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July 10, 2009/
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 22 2009

Mr. Mark Moyer
Vice President, U.S. Deputy Head, Regulatory Development
Sanofi-Aventis US LLC, a subsidiary of Sanofi-Aventis
9 Great Valley Parkway
Malvern, PA 19355-1304

Re: Docket No. FDA-2006-P-0025

Dear Mr. Moyer:

This letter responds to your petition dated December 19, 2006 (Petition), and supplements to that petition dated April 23, 2007 (First Supplement) and April 28, 2009 (Second Supplement).[1] You request that the Food and Drug Administration (FDA) give special consideration for any abbreviated new drug application (ANDA) referencing Eloxatin (oxaliplatin injection) containing added acid (other than oxalic acid), or conjugate base thereof, or containing an added sugar or sugars (e.g., lactose). You also request that FDA require such an application to demonstrate through sufficient preclinical and/or clinical testing that any new compound resulting from the addition of an added acid, or its conjugate base, or an added sugar to oxaliplatin does not compromise the safety or efficacy of the drug product.

For the reasons that follow, your petition and supplements are granted to the extent described and are otherwise denied.

I. BACKGROUND

Eloxatin is a platinum compound approved for the adjuvant treatment of stage III colon cancer and for the treatment of advanced colorectal cancer. Eloxatin is approved in two dosage forms: (1) a lyophilized powder that is reconstituted for injection, containing lactose, which has been withdrawn from sale (new drug application (NDA) No. 21-492) and is listed in the "Discontinued Drug Product List" section of FDA's *Approved Drug Products with Therapeutic Equivalence* Evaluation (Orange Book) (27th ed.),[2] and (2) an aqueous solution that contains neither added acid (or its conjugate base) nor added sugar (NDA No. 21-759). The subject of this petition is the currently marketed Eloxatin aqueous solution.

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[1] This citizen petition was originally assigned docket number 2006P-0523/CP1. The number was changed to FDA-2006-P-0025 as a result of FDA's transition to its new docket numbering system (Regulations.gov) in January 2008.

[2] FDA determined that this product was not withdrawn from marketing for reasons of safety or effectiveness (72 FR 65968, November 26, 2007).

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD and that it has the same active ingredient or ingredients, dosage form, route of administration, strength, and labeling[3] as the RLD. The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that meet the following conditions are therapeutically equivalent and may be substituted for each other: (1) contain identical amounts of the same active ingredient(s) in the same route of administration and dosage form; (2) meet applicable standards of strength, quality, purity, and identity, and are manufactured in compliance with Current Good Manufacturing Practices regulations; and (3) are adequately labeled.

II. DISCUSSION

A. Review Under an ANDA Versus NDA

1. Added acid (other than oxalic acid) or its conjugate base

You state that because an application for generic oxaliplatin solution with an added acid, or conjugate base thereof, must contain necessary preclinical and/or clinical data, submission of an ANDA under section 505(j) of the Act would not be appropriate and that instead, the generic applicant must submit to FDA an NDA under section 505(b) of the Act (Petition at 3 and 12-13, citing section 505(j)(2)(C)(i) of the Act).

As a threshold matter, we think it is important to review the requirements for an ANDA for a parenteral drug product. A drug product intended for parenteral use generally must contain both the same active and inactive ingredients in the same concentration as the reference listed drug. There is, however, the following exception for differences in inactive ingredients under 21 CFR 314.94(a)(9)(iii):

> An applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

[3] 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)).

A buffer consists of a weak acid and its conjugate base. Therefore, inactive ingredients consisting of an acid and its conjugate base functioning as a buffer meet the exception for a buffer under 21 CFR 314.94(a)(9)(iii). Accordingly, FDA would accept for review an ANDA for generic oxaliplatin solution that contains an added buffer in the form of an acid (other than oxalic acid), or conjugate base thereof (buffered oxaliplatin), citing Eloxatin solution as the reference listed drug. An applicant would need to provide evidence that this buffer does not affect the safety or efficacy of the generic oxaliplatin solution.

