DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 1 2006

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Re: Docket No. 2004P-0074/CP1, SUP1, SUP2, SUP3, and SUP4

Dear Messrs. Allera, Segal, and Sullivan:

This letter responds to the citizen petition you submitted on behalf of Savient Pharmaceuticals, Inc. (Savient), dated February 16, 2004 (Petition), requesting that the Food and Drug Administration (FDA) establish specific bioequivalence requirements for oral drug products containing oxandrolone. You claim that these bioequivalence requirements are necessary because of several unique aspects of oxandrolone drug products, including (1) serious safety issues regarding interactions between oxandrolone and warfarin, and (2) certain aspects of oxandrolone drug products that present evidence of actual or potential bioequivalence problems under 21 CFR 320.33. You also claim that because of oxandrolone's unique properties, conventional methods for demonstrating bioequivalence do not provide sufficient assurance of safety to support approval of an abbreviated new drug application (ANDA) for oxandrolone.

To establish bioequivalence and safety of oxandrolone drug products, you request that FDA require that:

- Evidence from appropriately designed clinical studies address the bioavailability issues associated with oxandrolone, including its concomitant use with warfarin. Required studies must include drug-drug interaction studies with pharmacokinetic and pharmacodynamic (PK/PD) endpoints[1] based on the safety and effectiveness of warfarin.

- Warfarin interaction PK/PD studies produce results identical or nearly so to those in the labeling of the reference listed drug (RLD)[2] before approving any other oxandrolone drug product.

[1] Pharmacokinetic studies measure the absorption, distribution, metabolism, and elimination of a substance. Pharmacodynamic studies evaluate a substance's mode of action and/or effects.

[2] *Reference listed drug* means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application (21 CFR 314.3(b)). A listed drug is a "new drug product that has an effective approval . . . Listed drug status is evidenced by the drug product's

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- Labeling be identical to the approved labeling for the RLD for oxandrolone as required by the Federal Food, Drug, and Cosmetic Act (the Act) and FDA's regulations. Require that evidence to support the labeling come from appropriately designed clinical studies establishing the PK/PD of drug interactions between the proposed oxandrolone drug product and warfarin.

- As has been established for the RLD, each ANDA for oxandrolone have additional chemistry, manufacturing, and controls (CMC), such as a well-controlled active pharmaceutical ingredient (API) particle size requirement and test procedure superior to that generally in place for an API in a solid dosage form, to ensure acceptable product quality, because oxandrolone is a potentially problematic drug product.

- Each ANDA for oxandrolone that contains more than one dosage strength of the drug demonstrate dose proportionality through pharmacokinetic studies in human subjects, or provide specific warfarin dose adjustment guidance for each dosage strength.

In addition, you request that FDA apply stringent standards for impurities in generic oxandrolone drug products based on recommendations in Agency guidance and proposed changes to the USP.

In reaching its decision, FDA has considered the information in the petition, supplemental data submitted to the petition, comments opposing the petition, and other information available to the Agency. The Agency has carefully considered the requests and arguments raised in the petition and, for the reasons set forth below, grants your petition in part with respect to your requests for the Agency to apply the statutory requirements for sameness of labeling and all appropriate impurity standards. You offer no convincing evidence (i.e., data or other information) that any of your proposed changes to current Agency practices are needed with respect to bioequivalence determinations, or CMC and impurity standards. Accordingly, because the Agency was not presented with any basis for departing from our established practices, we deny your petition in all other respects.

I. Background

A. Oxandrin

Savient, formerly Bio-Technology General Corp., is the holder of new drug application (NDA) 13-718 for Oxandrin (oxandrolone). Savient markets Oxandrin in oral tablets of 2.5-milligram (mg) and 10-mg dosage strengths. Oxandrin, an anabolic steroid, was approved July 21, 1964, and is indicated as adjunctive therapy to (1) promote weight gain

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identification as a drug with an effective approval in the current edition of FDA's Approved Drug Products with Therapeutic Equivalence Evaluations . . . ." Id.

after weight loss following extensive surgery, chronic infections, or severe trauma; (2) promote weight gain in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight; (3) offset the protein catabolism associated with prolonged administration of corticosteroids; and (4) relieve the bone pain frequently accompanying osteoporosis.

B. Warfarin

Warfarin is an anticoagulant used for the prevention and treatment of thrombosis, embolism, and other blood-clotting disorders. Warfarin's pharmacologic effect results from the inhibition of clotting factors and coagulation. The therapeutic or anticoagulant effect of warfarin is usually monitored in terms of its prothrombin time (PT)/international normalized ratio (INR), which are standardized laboratory measures of anticoagulant effect often employed to assess the adequacy of drugs to prevent blood clots. Warfarin is a narrow therapeutic range drug, which means that a small margin exists between a therapeutic and toxic dose (see 21 CFR 320.33(c)). Warfarin anticoagulation effect can be influenced by a variety of factors, including diet, gender, activity level, concomitant administration of prescription and nonprescription medications, vitamins, and herbal supplements. Oxandrolone is one of the drugs known to interact with warfarin, and oxandrolone's labeling has long included a warning regarding interaction with anticoagulants. The labeling for warfarin emphasizes that patients taking warfarin must be carefully monitored, and the dose of warfarin adjusted to maintain an acceptable therapeutic level.

