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January 10, 2005

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

Re: Request for Advisory Opinion Concerning "*Orange Book*" Listing of Patents

Dear Sir or Madam:

The undersigned submits this request for an advisory opinion of the Commissioner of Food and Drugs, pursuant to 21 C.F.R. § 10.85, with respect to two questions regarding the listing of patents in the Orange Book. Specifically, whether patents of the following kind should be listed in FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the "*Orange Book*":

1. Patents claiming drug delivery devices that are an integral and non-separable part of a drug product when:
   i. the drug delivery device patents do not specifically "claim" the active ingredients contained in the drug product or
   ii. the patent specification fails to "mention" the active ingredients contained in the drug product.

2. Patents claiming the protective packaging or "overwrapping" of a drug product.

A. Issues involved.

If a patent claims a drug delivery device or elements of a drug delivery device approved as part of a New Drug Application ("NDA"), but the patent does not

2005A-0015

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specifically *claim* the active ingredient or *mention* the active ingredient or ingredients contained in the approved drug product, or if a patent *claims* the protective overwrapping of a drug delivery device, should information concerning that patent be submitted to the FDA for listing in the *Orange Book*?

B. Statement of facts and law.

1. Applicable statute and regulations

The Federal Food, Drug, and Cosmetic Act ("FFDCA") § 505(b)(1) states that:

> The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

See also FFDCA § 505(c)(2) (same requirement for patents issued after submission or approval of an NDA). This means that "a patent must be listed if it contains a product claim that reads on the drug that is the subject of the NDA." *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1344 (Fed. Cir. 2003). "The listing decision thus requires what amounts to a finding of patent infringement, except that the 'accused product' is the drug that is the subject of the NDA." *Id.*

FDA recently amended its regulations implementing the listing provisions. 68 Fed. Reg. 36676, 36703-04 (June 18, 2003). In pertinent part, 21 C.F.R. § 314.53(b) now reads as follows:

> (b) *Patents for which information must be submitted and patents for which information must not be submitted*--(1) *General requirements.* An applicant described in paragraph (a) of this section shall submit the required information on the declaration form set forth in paragraph (c) of this section for each patent that claims the drug or a method of using the drug that is the subject of the new drug application or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For purposes of this part, such patents consist of drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents. * * * For patents that claim a drug product, the

> applicant shall submit information only on those patents that claim a drug product, as is defined in § 314.3, that is described in the pending or approved application.

Section 314.3, referred to in the above-quoted regulation, reads in relevant part as follows:

> *Drug product* means a finished dosage form, for example, tablet, capsule, or solution that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

FDA has previously recognized that drug delivery devices, and their associated protective packaging, approved as part of a New Drug Application, are integral parts of the approved drug product. *See, e.g., Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (Apr. 2003) at lines 208-211:

> Nasal aerosols usually consist of the formulation, container, valve, actuator, dust cap, associated accessories, and protective packaging, ***which together constitute the drug product***. Similarly, nasal sprays usually consist of the formulation, container, pump, actuator, protection cap, and protective packaging, ***which together constitute the drug product***. (emphases added)

2. Patents on drug delivery devices generally

In recent rulemaking on patent listing, FDA has generally clarified that patents on drug delivery devices are listable, although circumstances arise – as described later in this request for an advisory opinion – in which more explicit guidance would be helpful. In the proposed rule, 67 Fed. Reg. 65448, 65451 (Oct. 24, 2002), FDA proposed that patents claiming the "packaging" or "container" of a drug product not be listed. However, in the preamble to the final rule, FDA endorsed a distinction that had been raised in comments between on the one hand, patents claiming drug packaging or containers that are "distinct" from the drug product, and on the other hand, patents claiming devices that are "integral" to a drug product, such as "metered dose inhalers and transdermal patches." 68 Fed. Reg. 36676, 36680 (June 18, 2003). The agency specifically noted that a patent of the former kind "fall[s] outside the requirements for patent submission," in contrast to a patent that "claims the finished dosage form of the approved drug product," *i.e.*, that claims the "drug product" within the meaning of 21 C.F.R. §314.3. *Id.* Any such patent claiming the drug product "***must*** be submitted for listing." *Id.* (emphasis added). "The key factor is whether the patent being submitted claims the finished dosage form of the approved drug product." *Id.*

As previously noted in the context of nasal aerosols and sprays, FDA has explicitly recognized that drug delivery devices and their associated protective packaging, approved as part of a New Drug Application, are integral parts of a drug product. Another example is inhalers, which the preamble to the final patent listing regulations specifically cites as an example of a type of drug product for which device patent listing is required. FDA unquestionably considers the delivery device aspects of metered dose inhalers (MDI) and dry powder inhalers (DPI) to be integral parts of those drug products. *See, e.g., Guidance for Industry: Integration of Dose-Counting Mechanisms into MDI Drug Products* (March 2003); *Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products* (October 1998) ("Draft Guidance").