We discuss in section II.B.1 of this document the circumstances under which we would require additional preclinical and/or clinical data to demonstrate that any new compound resulting from the addition of an added acid, or its conjugate base, does not compromise the safety or efficacy of the drug product. If clinical data were required, as you suggest, FDA would not review the application for generic buffered oxaliplatin solution under section 505(j) of the Act, but instead, would require that application to be submitted under section 505(b) of the Act. However, if FDA determined that preclinical data (e.g., toxicological studies, comparative preclinical studies) would be sufficient and clinical data is not necessary, FDA would review the generic application under section 505(j) of the Act.

2. Added sugar

You assert that because an application for generic oxaliplatin solution with added sugar or sugars must contain necessary preclinical and/or clinical data, submission of an ANDA is not appropriate and the application must be submitted as an NDA under section 505(b) of the Act (First Supplement at 12).

FDA agrees that an application referencing the aqueous form of Eloxatin that contained an added sugar must be submitted under section 505(b) of the Act. As discussed in section II.A.1 of this document, as a condition for ANDA approval of a drug product intended for parenteral use, the generic formulation must contain both the same active and inactive ingredients in the same concentration as the innovator's formulation, with the exception for preservative, buffer, or antioxidant described in 21 CFR 314.94(a)(9)(iii). Because an added sugar does not meet the definition of a preservative, buffer, or antioxidant in the exception, FDA would not accept for review an ANDA for a generic oxaliplatin solution that contains an added sugar, citing Eloxatin solution as the RLD. Under these circumstances, an application for oxaliplatin solution with an added sugar could be submitted under section 505(b)(2) of the Act. [4]

As discussed in section II.B.2 of this document, the criteria for evaluating whether preclinical and/or clinical data may be necessary to ensure the safety and efficacy of any new platinum complex that may contain a by-product (i.e., degradation product,

[4] An application described in section 505(b)(2) of the Act relies upon investigations described in section 505(b)(I)(A) that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

degradation impurity) as the result of the added sugar are the same for an ANDA submission as for an NDA submission.

B. Necessity for Preclinical/Clinical Trials to Demonstrate Safety and/or Efficacy

1. Added acid (other than oxalic acid) or its conjugate base

You state that FDA must require any ANDA referencing Eloxatin to contain data from preclinical and/or clinical testing sufficient to demonstrate that the addition of an acid (other than oxalic acid), or conjugate base thereof, does not significantly alter the safety or efficacy profile of the resulting product (Petition at 12-13). Specifically, you state that adding an acid (other than oxalic acid), or its conjugate base, to buffer the oxaliplatin solution may cause the formation of new platinum compounds (Petition at 6). You state that the platinum complexes resulting from these formulation changes may contain a new by-product (i.e., degradation product, degradation impurity) that may affect safety and/or efficacy (Petition at 6-12, citing Dr. Chaney, Dr. Farrell, other authors, and other literature). As an example, you state that a new platinum complex, tartaroplatin, is formed as a result of ligand exchange when tartaric acid is added to oxaliplatin (Petition at 10-11). In the recently submitted Second Supplement, you reported on an effort to analyze impurities present in a generic product containing tartaric acid approved in Europe.

We agree that:

- Adding an acid (other than oxalic acid), or its conjugate base, to buffer the oxaliplatin solution may result in the formation of new platinum complexes under anticipated storage conditions. Oxaliplatin formulations containing an added buffer may undergo chemical exchange reactions in which the conjugate base of the acid displaces the oxalate ligand bound to platinum, forming a new platinum complex.

- New platinum complexes may have an impact on the safety and/or efficacy of the drug product.[5] Therefore, preclinical and/or clinical studies may be necessary if significant amounts of new platinum complexes occur under anticipated storage and use conditions.

