Bloomberg Law®

bloombergbna.com

INSIGHT: Drug Delivery Devices in the FDA Orange Book After *In re Lantus*

By Jason P. Cooper, Zachary A. Higbee, and Madeline E. Byrd

While the FDA's rules are tailored for drug companies, third parties may find themselves caught up in the regulatory process and unsure of their footing. One such scenario occurs when third parties supply drug delivery devices that are then incorporated with drug companies' pharmaceuticals. In particular, the FDA requires submitters of New Drug Applications (NDA) to list ''drug-product patents'' in its database of Approved Drug Products with Therapeutic Equivalence Evaluations, commonly referred to as the ''Orange Book.'' Under the current state of the administrative guidance, these drug-product patents may include patents directed to drug-delivery devices even when such patents do not mention a specific drug (e.g., an active pharmaceutical ingredient), and it is an open question whether drug delivery device patents are required to be listed in the Orange Book.

The U.S. District Court for the District of Massachusetts in *In re Lantus Direct Purchaser Antitrust Litig.* recently took up this very issue and the lack of clear guidance from the FDA, and the court ultimately concluded that choosing to list or not list drug delivery device patents could be subjectively reasonable under the circumstances. 284 F. Supp. 3d 91 (D. Mass. 2018).

This article reviews the current state of the law and FDA regulatory scheme to provide guidance for third-party device manufacturers when dealing with the Orange Book in view of *Lantus*.

Current FDA Guidelines and the Need for a Clear Rule

The Orange Book is part of a larger regulatory scheme that directs patent litigation between brand-name and generic drug companies. In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch–Waxman Act. This Act requires brand-name companies looking to market a new drug to submit an NDA to the FDA for approval. Upon submitting an NDA, the submitter must list certain patents related to the new drug in the Orange Book. Later, when a generic company wishes to market a drug that has already been approved by the FDA, it must submit an Abbreviated New Drug Application (ANDA). Upon submission of the ANDA, the submitter must ''certify'' against each patent listed in the Orange Book. If a generic manufacturer plans to market its product before a listed patent expires, it must file a paragraph IV certification stating that the patent is either invalid or will not be infringed. Filing a paragraph IV certification against a listed patent triggers the litigation process. *See* 35 U.S.C. § 271(e)(2).

After a paragraph IV certification is filed, the patent holder has 45 days to respond with a patent-infringement lawsuit. If the patent holder does so, then the FDA cannot approve the generic-drug application for 30 months. If a patent is not listed in the Orange Book, the brand-name company does not get the advantage of the 30-month stay. Because this 30-month stay

is a valuable exclusivity period, the question of which patents can be listed in the Orange Book is significant.

In the case of drug delivery device patents that do not claim a specific drug, the FDA's answer to this question has been vague. The FDA states that an NDA submitter must list any ''drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents'' in the Orange Book. 21 C.F.R. § 314.53(b)(1). On the other hand, the submitter must not list ''[p]rocess patents [and] patents claiming packaging.'' For years, players in the pharmaceutical industry have asked the FDA to clarify whether drug delivery device patents should be listed in the Orange Book. *See Lantus*, 284 F. Supp. 3d at 105-07. The FDA has responded by stating that ''drug product patents'' may include medical-device patents if they also claim the ''finished dosage form'' of the drug. 68 Fed. Reg. 36,676, 36,680 (June 25, 2003). Examples of finished dosage forms include tablets, capsules, solutions, aerosols, gels, and ''pre-filled drug delivery systems.'' Left unanswered in this requirement is whether a *specific drug* must be claimed as part of the finished dosage form. *See Lantus*, 284 F. Supp. 3d at 105-07. Because the manufacturers of the drug delivery systems are often suppliers to the drug manufacturers, the delivery-system manufacturers typically do not want their patents to be limited to being pre-filled with specific drugs but would instead want them to cover the novel features of the delivery system itself without a specific drug being pre-filled.

There are two classes of drug delivery device patents to consider: (1) drug delivery device patents that claim a specific drug and (2) general drug delivery device patents (patents that do not claim a drug) but that can be used as part of a finished dosage form for one or more drugs listed in the Orange Book. Patents belonging to the first group count as a ''pre-filled drug delivery system'' inasmuch as they expressly require a specific drug regulated by the Orange Book. Regarding the second category, however, it is unclear whether general drug delivery device patents constitute pre-filled drug delivery systems or whether they belong to the class of packaging patents that cannot be listed in the Orange Book.

In re Lantus Direct Purchaser Antitrust Litigation

Recently, this issue was addressed by a district court, which found that general drug delivery device patents do not fit neatly into either category. In *Lantus*, plaintiffs FWK Holdings LLC and Cesar Castillo Inc., brought an antitrust claim against Sanofi-Aventis for allegedly improperly listing its drug delivery device patents related to the Lantus Solostar in the Orange Book. One of the central patents in the dispute, U.S. Patent No. 8,556,864 (''the '864 patent''), claims a ''drive mechanism for use in a drug delivery device'' with no corresponding drug and no mention of a drug beyond the designation ''for use in a drug delivery device.'' Sanofi-Aventis listed the '864 patent in the Orange Book in conjunction with the insulin-glargine recombinant active pharmaceutical ingredient.

