Bloomberg BNA

BNA's
Patent, Trademark & Copyright Journal®

PATENTS

The authors assess the status of the Hatch-Waxman Act infringement safe harbor in the wake of recent case law.

Patent Infringement After FDA Approval: New Developments

BY DAVID P. HALSTEAD AND MELISSA S. RONES

Decades ago, innovator companies lost years of patent protection for their products to lengthy clinical trials, while generic companies were blocked from starting to develop their products until the innovator's patents had expired. The landmark 1984 Hatch-Waxman Act rebalanced the relationship between innovator and generic companies in two major ways: (1) innovator products would be eligible for up to five years of patent term extension to compensate for patent term effectively lost during the conduct of clinical trials prior to Food and Drug Administration approval; and (2) pre-approval activities by generic companies preparing to market their product would be exempt from patent infringement, allowing them to enter the market as soon as the relevant patents had expired. The second of these changes arises from 35 U.S.C. § 271(e)(1), which reads:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

Halstead is an IP rights management partner at Ropes & Gray. He is based in the firm's Boston office. Rones is an IP rights management associate also based in Boston.

In the nearly three decades since its passing, two major Supreme Court cases have elucidated the scope of this statutory infringement exemption. *Eli Lilly v. Medtronic*, 496 U.S. 661, 15 USPQ2d 1121 (1990), clarified that the exemption applies to medical devices as well as drugs, as the Federal Food, Drug, and Cosmetics Act of 1983 regulates both types of products. *Merck KGaA v. Integra Lifesciences I Ltd.*, 545 U.S. 193, 74 USPQ2d 1801 (2005) (70 PTCJ 198, 6/17/05), interpreted the exemption to cover at least some early stage drug discovery activities by innovators, even where the resulting data was not ultimately submitted to the FDA, provided that the experiments were performed with an intent to develop a drug and under a belief that information of potential relevance to an FDA submission might result. Together, these decisions pushed the exemption beyond the simple innovator/generic dichotomy and established a relatively broad exemption for pre-approval clinical and even pre-clinical research related to a product regulated by the FDCA.

 ISSN 0148-7965

Cases Address Post-Approved Activities. Recently, two Federal Circuit decisions have addressed the question of whether *post*-approval activities are protected by the Section 271(e)(1) exemption. *Classen Immunotherapies Inc. v. Biogen Idec*, 659 F.3d 1057, 100 USPQ2d 1492 (Fed. Cir. 2012) (82 PTCJ 650, 9/16/11), considered the issue in the context of a patent covering methods of immunizing a patient using an immunization schedule that poses a lower risk of inducing a chronic immune disorder than other tested schedules. The panel held that the safe harbor did not apply to ''information that may be routinely reported to the FDA, long after marketing approval has been obtained,'' and further suggested that the safe harbor would not protect any post-approval activities.

Soon thereafter, *Momenta Pharmaceuticals Inc. v. Amphastar Pharmaceuticals Inc.*, 686 F.3d 1348, 103 USPQ2d 1800 (Fed. Cir. 2012) (84 PTCJ 616, 8/10/12), addressed patent claims covering a method for analyzing the chemical composition of enoxaparin, a method Momenta alleged Amphastar employed to monitor its production batches of enoxaparin after approval. Here, the Federal Circuit held that the safe harbor did apply, because Amphastar was using the method to ensure that the enoxaparin it produced met the FDA standards required for compliance with its approval.

Because the FDA regulates the sale of enoxaparin and requires manufacturers to prepare and maintain batch records showing that the material sold met its quality standards, the court reasoned that Amphastar's use of the methods was reasonably related to the development and potential submission (on FDA request) of the batch records. In distinguishing *Classen*, the court noted that this information was not generated primarily for non-FDA purposes or for a ''routine submission,'' but was in fact a strict requirement pursuant to a specific statute to legally sell the enoxaparin in the US. The fact that the batch records were never actually requested or submitted to FDA did not alter the majority's view of the facts or the distinctions from *Classen*.

Conflict Over Safe Harbor Expansion. In a simpler world, this distinction would seem to have some merit. While the defendants in *Classen* could have been performing their studies primarily to improve the safety profile of their products—a worthy goal, but one not required by the FDA pursuant to their existing approval—Amphastar was under an ongoing requirement to verify the quality of its drug product, even though it might have done so using methods not protected by the patent at issue. Viewed in this way, a distinction centering on the statutory language ''reasonably related to the development and submission of information'' for the FDA is a tenable one.

