DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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DEC 1 2006

Re: Docket No. 2005P-0383/CP1 & SUP1

Dear Mr. Allera and Mr. Sullivan:

This responds to your citizen petition dated September 19, 2005 (petition), and your related supplement submitted February 2, 2006, on behalf of Savient Pharmaceuticals, Inc. (Savient). In the petition, you request that the Food and Drug Administration (FDA or the Agency) verify the scope of Savient's three-year exclusivity for geriatric[1] use information, which was granted based on geriatric studies Savient conducted for Oxandrin (oxandrolone). As part of this request, you ask FDA to refuse to approve any abbreviated new drug applications (ANDAs) for generic[2] oral products containing oxandrolone until Savient's exclusivity expires on June 20, 2008.

Essentially, your petition argues that the geriatric use information added to the Oxandrin label cannot be omitted from the labeling for generic oxandrolone products because this information is necessary to ensure the safe and effective use of those products. You conclude that the Agency, therefore, cannot approve ANDAs for generic oxandrolone products until the expiration of the three-year exclusivity period granted to Savient. We disagree for the reasons discussed in this response. This decision is based on a review of the petition, supplement, and comments, as well as other information available to the Agency.

I. Summary

Your petition raises a question the Agency has not previously addressed: whether geriatric labeling that is protected by exclusivity can be omitted from the labeling of generic products. To resolve this question, we must consider the regulations governing omission of protected information from ANDA labeling, the regulations regarding geriatric labeling for drug products, and the public health considerations underlying these two sets of regulations.

On one hand, the Agency has statutory authority to permit the labeling of a generic product to differ from that of the referenced innovator drug product (21 U.S.C. 355(j)(2)(A)(v)). Agency regulations at 21 CFR 314.94(a)(8)(iv) and 314.127(a)(7) (ANDA labeling regulations) implementing that authority allow a generic applicant to omit from its labeling aspects of the

[1] The term *geriatric* is defined for purposes of the geriatric labeling regulations as referring to persons aged 65 and older unless the specific labeling expressly states otherwise (see 21 CFR 201.80(f)(10)(i) and the final rule that published in the Federal Register of August 27, 1997 (62 FR 45313 at 45317)).

[2] The term *generic* is not defined in the Act or FDA's regulations. It is used in this response to refer to drug products for which approval is sought under an ANDA.

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innovator drug's labeling that are protected by exclusivity. One of these regulations, § 314.127(a), requires that the omission not render the generic product less safe or effective than the innovator's product for the remaining, nonprotected conditions of use. If this safety and effectiveness standard is satisfied, the omission is permitted under the ANDA labeling regulations. On the other hand, Agency labeling regulations at 21 CFR 201.80(f)(10) (geriatric labeling regulations) require labeling for new drugs, whether approved under new drug applications (NDAs) or ANDAs, to include available geriatric use information.[3]

To resolve the issue raised in your petition, the Agency must address the relationship between the ANDA labeling regulations and the geriatric labeling regulations. The Agency has determined that both these sets of regulations are most appropriately interpreted to permit ANDA sponsors to omit protected geriatric labeling as long as the generic product will remain as safe and effective as the innovator's product for the remaining, nonprotected conditions of use. In short, protected geriatric labeling can be omitted if the omission comports with the safety and effectiveness requirements of 21 CFR 314.127(a)(7).

Having made this determination, the Agency has assessed whether omission of the particular geriatric use information at issue for oxandrolone would make generic oxandrolone products less safe or effective than Oxandrin for all remaining, nonprotected conditions of use. Our review has determined that all of the safety and effectiveness issues addressed in the new geriatric use labeling are adequately addressed elsewhere in the label. Accordingly, we have concluded that the omission of the new geriatric use labeling would not render generic oxandrolone products less safe or effective than Oxandrin for all remaining, nonprotected conditions of use. Therefore, ANDAs for generic oxandrolone that omit Oxandrin's geriatric labeling can be approved during the exclusivity period. The Agency has also determined that the geriatric labeling regulations and ANDA labeling regulations permit generic oxandrolone applicants to include a statement in the geriatric use section of the label indicating that information has been omitted because it is protected by exclusivity.

This response is organized in two parts. The first part (section II) describes the ANDA labeling regulations and geriatric labeling regulations and articulates the Agency's reasons for concluding that protected geriatric information can be omitted from generic labeling so long as the generic product satisfies the § 314.127(a)(7) safety and effectiveness standard. The second part (section III) describes the new geriatric use information for Oxandrin and states the Agency's reasoning for concluding that omission of this particular information from the labeling for generic oxandrolone products comports with the § 314.127(a)(7) standard.

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[3] Effective June 30, 2006, the Agency's regulations at 21 CFR 201.57 were redesignated as 21 CFR 201.80, and a new § 201.57 was added to the regulations (see 71 FR 3988 (January 24, 2006)). The new regulations at 21 CFR 201.57 apply to prescription drugs for which an NDA or efficacy supplement was approved, pending, or submitted after June 30, 2006 (21 CFR 201.56(b)). The Oxandrin labeling at issue in this petition was approved on June 20, 2005, and no changes have been made to this labeling since that time. Accordingly, the former 21 CFR 201.57, now designated 21 CFR 201.80, applies to it. We note, however, that the substance of the geriatric use labeling requirements under the new regulations at § 201.57(c)(9)(v) remains the same as the earlier requirements now codified at § 201.80(f)(10).

II. Applicable Regulations Permit ANDA Applicants to Omit Protected Geriatric Use Information From Generic Labeling in Certain Circumstances

The Agency has reviewed the ANDA labeling regulations, the geriatric labeling regulations, and relevant case law and guidance to determine whether protected geriatric use information may be omitted from generic drug labeling. We have concluded that the applicable authorities can and should be interpreted to permit omission from generic labeling of protected geriatric information so long as the generic product will remain as safe and effective as the innovator's product for all remaining, nonprotected conditions of use, in accordance with § 314.127(a)(7).

A. The ANDA Labeling Regulations and the Geriatric Labeling Regulations

1. Three-Year Exclusivity and the ANDA Labeling Regulations

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) (21 U.S.C. 355(j)) of the Federal Food, Drug, and Cosmetic Act (the Act), which established the current ANDA approval process. Under section 505(j) of the Act, an applicant may obtain approval of an ANDA for a generic form of an innovator drug by providing evidence to FDA that, among other things, the proposed product is bioequivalent to the innovator's product and has the same active ingredient, dosage form, strength, route of administration, and labeling as the approved product. The Hatch-Waxman Amendments were intended to strike a balance to maintain incentives to promote pharmaceutical innovation and to facilitate more rapid approval of generic products and thereby increase competition in the pharmaceutical marketplace (see, e.g., 59 FR 50338 (October 3, 1994)).

