BNA

Pharmaceutical Law & Industry Report®

Orange Book Listing Opportunities for Drug-Device Combinations



BY TERRY G. MAHN, MICHAEL A. SIEM, AND ELIZABETH M. FLANAGAN

With many blockbuster drugs coming off patent in the next several years, Branded Pharmaceutical Companies are looking for more and more ways to protect their products. Increasingly, such companies are listing patents covering medical devices integral to drug delivery in the Orange Book as a means to do so. As described below this practice appears to be proper and presents an intriguing strategy to protect market share.

A. The Hatch-Waxman Act

By way of background, the Food, Drug & Cosmetic Act as amended (''FDCA'') provides for an applicant seeking approval for a new drug to file, in conjunction with the application, patents related to the drug as follows:

> 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.

21 U.S.C. § 355(b)(1) (2006).

Terry G. Mahn is head of the Regulatory and Government Affairs Group at Fish & Richardson in Washington, and a member of the advisory board for BNA's Pharmaceutical Law & Industry Report. Michael A. Siem is a principal in Fish's Intellectual Property Litigation Group in New York. Elizabeth M. Flanagan is an associate in the firm's Twin Cities office. They can be reached at mahn@fr.com, siem@fr.com, and eflanagan@fr.com.

Such patents are then listed in the Orange Book. *See id.* § 355(j)(7)(A). Of note, courts have recognized that the term ''drug'' has been properly construed by FDA as meaning ''drug product.'' *Pfizer, Inc. v. FDA*, 753 F. Supp. 171, 176 (D. Md. 1990); *see also Baker Norton Pharm., Inc. v. FDA*, 132 F. Supp. 2d 30 (D.D.C. 2001) (FDA has varying interpretations of ''drug'' according to context of FDCA).

Under the Hatch-Waxman Act, a generic applicant may submit an Abbreviated New Drug Application (''ANDA'') if it demonstrates that the generic drug is the ''same as'' the pioneer drug – that is, the generic drug has the same active ingredient, route of administration, dosage form and strength, and proposed labeling as the pioneer drug. 21 U.S.C. § 355(j)(2)(A)(iii). The ANDA applicant must also demonstrate that the generic drug is ''bioequivalent'' to the pioneer drug. *Id.* § 355(j)(2)(A)(iv). The FDCA establishes that a generic drug shall be considered bioequivalent to a pioneer 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.'' *Id.* § 355(j)(8)(B)(i). Certain changes from the listed pioneer drug are allowed because the drug is ''produced or distributed by different manufacturers''[1] or through a petitioning process when the proposed generic drug has a different active ingredient, route of administration, dosage form or strength. *Id.* § 355(j)(2)(C).

[1] 21 C.F.R. §§ 314.94(a)(8)(4), 314.127(a)(7).

 ISSN 1542-9547

Along with its ANDA, an ANDA applicant must also submit patent-related information in the form of a certification regarding each patent listed in the Orange Book for the relevant NDA. *Id*. § 355(j)(2)(A)(vii). Alternatively, for method of use patents, the ANDA applicant may ''carve-out'' of its proposed labeling any patented indication or method for which it does not seek approval. *Id*. § 355(j)(2)(A)(viii).

B. Orange Book Listings

FDA has promulgated regulations regarding the listing of patents in the Orange Book. Patent Submission Rules for Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36,676 (June 18, 2003) (codified at 21 C.F.R. pt. 314). The regulation mirrors the language of § 355(b)(1) set forth above, and additionally specifies that it concerns ''drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents.'' 21 C.F.R. § 314.53(b) (2011). The regulations prohibit the listing of ''process patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates.'' *Id*. However, these rules have not been interpreted to exclude delivery devices to administer drugs.

C. The Listability of Patents Claiming Devices Used to Administer Drugs

1. ''Drug Product'' May Include Mechanical Aspects of the Drug Delivery System

Regarding drug delivery systems, the FDA points to the definition of ''drug product'' found in its regulations, which defines a ''drug product'' as ''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.'' 21 C.F.R. § 314.3 (2011). FDA then cited the Orange Book, and noted several representative dosage forms for approved drug products including ''metered aerosols, capsules, metered sprays, gels and pre-filled drug delivery systems.'' Patent Submission Rules for Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. at 36,680. The ''key factor'' in determining whether a patent must be listed is ''whether the patent being submitted claims the finished dosage form of the approved drug product.'' *Id*.