C. Oxandrin-Warfarin Interaction

On April 21, 2003, FDA approved a supplemental application for a labeling change in the *Precautions* section for Oxandrin based on the results of a clinical study conducted by Savient on the interaction between oxandrolone and warfarin. The results of the study showed that a significant decrease (80 to 85 percent) in warfarin dose is needed to achieve therapeutic effect when oxandrolone is taken concurrently with warfarin. On the advice of the Agency, Savient issued a *Dear Health Care Professional* letter to health care professionals on April 24, 2003, about the oxandrolone-warfarin interaction. The letter reports on the results of the study and states that "[c]oncurrent dosing of oxandrolone and warfarin may result in large increases in the International Normalized Ratio (INR) or PT. When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain a desirable INR level and diminish the risk of potentially serious bleeding," and that physicians "should instruct patients to report immediately any use of warfarin and any bleeding."

The *Precautions* section of Oxandrin's labeling as revised by the 2003 supplement includes the following:

> PRECAUTIONS
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> Current dosing of oxandrolone and warfarin may result in unexpectedly large increases in the INR [International Normalization Ratio] or prothrombin time (PT). When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain the desirable INR level and diminish the risk of potentially serious bleeding. (See PRECAUTIONS: Drug Interactions).
>
> Drug interactions
>
> Warfarin: A multidose study of oxandrolone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin half-life from 26 to 48 hours and AUC from 4.55 to 12.08 ng*hr/mL; similar increases in R-warfarin half-life and AUC were also detected. Microscopic hematuria (9/15) and gingival bleeding (1/15) were also observed. A 5.5-fold decrease in the mean warfarin dose from 6.13 mg/day to 1.13 mg/day (approximately 80-85% reduction of warfarin dose), was necessary to maintain a target INR of 1.5. When oxandrolone therapy is initiated in a patient already receiving treatment with warfarin, the INR or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has been achieved. Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dosage if indicated are recommended when the oxandrolone dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.

D. Statutory and Regulatory Basis for Approval of ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. No. 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Act (21 U.S.C. 355(j)), which established the current ANDA approval process. To gain approval, an ANDA applicant generally must show, among other things, that its generic[3] drug product is bioequivalent to a listed drug (i.e., a drug product previously approved for safety and effectiveness), and has the same active ingredient or ingredients, dosage form, route of administration, strength, and labeling,[4] as the listed drug. The specific listed drug to which an ANDA refers is known as the reference listed drug (RLD).

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

[4] An ANDA must contain the same drug product labeling as the RLD, except for differences approved under a suitability petition, or differences required because the proposed drug product and the RLD are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the Act and 21 CFR 314.94(a)(8)).

The scientific premise underlying the Hatch-Waxman Amendments is that a drug product that meets the approval requirements of section 505(j) of the Act is as safe and effective as the RLD. When a drug product approved under section 505(j) is therapeutically equivalent to the RLD, the drug product may be substituted for the RLD. Therapeutic equivalence requires a showing that the products are pharmaceutical equivalents (see 21 CFR 320.1(c)) and are bioequivalent.[5]

FDA regulations at § 320.1(c) define pharmaceutical equivalents as follows:

> *Pharmaceutical equivalents* means drug products in identical dosage forms that contain identical amounts of the identical active ingredient, i.e., the same salt or ester of the same therapeutic moiety, [but] do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard[s] of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

FDA regulations specify that two drug products are bioequivalent if there is an:

> . . . absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose[6] under similar conditions in an appropriately designed study. (21 CFR 320.1(e); see also 21 CFR 320.23(b)).

FDA regulations at § 320.24 discuss the types of evidence required to establish bioequivalence. FDA has considerable discretion in determining how the bioequivalence requirement is met (see, e.g., 21 U.S.C. 355(j)(8)(C) and 21 CFR 320.24(a) and (b)(6)). FDA's determination regarding appropriate bioequivalence methodology need only be based on a "'reasonable and scientifically supported criterion, whether [the Agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs . . . .'" (*Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 218 (D.D.C. 1996) (quoting *Schering v. Sullivan Corp.*, 782 F. Supp. 645, 651 (D.D.C. 1992), *vacated as moot sub nom, Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993))). The Agency's standards and evidentiary requirements for demonstrating bioequivalence are described in detail in section II.A.

Among the various other requirements that ANDA applicants, like NDA applicants, must satisfy are standards for CMC to assure and preserve the drug's identity, strength, quality, and purity (see 21 U.S.C. 355(j)(4)(A) and 21 CFR 314.94(a)(9)(i)).

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[5] Section 505(j) of the Act permits approval of ANDAs for products that are not pharmaceutical equivalents to the listed drug under the suitability petition process at section 505(j)(2)(C). These products would not be therapeutic equivalents to the listed drug, and thus would not be substitutable.

[6] The phrase *same molar dose* means a dose containing the same number of molecules of the active moiety.

II. Discussion

A. FDA's Standard Bioequivalence Criteria Are Sufficient to Establish Bioequivalence of Generic Oxandrolone Drug Products.

You assert that FDA's established criteria for measuring bioequivalence (absorption parameters falling between 80 and 125 percent of the reference product) could result in generic oxandrolone drug products that vary in bioavailability by as much as 25 percent from the RLD and more than 50 percent from each other. You assert that such a relatively wide range in bioavailability, when combined with oxandrolone's effect on warfarin, a narrow therapeutic range drug, creates a significant safety risk to patients concomitantly administered oxandrolone and warfarin (Petition at 3, 10, and 11). We disagree. You offer no evidence that FDA's established criteria would be inadequate to determine bioequivalence for oxandrolone products or inappropriate to apply in light of oxandrolone's interaction with warfarin.

As noted in section I.D of this response, a generic drug is bioequivalent to a listed drug if "the rate and extent of absorption of the drug do not show a *significant difference* from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . . ." (emphasis added) (section 505(j)(8)(B)(i) of the Act; see also 21 CFR 320.1(e) and 320.23(b)).