Section 505(j)(5)(F)(iv) of the Act establishes three-year exclusivity for certain changes to new drugs made through supplements to NDAs, when such changes are based on new clinical investigations, other than bioavailability studies, that are essential to the approval of the change.[4] If this exclusivity is granted, FDA may not approve an ANDA for three years for the change described in the supplement. However, as explained in section II.B, under certain circumstances the protected labeling for the change can be omitted from ANDA labeling, allowing approval of the ANDA during the exclusivity period.

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[4] Section 505(j)(5)(F)(iv) states:

> If a supplement to an application approved under subsection (b) [i.e., an NDA] is approved after the date of enactment of this subsection and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection [subsection (j), i.e., an ANDA] for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

Section 505(c)(3)(E)(iv) of the Act establishes an equivalent three-year exclusivity delaying approval of NDAs described under section 505(b)(2) (21 U.S.C. 355(b)(2)) (see also 21 U.S.C. 355(c)(3)(E)(iii) and (j)(5)(F)(iii) (establishing equivalent three-year exclusivity protections against approval of 505(b)(2) applications and ANDAs, respectively, for the same conditions of use for which the Agency has approved an NDA for a drug containing a previously approved active ingredient)).

Section 505(j)(2)(A)(v) of the Act requires that the labeling for products approved under ANDAs be the same as that for the listed drug[5] that the generic is seeking to duplicate (the reference listed drug) unless an exception applies.[6] Failure to satisfy this labeling requirement is grounds for not approving an ANDA.[7] One of the exceptions to this statutory same-labeling requirement permits labeling "changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers" (21 U.S.C. 355(j)(2)(A)(v)) (different manufacturers exception). Consistent with this statutory exception, FDA's ANDA labeling regulations at §§ 314.94(a)(8)(iv)[8] and 314.127(a)(7)[9] permit generic labeling to omit an indication or other aspect of the reference listed drug's labeling that is protected by a patent or exclusivity. Section

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[5] A *listed drug* is a drug for which an approved application is listed in FDA's *Approved Drugs Products with Therapeutic Equivalence Evaluations* (informally referred to as the Orange Book) (see 21 U.S.C. 355(j)(2)(A)(i) and 355(j)(7) of the Act and 21 CFR 314.3(b)).

[6] Section 505(j)(2)(a) states:

> A[n] abbreviated application for a new drug shall contain— . . . (v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the [reference] listed drug . . . except for changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers.

[7] Section 505(j)(4) states:

> . . . [T]he Secretary shall approve an [ANDA] for a drug unless the Secretary finds—. . .
> (G) information submitted in the application insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required . . . because the drug and the listed drug are produced or distributed by different manufacturers.

[8] Section 314.94(a)(8)(iv), regarding required content for ANDAs, states:

> Labeling . . . proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug 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 indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act [now section 505(j)(5)(F)].

[9] Section 314.127(a)(7), regarding bases for refusing to approve an ANDA, states that one ground for refusal would be if:

> Information submitted in the abbreviated new drug application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the abbreviated new drug application except for changes required because of differences approved in a petition under 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use.

314.127(a)(7) requires that the omission "not render the proposed [generic] drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use."

The Court of Appeals for the District of Columbia Circuit has upheld the ANDA labeling regulations. The court concluded that the different manufacturer exception must authorize a generic drug's omission of labeling protected by exclusivity because three-year exclusivity would otherwise prevent approval of all generic versions of the drug, not just those labeled for the protected "change" approved under the supplement. The court concluded that interpreting the exception otherwise would expand the exclusivity beyond the scope intended by Congress (*Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996) (*Bristol-Myers*)).

The court in *Bristol-Myers* considered the argument that permitting ANDA applicants to omit protected labeling reduces the value of the exclusivity, by allowing generic products onto the market during the exclusivity period. However, the court concluded that Congress intended that, although the generic applicant would not have the benefit of including the protected information in its product labeling, its product could still compete with the innovator's product. Further, as that court acknowledged, the alternative interpretation, which would not permit ANDA applicants to enter the market at all during the exclusivity period, could allow innovators to delay generic competition indefinitely. An innovator could submit a new supplement every three years, thereby continually delaying generic product entry for one additional three-year period after another. The ANDA labeling regulations prevent such "evergreening" (*see Bristol-Myers*, 91 F.3d at 1500). They expedite competition from generic products, which are typically less expensive than the innovator's product, while ensuring that these generic products are just as safe and effective as the innovator's product for all remaining, nonprotected conditions of use.

2. The Geriatric Labeling Regulations

In 1990, FDA proposed amendments to its regulations governing the content and format of labeling for human prescription drug products to require sponsors to include in drug labeling available information pertinent to the appropriate use of drugs in the elderly (55 FR 46134 (November 1, 1990)). In 1997, the Agency published the final geriatric labeling regulations now codified at § 201.80(f)(10) (formerly designated § 201.57(f)(10)) (62 FR 45313 (August 27, 1997)).[10] The geriatric labeling regulations require that drug labeling include a geriatric use section addressing available information on geriatric use, and also include more detailed discussion of issues addressed in the geriatric use section, as appropriate, in other sections of the

[10] The publication of the geriatric labeling regulations was part of a larger effort by the Agency to encourage increased awareness and understanding of drug effects in the geriatric population. For example, FDA issued a guidance for industry entitled *Study of Drugs Likely to be Used in the Elderly* (the elderly guidance) (available on the Internet at http://www.fda.gov/cder/guidance/index.htm). This guidance concerns the importance of evaluating the effects of drugs in the geriatric population and sound methods for pursuing such evaluation. The geriatric labeling regulations relates to the elderly guidance in that these regulations establish labeling requirements to bring the results of such evaluations to the attention of practitioners. The Agency issued another guidance for industry entitled *Studies in Support of Special Populations: Geriatrics* (the geriatrics guidance) (available on the Internet at http://www.fda.gov/cder/guidance/index.htm) as part of an effort to facilitate international harmonization of standards for clinical testing programs. The geriatrics guidance is consistent with the elderly guidance and reflects sound scientific principles for evaluation of drugs in the geriatric population.

label (21 CFR 201.80(f)(10)(i)). The regulations expressly permit omission of geriatric labeling under certain circumstances.[11]

The preamble to the final regulations reflects the Agency's view that available geriatric information had not been consistently disclosed in product labeling before the geriatric labeling rulemaking.[12] Through the rulemaking, the Agency established labeling requirements for geriatric use information in the belief "that improving access to information that is important to the elderly will facilitate safe and effective use of prescription drugs in older populations" (62 FR 45313). Although the preambles to the proposed and final rule encourage development of geriatric use data, the regulations do not require the development of such data (see, e.g., 55 FR 46134 at 46135 and 62 FR 45313 at 45314).

