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

**Re: Docket No. 2005P-0383 - Response to Citizen Petition filed by Savient  
Pharmaceuticals, Inc.**

Dear Sir or Madam:

This letter is submitted on behalf of Savient Pharmaceuticals, Inc. ("Savient") in response to recent comments filed on February 28, 2006 by Frommer Lawrence & Haug LLP ("Frommer")<sup>1</sup> with regard to Savient's September 2005 Citizen Petition.<sup>2</sup> This letter is in full agreement with the original 2005 petition, and does not restate the complete basis for Savient's position, but instead only responds to the Frommer comments.

In its comments, Frommer argues that Savient's petition should be denied, and that FDA should not have granted three-year exclusivity for the Oxandrin<sup>®</sup> geriatric dose supplement because Frommer believes that the supplement was not supported by new clinical data. Additionally, Frommer incorrectly characterizes the geriatric dosing recommendation as a change in mandatory safety information, and not a change for which exclusivity can be granted. Finally, Frommer argues that despite Savient's exclusivity, applicants for generic versions of oxandrolone should be able to "carve out" the geriatric dose information. As discussed below, Frommer's comments are factually and legally inaccurate.

**I. Frommer's Response is factually inaccurate with regard to Savient's clinical studies supporting geriatric labeling exclusivity.**

The Frommer Response bases several of its arguments that the Savient Citizen Petition should be denied on factual assumptions that are incorrect.

<sup>1</sup> Letter from Frommer Lawrence & Haug LLP to Division of Dockets Management, Docket No. 2005P-0383 (Feb. 28, 2006) ("Frommer Response").

<sup>2</sup> Citizen Petition, Docket No. 2005P-0383 (Sep. 19, 2005) ("Savient Citizen Petition").

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**RC 1**

First, the Frommer Response asserts that Savient should not receive geriatric labeling exclusivity because its request was based on "re-analyzed, formerly-submitted clinical studies." Frommer Response at 1. The Frommer Response states that Savient's clinical data used to obtain geriatric labeling exclusivity "were most likely obtained entirely from clinical studies submitted in 1995 or earlier to support the approval of Oxandrin®." *Id.* at 10. The response also states that Savient "acknowledges that its 'clinical studies' were not new" and that Savient "merely complied with the geriatric labeling requirements . . . by comparing already available pharmacokinetic data comparing elderly and younger patients." *Id.* at 10, 11.

This assertion that Savient based its geriatric labeling exclusivity on re-analyzed formerly submitted data from previous clinical trials is totally inaccurate. Savient based its application for geriatric labeling exclusivity upon the data gathered from four different clinical trials and other studies all of which were conducted after the 1997 final geriatric labeling rule.<sup>3</sup> One of these clinical trials specifically targeted the safe use of Oxandrin® in the elderly, and the others evaluated use of Oxandrin® for conditions that significantly impact the geriatric population. These clinical trials provided the data for Savient's supplemental NDA, and were "reports of new clinical investigations" as required by section 505(b) of the Federal Food Drug and Cosmetic Act ("FFDCA") for the grant of three-year exclusivity. Thus, Frommer's argument, on which the petition response is largely based, that Savient should not receive exclusivity because its application was based on data that was merely re-analyzed, is factually incorrect and should be ignored.

## **II. Frommer's Response incorrectly characterizes the geriatric dosing recommendation as safety labeling for which exclusivity cannot be granted.**

Savient's three-year exclusivity for new geriatric dosing recommendations for Oxandrin® was properly granted by FDA. The Frommer Response mistakenly categorizes Savient's labeling change as new risk or warning information for which exclusivity cannot be granted. In support of its position, Frommer selectively cites statements made by FDA in the preamble to the final ANDA regulations that exclusivity would not apply to "changes in labeling that involve warnings or other such risk information that must be included in the labeling of generic competitors."<sup>4</sup> Frommer reads this statement in an artificially narrow way, since most labeling changes that are properly granted exclusivity by FDA contain statements that involve warnings or other risk information.

In the instant situation, Savient's exclusivity was not granted for changes made to warnings or risk information. Such changes were incidental to the labeling change that was the basis for the grant of exclusivity, *i.e.* the geriatric dosing recommendation.

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<sup>3</sup> 62 Fed. Reg. 45,313 (Aug. 27, 1997), codified at 21 C.F.R. part 201.

<sup>4</sup> 59 Fed. Reg. 50,338, 50,357 (Oct. 3, 1994).

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New indications, new dosing information, and pediatric labeling are regularly granted exclusivity by FDA, and they will generally include as a subordinate element, warnings and risk information that is associated with that new indication, dosing information or pediatric data. Thus, it is only supplements with new warnings or risk information that do not include a separate underlying basis for exclusivity that are the subject of FDA's statement. That is not the case here.