The purpose of a bioequivalence study of a generic drug product is to show that the bioavailability of the product is not significantly different from that of the reference (i.e., the RLD). In a standard bioequivalence study, single doses of the test and reference products are administered to each volunteer, and the rate and extent of absorption of the drug is determined from the measured plasma concentrations over time for each subject participating in the study. The extent of absorption (i.e., how much of the drug in the given dose was absorbed) is reflected through the *area under the concentration vs. time curve* (AUC). The maximum or *peak* drug concentration (Cmax) is used to reflect the rate of absorption.

It is important to analyze these pharmacokinetic parameters statistically because of the variability inherent in human subjects. This variability means that if the *same* subject receives the *same* drug product on two different occasions, the resulting plasma concentrations will not be exactly the same. Because of this inherent variability, if a single individual takes two *different* drug products on separate occasions, and there is a measurable difference in the pharmacokinetic parameters, it may not be clear whether this difference is the result of a difference between the products, or the result of inherent individual variability. Thus, FDA calls for ANDA and NDA applicants to use statistical methods to estimate more accurately those differences in pharmacokinetics that result from any differences in the two product formulations (see 21 CFR 320.23(a)).

To understand the statistical tests for bioequivalence, one must first understand the relevant statistical terms, particularly the definition of *mean* and *confidence interval*. The statistical term *mean* is frequently used in describing bioequivalence study results. The mean is the average of all the differences in pharmacokinetic values observed in the group of study subjects. If the same bioequivalence study is repeated in another small group of subjects, the second study's mean may be different from the first study's mean. FDA defines a *confidence interval* to address this potential for variation in the mean pharmacokinetic values of treatment groups. The mean for the study subjects lies at the center of the confidence interval. Essentially, the confidence interval provides an estimated range for the likely value of the mean if the drug were given to the entire patient population. The confidence interval specifies the preferred degree of *confidence* (i.e., likelihood) that this range accurately reflects what the results would be in the entire patient population.

In analyzing bioequivalence studies, FDA uses a 90 percent confidence interval. For example, the ratio of the mean AUC or Cmax value for the generic to that of the reference (reflecting the average difference between the test and reference products for all of the study subjects) could be 99 percent. A statistical analysis of the data could then determine that the 90 percent confidence interval for this study has a range of 90 percent to 110 percent for the ratio of these pharmacokinetic values. This confidence interval shows that for the entire patient population, the ratio of the mean AUC or Cmax between test and reference products is likely (with a 90 percent probability) to be between 90 percent and 110 percent. If a study includes a greater number of subjects, it can be expected to more accurately approximate what the results would be for the entire patient population. Consequently, the 90 percent confidence interval would be narrower (such as 95 to 105 percent), reflecting the greater likelihood that the mean values obtained for the study population approximate the mean values for the entire patient population.

FDA determines whether a study shows that two products are bioequivalent based on the confidence interval. Under this approach, the entire 90 percent confidence interval is expected to fall within the *acceptance interval* of 80 to 125 percent for FDA to conclude that the study demonstrates bioequivalence.[7] In other words, the acceptance interval (also referred to as *acceptance limits*) provides an upper and lower limit that the entire confidence interval must fall within. The acceptance interval is a fixed standard, while the size of the 90 percent confidence interval is derived from the data in a particular study.

The choice of the 80 to 125 percent acceptance interval reflects decades of scientific data on the variability of product characteristics within and between batches, as well as biological variability in patients. From these data, FDA concluded that the variability in pharmacokinetic values allowed under this acceptance interval would not adversely affect clinical outcomes, and that this variability is in fact reflective of the range of pharmacokinetic values that can arise for any particular manufacturer's product because

[7] See FDA's *Approved Drug Products with Therapeutic Equivalence Determinations* 26th Ed. viii (the Orange Book).

of product-specific and biological factors.[8] Having found thousands of drug products, including narrow therapeutic range drug products, to be bioequivalent based upon its current criteria, FDA has not identified any clinical problems arising from its reliance on these criteria.

B. Drug-Product Specific Interaction Studies Are Unnecessary.

You assert that the data in your Oxandrin-warfarin drug interaction study and the labeling precaution describing the study results are specific to Oxandrin. You claim that the results of your study are inapplicable to other oxandrolone drug products because of the "considerable variability in bioavailability permitted by FDA's usual criteria for bioequivalence" and the corresponding difference in warfarin anticoagulation effect that the variability could produce (Petition a 3). You claim that the increased potency in patients coadministered oxandrolone and warfarin represents a potential safety issue, requiring accurate, drug product-specific information for safe and effective patient care (Petition at 10).

FDA disagrees that clinical studies demonstrating drug interactions between generic oxandrolone drug products and warfarin are necessary for ANDA approval. As noted in section I.D of this response, ANDA sponsors are not required to conduct clinical studies to demonstrate that a product is safe and effective, as are sponsors of NDAs. Instead, an ANDA sponsor relies on the Agency's previous finding that (1) the RLD is safe and effective, by showing that the drug product proposed in the ANDA is bioequivalent to the RLD, and (2) the product also meets other ANDA requirements specified in the Act and FDA regulations. If an applicant makes that showing, the drug product described in the ANDA can be approved. Generic drug products that are bioequivalent and pharmaceutically equivalent to the RLD are considered to have established therapeutic equivalence, and thus can be expected to produce the same clinical effect and safety profile as the innovator product.[9] Moreover, if two drug products containing the same active ingredient are shown to be pharmaceutically equivalent and bioequivalent, their interaction with other drugs can be expected to be equivalent. Therefore, if a generic oxandrolone drug product meets the other ANDA approval requirements and is bioequivalent to Oxandrin, the RLD, its drug interaction with warfarin can be expected to be equivalent to the interaction between Oxandrin and warfarin. None of the safety and efficacy studies, including drug interaction studies, conducted for the RLD need to be repeated for the generic product.