With regard to clinical studies, the regulations require inclusion of one of three specific statements in the geriatric use section. One statement applies if clinical studies "did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences" (21 CFR 201.80(f)(10)(ii)(A)). Another applies "[i]f clinical studies . . . included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences" (21 CFR 201.80(f)(10)(ii)(B)). The third applies "[i]f evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment" (21 CFR 201.80(f)(10)(ii)(C)).

The regulations also provide that " . . . specific pharmacokinetic or pharmacodynamic studies that have been carried out . . . shall be described" (21 CFR 201.80(f)(10)(iii)(A)), and that sponsors must include a specified statement "[i]f a drug is known to be substantially excreted by the kidney" (21 CFR 201.80(f)(10)(iii)(B)). The regulations further state that "[i]f use of the drug in the elderly appears to cause a specific hazard, the hazard shall be described . . . ." (21 CFR 201.80(f)(10)(iv)). In addition, the regulations permit inclusion of additional statements "if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation" (21 CFR 201.80(f)(10)(v)).

The regulations authorize the Agency to permit a sponsor to not include any geriatric use information if none of the requirements and options for geriatric labeling content offered in § 201.80(i) through (v) are "appropriate" or "relevant." It also authorizes the Agency to permit the

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[11] The Agency issued a guidance on *Content and Format for Geriatric Labeling* (available on the Internet at http://www.fda.gov/cder/guidance/index.htm) to provide industry with information on submitting geriatric labeling in accordance with the regulation.

[12] See 62 FR 45313 at 45315 ("FDA acknowledges that some prescription drug labeling consistent with existing FDA [guidance] and regulations contains information on use in the elderly. . . . The final rule is intended to make geriatric labeling format and content more consistent . . . .").

sponsor to include an alternative statement if the Agency determines that this statement is "accurate" and "appropriate" (21 CFR 201.80(f)(10)(vi)).[13]

The Agency has interpreted the geriatric labeling regulations to require that product labeling reflect only relevant information that is "available" to that sponsor pertaining to use in the geriatric population. The Agency has explained that "available" information is information in the sponsor's possession, from published studies or in the professional literature (see 55 FR 46134 and 62 FR 45313 at 45316).

B. Geriatric Labeling May Be Omitted from ANDA Labeling on a Drug-Specific Basis in Accordance with the Safety and Efficacy Requirements of Section 314.127(a)(7)

Your petition suggests that omission of geriatric labeling should never be permitted, arguing that Agency guidance calls for generic labeling to include geriatric labeling that is based on the reference listed drug's geriatric use section. We disagree with your interpretation of the relevant authority and with your conclusion.

To determine whether geriatric labeling protected by exclusivity can be omitted from the labeling for generic products, the Agency must consider the ANDA labeling regulations and the geriatric labeling regulations. Neither of these sets of regulations expressly addresses their relationship to the other. As described in section II.A, each of these sets of regulations has a distinct purpose and furthers a specific public health goal. The ANDA labeling regulations permit prompt approval of generic drugs, even when certain labeling for the listed drug is protected by exclusivity, and therefore must be omitted, as long as the generic product will remain as safe and effective as the reference listed drug for all remaining, nonprotected conditions of use. The geriatric labeling regulations are intended to improve disclosure of information related to the use of approved prescription drug products in geriatric patients, to promote safe and effective use of those drugs in that population.

The Agency has concluded that it can most effectively accommodate the public health goals of both these sets of regulations by applying the approach described in § 314.127(a)(7), i.e., the Agency will permit omission of geriatric labeling for a specific generic drug product if the omission would not render the generic drug less safe and effective than the listed drug for all remaining, nonprotected conditions of use. If the omission would render the generic drug

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[13] Section 201.80(f)(1)(vi) states:

> If the sponsor believes that none of the requirements described in paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the [A]gency determines that such statement is accurate and appropriate.

See also 62 FR at 45315 ("FDA may permit an omission . . . if FDA determines that the statements described in [201.80(i) through (v)] are inappropriate or not relevant to the drug's labeling . . . ").

product less safe or effective for any of the remaining conditions of use, in the geriatric population or otherwise, the omission will not be permitted.

1. *There Is No Categorical Prohibition on Omission of Geriatric Use Information From ANDA Labeling*

The permissibility of omitting protected geriatric use information from ANDA labeling is an issue of first impression for the Agency. Neither the Agency's ANDA labeling regulations at 21 CFR 314.94(a)(8) and 314.127(a)(7), nor any applicable case law or Agency guidance, indicates that the authority to omit protected information from ANDA labeling is limited to certain categories, portions, or sections of labeling. In fact, the ANDA labeling regulations provide that any protected "aspect of" the listed drug's labeling may be omitted from ANDA labeling as long as the generic product would be no less safe and effective than the listed drug for the remaining, nonprotected conditions of use as required by § 314.127(a)(7).

The geriatric labeling regulations at § 201.80(f)(10) also do not include any limitation on the scope of the ANDA labeling regulations at §§ 314.94(a)(8) and 314.127(a)(7). FDA guidance on the geriatric labeling regulations likewise does not address whether the Agency intended that these regulations should limit the applicability of the ANDA labeling regulations to prevent omission of protected geriatric labeling. Further, the geriatric labeling regulations provide that the Agency may permit a sponsor to omit geriatric labeling if the Agency determines that the labeling is not "appropriate" or "relevant" (21 CFR 201.80(f)(10)(vi); 62 FR at 45315). Even assuming that geriatric use information was "relevant," if that information cannot be included in ANDA labeling because it is protected, and its omission would not render the product less safe or effective than the reference listed drug for all remaining, nonprotected conditions of use, it is reasonable to conclude that it is not "appropriate" to include this information for purposes of the geriatric labeling regulations and that the information, therefore, may be omitted in accordance with these regulations.[14]

Permitting omission of protected geriatric labeling under the geriatric labeling regulations also would follow from the Agency's interpretation of the geriatric labeling regulations as requiring a sponsor to address in its labeling only the geriatric use information that is "available" to that particular sponsor (see, e.g., 55 FR 46134 and 62 FR 45313 at 45316). Generic drug applicants cannot include information protected by exclusivity in their labeling and, therefore, this information is reasonably considered not to be available to them. If the protected information is, in addition, not needed for the generic product to be as safe and effective as the reference listed

[14] Although the Agency has not previously had occasion to interpret the term "appropriate" under § 201.80(f)(10)(vi) for purposes of omitting protected labeling, the Agency has offered examples of situations in which geriatric use statements would not be appropriate. In particular, the Agency has stated that "[a]lthough the geriatric statements provided in the final rule will be appropriate for most drug products, there are certain drugs that are not indicated for geriatric use *or for which the specified geriatric statements are not needed*" (62 FR 45313 at 45314 (emphasis added)). Here, for the reasons discussed in section III.B.1, based on the specific facts of this particular case, we have concluded that geriatric labeling for Oxandrin is not needed for generic oxandrolone products because they would remain as safe and effective as the reference listed drug for all remaining, nonprotected conditions of use.

drug for all remaining, nonprotected conditions of use, the omission also would be permissible under § 314.127(a)(7).