According to the October 1998 Draft Guidance, lines 1921-1924:

> Drug products for MDIs and DPIs may be defined as follows: for MDIs, the formulation, container, valve, the actuator, and any associated accessories (e.g., spacers) or protective packaging ***collectively constitute the drug product*** and for DPIs, the formulation, and the device with all of its parts including any protective packaging (e.g., overwrap) ***constitute the drug product***. (emphases added)

3. Patents that do not mention particular drug substances

There should be little question, particularly in light of the preamble discussion described above, that FDA's regulations generally require submission and listing of patents claiming elements of drug delivery devices that are approved as part of a New Drug Application. In such cases, the delivery device is integral to and "used and approved in combination with a drug," 68 Fed. Reg. 36676, 36680, and as a practical matter, cannot be separated from the delivery device (as is possible with packaging or a container housing a capsule or tablet).

However, FDA has yet to be explicit on the question of whether the listing requirement applies to patents that:

1) do not *claim* the drug substance generally (as in "medicament") or by class, (as in "antiinflammatories" or "bronchodilators") or specifically (as in "albuterol" or "terbutaline") or by chemical name (as in "9-chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate") in conjunction with the drug delivery device or,

2) otherwise do not reference the drug substance in any manner in the patent, such that the topic, theme or premise of the patent is directed to the device itself (most typically, to device-related mechanical aspects of the drug product).

It is the lack of explicit guidance in the above situations that occasions this request for an advisory opinion.

4. The conflict in regards to protective packaging

In regards to the issue regarding protective packaging, the question seems clear. Should persons submit to FDA, for subsequent listing in the *Orange Book*, patents claiming the protective packaging for drug products?

Even though the question seems simple enough; the conflict arises when struggling whether to follow the agency's *Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (Apr. 2003), lines 208-211 (stating that "protective packaging" constitutes part of the drug product), the *Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products* (October 1998) (stating that for MDI's associated accessories including any associated protective packaging constitutes the drug product and for DPI's the device with all of its parts including any protective packaging constitutes the drug product). Conversely, consider the guidance given in 67 Fed. Reg. 65448, 65451 (Oct. 24, 2002), where FDA stated that patents claiming the "packaging" or "container" of a drug product should not be listed.

This question becomes even more perplexing when you consider the preamble in the final rule where FDA endorsed a distinction between patents claiming drug packaging or containers that are "distinct" from the drug product, and patents claiming devices that are "integral" to a drug product. 68 Fed. Reg. 36676, 36680 (June 18, 2003). Here the difficulty arises as in one place FDA states that drug product includes protective packaging, in another patents claiming packaging or containers should not be listed.

5. The need for more explicit guidance

It is the very nature of patents that there is no uniform way to define an invention. Patents have varied scope, and different parts of an invention can be claimed in one or more patent claims, and even in different patents altogether.

The overall invention embodied in a drug product can have many different elements. It is possible to obtain patents that claim the specific approved delivery

mechanism, yet do not recite specifically *in the claims* the particular drug substance or drug substances incorporated in the approved drug product. Outside of the *claim* language, in the patent's specification (the text explaining the invention), some patents may refer either to drug substance in general (*e.g.*, "medicament" or "anti-inflammatory") or to the specific drug substance or substances. However, some may not refer to particular substances anywhere within a patent claiming a necessary and integral drug delivery device.

In regard to protective packaging, there is a conflict between the various guidance statements made by the agency. Where protective packaging is included within the definition of drug product it seems that patents covering the protective packaging should be listed with FDA. However, FDA has also, in its listing guidance, stated that packaging should not be listed. It seems logical that where packaging is protective of the product, rather than simply utilitarian, and enhances, maintains or prolongs product performance, that patents covering packaging of this kind are integral to, if not part, of the drug product and should be listed. However, further guidance is necessary to answer this question.