You offer no evidence that FDA's established bioequivalence criteria for systemically absorbed drugs would be inadequate to assess the bioequivalence of oxandrolone products. Specifically, we note that your drug interaction study evaluating the effect of two doses of oxandrolone, 10 mg and 5 mg, each administered twice a day, offers no

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[8] Dighe, S.V., and Adams, W.P., "Bioequivalence: A United States Regulatory Perspective," in *Pharmaceutical Bioequivalence* (Welling P.G. et al., eds.), pp. 347-380, 1991.

[9] See, e.g., the Orange Book at vi.

evidence that permissible variation of bioavailability among bioequivalent oxandrolone products would have any effect on warfarin levels. The effect on warfarin levels of the two oxandrolone doses you studied was not significantly different, suggesting that the maximum inhibitory effect on warfarin metabolism may have been reached with the 5-mg dose. You offer no evidence that there would be any effect on warfarin levels because of the difference in bioavailability between a generic product and Oxandrin or between two generic products, if the generic products have an AUC and Cmax within 80 to 125 percent of Oxandrin. It also bears noting in this regard that, as discussed in section II.H of this response, the labeling for oxandrolone adequately addresses the need to monitor and adjust warfarin dosing in light of oxandrolone-warfarin interaction, and of the numerous other drug interactions and other factors that can affect warfarin dosage and administration.

Accordingly, generic applicants of oxandrolone drug products will not be required to conduct drug-specific drug interaction studies on their own products if they meet the criteria for bioequivalence and pharmaceutical equivalence. To require such drug interaction studies would be contrary to one of the guiding principles for in vivo bioavailability studies: that no unnecessary human research should be conducted (21 CFR 320.25). The existence of oxandrolone-warfarin interaction has already been established by studies conducted on Oxandrin and does not need to be separately studied by each ANDA applicant for a generic oxandrolone drug product.

You also assert that if FDA allows generic applicants to rely on your oxandrolone-warfarin drug interaction study data, it would abridge your trade secret and proprietary rights and would violate due process (Petition at 12). We disagree with these unsupported claims. The drug interaction information in the approved Oxandrin labeling is not subject to any existing patent or exclusivity protection. As noted in section I.D of this response, the Hatch-Waxman Amendments permit a generic drug applicant to rely on the Agency's findings of safety and effectiveness for the RLD. Such reliance is subject to applicable patent and exclusivity protections (21 U.S.C. 355(j)(5)(B) and (j)(F)). In authorizing reliance by ANDA applicants upon the finding of safety and effectiveness for a listed drug, Congress intended the ANDA approval process to ". . . assist the Agency in avoiding duplicative reviews of safety and effectiveness information about already approved drugs" (54 FR 28872 at 28890 (July 10, 1989)). FDA's review of ANDAs under the Act does not involve disclosure of the data in the innovator NDA to the ANDA applicant or to the public. Thus, the confidentiality of any trade secret or other proprietary data is maintained, and any rights in that information would be unabridged. In reviewing an oxandrolone ANDA application, including its labeling, FDA would be complying with its statutory mandate under section 505(j) of the Act, just as the Agency has in reviewing thousands of other ANDAs for over 20 years since the passage of the Hatch-Waxman Amendments. We see no violation of due process arising from review of oxandrolone ANDAs, and you cite no authority to the contrary.

C. Generic Applicants Are Not Required To Show an Identical Effect or Nearly Identical Effect on Warfarin-Induced INR Levels by Conducting PK/PD Studies to Establish Bioequivalence and Safety.

You claim that generic applicants of oxandrolone must demonstrate an identical or nearly identical effect on warfarin-induced INR levels by conducting PK/PD studies to show bioequivalence and safety (Petition at 12). We disagree.

The purpose of the bioequivalence requirement is not to show that two products have identical bioavailability, but rather to show "the absence of a significant difference" in bioavailability (see 21 CFR 320.1(e); see also section 505(j)(8)(B) of the Act). FDA regulations at 21 CFR 320.24(b) describe the types of in vivo and in vitro studies acceptable to FDA for documenting bioequivalence. These include, in descending order of accuracy, sensitivity, and reproducibility: pharmacokinetic, pharmacodynamic, clinical, and in vitro studies. For dosage forms such as oxandrolone tablets, which are "intended to deliver the active moiety to the bloodstream for systemic distribution within the body," bioequivalence should preferably be established by pharmacokinetic tests described in § 320.24(b)(1)(i). This approach provides for "[a]n in vivo test in humans in which the concentration of the active ingredient or active moiety, and when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time."

An alternative method, including use of a pharmacodynamic endpoint such as warfarin INR levels, generally should be used only when the active ingredient cannot be measured directly in biological fluids (see 21 CFR 320.24(a) and (b)). Thus, applicants would not use a pharmacodynamic method to establish bioequivalence when adequate methods are available to measure drug concentration in biological fluids. Oxandrolone is readily measurable in plasma; therefore, pharmacodynamic tests are not recommended for establishing bioequivalence of oxandrolone drug products.