The nature and scope of the geriatric labeling requirements themselves suggest that geriatric labeling information is not categorically necessary for the safe and effective use of all drugs. The purpose of the regulations is to improve access to information on geriatric use to facilitate safe and effective use of prescription drugs in this population (62 FR 45313 at 45315). However, as noted in section II.A.2, it does not require development of data. Rather, the regulations require sponsors to address existing, available information in drug product labeling. The significance of the available data may vary. In some cases, it may be of great importance to ensure the safety and effectiveness of the drug in the geriatric population. In other cases, the information may be of limited value. Applicants holding NDAs approved before publication of the geriatric labeling regulations (such as Savient's NDA for Oxandrin) were required to submit labeling supplements to comply with the geriatric labeling requirements. In some cases, the new geriatric use information the applicants added to the labeling for these older products might address new safety or effectiveness issues; in others, it might merely address issues already adequately addressed elsewhere in the label.

In short, the Agency views assessment and disclosure of geriatric use information to be important goals in furtherance of product safety and effectiveness, and views the geriatric labeling regulations as providing an important mechanism for achieving these goals. However, it is not necessary to conclude, based on the content of these regulations or the purposes underlying them, that geriatric labeling can never be omitted. The appropriate approach is to assess each generic drug product independently, to determine whether omission of protected geriatric labeling would render that drug product less safe or effective than the listed drug that includes the protected labeling.

The Agency, therefore, considers it reasonable to interpret the geriatric labeling regulations in a manner consistent with the language and objectives of the ANDA labeling regulations. The ANDA labeling regulations at §§ 314.94(a)(8) and 314.127(a)(7) serve to expedite approvals of generic products by permitting omission of protected labeling so long as, in accordance with § 314.127(a)(7), such approvals can be accomplished without compromising product safety or effectiveness. Omission of protected geriatric labeling would, therefore, be permitted only if the product would remain as safe and effective as the reference listed drug for all remaining, labeled uses, including in the geriatric population.

As you discuss, Agency guidance states that labeling for products approved under ANDAs must be the same as that of the reference listed drug and should include geriatric information.[15] However, the Agency has not expressly addressed in any guidance the permissibility of omitting geriatric use information protected by exclusivity. Our existing guidance on the geriatric

[15] See 55 FR 46134 at 46135 (". . . FDA proposes to require [ANDA] sponsors to adopt revised labeling that is the same as the labeling for the listed drug . . . "and". . . drug products whose labeling is not in compliance with the rule will be misbranded . . ."), 62 FR 45313 at 45320 ("FDA will notify all holders of approved abbreviated applications of the changes in the listed product's geriatric labeling and provide directions on how to incorporate the new text in the labeling"), and geriatric labeling guidance at 2 and 5 ("All holders of ANDAs . . . should revise their labeling in accordance with the last approved labeling of the reference listed drug").

labeling regulations is reasonably interpreted as intended to inform ANDA applicants of the general obligation to update their labeling to include geriatric changes to the labeling for the reference listed drug. The alternative interpretation you propose would ascribe to our guidance an intent to categorically limit the scope of the ANDA labeling regulations, a matter on which the guidance is entirely silent. It is more reasonable to conclude that if we had intended to limit our own regulatory authority so dramatically, we would have affirmatively stated as much.

We interpret the Agency guidance on the geriatric labeling regulations to reflect the general obligation for generic applicants to update their labeling to include changes to labeling for the listed drug, unless one of the statutory exceptions applies. The different manufacturers exception (21 U.S.C. 355(j)(2)(A)(v)) applies to protected geriatric labeling, and the guidance does not render the ANDA labeling regulations implementing that exception inapplicable to protected geriatric labeling.[16]

The objectives both of the ANDA labeling regulations and of the geriatric labeling regulations can be met through application of the § 314.127(a)(7) safety and effectiveness standard. Applying this standard to permit omission of geriatric use labeling protected by exclusivity enables the Agency to expedite approval of safe and effective generic products. The Agency has, therefore, concluded that the permissibility of omitting protected geriatric use information from ANDA labeling should be considered on a drug product-specific basis and will depend upon whether the particular omission complies with § 314.127(a)(7).

2. *Permitting Omission of Protected Geriatric Use Information Is Consistent With the Case Law*

The determination to allow omission of protected geriatric labeling if the omission comports with § 314.127(a)(7) is consistent with the ruling of the Court of Appeals for the District of Columbia in *Bristol-Myers*. As discussed in Section II.A, that court concluded that omission of the protected labeling had to be permissible because the Act expressly limits the scope of three-year exclusivity to the change for which the exclusivity is granted. If the labeling associated with the protected change could not be omitted, the exclusivity would block approval of all generic versions of the drug, not just those labeled for the protected change. It follows from the court's reasoning that omission of protected geriatric use information is permissible as long as omission satisfies the safety and efficacy requirements of § 314.127. Otherwise, the exclusivity would block approval of all generic versions of the drug even if their labeling does not need to include the new geriatric use information for the generic to remain as safe and effective as the listed drug for all remaining, nonprotected conditions of use.

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[16] We also note that the Agency's regulations on good guidance practices expressly state that Agency guidance cannot establish legally binding obligations for the public or the Agency (see 21 CFR 10.115(d)). You cite the decision of the Court of Appeals for the District of Columbia in *Alaska Professional Hunters Assoc., Inc. v. FAA* (177 F.3d 1030 (D.C. Cir. 1999)) as authority for your argument that the Agency is bound by its guidance on the geriatric use regulations. However, that court has expressly ruled that the standard announced in *Alaska Hunters* did not apply where an agency had not adopted an express, direct, uniformly applied interpretation upon which the public had relied. *Ass'n. of American Railroads v. DOT*, 198 F.3d 944 (D.C. Cir. 1999). In contrast, the Agency guidance on the geriatric labeling regulations does not even explicitly speak to the question of whether ANDA applicants should be permitted to omit protected geriatric labeling.

III. Geriatric Use Information May Be Omitted from the Labeling for Generic Oxandrolone Products

Having determined that geriatric labeling protected by exclusivity can legally be omitted as long as the generic product remains as safe and effective as the reference listed drug for all remaining, nonprotected conditions of use, we turn now to the scientific and policy question of whether the protected geriatric information for Oxandrin in particular may be omitted from the labeling for generic oxandrolone products.

A. Background on Oxandrin

Oxandrin is an anabolic steroid approved by FDA in 1964. The INDICATIONS and USAGE section of the labeling states that Oxandrin is currently indicated for:

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

FDA's review of past Oxandrin labeling found that these indications have remained essentially the same since at least 1975. Oxandrin is available in 2.5-milligram (mg) and 10-mg strengths.