Support for the proposition that labeling exclusivity is properly granted despite new risk or warning information being included is found in FDA regulations. The ANDA regulations regarding the "carving out" of exclusive indications states that such protected labeling can be excluded so long as FDA finds that the differences in labeling that would result from such a carve out would not "render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."<sup>5</sup> This regulation presupposes that new labeling protected by exclusivity may contain information that cannot be carved out without making the drug less safe. Thus, FDA foresaw that some warnings and risk information that is integral to properly protected labeling can be included in the grant of exclusivity.

The ANDA final rule preamble that was cited by Frommer supports the grant of exclusivity to Savient. In that preamble, FDA states that exclusivity could be granted for a variety of labeling changes, including "changes in active ingredient, strength, dosage form, route of administration, or conditions of use," and the preamble further states that "the agency did not intend to suggest that other types of changes would not qualify. For example, changes in dosing regimen have resulted in grants of 3-year exclusivity."<sup>6</sup> Thus, FDA's grant of exclusivity for the geriatric dosing information for Oxandrin<sup>®</sup> was proper and in accordance with long-standing FDA policy and practice.

**III. The geriatric dose recommendation contains information that cannot be omitted from the Oxandrin<sup>®</sup> labeling without rendering the drug less safe or effective.**

As discussed in the preceding section of this letter, FDA regulations prohibit the "carving out" of exclusive labeling, when such an omission would "render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."<sup>7</sup> As stated in more detail in Savient's original 2005 petition, the geriatric dose recommendations for which exclusivity was granted are essential to the safe use of the drug in a significant segment of the drug's target treatment population. The changes to the labeling included additions to the clinical pharmacology section and the dosing and administration section, as well as to a new statement regarding geriatric use under the precautions section. The geriatric dose information is not limited to any particular indication for use, and broadly applies to all uses of the drug in the geriatric population.

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<sup>5</sup> 21 C.F.R. § 314.127(a)(7).

<sup>6</sup> 59 Fed. Reg. 50,338, 50,357 (Oct. 3, 1994).

<sup>7</sup> 21 C.F.R. § 314.127(a)(7).

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The exclusivity-protected geriatric dosing information may not be included in any generic version of Oxandrin<sup>®</sup>, and because the exclusion of this information would make the drug less safe and effective for the geriatric patients who rely upon the drug, this protected labeling cannot be omitted from any oxandrolone drug product that relies on the data and information in Savient's reference listed version of the drug. The Frommer Response attempts to overcome the clear intent and plain language of the FDCA and FDA regulations through two examples of drugs where certain information was successfully "carved out," and through a factually and legally unsupportable assertion that the dosing recommendation included in the new Oxandrin<sup>®</sup> labeling is obvious, and that physicians would automatically know how to dose their geriatric patients.

A. The examples provided in the Frommer letter do not support carving out the protected geriatric information.

The two examples provided in the Frommer Response as illustrative of the principle that protected dosing information can be omitted from the labeling of generic drugs were both adequately addressed and distinguished in Savient's original 2005 petition, and the key points will be restated herein.

Frommer first argues that FDA's allowance of the omission of protected dosing information for the drug Ultram<sup>®</sup> (tramadol) is applicable to Oxandrin<sup>®</sup>. In that case, Ultram<sup>®</sup>'s sponsor first submitted revised dosing information that involved a titration schedule that was intended for a substantial portion of the intended patient population. FDA never addressed the question as to whether this dosing information could be omitted from the labeling of generic tramadol products, and the point became moot when the exclusivity for this dosing information expired. Subsequent to the approval of the dosing supplement, Ultram<sup>®</sup>'s sponsor gained approval of a second dosing supplement, which was also granted exclusivity. This second dosing label change was only applicable to a very small subset of tramadol patients, and for majority of patients would represent an inferior dosing scheme. FDA permitted generic drug applicants to omit the labeling from the second supplement, but required the inclusion of the information on dosing from the first supplement.

The Ultram<sup>®</sup> situation is easily distinguishable from the Oxandrin<sup>®</sup> geriatric dose situation. In the case of the former, the dosing information was only applicable to a very small subset of patients using the drug, while for Oxandrin<sup>®</sup>, the geriatric dosing information is applicable to a significant portion of the target treatment population. Frommer has not demonstrated that the geriatric population is a very small subset of patients using Oxandrin<sup>®</sup>. Absent such proof, the geriatric dosing information cannot be excluded from the labeling without affecting the safety of the public.