Bioequivalence testing that measures oxandrolone plasma concentrations in the test and reference products is adequate to ensure that the potential for a drug-drug interaction between a generic oxandrolone tablet and warfarin will be equivalent to that for Oxandrin and warfarin. The purpose of bioequivalence testing is to ensure that two formulations provide an equivalent rate and extent of absorption of the active ingredient. Two drug products with an equivalent rate and extent of absorption of the drug will have equivalent blood concentrations and concentrations at the site of action. Because the magnitude of a drug-drug interaction is related to blood concentrations of the interacting drugs, it is reasonable to conclude that two oxandrolone products that produce equivalent blood concentrations will interact with a coadministered warfarin product to an equivalent degree. You offer no evidence to support a contrary conclusion. Once an ANDA sponsor has demonstrated that two oxandrolone products produce equivalent concentrations of the active ingredient in blood, it can be expected that the products will exhibit equivalent clinical performance, including potential for drug-drug interactions. Accordingly, a generic oxandrolone drug product that is shown to be bioequivalent to

Oxandrin can be expected to have a potential for interaction with warfarin equivalent to that of Oxandrin.

D. Your Reliance on 21 CFR 320.33(e) as a Bar to Establishing Bioequivalence and Designation of an AB Rating Is Misplaced.

You claim that oxandrolone is a drug with actual or potential bioequivalence problems, asserting that oxandrolone has the following five of the six physiochemical properties listed in § 320.33(e): (1) low aqueous solubility, (2) slow dissolution rate, (3) critical particle size, (4) complex morphology, and (5) a high excipient to API ratio (Petition at 13-15 and 17). You claim that "[t]hese characteristic[s] will likely render oxandrolone drug products not bioequivalent . . ." (Petition at 17).

We agree that oxandrolone possesses some of the physiochemical properties that you cite. However, your reliance on 21 CFR 320.33(e) to support your claim of potential bioinequivalence is misplaced. Section 320.33 sets forth criteria and evidence to be used in evaluating whether pharmaceutical equivalents and pharmaceutical alternatives[10] are not or may not be bioequivalent to one another. FDA considers the criteria in § 320.33 in determining whether to establish a bioequivalence requirement for pharmaceutical equivalents and pharmaceutical alternatives that are not subject to section 505(j) of the Act (see 21 CFR 320.32(a)). No such determination is needed for generic drug products that are subject to section 505(j) of the Act, such as oxandrolone, because the Hatch-Waxman Amendments establish bioequivalence requirements for all such drug products. In fact, by its terms, § 320.32 – which sets forth conditions in accordance with which FDA may seek to establish bioequivalence requirements – applies only to "a product not subject to section 505(j) of the [A]ct."

In any event, the fact that oxandrolone possesses some of the properties detailed in § 320.33 does not mean that bioequivalence may not be established between a generic oxandrolone drug product and the RLD, as you claim. As explained in section II.A of this response, an ANDA for an oxandrolone product can demonstrate bioequivalence if it can show that the plasma concentration parameters for the generic product fall within 80 to 125 percent of those for Oxandrin. Accordingly, we also disagree with your assertion that, because oxandrolone possesses characteristics of a drug with actual or potential bioequivalence problems, generic oxandrolone drug products cannot be rated AB, as therapeutically equivalent to the RLD (Petition at 15). An ANDA applicant can demonstrate the therapeutic equivalence of its generic oxandrolone product to Oxandrin

[10] As stated in the Orange Book (vi):

> Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths . . . . Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate-release or standard-release formulations of the same active ingredient.

See 21 CFR 320.1(d).

if it can demonstrate that its product satisfies these same bioequivalence requirements, and that its product is pharmaceutically equivalent to Oxandrin (i.e., it contains identical amounts of the same active drug ingredient in the same dosage form and route of administration, and meets compendial or other applicable standards of strength, quality, purity, and identity).

E. Current Statutory and Regulatory Requirements Ensure That Adequate Information Regarding the Physical and Chemical Characteristics of a Generic Oxandrolone Drug Product Is Included in the ANDA.

1. Your Concerns Regarding Chemistry, Manufacturing, and Controls in an ANDA for Generic Oxandrolone Drug Products

You request that the Agency require applicants for generic oxandrolone drug products to have the same CMC specifications as have been established for the RLD, which you describe as including a well-controlled API particle size requirement and a test procedure superior to that generally in place for an API in a solid dosage form, to ensure acceptable quality (Petition at 5).

Your apparent concern that generic oxandrolone drug products will not satisfy the statutory and regulatory CMC standards is misplaced. As part of the review of an ANDA, the Agency evaluates, among other things, the physiochemical characteristics of the drug substance described in § 320.33(e) (that you claim make the bioavailability of oxandrolone problematic) and sets appropriate CMC specifications. Under section 505(j)(4)(A) of the Act, the Agency may approve an ANDA only if the methods used in, or the facilities and controls used for, the manufacture, processing, and packaging of the drug are adequate to assure and preserve its identity, strength, quality, and purity.

To that end, an ANDA applicant must submit the same type of CMC information as required in an NDA (see 21 CFR 314.94(a)(9)(i) (incorporating 21 CFR 314.50(d)(1)). ANDA applicants must submit, among other things:

> A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, tests, analytical procedures, and acceptance criteria relating to stability, sterility, particle size, and crystalline form . . . .
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> A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product) and a statement of the composition of the drug product; the specifications for each

> component; the name and address of each manufacturer of the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product, including for example, tests, analytical procedures, and acceptance criteria relating to sterility, dissolution rate, container closure systems; and stability data with proposed expiration dating.
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> . . .[F]or each batch of the drug product used to conduct a . . . bioequivalence study . . . the specification[s] for each component and for the drug product; . . . and the [test] results of any test performed on the components used in the manufacture of the drug product as required by [21 CFR] § 211.84(d) . . . and . . . § 211.165 . . .

(21 CFR 314.50(d)(1)).