1. Savient's Geriatric Labeling Supplement

In August 2002, in accordance with FDA's requirement at 21 CFR 201.80 for applicants to provide available information on geriatric use in the labeling for prescription drug products, Savient submitted a geriatric labeling supplement (NDA 13-718/supplement 023) to the Agency to change the Clinical Pharmacology, Precautions, and Dosage and Administration sections of the package insert. This labeling supplement included data from three double-blind, placebo-controlled clinical studies and two open-label uncontrolled studies, which Savient conducted to study various uses of oxandrolone.[17]

[17] Four of the studies from which Savient obtained the data supporting the labeling change were phase 2 studies that Savient had previously conducted but had not submitted to the Agency. Savient submitted abbreviated study reports for these four studies. The abbreviated reports presented only data on body weight gain from baseline. One of these studies was a 4-month, dose-ranging study in patients 40 years and older with Chronic Obstructive Pulmonary Disease (COPD) that Savient had conducted to evaluate the effect of oxandrolone on respiratory muscle strength. Another was a 4-month study in patients 18 years and older conducted to evaluate the effect of oxandrolone on the treatment of ulcers. The third was a 3-month study in men 60 years and older conducted to evaluate the effects of oxandrolone on body composition, skeletal muscle strength, physical function and quality of life, serum lipids and liver function, and safety profile. The fourth was a 4-month study conducted in patients 40 years and older with COPD to evaluate the effects of oxandrolone on body weight and composition and pulmonary function. The fifth study was described as a pharmacokinetics study in elderly subjects.

Savient relied on data from these studies to support labeling stating that oxandrolone has similar effects on weight gain in the geriatric and nongeriatric populations. Although no single study had sufficient data to support a conclusion as to relative weight gain in the geriatric--as opposed to nongeriatric--adult population, FDA concluded that, collectively, the data derived from these various studies provided sufficient evidence for the labeling change. In addition, Savient relied on these five studies to support new labeling regarding the relative adverse event profiles for the geriatric and nongeriatric populations and a new dosing recommendation for the geriatric population.

The Agency approved Savient's labeling supplement on June 20, 2005, and granted Savient three-year marketing exclusivity that expires on June 20, 2008.

2. *The New Geriatric Labeling*

The geriatric use information added to the Oxandrin labeling upon approval of the supplement is described below:

The CLINICAL PHARMACOLOGY section was revised to add the following:

> In a single dose pharmacokinetic study of Oxandrin in elderly subjects, the mean elimination half-life was 13.3 hours. In a previous single dose pharmacokinetic study in younger volunteers, the mean elimination half-life was 10.4 hours. No significant differences between younger and elderly volunteers were found for time to peak, peak plasma concentration or AUC [area under the concentration vs. time curve] after a single dose of Oxandrin. The correlation between plasma level and therapeutic effect has not been defined.

The PRECAUTIONS section was revised to add the following information:

> *Geriatric Use*: Oxandrin, at daily doses of 5 mg bid and 10 mg bid, was evaluated in four clinical trials involving a total of 330 patients with different underlying medical conditions. The maximum duration of treatment was 4 months with the average duration of treatment from 68.5 days to 94.7 days across the studies. A total of 172 elderly patients ($\geq$ 65 years of age) received Oxandrin treatment. Mean weight gain was similar in those $\geq$ 65 and those < 65 years of age. No significant differences in efficacy were detected between the 5 mg bid and 10 mg bid daily doses. The adverse event profiles were similar between the two age groups although the elderly, particularly in women, had a greater sensitivity to fluid retention and increases in hepatic transaminases. A single dose pharmacokinetic study in elderly volunteers revealed an increased half-life compared to younger volunteers. (see Clinical Pharmacology) Based on greater sensitivity to drug-induced fluid retention and transaminase elevations, a lower dose is recommended in the elderly (see Dosage and Administration).

The DOSAGE AND ADMINISTRATION section was revised to add the following: *"Geriatric Use:* Recommended dose for geriatric population is 5 mg bid."

B. Assessment of Safety and Effectiveness for Generic Oxandrolone Products that Omit Geriatric Labeling

In addition to suggesting that geriatric labeling required under the geriatric labeling regulations cannot be omitted as a categorical matter, you argue that the new geriatric use information for Oxandrin in particular cannot be omitted from the labeling for generic oxandrolone products. You assert that generic oxandrolone products would not be as safe and effective as Oxandrin if this labeling were omitted. In addition, you claim that generic oxandrolone products would be misbranded because they would fail to provide adequate directions for use, and that permitting omission of the new geriatric use information would be inconsistent with past Agency practice and the objectives of the Hatch-Waxman Amendments. We disagree.

The labeling for oxandrolone is unusual because all the safety and effectiveness issues addressed in the new geriatric use information are of concern within the general adult population and, as a consequence, are adequately addressed elsewhere in the label. As set forth in the following subsection, the Agency has determined that omission of the new geriatric use information would not affect the safety or effectiveness of generic oxandrolone products, that generic oxandrolone products would not be misbranded, and that permitting omission of this information would be consistent with the Agency's past practice and the objectives of the Hatch-Waxman amendments.[18]

1. Omission of the New Geriatric Use Information From the Labeling for Generic Oxandrolone Products

The new geriatric use labeling (quoted in subsection III.A.2) reflects that the studies submitted by Savient did not demonstrate a difference in efficacy between the geriatric and nongeriatric populations. These studies also did not demonstrate any difference in efficacy between 5 mg bid[19] and 10 mg bid dosing in either the geriatric or nongeriatric population. The studies indicated some safety considerations for the geriatric population, however. Specifically, these studies indicated that the geriatric patients may have greater sensitivity to drug-induced fluid retention (edema) and exhibit elevated transaminases (liver toxicity), and that the drug may have a longer half-life in the geriatric population, which could exacerbate both of these risks. The results of these studies are reflected in the new labeling for the Clinical Pharmacology section (half-life) and the geriatric use section under Precautions (efficacy, edema, liver toxicity, half-life). In light of these study results, the new geriatric labeling also includes a statement in the Dosage and Administration section recommending 5 mg bid dosing in the geriatric population.

[18] This conclusion regarding the safety and effectiveness of oxandrolone products if geriatric information were omitted from the labeling does not reflect any Agency judgment as to the safety or effectiveness of any other products if geriatric use information were similarly omitted. Rather, this conclusion is based on a case-specific analysis of oxandrolone.

[19] The term *bid* means twice daily (in the morning and evening).

After reviewing the content of the geriatric use section, and the related, new geriatric labeling included in the labeling for Oxandrin, we have concluded that, if the new geriatric labeling were omitted, generic oxandrolone products would remain as safe and effective as Oxandrin for all remaining, nonprotected conditions of use. This is based on the determination that the labeling for generic oxandrolone would still contain adequate information to permit appropriate use and to minimize risks in all adults, including the geriatric population, with regard to each of the safety considerations also identified in the new geriatric labeling: edema, liver toxicity, and dosing.

a. Edema

Edema is addressed in the new geriatric labeling, but also has long been addressed in the nonprotected Warnings and Adverse Reactions sections of the labeling. The current, nonprotected labeling reads:

> WARNINGS
> Edema with or without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal or hepatic disease....
>
> ADVERSE REACTIONS - Fluid and Electrolytes
> Edema, retention of serum electrolytes. . . .

