinephrine reuptake inhibitor (SNRI), was initially developed by Wyeth as an immediate release (IR) formulation. An extended release (XR) formulation was subsequently developed that accomplished the following relative to the IR formulation: 1) lower  $C_{max}$  (peak concentration) and 2) lower frequency of dosing (to once per day).

## **RECOMMENDED STUDIES**

### **Wyeth Comments/Proposal**

The proposed guidance would require 2 single dose studies examining bioequivalence between Effexor XR and the generic formulation under fed conditions with 150 mg administered orally. One study would administer Effexor XR and the generic as a single capsule and in the second study Effexor XR and the generic would be sprinkled on a teaspoon of applesauce. Bioequivalence would be based on 90% confidence intervals for venlafaxine. This proposed guidance also states that due to safety concerns, bioequivalence studies under fasting conditions are not recommended.

Wyeth is not in agreement that the 2 recommended studies are adequate to assure comparable safety, tolerability and efficacy for patients who might be administered a generic version of Effexor XR. In addition, Wyeth does not agree that safety concerns should preclude evaluation under fasting conditions in the conduct of bioequivalence studies with generic venlafaxine hydrochloride extended release products.

Wyeth recommends that 2 additional studies be required. The third study would be a fed vs. fasted bioequivalence study to assure the pharmacokinetics of the generic are not altered by a patient's dietary habits. Additionally, ensuring bioequivalence under fed and fasted conditions would limit the potential for dose dumping following meals of varying fat content. The fourth study that should be required is a bioequivalence study under multiple dose (steady-state) conditions.



## Justification

The labeling for Effexor XR states, "Effexor XR should be administered as a single dose with food either in the morning or in the evening at approximately the same time each day." This recommendation is not based on safety concerns but rather is intended to improve tolerability and patient compliance. Effexor XR can be taken without regard to meals, as supported by the successful demonstration of bioequivalence under fed and fasting conditions by Wyeth (results on file in Effexor XR NDA). Moreover, the FDA's summary basis of approval (SBA) for Effexor XR concludes that there is no food effect on the bioavailability of venlafaxine and its metabolite ODV (O-desmethylvenlafaxine), and that patients may take Effexor XR with or without meals (1).

Appetite and meal content for major depressive disorder (MDD) patients can vary considerably from extensive fasting (i.e., anorexia) to over consumption. Craving specific foods and appetite changes can be severe resulting in large weight loss or gain (2).

Therefore, any generic venlafaxine extended release capsules must provide a consistent pharmacokinetic profile under a variety of meal conditions. This attribute will limit the occurrence in patients of adverse events such as nausea, vomiting, dizziness, and orthostatic hypotension due to a generic product displaying a different pharmacokinetic profile under either fasted or fed conditions. Bioequivalence between fed and fasted conditions should therefore be required in order to ensure that the pharmacokinetic parameters for  $C_{max}$  and AUC for 150 mg of a generic product are bioequivalent to 150 mg of Effexor XR. As such we recommend that the final guidance require a single dose study to specifically evaluate the effect of a high fat meal on pharmacokinetics in comparison to the fasting state.

Secondly, we propose that the guidance require generic applicants to demonstrate bioequivalence to Effexor XR under multiple dose (i.e., steady state) conditions for 150 mg. Although single dose pharmacokinetic studies are more sensitive, the FDA guidance for industry on "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" (March 2003) delineates the need to evaluate a modified release dosage form under steady state conditions. This is to ensure that the peak/trough variability in plasma levels is minimized and meets the pharmacokinetic requirements for a once-per-day dosing interval. It is important that generic venlafaxine HCl extended release products

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have similar accumulation rates and peak/trough variability to Effexor XR, which is dependent on a similar terminal half-life. Because the pharmacokinetics following administration of Effexor XR is characterized by 'flip-flop' kinetics, the terminal half-life can potentially be altered if the rate of absorption is altered.

## **Conclusion**

In conclusion, Wyeth recommends that in order to assure bioequivalence between Effexor ER and generic venlafaxine HCl extended release products, 2 additional studies be included in the "Guidance on Venlafaxine Hydrochloride." These 2 additional studies would be: 1) fed (high-fat meal) versus fasted study demonstrating bioequivalence of 150 mg of the generic under fasted and fed conditions, and 2) a demonstration that the generic product is bioequivalent to 150 mg of Effexor XR under multiple dose (i.e., steady state) conditions.

## **DISSOLUTION TEST METHOD**

### **Wyeth comment/Proposal**

The proposed guidance references a Dissolution Methods Database and requires comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. In addition, for modified release products, dissolution profiles on 12 dosage units of test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted.

The Effexor XR commercial product is designed as a pH independent formulation, releasing the drug over an extended period of time. Additionally, the pellets in the capsule may also be sprinkled on applesauce and administered. Based on our in-vitro experience, Wyeth proposes that at a minimum, the dissolution media required for comparison of the in-vitro release of our product and similar products must include: water, 0.9% sodium chloride, 0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, Simulated Intestinal Fluid without enzymes (feSIIF) pH 5.0, feSIIF pH 6.8, and water after exposure to applesauce (pH 4.0). For comparison of multipoint dissolution profiles obtained in multiple media, similarity testing should be performed using pairwise dissolution profiles obtained in each individual medium (3). An  $f_2$  value between 50 and 100 must be met in each media. The dissolution procedure must be validated for testing in any of the dissolution media and the specification must be met.

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## Justification

Wyeth has examined the effect of dissolution apparatus, agitation and pH on the in vitro release of venlafaxine from 75 mg, 100 mg and 150 mg clinical batches of Effexor XR. Dissolution experiments were conducted using USP Apparatus 1 (baskets) and Apparatus 2 (paddles) at 50, 75 and 100 rpm. Dissolution media included water, simulated gastric fluid (without enzyme) and simulated intestinal fluid (without enzyme). The in vitro release of venlafaxine was unaffected by any of the test conditions as indicated by similarity factor ( $f_2$ ) calculations all having values greater than 50 (4). These data indicate the robustness of the formulation under multiple in vitro test conditions, and provide evidence that the in vivo release of venlafaxine would not be affected by gastrointestinal volume, composition, pH, surface tension, viscosity, or motility.

## Conclusion

In conclusion, Wyeth proposes that in order to assure comparability between Effexor XR and generic products, dissolution profiles be obtained in the following media:

- Water
- 0.9% sodium chloride
- 0.1N HCl
- pH 4.5 acetate buffer
- pH 6.8 phosphate buffer
- (feSIIIF) pH 5.0
- (feSIIIF) pH 6.8
- Water after exposure to applesauce (pH 4.0)

For comparison of multipoint dissolution profiles obtained in multiple media, similarity testing should be performed using pairwise dissolution profiles obtained in each individual medium (3). An  $f_2$  value between 50 and 100 must be met in each media. The dissolution procedure must be validated for testing in any of the dissolution media and the specification must be met.

## References:

- (1) FDA summary basis of approval (SBA) for Effexor XR

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- (2) Diagnostic and Statistical Manual of Mental Disorders (DSM IV- TR); 4<sup>th</sup> edition; 2000; Chapter "Mood Disorders"; American Psychiatric Association; Washington, DC
- (3) FDA, Guidance for Industry, SUPAC MR: Modified Release Solid Oral Dosage Forms, September 1997
- (4) Smith, D., The Development and Validation of a Level A In Vitro/In Vivo Correlation (IVIVC) for Effexor XR Capsules: Final report. Wyeth Research RPT-62046, 2005