The CMCs for a drug are product-specific. Accordingly, the CMC specifications for a generic version of a drug may differ in some respects from those for the RLD (or another generic). The reasons for these differences include that an ANDA product may be produced by a different manufacturing process than the RLD, may use a different source for its active ingredient, or may contain different inactive ingredients. FDA carefully reviews the CMC specifications set forth in an ANDA to ensure that those specifications assure and preserve the identity, strength, quality, and purity of the drug as required by section 505(j)(4)(A) of the Act and the Agency's implementing regulations. Differences between ANDA and RLD products may require different specifications to meet the statutory and regulatory requirements. For example, if the RLD uses solvent A in its manufacturing process, and the ANDA product uses solvent B, then to meet a quality standard on removal of solvent, there would be a specification for solvent A for the RLD and a specification for solvent B for the ANDA product. These different specifications would ensure both products meet the same quality standard. The Agency will not approve a generic oxandrolone product unless, in addition to satisfying all other requirements for approval, its CMCs are adequate to assure and preserve product identity, strength, quality, and purity.

You specifically raise the issue of a particle size specification for the API. All approved ANDAs for oxandrolone will have appropriate particle size specifications for the API. Particle size specifications may differ because particle size is only one of many factors that can affect product quality attributes, such as dissolution. For example, product A may use a small particle size to obtain rapid dissolution while product B uses a different excipient to obtain rapid dissolution. In this case, products A and B would both need particle size specifications to assure consistent quality for that product, but the particle size would differ between products. In short, with respect to generic oxandrolone products, the particle size specification for each ANDA may be different, but the specifications for every ANDA will ensure product quality.

2. Your Concern About Impurity Profiles

You express concern that differences between the impurity profiles for a proposed generic oxandrolone drug product and for Oxandrin could potentially represent a safety issue, and request that FDA apply all appropriate impurity standards to the drug substances used in oxandrolone drug products (Supplement 3, pp. 1 and 2). You cite two Agency guidances[11] that you state reflect current standards and FDA's views on impurities in drug substances. You request that FDA apply the impurities standards described by these guidances in reviewing generic oxandrolone drug products. We agree that impurities may be a potential safety issue for drug products, and will apply all appropriate impurity standards, including, as appropriate, the standards in the guidances you cite, when reviewing generic oxandrolone drug products. Therefore, your request that FDA apply all appropriate impurity standards to the drug substances used in oxandrolone drug products is granted.

As you note, FDA regulations and policy provide for review of impurities in ANDA drug products before approval of the ANDA. As discussed in section II.E.1 of this response, under section 505(j)(4)(A) of the Act, the Agency approves an ANDA when the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve its identity, strength, quality, and purity. FDA, therefore, requires ANDA applicants to submit information regarding impurities under the CMC section of the ANDA (see 21 CFR 314.94(a)(9) and 314.50(d)(1)).

You also state that the United States Pharmacopeia (USP) has published a proposed method for identifying and quantifying impurities in the oxandrolone drug substance (see the USP *Pharmacopeial Forum*, Volume 31, #1 (January – February 2005), In-Process Revision section, pages 64-67). You state that you will use the proposed method as soon as it becomes official. You request that the Agency apply the proposed USP method in reviewing generic oxandrolone drug products (Supplement 3, pp. 5-8).

The Act recognizes the USP as an official compendium (see 21 U.S.C. 321(j)), and FDA accepts USP specifications for the approval of drug products (see 57 FR 17950 at 17958-59 (April 28, 1992)). Thus, an ANDA applicant for a generic oxandrolone drug product might be able to show adequate controls for impurities by demonstrating that its product meets the official USP specifications for impurities if there were such specifications (21 CFR 314.50(d) and 314.94(a)(9)). As you acknowledge, however, the USP is still considering whether to adopt the proposed method. It has not become official and could possibly be revised or abandoned. Accordingly, your request regarding application of this proposed USP method is denied.

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[11] *ANDAs: Impurities in Drug Substances* and *Q3A Impurities in New Drug Substances (Q3A)(R)*, available on the Internet at http://www.fda.gov/cder/guidance/default.htm.

F. Multiple-Dose Studies Are Unnecessary.

You state that "multiple-dose oxandrolone-warfarin interaction studies may be necessary to determine the range of possible effects of oxandrolone on warfarin's action" (Comment 4, section VII.). We do not believe that interaction studies are needed, and you offer no evidence to the contrary. As explained in section II.B of this response, a showing of bioequivalence between a generic oxandrolone and Oxandrin, the RLD, is sufficient to demonstrate that the interaction of the generic oxandrolone with warfarin will be equivalent to the interaction of Oxandrin with warfarin.

Further, we do not believe that a multiple-dose bioequivalence study is necessary before a generic oxandrolone drug product may be determined to be bioequivalent to Oxandrin, and you offer no data to support a contrary conclusion. For orally administered immediate-release drug products such as oxandrolone, a single-dose bioequivalence study is considered more sensitive than a multiple-dose study "in assessing release of the drug substance from the drug product into the systemic circulation . . . ." (see the guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, page 8, available on the Internet at http://www.fda.gov/cder/guidance/default.htm). In addition, although FDA regulations at 21 CFR 320.27(a)(3) define conditions in which a multiple-dose study may be necessary to determine bioavailability, none of those conditions apply here.

G. Demonstration of Dose Proportionality May Be Unnecessary.

You claim that applicants seeking approval of different dosage strengths of oxandrolone must demonstrate dose proportionality using pharmacokinetic studies in human subjects because oxandrolone presents bioequivalence problems. You assert that lack of dose proportionality among generic oxandrolone products raises additional safety concerns because of the interaction between oxandrolone and warfarin. Such lack of dose proportionality, you contend, has the potential to significantly affect warfarin potency, requiring specific warfarin dose adjustment guidance in the labeling for each dosage strength of oxandrolone, which must be supported by drug- and dosage strength-specific clinical data (Petition at 15-16). We disagree.