This warning and this adverse reaction information related to edema would be included in the approved labeling for generic oxandrolone products. The edema adverse reaction is a well-established side effect of all anabolic steroids, including oxandrolone. As in the general adult population, geriatric patients with underlying cardiac, renal, and hepatic disease would be at greatest risk of a serious clinical complication from edema.

Because the oxandrolone labeling would retain the above warning and adverse reaction information related to edema in adult patients, the absence of a specific geriatric use statement that edema occurred more frequently in the elderly patients in certain clinical studies will not render generic products less safe or effective than Oxandrin in the geriatric population. The labeling would still provide adequate notice of these risks to enable monitoring, timely detection, and treatment as appropriate in the clinical setting.

b. Liver toxicity

Hepatotoxicity (liver toxicity) is a serious side-effect of anabolic steroids, which the labeling for Oxandrin has long addressed. In addition to the new geriatric labeling regarding elevated transaminases, the label for oxandrolone currently contains several statements concerning liver toxicity that are not protected. A *Boxed Warning* describes the occurrence of peliosis hepatis and liver cell tumors.[20] In addition, the PRECAUTIONS section states the following: "Because of

[20] The boxed warning states:

the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically." This safety concern is again discussed under the ADVERSE REACTIONS section as follows:

> Cholestatic jaundice with, rarely, hepatic necrosis and death. Hepatocellular neoplasms and peliosis hepatis with long-term therapy (see Warnings). Reversible changes in liver function tests also occur including increased BSP retention, changes in alkaline phosphatase and increases in serum bilirubin, aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT).

In short, if the new geriatric use information were omitted, the label for generic oxandrolone would still contain a thorough discussion of the risk of liver toxicity and include recommendations for liver function testing.[21] Consequently, exclusion of the statement that elderly patients in the clinical studies exhibited a higher incidence of increases in hepatic transaminases will not render generic versions of the drug less safe for use in the geriatric population.

c. Dosing instructions

The change to the DOSAGE AND ADMINISTRATION section of oxandrolone as a result of the labeling supplement was based on the observation that efficacy was similar between the 5 mg and 10 mg bid dosing, the two dosing levels assessed in the studies Savient conducted. In light of the dose-related adverse reactions, the new geriatric use labeling advises prescribers to use the

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> PELIOSIS HEPATIS, A CONDITION IN WHICH LIVER AND SOMETIMES SPLENIC TISSUE IS REPLACED WITH BLOOD-FILLED CYSTS, HAS BEEN REPORTED IN PATIENTS RECEIVING ANDROGENIC ANABOLIC STEROID THERAPY. THESE CYSTS ARE SOMETIMES PRESENT WITH MINIMAL HEPATIC DYSFUNCTION, BUT AT OTHER TIMES THEY HAVE BEEN ASSOCIATED WITH LIVER FAILURE. THEY ARE OFTEN NOT RECOGNIZED UNTIL LIFE-THREATENING LIVER FAILURE OR INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. WITHDRAWAL OF DRUG USUALLY RESULTS IN COMPLETE DISAPPEARANCE OF LESIONS.
>
> LIVER CELL TUMORS ARE ALSO REPORTED. MOST OFTEN THESE TUMORS ARE BENIGN AND ANDROGEN-DEPENDENT, BUT FATAL MALIGNANT TUMORS HAVE BEEN REPORTED. WITHDRAWAL OF DRUG OFTEN RESULTS IN REGRESSION OR CESSATION OF PROGRESSION OF THE TUMOR. HOWEVER, HEPATIC TUMORS ASSOCIATED WITH ANDROGENS OR ANABOLIC STEROIDS ARE MUCH MORE VASCULAR THAN OTHER HEPATIC TUMORS AND MAY BE SILENT UNTIL LIFE-THREATENING INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. BLOOD LIPID CHANGES THAT ARE KNOWN TO BE ASSOCIATED WITH INCREASED RISK OF ATHEROSCLEROSIS ARE SEEN IN PATIENTS TREATED WITH ANDROGENS OR ANABOLIC STEROIDS. THESE CHANGES INCLUDE DECREASED HIGH-DENSITY LIPOPROTEINS AND SOMETIMES INCREASED LOW-DENSITY LIPOPROTEINS. THE CHANGES MAY BE VERY MARKED AND COULD HAVE A SERIOUS IMPACT ON THE RISK OF ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE.

[21] The geriatric use section discusses increases in hepatic transaminases (a type of enzyme). The label does not expressly refer to transaminase levels otherwise. Instead, the label includes recommendations for "liver function tests." Liver function testing would include monitoring of transaminase levels, among other function tests.

lower (5 mg bid) of these two doses for which Savient's studies provided data on use in the elderly population.

If the new geriatric use recommendation were omitted, the DOSAGE AND ADMINISTRATION section would state:

> Adults: The response of individuals to anabolic steroids varies. The daily adult dosage is 2.5 mg to 20 mg given in 2 to 4 divided doses. The desired response may be achieved with as little as 2.5 mg or as much as 20 mg daily. A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated intermittently as indicated.

The statements that "daily adult dosage is 2.5 mg to 20 mg" and that "desired response may be achieved with as little as 2.5 mg daily" are particularly noteworthy because 2.5 mg daily is a lower dose than the 5-mg twice-daily dose recommended for geriatric patients under the new labeling. This nonprotected dosing information regarding the effectiveness of an even lower dose and limiting the duration of dosing, along with the nonprotected safety information discussed previously regarding edema and liver toxicity, would provide appropriate guidance to practitioners for safe and effective dosing of oxandrolone. Omission of the new dosing information for the geriatric population would therefore not render generic oxandrolone products any less safe or effective than Oxandrin.

d. New geriatric information may be omitted from oxandrolone ANDA labeling

In short, the Agency has determined that it may approve ANDAs for drug products referencing Oxandrin that omit from their labeling the new geriatric use information for Oxandrin because omission of this labeling will not render these generic drugs less safe or effective than Oxandrin for the remaining, nonprotected conditions of use. The new geriatric use labeling for Oxandrin includes information relevant to all the listed indications because the drug may be used in the geriatric population for all of them. However, generic oxandrolone products would be as safe and effective as Oxandrin for all of these indications if the new geriatric use information were omitted, because the concerns addressed in the new Oxandrin geriatric labeling apply within the general adult population (not just the geriatric population) and are, as a result, adequately addressed by the labeling applicable to all adults.[22]

[22] You state that Savient generated the data supporting its new geriatric use labeling "in response to a request from the Agency for data on the safe use of drugs in the elderly" (petition at 4). If this statement is intended to suggest that the Agency requested that Savient develop or submit new data, the statement is not correct. As stated in the preambles to the proposed and final geriatric labeling regulation, the Agency has encouraged sponsors to develop geriatric use data; however, the regulations do not require development of new data, and the Agency did not request development or submission of any new data on oxandrolone in particular. Rather, as described in section III.A.1, Savient chose to review existing studies it had conducted for various purposes, to determine whether the studies included information on geriatric use, to submit abbreviated reports concerning the geriatric use information derived from these studies, and to conduct and submit a small study addressing pharmacokinetics.