FDA has recognized that drug delivery devices, and their associated protective packaging, approved as part of an NDA, are integral parts of the approved drug product. *See e.g*., FDA, Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action 7 (2003) (acknowledging that for a nasal aerosol, the ''container, valve, actuator, dust cap, associated accessories, and protective packaging'' constitute part of the nasal aerosol drug product; similarly for nasal sprays). In the context of a draft Guidance regarding MDIs (meter dose inhalers)—a dosage form exemplified in the preamble to the Patent Submission Rules as being within the definition of drug product—FDA appears to consider the device aspects of MDIs and DPIs (dry powder inhalers) as part of the drug product. That Guidance defines drug product 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***. For DPIs, the formulation, and the device with all of its parts including any protective packaging (e.g., overwrap) ***constitute the drug product***.
>
> FDA, Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products 60 (1998) (emphases added) (hereinafter FDA, MDI Draft Guidance).

These draft Guidances may be reconciled with the Orange Book listing regulations—and the prohibition against listing ''packaging''—by accepting that in the case of nasal sprays, nasal aerosols, MDI and DPI products, the structure and function of the delivery device is critical to the dosage administered to the patient. In a sense, these mechanical components work in concert with the drug substance and inactive ingredients to safely and effectively deliver a therapeutic dose in ways that are not easily reproduced by other structures, and therefore are considered ''integral'' to the drug product. The same can be said for transdermal patches, which FDA also cited as an example of a drug delivery system falling within the rubric of ''drug product.'' Patent Submission Rules for Applications for FDA Approval to Market a New Drug 68 Fed. Reg. at 36,680. However, it cannot be said that a container for tablets or capsules has any effect on the dose delivered—thus these are properly viewed as distinct from the drug product.

FDA provided some insight as to why it considers the mechanical aspects of MDIs and DPIs to be part of the ''drug product.'' For example, ''[o]ne significant difference between MDI drug products and other, more conventional drug products is that the clinical efficacy of MDIs may be directly dependent on the design, reproducibility, and performance characteristics of the container and closure system.'' FDA, MDI Draft Guidance at 805-810. ''As with MDIs, the clinical efficacy of a DPI drug product may be directly dependent on the design, reproducibility, and performance of the container and closure system.'' *Id*. at 1101-04.[2] FDA's interpretation here makes sense, considering that a change in any of the valve, propellant, actuator or casing may very well lead to a change in the dose administered to the patient (either in terms of amount of drug substance delivered, or rate and extent of absorption), thus raising safety and efficacy issues that FDA would need to review.

2. Application of the Two-Step Analysis to Listing Patents that Claim Drug Delivery Systems

One seeking to list a patent in the Orange Book that claims drug delivery systems should engage in a two-step inquiry. The first prong of the submission inquiry requires a determination of whether the patent claims any part of the drug delivery system or its use which is ''integral'' to FDA approval of the NDA. Or, stated differently, the question is whether any of the claimed features or uses could potentially impact the safe or effective administration of the drug. If the answer is ''yes,''

[2] There are several other passages reflecting the same rationale. *E.g*., FDA, MDI Draft Guidance at 157-59 (''MDIs and DPIs are complex units, the quality and reproducibility of which can be better ensured by appropriate controls of all components (active ingredients, excipients, device components, protective packaging) used in the drug product. . . .''); *Id*. at 919-23 (''The valve should repeatedly dispense the aerosolized drug in discrete, accurate, small doses in the desired physical form. The performance of the valve and its compatibility with other drug product components should be thoroughly investigated before initiating critical clinical and/or bioequivalence studies.'').

  PLIR ISSN 1542-9547

the first prong of the analysis is met. A patent claiming these features or uses should be listable even where the patent does not ''claim'' (in a patent law sense) the related drug substance, either explicitly, by genus, species or some other category.[3]

The second prong of the inquiry is to consider whether it is reasonable to conclude that the patent will be infringed if the drug product is manufactured, used or sold by one not licensed to practice the patent. This second step serves to prevent over-reaching by a NDA-holder by requiring an infringement analysis of the drug product *as labeled*. Significantly, however, this step does not require a finding that the drug product could not reasonably be approved with a different label than the pioneer label even if only to avoid infringement. Under FDA regulations, ANDA applicants are permitted to ''carve out'' indications and ''other aspects of labeling'' protected by patents provided the generic drug (as labeled) is not rendered less safe or effective than the pioneer drug. 21 C.F.R. § 314.94(a)(8)(iv) and § 314.172(a)(7) (2011). An NDA-holder cannot know whether a future ANDA applicant might seek to carve out protected language or whether such labeling changes would even be permitted. Thus, it seems to be sufficient that the NDA-holder make its reasonableness determination based on the labeling language approved for its drug product.[4]

3. Claim Construction as a Factor in the Second Prong of the Listing Test

If patent claims and the approved drug labeling do not match, the second prong of the listing test may turn on claim construction. FDA regulators and Patent and Trademark Office examiners do not always speak the same language and may have different ideas as to the meaning of certain key terms. For example, FDA will not allow label language that is ambiguous or confusing to patients even though such language might be clear to one ''skilled in the art.'' The result could lead to similar concepts potentially being described with different terminology. Therefore, before listing, an applicant will need to analyze and compare the approved label language with the patent claims to determine whether the patent is eligible for listing under the two-prong inquiry. Implicit in a successful analysis, therefore, is a finding that the approved label recites each and every element in at least one patent claim, either explicitly or by reference to a proprietary device claimed by such patent.