The second example cited by Frommer is even less applicable to the Oxandrin<sup>®</sup> labeling issue. In that case, the drug Rebetal<sup>®</sup> was indicated for use in combination with either the drug Intron<sup>®</sup> or PEG-Intron<sup>®</sup>. The labeling for the combination of Rebetal<sup>®</sup> with PEG-Intron<sup>®</sup> was protected by labeling exclusivity. FDA permitted the exclusion of the labeling related to the combination with PEG-Intron<sup>®</sup>, stating that the combination of Rebetal<sup>®</sup> with Intron<sup>®</sup> was not subject to protected labeling, and that the exclusion of the protected PEG-Intron<sup>®</sup> labeling would not make the drug less safe for the non-protected use. FDA's actions are clearly supported by the ANDA regulations and ordinary analysis that permit the omission of one indication when such omission does not render other, non-protected, uses less safe or effective. The use of the Rebetal<sup>®</sup>/Intron<sup>®</sup> combination is in no way effected by the omission of the Rebetal<sup>®</sup>/PEG-Intron<sup>®</sup> combination labeling. In contrast, all uses for Oxandrin<sup>®</sup> are potentially rendered less safe with the omission of the protected geriatric labeling.

- B. The information contained in the protected Oxandrin<sup>®</sup> labeling is not self-evident, and inclusion of that information in the labeling is required to most effectively protect geriatric patients.

The Frommer Response states that physicians would start geriatric patients at a "lower effective dose to prevent further impaired renal function" even without Savient's geriatric labeling information for Oxandrin<sup>®</sup>. Frommer Response at 11. In essence, Frommer argues that the proposed geriatric dosing recommendation is inherently obvious, and should be self-evident to physicians.

The response assumes that physicians would prescribe a lower dose because of the adverse events associated with the Oxandrin<sup>®</sup>. Because Oxandrin<sup>®</sup> is metabolized by the liver and excreted by the kidneys, any impairment of these functions could increase adverse events associated with Oxandrin<sup>®</sup>. A physician would be correct to use this knowledge to recommend a lower dosage than those typically recommend to his patients. Nevertheless, without the benefit of Savient's clinical data, a physician would not know that all geriatric patients, including those without renal function problems, should receive a starting dosage of 5 mg bid. Therefore, Savient's additional labeling information has helped ensure that geriatric patients will receive a more appropriate dosage level of Oxandrin<sup>®</sup> that balances both the risks of adverse events and the therapeutic benefits of the drug.

In contrast to Frommer's suggestion, relatively little is known about anabolic steroids generally, and oxandrolone in particular, in geriatric patients. Most studies in this class of drugs were conducted in children, young adults, and middle aged adults. The comparative amount of data in geriatric subjects is lacking. Therefore, Savient's studies in Oxandrin<sup>®</sup> represent significant and important new data. Generally speaking, it is often assumed that the elderly should receive lower doses of many drugs due to less efficient metabolism. However, absent the drug specific data such as that generated by the Oxandrin<sup>®</sup> studies, these assumptions are only

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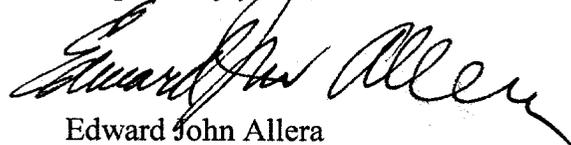
the physician's best guess. Absent specific data, it is not possible for the physician to make an informed decision about the correct starting dose.

**IV. Frommer's accusation of abuse of the petition process is baseless.**

Frommer makes an accusation that Savient's 2005 petition represents an abuse of the citizen petition process; however, Frommer provides no basis for this accusation other than some general statements that other pioneer drug companies have used the process for delay. These general statements have no more basis than Frommer's allegations that Savient's studies are nothing more than re-analyzed data from old studies. The alleged abuse of the citizen petition process by some minority of the regulated industry does not remove the right of companies, such as Savient, to protect their valid legal rights to exclusivity.

Savient's concerns with regard to the exclusive geriatric labeling for Oxandrin<sup>®</sup> raise important legal and scientific issues and cannot be wished away by potential generic competitors. A generic drug company's desire to bring a product to market does not automatically trump the legitimate scientific and regulatory concerns of the pioneer. FDA has indeed recognized that the petition process has in some situations been abused by companies seeking to delay FDA action on any number of issues; however, Frommer fails to provide any meaningful evidence in its erroneous memo that would lead to the conclusion that Savient's concerns with regard to the protection of its exclusivity rights granted by FDA are anything other than legitimate.

Respectfully yours,



Edward John Allera  
Theodore Sullivan