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February 28, 2006

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

Re: Proposed Citizen Petition Response to Savient's 2005P-0383; Oxandrolone

Dear Sir/Madam:

The following comments submitted in opposition to the above-referenced Citizen Petition ("Savient Petition") filed September 19, 2005 on behalf of Savient Pharmaceuticals Inc. ("Savient").

The Savient Petition should be denied in an expeditious manner. Savient should not have received any geriatric labeling exclusivity in the first place, because its geriatric labeling was evidently based on re-analyzed, formerly-submitted clinical studies, or the labeling consists of mandatory safety information not warranting exclusivity. Alternatively, the labeling exclusivity should not prevent the marketing of generic oxandrolone products that "carve out" such labeling. The Savient Petition, manifestly intended to delay generic competition in the oxandrolone market, must be rejected.

A. Labeling Exclusivity Based on New Clinical Investigations

The Federal Food, Drug, and Cosmetic Act, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) ("Hatch-Waxman"), established a mechanism where a generic, bioequivalent version of a reference listed drug (RLD) may be filed and approved as an ANDA for marketing in interstate commerce in the United States. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1358 (Fed. Cir. 2003) (citing 21 U.S.C. § 355(j)); *see also* Hatch-Waxman Title I; 21 C.F.R. § 314.94. An RLD is a drug previously approved for marketing by FDA and listed as such in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"), previously published and now *available at*

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http://www.fda.gov/cder/orange/default.htm. *See* 21 U.S.C.A. § 355(j)(7); 21 C.F.R. 314.3(b); FDA Draft Guidance for Industry: Listed Drugs, 30 Month Stays, and Approval of ANDAs and 505(b)(2) Applications Under Hatch-Waxman, as Amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 Questions and Answers, *available at* http://www.fda.gov/cder/guidance/6174dft.pdf (October 2004). Following the enactment of the MMA, FDA did not amend the RLD definition. *Id.* at 2.

If FDA approves a supplement submitted by the RLD holder under FD&C Act § 505(b) containing reports of new clinical investigations (other than bioavailability studies) essential for approval of the supplement, and the studies were conducted or sponsored by the RLD holder, FDA may grant three years of marketing exclusivity for the new labeling. *See* 21 U.S.C.A. § 505(j)(5)(F)(iv). While FDA has not expressly stated what types of supplemental applications would warrant three years of exclusivity, FDA has determined that changes in warnings or risk information would not qualify for such exclusivity, because excluding such information would serve no public health interest. FDA noted in the preamble to its final ANDA regulations:

> FDA declines to define in the regulations the kinds of supplemental applications that, if supported by clinical investigations, would warrant 3-year exclusivity. Although the preamble to the proposed rule identified certain types of changes in a product that would normally warrant exclusivity (changes in active ingredient, strength, dosage form, route of administration, or conditions of use), the agency did not intent to suggest that other types of changes would not qualify. For example, changes in dosing regimen have resulted in grants of 3-year exclusivity. Changes that would not warrant exclusivity are, as discussed in the proposed rule, changes in labeling that involve warnings or other such risk information that must be included in the labeling of generic competitors. Applicants containing approval for such changes in labeling would, in any event, have no valid interest in precluding such information from the labeling of other products.

Abbreviated New Drug Regulations; Patent and Exclusivity Provisions ("Final Patent and Exclusivity Regulations"), 59 Fed. Reg. 50,338, 50,357 (Oct. 3, 1994) (codified at 21 C.F.R. pt. 314).

B. Labeling "Carve Out": Section viii Statement of Non-Applicable Use

In Hatch-Waxman, Congress provided that FDA may approve an ANDA with less than all of the RLD's labeling. *See Warner-Lambert*, 316 F.3d at 1359-61; *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1495-96 (D.C. Cir. 1996); 21 C.F.R. § 314.107. While ideally a generic drug would be labeled the same as the RLD, Congress realized that there would be some differences between the generic and RLD labeling. For instance, Congress permitted differences in the two sets of labeling, because the generic is manufactured by a different entity than the RLD. *See* 21 U.S.C.A. §§ 355(j)(2)(A)(v), 355(j)(4)(G) (2005).

