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June 21, 2007

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2007 JUN 22 P 3:11

BY HAND AND FIRST CLASS MAIL

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

Re: Request for an Advisory Opinion --"Orange Book" Listings of Patents

Dear Sir or Madam:

On behalf of AstraZeneca, and as provided by 21 C.F.R. § 10.85, the undersigned herewith submits this request for an advisory opinion of the Commissioner of Food and Drugs with respect to the requirement to list certain types of patents in the publication *Approved Drug Products With Therapeutic Equivalence Evaluations* ("Orange Book"), pursuant to Sections 505(b)(1) and 505(c)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA").

A. Issues Involved

The issues involved in this request are: (1) what constitutes an approved pre-filled drug delivery system for the purposes of determining whether patents relating to that system should be listed; and (2) whether patents relating to an approved pre-filled drug delivery system should be listed if they (a) disclose but do not claim the active ingredient or formulation of the approved drug product or (b) neither disclose nor claim the active ingredient or formulation of the approved drug product.

B. Statement of Facts and Law

21 C.F.R. § 314.53 requires that New Drug Application ("NDA") applicants submit for listing in the Orange Book the patent numbers and expiration dates of any patent that claims the drug or a method of using the drug that is the subject of the NDA "with respect to which a claim of patent infringement could reasonably be asserted . . . " *Id.* The regulation states that patents

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that claim the "drug product" that is the subject of the NDA must be listed, but also states that patents claiming "packaging" must not be listed. 21 C.F.R. § 314.53(b)(1)

In June 2003, FDA sought to clarify the listing requirements for NDAs by amending these regulations. 68 Fed. Reg. 36676 (June 18, 2003). In response to FDA's proposal, certain comments stated that patents claiming delivery devices or containers that are "integral" to a drug product or require prior FDA approval should be submitted and listed. 68 Fed. Reg. 36676, 36680. The comments distinguished between packaging and devices such as metered dose inhalers and transdermal patches, which are drug delivery systems used and approved in combination with a drug. *Id.*

In response to these comments, FDA indicated that it clarified the rule to ensure that if the patent claims the drug product as defined in § 314.3, the patent must be submitted for listing. The agency went on to state that the key factor is "whether the patent being submitted claims the finished dosage form of the approved drug product." *Id.* In this connection, FDA indicated that the appendix in the Orange Book lists current dosage forms for approved drug products, and that list includes metered aerosols, capsules, metered sprays, gels, and "pre-filled drug delivery systems." 68 Fed. Reg. 36676, 36680.

The FDA's endorsement of the comments' distinction between packaging and drug delivery systems leaves certain questions unanswered and in need of further clarification. First, it remains unclear as to what types of products fall within the meaning of the term "pre-filled drug delivery systems," particularly when such products are not expressly identified in the definition of dosage forms or listed in Appendix C of the Orange Book. This is also especially true when the agency has not in other contexts, such as guidance documents, expressed any opinion on such questions. For example, while AstraZeneca believes that the term "pre-filled drug delivery system" encompasses, among other things, pre-filled syringes approved to deliver an approved drug product, FDA has not directly addressed that point.

Second, FDA has not directly addressed the question whether the listing requirement applies to patents for approved drug delivery systems where the patents disclose but do not claim, or neither disclose nor claim, the active ingredient or formulation of the approved drug product. On January 10, 2005, GlaxoSmithKline ("GSK") requested an advisory opinion on whether patents relating to a drug delivery system should be listed if they do not specifically claim the active ingredients contained in the drug product. GSK also requested an advisory opinion on whether listing is required when the patent specification fails to mention the active ingredients in the drug product. (Docket No. 2005A-0015) Subsequently, on August 10, 2006, AstraZeneca submitted a similar request for an advisory opinion from FDA. (Docket No. 2006A-0318). To date, FDA has not responded in a substantive manner to these requests for advisory opinions.

As explained in AstraZeneca's previous request for an advisory opinion, an important goal of the Hatch-Waxman Amendments is to provide generic manufacturers with notice of the patents that would be infringed by their manufacture, use and sale of a generic copy of the branded product. The Amendments were also designed to allow for early resolution of challenges to patents before marketing begins. Similarly, the statute provides an incentive to generic manufacturers to challenge listed patents by awarding them a 180-day exclusivity period for successful challenges to the validity, enforceability or infringement of listed patents. 21 U.S.C. § 355(j)(5)(B)(iv).

AstraZeneca believes that listing in the Orange Book of patents claiming an approved pre-filled drug delivery system and/or one identified in the labeling of the product would further the goals of the Hatch-Waxman Amendments, even if the approved formulation or active ingredient is not claimed but is disclosed in the patent or the active ingredient is neither claimed nor disclosed in the patent. Listing such patents would provide generic manufacturers with notice of their potential infringement and an opportunity to challenge the patents early on before introducing the generic product into the marketplace. In fact, because such patents may not claim or disclose the formulation or active ingredient specifically, a generic manufacturer searching for patents that refer to the product might not uncover them if they are not listed in the Orange Book.

On the basis of the foregoing, AstraZeneca seeks an advisory opinion on (1) what constitutes an approved pre-filled drug delivery system for the purposes of determining whether patents relating to that system should be listed; and (2) whether patents relating to approved pre-filled drug delivery systems should be listed if they (a) disclose but do not claim the active ingredient or formulation of the approved drug product or (b) neither disclose nor claim the active ingredient or formulation of the approved drug product. AstraZeneca believes that that the term "pre-filled drug delivery system" encompasses, among other things, pre-filled syringes approved to deliver an approved drug product. AstraZeneca also believes that Orange Book listing is required for patents directed to such drug delivery systems even if the patents disclose but do not claim, or neither disclose nor claim, the active ingredient or formulation of the approved drug product. Accordingly, AstraZeneca will continue to list these patents unless and until it otherwise receives guidance or an advisory opinion from FDA that such listings are improper.

C. Certification

The undersigned certifies that, to the best of his knowledge and belief, this request includes all data, information, and views relevant to the matter, whether favorable or unfavorable to the position of the undersigned, which is the subject of the request.

Respectfully submitted,

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