ROPES & GRAY LLP
ONE METRO CENTER 700 12TH STREET, NW SUITE 900 WASHINGTON, DC 20005-3948 202 508-4600 F 202 508-4650
BOSTON NEW YORK PALO ALTO SAN FRANCISCO WASHINGTON, DC www.ropesgray.com

Denise L. Loring
212-596-9069
646-728-2543 fax
Denise.Loring@ropesgray.com

August 10, 2006

BY HAND

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

Request for Advisory Opinion Concerning "Orange Book" Listing of Patents

Dear Sir or Madam:

Pursuant to 21 C.F.R. § 10.85, the undersigned submits this request for an advisory opinion of the Commissioner of Food and Drugs with respect to the question whether patents directed to drug delivery systems, such as inhalation devices, that do not recite the approved active ingredient or formulation should be listed in the *"Approved Drug Products With Therapeutic Equivalence Evaluations,"* (the "Orange Book").

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 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. *Id.*

On June 23, 2003, FDA published its final rules, amending the patent listing regulations. *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug is Invalid or Will Not Be Infringed*, 68 Fed. Reg. 36676 (June 18, 2003). In the preamble to the final rules, FDA stated that drug products , as defined in 21 C.F.R. § 314.3, include "metered aerosols, . . . metered sprays . . . and pre-filled drug delivery systems" and that patents claiming such drug products should be listed in the Orange Book. FDA noted that "[t]he key factor is whether the patent being submitted claims the finished dosage form of the approved drug product." *Id.* at 36680; *see also* 36697.

2006A-0318

AP 1

In a Draft Guidance relating to metered dose inhalers (MDIs) and dry powder inhalers (DPIs), FDA stated that the "drug product" includes the entire inhalation drug delivery system, including the inhaler and its protective packaging:

> For MDIs, the formulation, container, the valve, the actuator, and any associated accessories (e.g., spacers) or protective packaging collectively constitute the drug product. For DPIs, the formulation, and the device with all of its parts including any protective packaging (e.g., overwrap) constitute the drug product.

Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products, lines 1921-24 (October 1998); see also Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, lines 208-12 (April 2003).

FDA has not, however, directly addressed whether patents directed to drug delivery systems, such as inhalers that are approved along with the formulation, that do not recite the approved active ingredient or formulation should be listed in the Orange Book.

In January 2005, GlaxoSmithKline ("GSK") submitted to FDA a request for an advisory opinion directed to this precise question: whether patents that claim a drug delivery device or element of a drug delivery device that do not claim or recite the active ingredient of the approved product should be listed in the Orange Book (Tab A). As far as we can determine, FDA has not publicly responded to GSK's request.

AstraZeneca submits that the requirement for listing drug products that are finished dosage forms, such as MDIs and DPIs, should encompass patents directed to the inhalation device of the approved drug product, even if the formulation or active ingredient is not specifically mentioned or claimed in the patents.

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 and to permit early resolution of challenges to patents before marketing begins. *See* 68 Fed. Reg. at 36676. Similarly, the Hatch-Waxman Amendments provide 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).

Listing in the Orange Book of patents claiming inhalation devices would further all of these goals of the Hatch-Waxman Amendments, even if the active ingredient of the finished dosage form is not specifically claimed or referred to in the patent. It would provide generic manufacturers with notice of their potential infringement of these patents and an

opportunity to challenge the patents early, before obtaining FDA approval of their Abbreviated New Drug Application and introducing the generic product into the marketplace. Indeed, because these patents do not claim the formulation or active ingredient specifically, a generic manufacturer searching for patents that refer to the active ingredient might not uncover them if they are not listed in the Orange Book.

AstraZeneca accordingly seeks an advisory opinion on the listability of patents that are directed to inhalation devices under the circumstances where the inhalation device is approved by FDA along with the formulation and the patents do not claim or refer to the formulation or active ingredient of the drug product. Because AstraZeneca believes that such patents should be listed, AstraZeneca will continue to list them unless it receives guidance from FDA that such listings are improper.

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,

Denise L. Loring
Ropes & Gray LLP
1251 Avenue of the Americas
New York, NY 10020
212-596-9000

DLL:alc
Enclosure