Regarding RLD indications protected by an Orange Book patent, Congress further expanded this labeling exception in Hatch-Waxman with a provision that permits a generic applicant to submit an ANDA with labeling that omits RLD labeling for indications protected by patent. Assuming that an RLD labeling containes more than one indication, therefore, a generic drug applicant can submit an application for the same drug substance along with a "section viii" statement that the ANDA did not claim a patent-protected use. *See* 21 U.S.C.A. § 355(j)(2)(A)(viii). Congress enacted this provision, with full knowledge of the concepts of patent infringement and new labeling exclusivities for supplements containing reports of new clinical investigations, which were also addressed in Hatch-Waxman in this context.[1] The report submitted with the House bill for Hatch-Waxman explained this provision:

> The Committee has adopted the FDA's policy of utilizing the term "same" except that the bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved. For example, if the listed

[1] *See, e.g.*, 35 U.S.C.A. § 271(e), which distinguished that it would not be an act of infringement to use a develop and submit a generic drug for an RLD drug without RLD labeling protected by a patent, while it would be an infringement to market such ANDA for the patent protected used following market approval, whether or not the ANDA product contained such protected labeling. New labeling exclusivities are also directly provided for in the statute. *See, e.g.*, 21 U.S.C.A .§505(j)(5)(F)(iv).

> drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

H.R. Rept. No. 857 (Part I), 98th Cong., 2d Sess. at 21-22, reprinted in 1984 U.S.C.C.A.N. 2654-55. The legislative history does not indicate that Congress intended to limit this provision in any way, *e.g.*, based on actual market sales of any particular indication or use of a RLD.

FDA promulgated corresponding regulations and guidances to implement and expand these Hatch-Waxman provisions. FDA's regulations provide that generic drugs can include labeling differences to comply with current FDA labeling guidelines or other guidance, or omit an indication protected by patent *or exclusivity*. *See* 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added). FDA's regulations further provide that if an ANDA omits an indication protected by patent or exclusivity, FDA must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." Letter from Janet Woodcock, Director, FDA Center for Drug Evaluation and Research (CDER) to Apotex Corporation, Teva Pharmaceuticals USA and Winston & Strawn (for Caraco Pharmaceutical Labs, Limited) (FDA Docket Nos. 01P-0495, 02P-0191, and 02P-0252) (June 11, 2002) ("FDA Tramadol Response") at 5 (regarding generic tramadol Section viii labeling and quoting 21 C.F.R. § 314.127(a)(7)). FDA's guidances send a similar message. *See, e.g.*, FDA Draft Guidance for Industry: Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications, *available at* http://www.fda.gov/cder/guidance/3660dft.pdf (October 2000) ("Discontinued Labeling Guidance") at 2 (explaining, for example, that FDA permits generic applicants to omit labeling protected by patent or exclusivity if the resultant labeling does not render the product unsafe for the remaining uses).

FDA's authority to approve an ANDA for its labeled intended use that does not contain RLD indications protected by patent or exclusivity has been consistently affirmed by the counts. *See, e.g., Bristol-Myers Squibb*, 91 F.3d at 1500 (citing 21 U.S.C. § 355(j)(2)(A)(v) and the Congressional intent to permit ANDAs that omit RLD labeling indications protected by patent); *Sigma-Tau Pharm., Inc. v. Schwetz*, 288 F.3d 141, 148 (4th Cir. 2002). Without evidence to the contrary, FDA presumes that the intended use of an ANDA is contained in the product's labeling, regardless how it is prescribed by physicians or dispensed by pharmacists. *See Sigma-Tau*, 288 F.3d at 147.

C. Examples of Section viii "Carve Outs" - Ribavirin, Tramadol, and More

Two recent examples where FDA permitted section viii "carve outs" involved the drug products tramadol (Ultram®) and ribavirin (Rebetol®).