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[5] For example, by-products may have a leaving group ligand bound to platinum that is different from the oxalate leaving group ligand in oxaliplatin. The rate of substitution of this leaving group ligand, in part, affects biological activity and toxicity. By-products with leaving group ligands having fast dissociation rates may give rise to highly toxic complexes (e.g., diaquoPt(DACH)). Conversely, by-products with leaving group ligands having slow disassociation rates may yield inactive and nontoxic complexes (Schwartz, P., et al., "Preparation and antitumor evaluation of water-soluble derivatives of dichloro(1,2-diaminocyclohexane)platinum(II)," *Cancer Treatment Reports* (1977) 61:1519-1525; Cleare, M.J., et al., "Studies on the antitumor activity of Group VIII transition metal complexes. Part I. Platinum(II) complexes," *Bioinorganic Chemistry* (1973) 2:187-210).

- Potential biological activity and toxicity of new platinum complexes cannot be predicted based solely on the determination of structural similarity to other platinum-containing drug products.

However, preclinical and/or clinical studies may not be necessary to demonstrate that an added acid, or its conjugate base, has an impact on the safety or efficacy profile of the resulting oxaliplatin drug product. The need for preclinical and/or clinical safety evaluation is dependent, in part, upon the extent to which new degradation impurities are formed in the product formulation during storage.

Each ANDA or NDA applicant must satisfy various requirements, including the standards for chemistry, manufacturing, and controls (CMC). The purpose of the CMC review is to ensure that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug product are adequate to assure and preserve its identity, strength, purity, and quality (21 CFR 314.127(a)(l); section 505(j)(4)(A) of the Act). ANDA applicants must submit, with one exception not relevant here, the same type of CMC information as required in an NDA (21 CFR 314.94(a)(9)(i)). The required CMC information includes, among other things, "the specifications necessary to ensure the identity, strength, quality, [and] purity... of the drug product..." (21 CFR 314.50(d)(l)(ii)(*a*) and 314.94(a)(9)).

FDA's CMC review carefully evaluates any application submitted under section 505 of the Act referencing Eloxatin injection for any oxaliplatin degradation products that may be generated during the product's labeled shelf-life. Any degradation impurities or new platinum complexes are evaluated and controlled, as specified for ANDAs in FDA's draft guidance for industry, *ANDAs: Impurities in Drug Products*[6] (ANDA impurities guidance), and as specified for NDAs in FDA's ICH[7] guidance for industry, *Q3B(R2) Impurities in New Drug Products* (ICH guidance) (both of these guidance documents are available on FDA's web site at http://www.fda.gov/cder/guidance/default.htm).

As described in the ANDA impurities guidance at 2, we recommend that applicants specify any degradation product observed during stability studies conducted at the recommended storage condition (see also ICH guidance at 2-3). FDA will examine evidence that the analytical procedures have been validated and are suitable for the detection and quantification of degradation products (ANDA impurities guidance at 2-3; ICH guidance at 3-5). FDA will ensure that analytical procedures are validated to demonstrate specificity for the specified and unspecified degradation products (Id.).

The ANDA impurities guidance and the ICH guidance describe the qualification threshold (i.e., the limit above which a degradation product/impurity must be appropriately qualified). In general, a degradant or impurity does not need to be qualified

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[6] A notice of availability for this draft guidance published in the *Federal Register* on August 29, 2005. When finalized, this guidance will represent FDA's current thinking on this topic.

[7] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

if it occurs in a concentration below the qualification threshold. *Qualification* is the process of acquiring and evaluating data that establish the biological safety of an individual degradation product or a given degradation profile at the level or levels being considered (ICH guidance at 6; ANDA impurities guidance at 4-5). The ICH guidance spells out qualification thresholds expressed either as a percentage of the drug substance or as the total daily intake of the degradation product based on the amount of drug substance administered per day (maximum daily dose) (e.g., for a maximum daily dose between 100 milligrams (mg) to 2 grams, the qualification threshold is 0.2 percent or 3 mg total daily intake, whichever is lower) (ICH guidance at Attachment 1). Higher or lower thresholds for qualification of degradation products may be appropriate for some individual new drug products based on scientific rationale and the level of concern, including drug class effects and clinical experience (ICH guidance at 6; ANDA impurities guidance at 4-5).