An important function of the *Orange Book* is to provide notice to generic companies of patents that would be infringed if they were to develop a generic copy of a listed drug or drug product. It serves that notice function to require listing of all patents (other than process patents, which are outside the statutory scope of the listing requirements) that would be infringed if a third party sold a copy of the listed drug or drug product. *See Apotex*, 347 F.3d at 1344 ("The listing decision thus requires what amounts to a finding of patent infringement"). If an integral drug delivery device, or a protective package, is approved as part of a New Drug Application, then patents claiming that device, elements of that delivery device or components necessary to protect or maintain the drug product should be listed in order to fulfill the notice function provided by the *Orange Book.* They, like other properly listed patents, would then be the subject of prompt (premarket) certifications and possibly patent infringement litigation, as authorized under the Hatch-Waxman Amendments, in the event of Paragraph IV certifications.

If a patent does not *claim* the drug substance(s) either generally or specifically, or otherwise mention or reference the drug substance(s) elsewhere in the patent, GlaxoSmithKline, and other NDA-holders, are put in a difficult position without further explicit guidance from FDA. Similarly, due to conflicting statements from FDA regarding exactly what constitutes drug product for Orange Book listing purposes and statements regarding patents that should not be listed, NDA-holders are in a quandary regarding patents covering drug product overwrapping.

If, in an abundance of caution, an NDA-holder does not list certain patents, it could be criticized for failing to give notice to generic applicants of patents that cover an approved product that could be enforced against them should they receive approval and bring the product to market. Conversely, should the NDA-holder list certain patents it could be criticized for inappropriate listing, on a theory (that GlaxoSmithKline believes unfounded) that the drug-device or FDA approved product-drug product definition nexus is insufficiently strong. Accordingly, GlaxoSmithKline is requesting explicit advice from FDA that patents are listable in the circumstances described herein. We reiterate that there are two distinct groupings of questions. In the first group, two categories of device specific patents should be specifically considered: 1) those that do not recite the drug substance in the *claims* of the patent but do mention the drug substance elsewhere in the patent (as in the specification), and 2) those that do not mention the drug substance in the patent anywhere, *i.e.,* patents that could be considered "pure" drug delivery device patents. In the second group is the question of protective packaging or overwrap patents. More precisely, please consider patents claiming protective packaging that, although discarded by the patient, nonetheless enhances, maintains or prolongs product performance. We ask that FDA explicitly confirm that patents in both groups are listable.

6. GlaxoSmithKline's current practice

This request for explicit guidance from FDA is to clarify FDA's position on the listability of certain patents in the FDA Orange Book. However, GlaxoSmithKline feels it is also important for FDA to understand its current practice when listing patents that claim a drug delivery device or elements of a drug delivery device approved as part of a NDA. As FDA has yet to clearly define whether certain kinds of patents are or should be listed, GlaxoSmithKline has not listed patents that do not *claim* the approved drug substance either generally or specifically. Further, with regard to patents covering protective packaging or overwrapping, GlaxoSmithKline has not listed these patents due to the conflicting guidance given by FDA.

These decisions were undertaken by GlaxoSmithKline in an attempt to meet statutory notice requirements, in a conservative and cautious manner. Without further clear and explicit guidance from FDA, however, NDA-holders remain in a difficult position, uncertain whether the kind of conservative, cautious approach that GlaxoSmithKline has adopted fully meets the statutory patent listing requirements as FDA would interpret them.

7. Conclusion

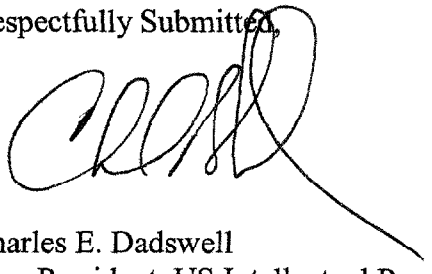
We accordingly seek an advisory opinion on the listability of patents in the circumstances described above.

We invite FDA to contact us should the agency feel it necessary for either clarification of our request or to discuss our request further.

C. *Certification.*

The undersigned certify, 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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cc: Gerald Masoudi, Esq., Acting Chief Counsel