Ultram® (tramadol) is indicated for "the management of moderate to moderately severe pain." Following its initial approval on March 3, 1995, the dosing schedule for Ultram® was modified twice, based on the submission of clinical studies, for which FDA granted three years of new labeling exclusivity in each instance, which also included a six month pediatric extension for each. The dosing regimen was modified sequentially as follows (FDA approval dates for labeling in parentheses): 1) 50 to 100 mg every 4 to 6 hours as needed, not to exceed 400 mg per day (March 3, 1995), 2) titrated dose of 50 mg per day for 3 days, with increasing increments of 50 mg per day for 3 days until an effective dose not exceeding 400 mg per day was reached after day 10 i.e., a 10-day titration schedule (August 21, 1998), and 3) titrated dose of 25 mg per day for three days, with increasing increments of 25 mg per day for 3 days until an effective dose not exceeding 400 mg per day was reached after day 16 i.e., a 16-day titration schedule (December 23, 1999). FDA Tramadol Response at 2-3.

FDA reviewed the approved labeling for Ultram® and determined that generic tramadol could be approved omitting the third listed dosing regimen above under 21 C.F.R. § 314.127(a)(7) i.e., the resultant labeling would not be less safe or effective "for all remaining, non-protected conditions of use." *Id.* at 10 (quotation from 21 C.F.R. § 314.127(a)(7)). FDA distinguished the two subsequent titration schedules, noting that the 10-day schedule included clinical data to demonstrate that the titration improved the tolerability of tramadol in the *general population* that did not require rapid relief. In contrast, the 16-day schedule provided "limited" utility, because it included clinical data to demonstrate that the titration improved the tolerability of tramadol only for patients who were previously intolerant to tramadol i.e., *not the general population. Id.* at 8-9. FDA also concluded that the 10-day schedule provided sufficient labeling information for physicians to determine whether the benefits of improved tolerability of a titration schedule outweighed more rapid relief without such a schedule. *Id.*

Rebetol® contained two combination uses, one for rivabirin with INTRON® A (interferon alfa-2b, recombinant) and the other for ribavirin with PEG-Intron® (peginterferon alfa-2b, recombinant). Both combination uses treat hepatitis C, but

in different patient populations. The INTRON® A and PEG-Intron® labelings also included directions for using these products with Rebetol®. While the combination use of ribavirin with PEG-Intron® was protected by new labeling exclusivity, FDA permitted generic ribavirin that omitted this combination use, because the combination use of ribavirin with INTRON® A was not protected, and would not be less safe or effective in the absence of the PEG-Intron® labeling. Letter from Steven K. Galson, Acting Director FDA/CDER to David M. Fox, Esq., counsel for Valeant Pharmaceuticals Inc. (RLD holder for Rebetol®) (FDA Docket No. 2003P-0321/CP1) (Apr. 6, 2004) ("FDA Ribavirin Response") at 21. Although Valeant argued in a Citizen Petition that the labeling for PEG-Intron® and common substitution use of generic products[2] would "misbrand" the product, FDA determined that absent the omitted labeling in generic ribavirin products, it would not be "reasonable" to conclude that either of these argued "uses" constituted labeling protected by the combination use exclusivity. *Id.*

In its response to Valeant's citizen petition, FDA noted that FDA had consistently approved generic products the omitted labeling protected by patent or exclusivity in a variety of situations:

> 1) Omitting a protected dosing schedule, *e.g.*, generic tramadol (FDA Docket Nos. 01P-0495, 02P-0191, and 02P-0252);[3]
>
> 2) Omitting indications with indication-specific dosing instructions, *e.g.*, generic captopril removing two protected indications with corresponding protected, indication-specific dosing information;
>
> 3) Generic versions of co-packaged products, *e.g.*, generic ifosfamide approved stand alone, which had been previously only marketed with mesna (relevant FDA Docket Nos. 01P-0061; Determination that IFEX (Ifosamide for Injection), 1-Gram and 3-Gram Vials, Was

[2] The common practice of substituting generic products when one exists, regardless of the labeling on the generic product, was argued to be a "foreseeable use" that would cause the generic product to be misbranded under section 505 of the FD&C Act. FDA Ribavirin Response at 27-29.

[3] Savient raises the argument that FDA would not have approved the generic labeling for tramadol if the patent and exclusivity for a dosing schedule consisting of a titration schedule had not expired prior to approval i.e., discontinued labeling that included only the non-titration dosing schedule. Savient Petition at 12-13. FDA did not address this issue, because "adequate" labeling remained on the labeling that was not protected by patent or exclusivity. FDA Tramadol Response at 2.

Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 67 Fed. Reg. 34,457 (May 14, 2002); and

4) Generic products with Medication Guides, *e.g.*, isotretinoin.[4]

FDA Ribavirin Response at 20.

In light of these and other considerations, Savient's assertions that generic oxandrolone products would be less safe or effective if they omitted new geriatric labeling (Savient Petition at 12) is specious and untimely, as discussed *infra*, in light of the prior safe use of oxandrolone since 1964 for the same indications in the same patient populations without such labeling.

D. Why Geriatric Labeling for Oxandrolone Should Not Have Received Labeling Exclusivity

1. Geriatric Labeling

Drug manufacturers have been placed on notice that their clinical studies should include sufficient numbers of elderly subjects as early as 1990. FDA has encouraged sponsors to include more elderly subjects in its initial clinical studies to approve prescription drugs, beginning as early as March 5, 1990. *See* New Drug Applications; Guideline for the Study of Drugs Likely to Be Used in the Elderly Availability, 55 Fed. Reg. 7,777, 7,778 (Mar. 5, 1990) (announcing the availability of a guideline entitled "Guideline for the Study of Drugs Likely to be Used in the Elderly"). The guideline did not require or anticipate new clinical studies would be necessary to evaluate a new therapy in the elderly, because patients over 65 already represented a significant portion of study subjects. This guidance did acknowledge, however, that it was unusual for sponsors to make a pharmacokinetic comparison between the elderly and other subjects to discern differences requiring dose adjustments or additional precautions. A re-analysis of previously submitted clinical data, however, would not normally be considered "new" clinical data.

In 1990, FDA proposed regulations to amend prescription labeling requirements to establish in the precautions section information about use of prescription drugs for the elderly. 55 Fed. Reg. 46,134 (Nov. 1, 1990). Four years thereafter, FDA published a guideline for the use of drugs in geriatric populations

[4] FDA further permitted generic products with risk management programs that preserved the "same essential elements" as the RLD, even if not identical. *See* FDA Docket No. 02P-0059 (FDA decision, Nov. 8, 2002).

entitled "Studies in Support of Special Populations: Geriatrics." *See* 59 Fed. Reg. 39,398 (Aug. 2, 1994). Three years after that, FDA enacted its final rule mandating a geriatric labeling section. Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection in the Labeling, 62 Fed. Reg. 45,313 (Aug. 27, 1997) ("Final Geriatric Labeling Rule") (codified in 21 C.F.R. part 201). This rule advised that at least 100 subjects age 65 years and older should be included in all clinical studies, to detect "clinically significant differences." *Id.* at 45,317. Following this final regulation, additional guidance was also made available to explain how to comply with the regulation without the need for additional clinical studies. Guidance for Industry: Content and Format for Geriatric Labeling (Oct. 2001) ("Geriatric Labeling Guidance").

2. The Warnings and Precautions in Geriatric Labeling Cannot Qualify for Exclusivity

While the geriatric rule and guidance do not explicitly address three-year exclusivity for new labeling, it is clear that new geriatric labeling, which adds warnings or precautions, even with clinical data, will not be granted three years of new labeling exclusivity. FDA's guidances and regulations establish that "[n]ew labeling will not be protected by exclusivity if it describes new risks or warnings." *See, e.g.,* FDA Guidance for Industry: Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications, Draft Guidance (Oct. 2000) at 6 n. 7 (citing Abbreviated New Drugs Application Regulations, 54 Fed. Reg. 28,872, 28,899 (proposed Jul. 10, 1989) (to be codified at 21 C.F.R. pts. 10, 310, 314, and 320) and Final Patent and Exclusivity Regulations, 59 Fed. Reg. 50,338, 50,356-57 (Oct. 3, 1994)).