If a degradation product is above the qualification threshold, it is considered qualified when certain conditions are met. A degradation product is qualified, for example, when the observed level and proposed acceptance criterion are comparable (i.e., qualified using comparative analytical studies) to the reference listed drug, when they are justified by the scientific literature, or when they do not exceed the level that has been adequately evaluated in toxicology studies (for other examples, see ICH guidance at 6, Attachment 3 and ANDA impurities guidance, section IV and Attachment 1, at 4-8).

For an aqueous oxaliplatin referencing Eloxatin injection, FDA uses appropriate CMC review to assess specific chemical information and data about whether the added conjugate base of the buffering agent replaces the oxalate ligand in the platinum complex. If new platinum complexes are generated as a result of this ligand exchange reaction, the CMC review evaluates the extent to which these new platinum complexes are generated under anticipated storage conditions. Based on these reviews, we assess whether these new platinum complexes are generated at a level below the qualification threshold, at a level requiring qualification, or at a level that would require preclinical and/or clinical studies.

If an oxaliplatin degradation product is present below the qualification threshold, or is appropriately qualified, as described in the ANDA impurities guidance and the ICH guidance, additional preclinical and/or clinical testing ordinarily would not be needed. Although we agree that it is possible that adding a buffering agent (e.g., tartaric acid) to oxaliplatin may have an impact on the safety and/or efficacy profile of the drug product, FDA will analyze the specific chemical information and stability data contained in each application to determine whether any specific degradation product requires additional preclinical and/or clinical studies to demonstrate its impact on safety or efficacy.[8]

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[8] The information and data included in your Second Supplement does not alter our analysis or conclusions. The level of any impurity in an Eloxatin product for which approval in the United States is sought (either as an ANDA or as a 505(b)(2) application) would be determined using a validated analytical method, and the standards set forth in the above-referenced ANDA impurities guidance and ICH guidance would be followed.

The Agency will not approve an application submitted under section 505 of the Act for an oxaliplatin product containing an added acid, or its conjugate base, unless, in addition to satisfying all other requirements for approval, the CMC information assures and preserves product identity, strength, quality, and purity. FDA will ensure that these formulations maintain their labeled potency throughout the product shelf-life. If new platinum complexes form as a result of the addition of an acid, or its conjugate base, these oxaliplatin degradation products will be evaluated and controlled in accordance with the recommendations provided in the ANDA impurities guidance or the ICH guidance. Therefore, FDA will ensure that the safety and effectiveness of buffered oxaliplatin would not differ from Eloxatin aqueous solution.

2. Added sugar

In the first supplement, you state that the addition of sugars to solutions of oxaliplatin raises the same concerns about by-products (i.e., degradation products, degradation impurities) as those raised by the addition of a buffer (First Supplement at 2). Accordingly, you request that the Agency require that any application for a generic version of oxaliplatin solution that contains an added sugar, citing Eloxatin as the reference listed drug, include preclinical and/or clinical studies to demonstrate safety and efficacy.

To support your argument, in addition to other literature, you submit an internal Sanofi report entitled "Stability of oxaliplatin solution in the presence of dissolved sugars" (the Report) (First Supplement, Appendix A). You state that the Report shows that the addition of sugar to an oxaliplatin aqueous solution causes increases in three types of new platinum complexes (i.e., diaquoPt(DACH), diqquoPt(DACH) dimer, and platinum (IV)[9]) in comparison to the control solution (plain aqueous solution) upon testing after 3 months in ambient (room temperature (25°C, 60 percent humidity) and accelerated conditions (40°C, 75 percent humidity) (First Supplement at 5-7). Based on these results, you argue that solutions stored at room temperature for any commercially relevant period of time (e.g., 6 months) would likely generate these complexes above 0.2 percent (First Supplement at 8, citing FDA guidance for industry, *Q1A(R2) Stability Testing of New Drug Substances and Products*). In the recently submitted Second Supplement, you reported on an effort to analyze impurities present in a generic product obtained commercially in Portugal.