D. Recent Requests for Clarification on Drug/Device Patent Listing

Citizen Petitions filed in recent years have requested clarification of the Orange Book listing requirements for drug delivery devices in situations where the relevant patent does not claim the drug substance described in the NDA. In 2005, GlaxoSmithKline (''GSK'') requested guidance on the listability of:

> (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; and (2) patents claiming the protective packaging or ''overwrapping'' of a drug product.

GlaxoSmithKline Request for Advisory Opinion Concerning 'Orange Book' Listing of Patents,'' January 10, 2005, FDA Docket No. 2005A-0015 at 1. GSK noted that its current practice was not to list patents that do not *claim* the approved drug substance either generally or specifically. It also said that it did not list patents covering protective packaging or overwrapping ''due to the conflicting guidance given by FDA.'' *Id*. at 7.

In August of 2006, AstraZeneca filed a similar request for an advisory opinion. AstraZeneca advanced the position that ''the requirement for listing drug products that are finished dosage forms, such as metered dose inhalers (''MDIs'') and dry powdered inhalers (''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.'' *See Ropes & Gray Request for Advisory Opinion Concerning 'Orange Book' Listing of Patents*, August 10, 2006, FDA Docket No. 2006A-0318 at 2. AstraZeneca noted, ''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.'' *Id*. at 3.

AstraZeneca renewed its request in June 2007, once more clarifying the issues it wished to have addressed:

> (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 (i) disclose but do not claim the active ingredient or formulation of the approved drug product or (ii) neither disclose nor claim the active ingredient or formulation of the approved drug product.

Ropes & Gray Request for an Advisory Opinion – 'Orange Book' Listings of Patents, June 21, 2007, FDA Docket No. 2007A.0261 at 1.[5]

Recently, the listability of drug delivery devices has been raised in courtroom litigation. In *King Pharmaceuticals Inc. et al. v. Intellijet, Inc.*, the defendant filed a counterclaim seeking a court order requiring plaintiffs to delist a patent from the Orange Book that relates to plaintiffs' EpiPen and EpiPen Jr. Auto-Injectors. (Civ.

[3] This is a direct result of the construction of the statutory phrase ''claims the drug,'' which the FDA interprets as claiming the ''drug product.'' As discussed above, the term ''drug product'' is broad enough to encompass mechanical elements. Therefore, a patent may ''claim the drug'' without actually being directed to the particular drug substance described in the relevant NDA.

[4] FDA requires a generic applicant to demonstrate ''that the route of administration [and] the dosage form . . . are the same as'' the pioneer drug. 21 U.S.C. § 355(j)(2)(A)(iii) (2006). Thus, an ANDA applicant referencing a drug approved in pre-filled delivery system will either have to copy the label of the approved drug specifying the same delivery system ''dosage form'' or reference a different delivery system that is shown to be substantially equivalent to the approved one. In the latter case, the drug review staff in FDA Center for Drug Evaluation and Research will be required to consult with the device review staff in FDA Center for Devices and Radiological Health to determine whether the two delivery systems are substantially equivalent *and* whether the substitute delivery system (used in place of the patented system that has been carved out) renders the drug product less safe or effective than the pioneer drug product.

[5] As of this writing, FDA has not issued a substantive response to either the GSK or AstraZeneca petitions.

No. 1:11-cv-65 (D. Del.).) The patent sought to be delisted, U.S. Patent No. 7,794,432, relates to an auto-injector for dispensing a pre-determined dose of medicine. Defendant's counterclaim alleges that the '432 patent does not claim either the drug for which plaintiff's NDA was approved or an approved method of using the drug, because the NDA in question is for epinephrine, 0.3 mg and 0.15 mg. (*Id.* Docket No. 11, ¶¶ 114-115).[6]

While every delivery system cannot be listed in the Orange Book, it is yet another option that Branded Pharmaceutical Companies should consider in attempting to utilize the full spectrum of its intellectual property to protect its products.

[6] As of this writing, Defendant's delisting counterclaim is still live.

  PLIR ISSN 1542-9547