However, Chief Judge Randall R. Rader—who wrote the *Classen* decision—disagreed. He vigorously dissented in *Momenta*, calling the expansion of the safe harbor to post-approval activities ''incorrect'' and ''a massive enlargement of the statutory exemption.'' Additionally, he raised concerns that applying the safe harbor to post-approval activities discouraged innovation by permitting free-riding. With the Federal Circuit internally conflicted over the proper construction of the safe harbor, it seems likely that the issue will be addressed by the court en banc or even by the Supreme Court. The outcomes for Biogen and Amphastar—and for others engaged in similar activities—hang in the balance.

The current conflict casts doubt on the commercial value of at least three categories of patents: (1) quality assurance/quality control (QA/QC) methods; (2) clinical trial protocols; and (3) research tools. QA/QC methods closely track the *Amphastar* case, whose holding directly implicates the ability to enforce patents covering methods of characterizing a regulated product for commercial sale. Scenarios of this sort can arise in the context of small molecules (e.g., if a finished product needs to be characterized in terms of levels of a difficult-to-remove impurity) and formulations (e.g., to show a characteristic release profile).

However, QA/QC methods may turn out to be most important for biologics and biosimilars. Because biologic products are large and complex, and are often composed of mixtures of molecules that cannot be fully elucidated at a structural level, ensuring consistency from batch to batch and manufacturer to manufacturer requires assessing a variety of structural and functional characteristics for comparison against a reference standard—analogous to the situation in *Momenta* for the complex carbohydrate enoxaparin.

Although the regulatory requirements that will apply to biosimilars are still in very preliminary stages, it seems highly likely that batch records like those generated by Amphastar will need to be prepared and maintained by biosimilar manufacturers as well. No doubt many originators of biologic products are hoping to gain an extra period of exclusivity by patenting methods of testing their products for characteristics that are important to their safety and efficacy. The decision in *Momenta*, if upheld, likely renders such patents useless.

In contrast, if the views set forth in Rader's dissent prevail, such patents could create a significant additional barrier to market entry for competitors. Biosimilar manufacturers would need to challenge the validity or enforceability of such patents, delay market entry, or convince the FDA that alternative, noninfringing methods are adequate to assess the similarity, safety, and efficacy of their product.

Patents on clinical trial protocols and other methods of assessing treatments align more closely with the *Classen* decision. While it seems undisputed that such patents are unenforceable against pre-approval activities, in the context of a product subject to FDA-mandated Phase IV trials or additional trials after an accelerated approval, there is room for optimism that these activities would be protected as well.

Issue Is Whether FDA Requires Activity. If upheld, the current distinction between *Classen* and *Momenta* turns on whether potentially infringing activity is specifically required by FDA, and in that context post-approval trials required by the FDA would probably qualify for the safe harbor. However, Rader's dissent in *Momenta* suggests that the safe harbor might not apply to post-approval trials if his interpretation of the statute ultimately prevails.

Patents on research tools have not been squarely addressed by any Federal Circuit decisions since the *Merck* decision first raised the question of whether their use in drug development might be exempt from claims of patent infringement. However, in addressing a patent covering an analytical method, the *Momenta*

   ISSN 0148-7965

opinion's reasoning raises the question of whether the same logic and broad statutory interpretation might apply to a patent covering an analytical instrument—or indeed any reagent, method, or device used to generate data useful to or required by the FDA pursuant to its regulatory powers. A sweeping decision harmonizing the outcomes in *Classen* and *Momenta* could have implications for research tools, potentially affecting technologies from analytical reagents to medical and biologic instrumentation.

At least with respect to generic and follow-on products, where the FDA is unlikely to require post-approval trials, traditional composition of matter, method of treatment, and method of diagnosis claims—claims that pertain directly to the approved product and its label and would be unrelated to any gathering or potential submission of post-approval information to the FDA—are likely to continue to offer innovators strong protection against other market entrants. These mainstays of protection for innovative pharmaceutical, biologic, and medical device products should retain their value. It is the exceptional cases, where creative innovators try to secure patents around anticipated FDA requirements for generic and biosimilar versions of their products, where the role of patents is uncertain.

Whether or not the safe harbor applies after approval may turn out to be only one of the relevant questions in this rapidly developing area of law. The appropriate remedy for infringement may also be at issue. In an industry accustomed to injunctions, could some types of patents fail the balancing test, delivering only a reasonable royalty or other monetary award?

While it seems likely that courts will continue to reward method of treatment and composition of matter claims with injunctions, outcomes for infringing quality control and clinical trial protocol patents have little precedent. Factors affecting the remedy could include the availability of alternative paths for testing/approval of generic or follow-on products, perceived inequities if the innovator is seen to have unfairly influenced the FDA to adopt requirements protected by its patents, and even the price disparity between innovator and follow-on products.

For the time being, innovators will continue to seek these patents, and generic and biosimilar manufacturers will continue to worry about them. Each side, knowing that the effectiveness of these patents is in question, awaits the next development from the courts.