Under the assumption of pharmacokinetic linearity, dose proportionality refers to a proportional increase in pharmacokinetics (AUC and Cmax) with an increase in dose. (see Center for Drug Evaluation and Research Data Standards Manual (definition of dose proportionality study)). That is, the AUC and Cmax would be about twice as high if two 10-mg tablets are administered instead of one if the pharmacokinetics increase proportionally with the dose, because the dose would be twice as high. Your claim relates to whether two strengths of the same applicant's drug product will provide a proportional dose. That is, if an applicant has a 5-mg and 10-mg strength tablet, will the AUC and Cmax for the 10-mg tablet be equivalent to that of two 5-mg tablets.

If a drug product is to be marketed in multiple strengths, an ANDA sponsor may not need to conduct in vivo bioequivalence studies for each strength of the drug product. Under § 320.22(d)(2) (21 CFR 320.22(d)(2)), applicants may request a waiver of in vivo bioequivalence data if the drug product is in the same dosage form, but in a different strength, and is "proportionally similar" in its active and inactive ingredients to another drug product for which the same manufacturer has conducted in vivo studies and obtained approval.

For immediate-release drug products, such as oxandrolone, including products that have narrow therapeutic ranges, FDA policy permits waivers of in vivo bioequivalence data of one or more lower strengths based on dissolution tests and an in vivo study on the highest strength (see 21 CFR 320.22(d)(2)). For example, if the 10-mg strength of a generic oxandrolone drug product is shown to be bioequivalent to the 10-mg strength of Oxandrin, in vivo studies may be waived for the lower strengths, provided the lower strengths are proportionally similar to the 10-mg strength, and meet an appropriate in vitro dissolution test approved by the Agency. This combination of in vivo and in vitro testing can be expected to detect whether the products have bioequivalence problems of the type you identify.

The waiver standards in § 320.22(d)(2), based on proportional similarity and acceptable in vitro dissolution testing for different strengths of a drug product line, are derived from basic principles of pharmacology and pharmaceutics. Two drug products with different excipients may show different bioavailability because differences in excipients may alter a drug's in vivo bioavailability. However, when an in vivo bioequivalence study on one strength demonstrates that the difference in excipients does not alter bioequivalence, then there is a strong likelihood that the absorption and resulting in vivo bioavailability of the active ingredient will be equivalent in different strengths of the same drug product line that have the same proportions of the same excipients.

To further confirm whether all strengths of a generic drug will be bioequivalent to corresponding strengths of the listed drug, the FDA asks that applicants conduct comparative in vitro dissolution testing between each strength of the test and reference product. If this testing yields evidence that waivers of in vivo testing of lower strengths are not scientifically justified, FDA would request an ANDA sponsor to conduct in vivo bioequivalence tests on more than one strength of the product. In the absence of evidence that a waiver may not be justified, if all strengths of a generic oxandrolone tablet formulation are formulated to be proportionally similar in their active and inactive ingredients and have dissolution equivalent to that of the corresponding strength of the reference product, one in vivo bioequivalence study can be expected to support the bioequivalence of all strengths of the generic product.

You offer no evidence that reliance on bioequivalence determinations that permit a waiver of strength-specific in vivo bioequivalence testing for oxandrolone products could result in approval of generic oxandrolone products that do not exhibit proportionally similar dosing across strengths. Further, we note with respect to your arguments that

generic oxandrolone should have dosage strength-specific interaction warnings, the Oxandrin labeling does not include dosage-specific interaction information.

H. Labeling

1. Generic Oxandrolone Drug Products Are Required to Have the Same Labeling as the RLD Except for Differences Permitted by Law.

An ANDA must contain the same drug product labeling as the RLD, except for differences approved under a suitability petition, or differences required because the proposed drug product and the RLD are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the Act and 21 CFR 314.94(a)(8)). Accordingly, we grant your request that labeling approved under section 505(j) of the Act for oxandrolone drug products be the same as labeling for the current RLD, Oxandrin, unless an exception to the same labeling requirement applies.

We do not agree, however, that support for labeling for an oxandrolone product submitted under an ANDA must come from clinical studies specific to each generic oxandrolone product (Petition at 17). As discussed in section II.B of this response, generic versions of oxandrolone shown to be pharmaceutically equivalent and bioequivalent to the RLD can rely on Agency findings of safety and efficacy for the RLD and be expected to have safety and effectiveness comparable to the RLD.

You also claim that patients administered generic oxandrolone "may face a significant health safety risk due to the relatively wide bioavailability range permitted for the generic oxandrolone, when combined with its effects on the narrow therapeutic range of warfarin" (Petition at 12). Thus, you claim that "drug product specific information is required to provide physicians the necessary tools for safe and effective patient care" (Petition at 10). As discussed in section II.A of this response, you have offered no evidence that FDA's established bioequivalence criteria would permit clinically meaningful variability among oxandrolone drug products or in their interaction with warfarin. As previously discussed, generic oxandrolone drug products shown to be therapeutically equivalent to Oxandrin can be expected to interact with warfarin in a manner equivalent to Oxandrin.

It follows that generic oxandrolone products can, as they legally must (subject to the exceptions noted previously), bear the same labeling as the RLD, including conditions of use, warnings, and other safety information. Therefore, with the exceptions noted previously, ANDAs referencing Oxandrin must include labeling that contains the same current information as Oxandrin, including with respect to oxandrolone-warfarin interaction.[12]

[12] The Agency is responding separately to a second citizen petition filed on behalf of Savient regarding the permissibility of omitting certain geriatric use information from the labeling of generic oxandrolone products (Docket No. 2005P-0383/CP1).