As the geriatric labeling regulations reflect, the geriatric population is a subset of the adult population (see 21 CFR 201.80(f)(10)(ii); see also 55 FR at 46134 and the geriatrics guidance at 3). In this particular instance, the Agency has concluded that, even with certain geriatric information omitted, the labeling for adults adequately addresses, for younger adults and geriatric patients alike, the specific safety issues also addressed in the new geriatric use labeling.

You suggest that the grant of three-year exclusivity shows that the new geriatric use labeling for Oxandrin is needed for generic oxandrolone products to be safe and effective. This assumption is incorrect. The grant of three-year exclusivity does not reflect an Agency determination that the new geriatric use information is needed to ensure safety or effectiveness of the drug.

FDA will grant three-year exclusivity if it determines that new clinical data submitted in support of approval of an NDA supplement satisfies all of the requirements of the exclusivity (see footnote 4 supra quoting the statutory standard), including the requirement that the data are "essential to the approval of the supplement" (21 U.S.C 505(j)(F)(iv)). In other words, if the data are needed to support the labeling change (and satisfy the other requirements for three-year exclusivity), the Agency will grant the exclusivity. However, granting the exclusivity does not preclude the Agency from determining that the protected information may be omitted from labeling for generic products because it is not needed for those products to be as safe and effective as the reference listed drug for all remaining, nonprotected conditions of use.

In the case of Oxandrin, the Agency determined that the clinical studies submitted in support of the geriatric labeling supplement were "essential" because they were needed to support the geriatric use labeling change, as the specific statements made in the new labeling regarding the results of those studies could not be made without relying on those studies. However, the Agency has now also determined that this geriatric information may be omitted from labeling for generic oxandrolone products because it is not needed for those products to be as safe and effective as Oxandrin for all remaining, nonprotected conditions of use.

We also note that we see no basis as a factual matter for your assertion that the new labeling is necessary to the product's safety and effectiveness. You offer no evidence to support your assertion. We note in this regard that oxandrolone has been on the market for over 40 years. Its labeling has included all of the same indications it now includes and warnings regarding edema and liver toxicity since at least 1975. Yet, the Agency is not aware of any evidence of safety or effectiveness concerns peculiar to the geriatric population relating to this drug with respect to edema, liver toxicity, or any other issue.[23]

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[23] Savient submitted a supplement to its citizen petition, dated February 2, 2006, providing the Agency a copy of an article describing a case of a 93-year-old woman who was treated chronically with the anti-coagulant warfarin for atrial fibrillation and who exhibited bleeding among other adverse effects. The supplement asserts that this article provides further evidence of the need to include the new geriatric use information to ensure product safety. The issue of oxandrolone-warfarin interaction is being considered in the Agency's response to a second citizen petition in which Savient focuses largely on this drug-drug interaction (Docket No. 2004P-0074/CP1). Savient submitted the article to the dockets for both petitions. We note here only that (1) oxandrolone has included warnings regarding interaction with anti-coagulants since at least September 1975; (2) the geriatric dosing information for Oxandrin contains no information on specific dosing for oxandrolone when taken with warfarin; (3) the labeling for warfarin includes extensive safety information on both use of warfarin in the geriatric population and on drug-drug interactions including express references to interaction with oxandrolone and with other anabolic steroids; and (4)

2. *Generic Products Will Not Be Misbranded if They Do Not Include Geriatric Labeling Protected by Exclusivity; Omission of This Labeling Is Consistent with Agency Practice and the Objectives of the Hatch-Waxman Amendments*

a. Misbranding

You argue that generic products would not provide adequate directions for use and would, therefore, be misbranded if they were not to include the new geriatric use information approved for Oxandrin. We disagree.

As you note, FDA regulations exempt prescription drugs from the statutory requirement at 21 U.S.C. 352(f)(1) for adequate directions for use, but require that labeling for prescription drugs bear information adequate for practitioners to use the drug safely for its intended uses (21 CFR 201.100(a) and (d)). We see no basis for concluding that a generic oxandrolone product would not bear information adequate for practitioners to use the drug safely for its intended uses if the new geriatric use information were omitted.

Of course, not every generic drug product would provide adequate information for practitioners if protected geriatric use information were omitted from its labeling; however, the omission would not be permitted under such circumstances. To ensure that prescription generic drug products bear information adequate for practitioners to use the drug safely for their intended uses, FDA regulations permit omission of protected information from the labeling for a generic drug only if the product will remain as safe and effective as the listed drug for all remaining, nonprotected conditions of use. Here, the Agency has concluded that a generic oxandrolone product whose labeling omits the protected geriatric information will be no less safe or effective than Oxandrin for all remaining, nonprotected conditions of use. Accordingly, the generic product would not be misbranded.[24]

b. Agency practice

Permitting ANDA applicants for generic oxandrolone products to omit the new geriatric labeling is consistent with past Agency practice with respect to omission of other protected labeling. In your petition, you suggest that permitting a labeling omission for oxandrolone is inconsistent with the Agency's determinations permitting ANDA applicants to omit information protected by three-year exclusivity from the labeling for generic ribavirin[25] and generic tramadol

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Savient has offered no evidence that exclusion of the new geriatric information from the labeling for generic oxandrolone products will make them less safe and effective than Oxandrin when geriatric patients are receiving concurrent warfarin treatment.

[24] We note as well, as discussed in section II.A.2, that the geriatric labeling regulations expressly provide for omission of labeling that is not relevant or appropriate to include (see 21 CFR 201.80(f)(10)(vi)).

[25] Letter dated April 6, 2004, from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research (CDER), to David M. Fox, Hogan & Hartson, L.L.P (Ribavarin citizen petition response, Docket No. 2003P-0321/CP1).

hydrochloride (tramadol).[26] We see no inconsistency between these two prior determinations and the Agency's determination to allow generic oxandrolone applicants to omit the new geriatric use information for Oxandrin.

In the case of ribavirin, the Agency permitted generic applicants to omit labeling referring to combination use of ribavirin with the drug PEG-intron (peginterferon alfa-2b). The Agency concluded that this information could be omitted because the generic products could still be labeled for combination use with another product, Intron A, and would remain as safe and effective as the reference listed drug for this remaining use. You offer no rationale for considering this determination inconsistent with the Agency's determination to permit generic oxandrolone applicants to omit the new geriatric use information. With oxandrolone, as with ribavirin, the Agency has made a product-specific determination, based on the nature of the drug and the content of the labeling, that generic versions of the particular drug will remain as safe and effective as the reference listed drug for all remaining, nonprotected conditions of use.