The plaintiffs argued that this was improper because the claims of the '864 patent allegedly fell into the ''patents claiming packaging'' category, which is excluded from listing in the Orange Book. Sanofi-Aventis contested that the '864 patent actually constituted a pre-filled drug delivery system, and thus was properly listed. The court found that ''while it may be debatable whether the Lantus SoloSTAR fits neatly into the category of patents that must be disclosed, it does not fit into the category of patents that must not be disclosed.'' It concluded that ''Sanofi's interpretation of the listing requirements was reasonable.'' In reaching its decision, the *Lantus* court concluded that it was reasonable to list patents related to the Lantus Solostar injector, ''including its components,'' in part because the FDA had approved the injector as a drug delivery system. The *Lantus* court also specifically noted the FDA's refusal to address the issue on numerous occasions and reasoned that Orange Book listing of drug delivery devices without a drug was still an open question, such that either listing or not listing such devices could be considered reasonable.

Sanofi-Aventis thus escaped antitrust liability because its reasonable conduct could not be an unambiguously wrongful monopolization under the Sherman Act. Although *Lantus* is not binding precedent in all jurisdictions, NDA submitters should be able to form a good-faith belief that drug delivery device patents covering some portion of a drug delivery device subject to NDA approval may or may not be listed at the discretion of the NDA submitter. Thus, in the wake of the FDA's ambiguity, either listing or not listing these patents is acceptable.

Whether to List These Patents in the Absence of Clear FDA Guidance

Although either approach may be acceptable, there is still a question of whether it is *advisable* to list general drug delivery device patents in the Orange Book. Numerous factors weigh for and against listing a drug delivery device patent in the Orange Book.

Legal Considerations From an antitrust perspective, improper listing in the Orange Book could give rise to potential antitrust litigation. Even though the court in *Lantus* did not find an antitrust violation, another court may come to the opposite conclusion. *Lantus* only involved a potential violation of section 2 of the Sherman Act because the patent holder and the NDA submitter were the same entity. If the patent holder is one entity, such as a general drug device supplier, and the NDA submitter is a different entity, such as a brand-name-drug manufacturer, there could be a potential issue of section 1 of the Sherman Act, which was not considered by the *Lantus* court.

From an intellectual property perspective, listing patents in the Orange Book also provides competitors a blueprint of the patent protection surrounding a given drug delivery device and requires the submitter to take a formal position on the scope of its patents, which may make avoiding infringement easier and less risky for competitors. In particular, the patent submitter may inadvertently limit its future claim interpretation options by listing in the Orange Book and, thus, take a formal position that the claims of a listed patent read upon a particular drug delivery device. Tipping the scales in the other direction, the FDA's 30-month stay of ANDA approval for drug delivery devices would provide an exclusivity period beyond the enforcement of the patent.

What's more, many general drug delivery device patent holders are suppliers that sell these devices to drug companies without producing the drugs themselves. Ultimately, it is not these suppliers' responsibility but the responsibility of the drug company that is submitting the NDA to list the proper patents in the Orange Book. 21 C.F.R. § 314.53(a). Third-party suppliers have even less motivation to seek Orange Book listing of their patents under the FDA's regulations.

Business Considerations Pragmatically, listing the '864 patent in the Orange Book forced Sanofi-Aventis to defend itself in both ANDA litigation and a costly antitrust litigation, whereas parties not listing in the Orange Book can wait and decide whether to bring suit when the device is actually released.

Finally, companies that supply general drug delivery devices to multiple drug manufacturers might worry about whether listing their patents in the Orange Book in conjunction with one of their customer's drugs will alienate other customers and potential customers. These non-pharmaceutical manufacturers may have multiple customers using the same drug delivery device for one or more drugs or may wish to sell the same delivery device to generic drug manufacturers in connection with an ANDA submission, so *not* listing may be the best business decision to keep every customer happy and avoid unwanted conflict.

On the other hand, pharmaceutical companies may wish to exclude pharmaceutical competitors from manufacturing drug delivery devices or delivering drugs using patented final dosage forms. These pharmaceutical companies may have a greater financial incentive to protect their drugs and less interest in separately selling drug delivery devices to third-party manufacturers and suppliers.

Conclusion

Each drug delivery device manufacturer should weigh the various factors with its own particular circumstances. Given the lack of an FDA mandate, unwanted attention, potential liability, potential for higher cost, and business concerns surrounding listing a patent against particular customers' pharmaceuticals, general drug delivery device manufacturers (as opposed to pharmaceutical companies) should generally not have their patents listed in the Orange Book until the FDA issues clearer requirements. This balance may shift in favor of listing patents for pharmaceutical companies (as opposed to third-party suppliers) who also patent the surrounding drug delivery devices to deliver their drugs because the attention, potential litigation, and business concerns are either mitigated or nonexistent for pharmaceutical companies already participating in the NDA/ANDA process.

Until the FDA issues further guidance, it remains unclear whether drug delivery device patents must be listed in the Orange Book, but parties are likely (although not guaranteed) to avoid antitrust issues under the current jurisprudence. Ultimately, listing general drug delivery device patents in the Orange Book appears riskier than it is rewarding for third-party drug delivery device manufacturers.

Jason P. Cooper *is a partner and co-chair of the Intellectual Property Practice at Alston & Bird, and* ***Zackary A. Higbee*** *is a senior associate in that practice.*

Madeline E. Byrd *is a former Alston & Bird summer associate.*