Actually, FDA anticipated that very few geriatric labeling supplements would require clinical data, because the agency advised including more geriatric patients in the initial approval studies, which generally had already been the case:

> The guideline did not call for, or anticipate, an increase in the number of patients or the number of clinical studies needed to evaluate a new therapy. Patients over 65 years of age already represented a significant portion of study subject in most cases, based on several FDA surveys. The principal new steps called for were to not exclude the very old, to analyze the data already collected, and to obtain modest additional pharmacokinetic data. Only in

> special cases (e.g., drugs especially targeted for older patients or where age-related differences or problems are anticipated) were separate studies in the elderly recommended.

Final Geriatric Labeling Rule, 62 Fed. Reg. at 45,313.

Indeed, many of the labeling changes associated with geriatric patients would be expected to be correlated to the impaired renal function that many elderly patients have as compared with younger patients. FDA's final geriatric labeling regulations note that for drugs that are substantially excreted by the kidney, care should be taken for geriatric patients in dose selection, which may be monitored by calculating creatine clearance.[5] Final Geriatric Labeling Rule, 62 Fed. Reg. at 45,314. In th is regard, an applicant may provide reasons or alternative labeling to justify omission of geriatric labeling for products that may be indicated for geriatric use. *Id.*

3. Pediatric Labeling Contrast

In contrast to geriatric labeling, pediatric exclusivity attaches six months of exclusivity to any exclusivity or patent protection listed in the Orange Book for any drug product containing the same active moiety. A second six-month period may be added if the additional pediatric studies are submitted in response to a request for such studies for a new use. In this situation, the supplemental new use must qualify for three years of new labeling exclusivity, which is the only period to which the additional six months of exclusivity will attach. *See* Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act (Revised, Sept. 1999) ("Pediatric Exclusivity Guidance") at 13-14.

FDA and Congress, however, added the provision for pediatric exclusivity, because pediatric patients were <u>not</u> generally included in clinical studies, unlike the recommendation and common enrollment of geriatric patients in clinical studies intended for NDA approval. For example, the final pediatric rule noted how previous voluntary steps to encourage pediatric studies had failed, resulting in labeling that merely noted that the safety and effectiveness of the drug had not been

[5] Increased serum creatine clearance indicates that significant renal dysfunction is present. Normal serum clearance levels, however, may not ensure that normal renal function is present. *See, e.g.,* Richard E. Lafayette, *Preventing disease progression in chronic renal failure,* American Family Physician, Nov. 1, 1995 (attached).

evaluated in pediatric patients. *See id.* As a result, pediatric exclusivity was provided as an incentive to further help encourage such studies. *See id.* As described above, geriatric labeling could be provided generally by reanalyzing clinical data that had already been collected for all patients. No additional incentive is necessary to include geriatric patients in clinical studies.

E. Geriatric Labeling for Oxandrin®

1. Savient's Studies Were Not New

Remarkably, Savient asserts that it submitted new clinical studies for oxandrolone to meet its requirement for geriatric labeling.[6] Savient attempts to cast its situation as "unique," where it "generated clinical data that led to unique labeling for safer drug use." Savient Petition at 4. FDA did (perhaps erroneously) grant Savient three years of new labeling exclusivity, assigned exclusivity code M-42 "ADDITION OF GERIATRIC USE SUBSECTION TO THE PRECAUTIONS SECTION OF THE PACKAGE INSERT AND GERIATRIC DOSING INFORMATION," approved on June 20, 2005.

Even Savient acknowledges that its "clinical studies" were not new.[7] Instead, Savient notes that "from four clinical studies conducted with Oxandrin® in 339 patients, 172 of which were geriatric patients. These studies were the basis of changes to the labeling for Oxandrin®, including changes to the precautions as well as the dosing and administration sections." *Id.* at 8. This statement indicates that Savient's geriatric clinical data were most likely obtained entirely from clinical studies submitted in 1995 or earlier, to support the approval of Oxandrin® (initially approved for marketing in 1964 by G.D. Searle). Savient bought rights to market the product from Searle, and began marketing the product in 1995, five years after FDA's initial geriatric guidance document put companies on alert to collect geriatric clinical data.

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[6] Oxandrolone is indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in patients who without definite pathophysiologic reasons fail to gain weight or maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis.