In the case of tramadol, the Agency permitted generic applicants to omit from their labeling protected dose titration information. Specifically, the Agency permitted omission of information regarding increasing the drug dose by 25 mg per day. The label also included information on increasing the dose by 50 mg per day. The Agency found the protected 25-mg dosing information unnecessary for generic products to be as safe and effective as the reference listed drug because, even without the 25-mg dosing information, the drug could be used safely and effectively based upon the 50-mg dosing information by those patients who had not previously reacted adversely to tramadol. Here, too, you fail to explain why this determination is in any way inconsistent with the Agency permitting generic oxandrolone applicants to omit the new geriatric use information for Oxandrin. You suggest that the tramadol determination reflects the importance of including adequate dosing information in product labeling. We agree that this is important. However, as discussed previously, the Agency has determined that generic oxandrolone labeling will include adequate dosing information if the new geriatric dosing information is omitted.

In short, we see no inconsistency between the tramadol determination and our determination to permit omission of geriatric use information for oxandrolone. In fact, we view the tramadol example as fully consistent with our determination with respect to oxandrolone. Generally, ANDA applicants seek to omit protected indications for the drug from the generic labeling and omit information related to those indications. In the case of oxandrolone, the geriatric use information that will be omitted is relevant to nonprotected indications that will remain in the label. The tramadol determination also permitted omission of information relating to an indication that would remain on the label. In both cases, the Agency found the omission permissible because it would not render the generic drug any less safe or effective than the listed drug for all remaining, nonprotected conditions of use.

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[26] Letter dated June 11, 2002, from Janet Woodcock, Director, CDER, to Marcy Macdonald, Associate Director, Regulatory Affairs, Apotex Corp., and Deborah A. Jaskot, Executive Director, Regulatory Affairs, Teva Pharmaceuticals USA, and James F. Hurst, Winston and Strawn (Tramadol citizen petition response, Docket Nos. 01P-0495/CP1, 02P/0191/CP1 and 02P/0252/CP1).

c. Objectives of the Hatch-Waxman Amendments

As noted in section II.A.1, the Hatch-Waxman Amendments were intended to strike a balance between promoting innovation and encouraging competition in the pharmaceutical marketplace (see, e.g., 59 FR 50338 (October 3, 1994)). The ANDA labeling regulations were issued to implement these amendments, and the courts have upheld these regulations and the resultant balancing of these interests. Accordingly, it follows that the Agency's reasonable application of these regulations is consistent with the objectives of the Amendments.

You argue that, in this particular case, permitting omission of the protected geriatric use information would be inconsistent with the objectives of the Hatch-Waxman Amendments because the omission would result in the generic product having "'better' or less restrictive labeling." You indicate that generic labeling would be "better" or "less restrictive" because it would not restrict dosing for geriatric patients to the same degree as the Oxandrin label containing the new geriatric dosing information. As explained in section II.B.1.c, if generic applicants omit the new labeling that recommends starting geriatric dosing at 5 mg bid, the labeling will still include dosing information indicating that dosing can begin at a level as low as 2.5 mg daily, one-fourth of the daily dosing recommended in the new geriatric dosage information. You do not explain why you would consider the Oxandrin label more restrictive as a result, or what bearing this has on consistency with the objectives of the Hatch-Waxman Amendments.

Regardless of whether the generic labeling would be less or more "restrictive" with the geriatric dosing information omitted, omission of the new geriatric use information will not make generic oxandrolone products less safe or effective and, therefore, is permissible under section 314.127(a)(7). We see no basis for considering the omission of the new geriatric use information inconsistent with the balance Congress intended the Hatch-Waxman Amendments to effect between promotion of innovation and encouragement of competition.

C. Including a Statement Regarding Omission of Geriatric Labeling in the ANDA Labeling

The Agency has determined that ANDA applicants may obtain approval of oxandrolone labeling that omits geriatric use information. As a result, the labeling for these generic products would not include the information contained in the new geriatric use section for Oxandrin or the associated new geriatric use information included elsewhere in the Oxandrin label.

The Agency will permit ANDA applicants to include a statement in the geriatric use section of their labeling to indicate the reason for the omission. Specifically, the Agency will permit the following statement in the geriatric use section: "Certain geriatric use information is protected by marketing exclusivity." This statement is consistent both with the geriatric labeling regulations and with the ANDA labeling regulations. Under the geriatric labeling regulations, if the Agency determines that labeling otherwise required or permitted can be omitted, the sponsor can include an alternative statement if the Agency determines that this alternative statement is "accurate and appropriate" (see 21 CFR 201.80(f)(10)(vi)). The above statement of reason is

undeniably accurate, and it is likewise appropriate as a means to inform the reader of the reason that the geriatric use information is not presented in the ANDA labeling.

The statutory authority at section 505(j)(2)(a)(v) of the Act for the ANDA labeling regulations does not dictate the nature or scope of permissible labeling changes. It simply authorizes labeling "changes" if required because of a difference in manufacturer. The ANDA labeling regulations themselves also do not preclude the Agency from permitting generic oxandrolone applicants from including an explanatory statement regarding the omission of protected labeling. Section 314.94(a)(8)(iv) describes types of permissible changes, stating that they may include among other differences "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity . . . ." Section 314.127(a)(7) states simply that labeling may include "changes required . . . because aspects of the listed drug's labeling are protected by patent, or by exclusivity . . . ." The Agency has previously relied on this statutory authority and these two regulatory provisions to permit insertion of additional language in generic labeling associated with a permissible difference in drug products, and this interpretation has been upheld by the courts (see *Zeneca, Inc. v. Shalala*, 213 F.3d 161 (D.C. Cir. 2000) (upholding an Agency decision to allow a generic product to include a different, permissible inactive ingredient and, therefore, to include in its labeling a warning consistent with Agency regulations for products containing that ingredient)).

IV. Conclusion

Your petition is denied. The Agency has the legal authority to permit the omission of protected geriatric use information from the generic drug labeling for oxandrolone. The Agency has determined, in accordance with this authority, that ANDAs referencing Oxandrin may be approved with labeling that omits the new geriatric use labeling for Oxandrin during the three-year exclusivity period, because the generic products will be no less safe or effective than Oxandrin for all remaining, nonprotected conditions of use. In addition, until the three-year exclusivity expires on June 20, 2008, ANDA labeling that omits the geriatric information also may contain a statement in the geriatric use section alerting the reader that certain geriatric use information has been omitted because of exclusivity.

Sincerely,

Steven K. Galson, M.D., M.P.H
Director
Center for Drug Evaluation and Research