2. Current Warfarin and Oxandrin Labeling Fully Inform Physicians of How to Address Concomitant Use of Oxandrolone and Warfarin to Ensure Patient Safety.

As your petition correctly states, "it is widely accepted that warfarin dosing must be carefully titrated to assure proper anticoagulation control" (Petition at 2). As warfarin labeling explains, dose adjustment or titration of warfarin, based on a patient's PT/INR levels, and close monitoring of these levels, is necessary because of warfarin's narrow therapeutic range and the fact that warfarin is affected by a number of factors, such as other drugs, dietary vitamin K, diet, age, sickness, and physical state. The labeling for warfarin lists dozens of drug classes and specific drug products that interact with warfarin, including both oxandrolone and the class steroids anabolic (17-Alkyl testosterone derivatives), to which oxandrolone belongs. Information from product-specific drug interaction studies would not alter this practice of careful titration and close monitoring; that is, regardless of whether a patient is administered Oxandrin or generic oxandrolone, the physician will need to titrate the patient for individualized therapy and closely monitor the patient when oxandrolone and warfarin are coadministered.

The warfarin labeling provides sufficient instructions on how to administer warfarin when the drug is coadministered with drugs, such as oxandrolone, which exhibit drug-drug interactions. Following are relevant excerpts from a warfarin drug product's current labeling:

> In a BLACK BOX WARNING:
>
> Regular monitoring of INR should be performed on all treated patients. . . . Patients should be instructed . . . to report immediately to physicians signs and symptoms of bleeding.
>
> Under WARNINGS:
>
> It cannot be emphasized too strongly that treatment for each patient is a highly individualized matter. [Warfarin], a narrow therapeutic range (index) drug, may be affected by factors such as other drugs . . . .
>
> Under PRECAUTIONS:
>
> Periodic determination of PT/INR or other suitable coagulation test is essential . . .
>
> Drug-Drug and Drug-Disease Interactions
> Numerous factors, alone or in combination, including changes in diet and medications, including botanicals, may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional PT/INR determinations in the period immediately after discharge from the hospital, and whenever other medications, including botanicals, are initiated, discontinued or taken irregularly.
>
> * * *

Potential drug interactions with [warfarin] are listed below by drug class and by specific drugs.
[Specific drugs include oxandrolone. Classes of drugs include steroid, anabolic (17-Alkyl testosterone derivatives), to which oxandrolone belongs.]

* * *

Because a patient may be exposed to a combination of the above factors, the net effect of [warfarin] on PT/INR response may be unpredictable. More frequent PT/INR monitoring is therefore advisable. Medications of unknown interaction with coumarins are best regarded with caution. When these medications are started or stopped, more frequent PT/INR monitoring is advisable.

Under DOSAGE AND ADMINISTRATION:

The dosage and administration of warfarin must be individualized for each patient according to the particular patient's PT/INR response to the drug. The dosage should be adjusted based upon the patient's PT/INR.

* * *

LABORATORY CONTROL . . . The PT should be determined daily after the administration of the initial dose until PT/INR results stabilize in the therapeutic range. Intervals between subsequent PT/INR determinations should be based upon the physician's judgment of the patient's reliability and response to [warfarin] in order to maintain the individual within the therapeutic range. Acceptable intervals for PT/INR determinations are normally within the range of one to four weeks after a stable dosage has been determined. To ensure adequate control, it is recommended that additional PT tests be done when other warfarin products are interchanged with warfarin sodium tablets, USP, as well as whenever other medications are initiated, discontinued, or taken irregularly (see PRECAUTIONS). . . .

In the warfarin MEDICATION GUIDE:

Get your regular blood test to check for your response to [warfarin].

* * *

Tell your healthcare provider about all the medicines you take. Do not stop medicines or take anything new unless you have talked to your healthcare provider. Keep a list of your medicines with you at all times to show your healthcare provider and pharmacist.

* * *

You must have regular blood tests and visits with your healthcare provider to monitor your condition.

* * *

Do not start, stop, or change any medicine without talking to your healthcare provider.

The Oxandrin labeling similarly provides:

PRECAUTIONS. . . Drug Interactions

> Anticoagulants: Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired prothrombin time. Patients receiving oral anticoagulant therapy require close monitoring, especially when anabolic steroids are started or stopped.
>
> Warfarin: ... When oxandrolone therapy is initiated in a patient already receiving treatment with warfarin, the INR or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has been achieved. Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dosage if indicated are recommended when the oxandrolone dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.

In sum, as the warfarin and the Oxandrin labeling indicate, treatment with warfarin must be individualized for each patient and closely monitored. Specific dosing instructions cannot be given because of the need to individualize dose adjustment for each patient. Data from drug-specific interaction studies would not obviate the need for patient monitoring and dose titration. The warfarin and the Oxandrin labeling fully inform physicians on how to address coadministration of oxandrolone and warfarin to ensure patient safety.

III. Conclusion

You have not identified, and FDA is not aware of, any specific properties of oxandrolone that warrant application of unique bioequivalence or safety requirements for approval of ANDAs for oxandrolone. Generic oxandrolone drug products that meet the Agency's current standards for establishing bioequivalence and fulfill the other ANDA requirements can be expected to have an effectiveness and safety profile equivalent to that of Oxandrin. Therefore, your request that the Agency establish specific bioequivalence requirements for generic drug products containing oxandrolone is denied. The Agency also declines to require ANDA applicants to submit drug-specific clinical study data on the interaction of its oxandrolone drug product with warfarin. The Agency will approve ANDAs for oxandrolone drug products where the applicants meet applicable statutory and regulatory requirements for approval.

Sincerely,

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