[7] Savient's supplement including the purported clinical studies in support of the geriatric labeling has not been posted on FDA's website for public viewing to date. Accordingly, the public presently must rely on Savient's own statements regarding the data that it submitted with its supplement.

In essence, Savient merely complied with the geriatric labeling requirements, as did other RLD manufacturers by comparing already available pharmacokinetic data comparing elderly and younger patients. *See* Final Geriatric Labeling Rule, 62 Fed. Reg. at 45,313. Savient even submitted a supplement for a dose in excess of its larger 10 mg dose approved in 2001, well after it had been put on notice about the requirements for obtaining geriatric clinical data for new approvals or supplements.

Oxandrin®'s labeling recommends that geriatric patients start with a dose of 5 mg to avoid drug-induced fluid retention and hepatic transaminases observed in elderly patients. This drug induced effect of reduced renal function is already evidenced by the adverse events of edema, retention of serum electrolytes, increased creatine excretion, and increases serum levels of creatine phosphokinase present on the labeling prior to the added geriatric labeling. In the absence of specific geriatric labeling, therefore, it would stand to reason that geriatric patients would start at a lower effective dose to prevent further impaired renal function.[8] By determining a lower effective dose for geriatric patients, Savient essentially provided new bioavailability data for geriatric patients, which would have been expected given the drug's known adverse events. As discussed *supra*, new clinical bioequivalence data does not qualify a product for three years of market exclusivity for information added in a supplement based on this type of data.

2. Geriatric Labeling for Oxandrin® Should Not Have Received Exclusivity

In the alternative, if Savient's citizen petition should convince FDA that all generic oxandrolone products (and perhaps all generic products for RLDs that include a sizable geriatric population) should contain the RLD's geriatric labeling, then Oxandrin® is not entitled to its three year new labeling exclusivity, because no new clinical studies appear to have been submitted. FDA's preamble to the final regulations for new labeling exclusivity already anticipated how the public interest to provide such warnings would supercede the exclusivity for a supplement based on new clinical studies, noting that "changes in labeling that involve warnings or

[8] Assuming that these conditions represent additional risk factors for use of oxandrolone in geriatric patients, Savient exacerbated this risk by offering a new 10 mg dose. The prior 2.5 mg dose provides for better titration of dosing. The labeling for Oxandrin®, moreover, notes that individual dosing should be adjusted from 2.5 to 20 mg given in divided doses, because the dose response to anabolic steroids, such as oxandrolone, varies. This information and the labeling for Oxandrin® provide further evidence that the product was adequately labeled prior to the new geriatric labeling, because it would have been expected that physicians would prescribe oxandrolone at a lower recommended dose for geriatric patients with impaired renal function.

other such risk information that must be included in the labeling of generic competitors" and there is "no valid interest in precluding such information [risk information] from the labeling of other products." *See* 59 Fed. Reg. at 50,357.[9] If FDA requires geriatric labeling for oxandrolone, this would no longer entitle Savient to three year new labeling exclusivity for Oxandrin®, because Savient would have successfully convinced FDA that the labeling is tantamount to warnings or risk information necessary for a sizable population that would use generic oxandrolone.

3. Geriatric Labeling for Oxandrin® Can Be Carved Out

Savient argues that generic drugs should not be permitted to be marketed with "less safe" labeling that omits the geriatric labeling protected by Savient's new labeling exclusivity, *i.e.*, Savient should be awarded *de facto* geriatric labeling exclusivity for three years based on a reanalysis of prior submitted clinical data. As support, Savient argues that the geriatric use of oxandrolone is mostly elderly patients, 40% who reside in long term health care facilities. Savient Petition at 2. Savient contends that as in Rebetol® (ribavirin), Docket No. 2003P-0321, FDA should not approve generic oxandrolone labeling without geriatric labeling, *i.e.*, the geriatric labeling "carve out", because the product would be less safe with the omitted uses. *Id.* at 11-12. Savient argues that FDA would not have approved Ultram® (tramadol), Docket Nos. 02P-0252, 02P-0191, and 01P-0495 had the exclusivity for a certain dose titration labeling not expired. *Id.* at 12-13. Savient further asserts that the geriatric labeling applies to all intended uses of the drug, so a "carve out" would not be applicable, given that geriatric patients are a significant portion of the drug's population. *Id.* at 13.