Again, we agree with you that there is a possibility that an added sugar (e.g., lactose, glucose) will result in the formation of new platinum complexes, analogous to the potential for an added acid (other than oxalic acid), or its conjugate base, to result in the formation of new platinum complexes. The underlying concepts are also analogous regarding biological activity, toxicity, and the impact on safety and/or efficacy of the drug product.

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[9] You note that platinum (IV) complex represents a new impurity (First Supplement at 6). FDA would evaluate and control for any platinum (IV) complex, as described in section II.A.1 of this document, as it would any other new platinum complexes.

FDA carefully reviewed the data provided in the Report. The data show that the sugars slowed down the formation of certain platinum complexes (i.e., diaquoPt(DACH) and diquoPt(DACH) dimer) but enhanced the formation of others (i.e., platinum (IV) complex and its related unspecified degradation impurities, as well as other unspecified degradation impurities related to diaquoPt(DACH) complex) under accelerated storage conditions. When stored in ambient conditions for a limited 3 months, none of the listed impurities appear to exceed 0.2 percent and the changes in the levels appear comparable to the control group (water). While these data are useful to FDA to identify specific degradation products and their potential characteristics, the study is not complete, in depth, and/or dispositive. For example, the data provide aggregate percentages of the drug substance for each degradation impurity category, as opposed to providing the percentages for each individual degradation impurity, making it unclear whether individually, any unspecified degradation impurity could have exceeded the qualification threshold under standard long-term and/or accelerated storage conditions. Therefore, we do not believe it is appropriate to assume that similar impurities would develop in solutions stored at room temperature for any commercially relevant period of time. Although FDA considers accelerated data useful for identifying areas of potential concern, we cannot generalize a need for preclinical and/or clinical studies based on the data presented in the Report. The information and data provided with your Second Supplement does not alter our analysis.

To assess whether preclinical and/or clinical studies are necessary, FDA will conduct the CMC review for drug product formulations having an added sugar in an analogous manner to that described in section II.A.1 for buffered oxaliplatin formulations. The CMC review will evaluate any application submitted under section 505(b) of the Act referencing Eloxatin injection for any oxaliplatin degradation impurities that may be generated as a result of ligand exchange during the product's labeled shelf-life. FDA will ensure that the analytical procedures are validated and are suitable for the detection and quantification of degradation products (ICH guidance at 3-5). We will analyze specifications for the proposed drug product, the real-time stability data, and the proposed maximum daily dose. Any new platinum complex degradation product will be evaluated and controlled as specified in the ICH guidance and as discussed in more detail in section II.A.1 of this document. Accordingly, if new platinum complexes or degradation products are appropriately controlled and qualified, we believe that preclinical and/or clinical studies to demonstrate safety and efficacy will not be necessary.[10]

[10] The Agency has reviewed and is approving an application under section 505(b)(2) in which the degradation impurity levels were below the ICH qualification threshold.

III. CONCLUSION

We agree with your petition that the potential exists for oxaliplatin solutions to develop impurities if an acid (other than oxalic acid), or a conjugate base thereof, is added, or if a sugar is added. We also agree that such impurities may have an impact on the safety and/or the efficacy of the product if they occur at certain levels of concentration. We do not believe, however, that this theoretical concern requires preclinical and/or clinical testing in all instances. Instead, we intend to closely examine the degradation impurity levels for all oxaliplatin solutions and ensure that degradation impurity levels are below the threshold described in our guidance documents, or that impurities are appropriately qualified. Otherwise, for the reasons stated above, your petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research