Savient's position, however, does not find any support in the statute, regulations, case law, FDA's guidances, or FDA's responses to other relevant citizen petitions. Furthermore, case law has consistently supported FDA approving ANDAs with less than all of the indications in the RLD, finding "unusually strong support" in the legislative history cited *supra* and the statutory provisions requiring an ANDA include "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed] drug." *Bristol-Myers Squibb*, 91 F.3d at 1500

[9] As noted in the context of copyright laws and Hatch-Waxman ANDA approvals, when two laws are in conflict, a resolution should be adopted by courts or a regulatory authority that preserve the "principal purposes" of each. *See SmithKline Beecham Consumer Healthcare, L.P. v. Watson Pharm.* 211 F.3d 21, 27-28 (2d Cir. 2000) (noting that Hatch-Waxman provisions requiring same labeling for generics "trumps" copyright laws for a user's guide and audio tape that constituted "labeling" for a drug product).

(citing 21 U.S.C. § 355(j)(2)(A)(i)). In particular, the court noted that this provision would have been redundant if the same labeling including same indications applied in all cases, which § 355(j)(2)(A)(v) does not. The court further noted that § 355(j)(3)(B) does not provide that one reason to disapprove an ANDA is for including less than all of the RLD indications. *Id.*

FDA's authority to approve generic drugs with less than all of the RLD labeling has also been upheld by the courts in a variety of similar situations. Orphan drug exclusivity was held to be limited to "disease-specific" labeling indications, even if the non-protected indication included in the generic product was only a minor use of the product. *Sigma-Tau*, 288 F.3d at 145. Courts have also upheld labeling changes adding warnings related to a difference in formulation, because the generic product used a different preservative than the reformulated RLD to avoid a new formulation exclusivity. *See, e.g., Zeneca, Inc. v. Shalala*, 213 F.3d 161, 169 (4th Cir. 2000) (permitting the generic drug to add health warnings for a preservative containing sulfite, finding the written warning sufficient to render the generic product as safe and effective as the reformulated RLD product that now contained a preservative with no sulfites and, hence, less potential for an allergic effect).

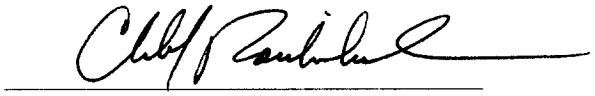
F. Savient's Abuse of the Citizen Petition Process

Manifestly, Savient filed its petition in an effort to delay generic oxandrolone approvals. As FDA has recognized, generic approvals have been often delayed by frivolous citizen petitions brought by RLD holders to slow down the review process with specious, untimely, or frivolous citizen petitions alleging "new" bioequivalence or labeling issues. FDA apparently is in the process of soliciting public input on how to reform this problem with the citizen petition process. *See, e.g.,* FDA Examining Citizen Petition Review Process to Speed Generic Approvals, FDC Reports "The Pink Sheet Daily" No. 002 (Feb. 28, 2005); Citizen Petition Reform Under Consideration by FDA, FDC Reports "The Pink Sheet Daily" No. 002 (Sep. 19, 2005). One solution proposed by FDA, for example, would be for FDA to consider the petition and ANDA approvals separately, if FDA is not ready to decide on the petition. FDA could also choose to comment in its response that the petition was filed in a specious, untimely, or other manner that appeared to hamper or delay competition. *See id.* FDA has already done the latter, in response to a late-filed petition to request that FDA immediately deny approval of an NDA product. *See, e.g.,* Letter of Steven Galson, M.D., M.P.H., Acting Director, Center for Drug Evaluation and Research to Geoffrey Allan, Ph.D., President and Chief Executive Officer, Insmed, Inc., of 8/30/2005 (Docket No. 2005P-0322).

Since oxandrolone has been on the market from 1964 until 2005 without any serious effects for a lack of geriatric labeling, the Savient Petition should be denied, and FDA should immediately permit section viii carve outs of the geriatric labeling for otherwise approvable ANDAs, even if FDA has not formally drafted a response to the Petition.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP

By: 

Charles J. Raubicheck