

THE SAFE HARBOR PROVISION OF HATCH-WAXMAN – IS THERE A “HOLE” IN THE SAFETY NET?

The Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Act) was enacted for the dual purpose of restoring patent term to pharmaceutical inventions caused by the lengthy regulatory approval process while at the same time ensuring that a *de facto* patent term extension didn't occur because a generic manufacturer could not initiate the manufacture and/or testing required for regulatory approval of a generic drug product without infringing, e.g., the pioneer patent covering the drug itself until that patent expired.¹

For generic companies, in addition to creating a new procedure for the regulatory review and approval of generic drugs (Abbreviated New Drug Applications, or ANDAs), the Act created what is commonly referred to in the trade as the “safe harbor provision,” intended to insulate activities of companies during the development of a pharmaceutical product from patent infringement actions. The safe harbor provision overruled legal precedent created by the courts that a drug manufacturer could not initiate the testing required for approval without infringing the pertinent patent until after the expiration of that patent.² Codified as 35 U.S.C. §271(e)(1), the Act provided an exemption from infringement for otherwise infringing activities that are reasonably related to obtaining FDA approval for a drug. The statute reads in pertinent part that “[i]t shall not be an act of infringement to make, use, offer to sell, or sell within 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.”

¹ Generally, the patentee has the right to exclude others from making, using, selling or offering to sell its patented technology. 35 U.S.C. §271 (a).

² See *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir.), *cert. denied*, 469 U.S. 856 (1984).

The legislative history of the safe harbor provision indicates that it was meant to allow a limited amount of testing so that generic companies could establish the bioequivalency of a generic substitute prior to the expiration of the patents covering a pioneer drug product.³

Early cases, focusing on the word “solely” in the phrase “solely for uses reasonably related” in the statutory language, held that any activity beyond bioequivalency testing for FDA approval constituted infringement. In one case, the court stated that because Genentech made and used plasma-derived and recombinant Factor VIII:C preparations for multiple purposes, including uses beyond meeting FDA requirements (such as preparation of a European patent application and supplying the product (with compensation) for the purpose of developing a commercial scale manufacturing process), those activities fell outside the safe harbor provision.⁴ Another court held that the collateral use of data submitted to FDA, in that case to promote or market the product, was outside the safe harbor provision.⁵

Certain activities appeared to be clearly outside the protection of the safe harbor. For example, the production of a pharmaceutical product in anticipation of FDA approval, and taking concrete steps in preparation for marketing the product have been deemed to fall outside the safe harbor provision. In one such case, 24 million dollars was spent to stockpile the drug and prepare to market the same immediately upon anticipated FDA approval was deemed outside the safe harbor provision.⁶ Commercial use was another activity deemed outside the safe harbor provision.⁷

³ H.R. Rep. No. 857 at 8; *Scripps Clinic and Research Found. V. Genentech*, 666 F. Supp. 1379 (N.D. Cal. 1987); *Integra Lifesciences I, Ltd. V. Merck KGaA*, 331 F. 3d 860 (Fed. Cir. 2003), citing *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F3d. 1162 (Fed. Cir. 1997).

⁴ *Scripps Clinic and Research Found. V. Genentech*, 666 F. Supp. 1379 (N.D. Cal. 1987).

⁵ *Ortho Pharmaceutical v. Smith*, 18 U.S.P.Q. 2d 1977 (E.D. Pa. 1990).

⁶ *Biogen, Inc. v. Schering AG*, 954 F.Supp 391 (D. Mass. 1996).

⁷ *American Standard, Inc. v. Pfizer, Inc.*, 722 F. Supp. 86 (D. Del. 1989); *Eli Lilly & Co. v. A.H. Robins Co.*, 228 U.S.P.Q. 757 (E.D. Va. 1985).

Activities Deemed Safe

The courts, when considering the issue of whether a particular activity falls under the safe harbor provision, more recently applied a test which tracks the statutory language of 35 U.S.C. §271(e)(1) and involves the consideration of whether the use in question was “reasonably related to the development and submission of information” to the FDA. The standard generally invoked by the courts until now has been, “[w]ould it have been reasonable, objectively, for a party in the defendant’s situation to believe that there was a decent prospect that the ‘use’ in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the processes by which the FDA would decide whether to approve the product?”⁸ As a result, the courts have decided that many pre-market activities fall within the safety net of the safe harbor provision and have generally given the benefit of the doubt to the alleged infringer concerning specific activities, as long as the infringing activity could in some way be used in a regulatory (FDA) submission.

In one landmark decision, the court considered pre-approval activities with respect to an implantable defibrillator device.⁹ The court held that the following activities fell within the safe harbor provision: using test data generated to obtain import approval from foreign governments; publication of articles describing features of the device; relying on the device to assist in raising capital; demonstrating the device at trade shows; obtaining foreign patents; manufacture of the device (where most were used to generate data for the FDA); sales of the device in the U.S. (for use only in clinical trials); sales to international distributors (for the limited purpose of having the device clear customs, for use in foreign clinical trials); and clinical trials conducted overseas, *in addition* to domestic testing.¹⁰

⁸ *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff’d*, 991 F. 2d 808 (Fed. Cir. 1993).

⁹ *Intermedics, Inc. v. Ventritex, Inc.*, 775 F.Supp. 1269 (N.D. Cal. 1991).

¹⁰ See also *NeoRx Corp., v. Immunomedics, Inc.*, 877 F. Supp. 202 (D. N.J. 1994), where the court held that the manufacture of commercial scale lots beyond that needed for FDA approval fell within the safe harbor provisions, in part because one could not predict whether FDA would require more information during the approval process.

In another landmark decision, a court considered whether any of six allegedly infringing activities undertaken by the defendants Hoechst and Transkaryotic amounted to patent infringement of Amgen's EPO patents or whether those activities fell under the safe harbor provision of §271(e)(1).¹¹ The court held that the following activities fall under the safe harbor provision: (i) export of EPO to Japan for use in evaluating an alternative manufacturing process (despite the fact that no approval had been sought for that new process); (ii) purity studies that were not submitted to FDA (because that use was calculated to lead to the submission of relevant information to FDA); (iii) the production of consistency batches (commercial scale production) which were not requested by FDA but were "objectively likely to generate useful information, even if the results were later discarded or abandoned for reasons unrelated to FDA approval"¹²; (iv) characterization of the carbohydrate structure of GA-EPO as compared to human urinary EPO (also useful for assessing the Defendants' patent position); (v) viral clearance tests designed to meet European regulatory standards (but the results of which were submitted to FDA); and (vi) unexecuted plans to conduct radiolabeling for studies unique to Japanese regulatory requirements.

The safe harbor was further deemed to be available with respect to a drug company's use of patented intermediates to develop a structure-activity relationship database ("SAR") to investigate and identify potential new drug candidates.¹³ Bristol Myer's Squibb had embarked on a taxane research program for the purpose of discovering a new product that could replace its Taxol product as a preeminent anti-cancer drug as soon as the taxol patents expired. The court ruled that it was reasonable, objectively, for Bristol Myer's to believe that there was a "decent prospect" that its use of RPR intermediates would contribute (relatively directly) to the generation of kinds of information likely to be relevant during the FDA approval process of a drug coming out of its SAR program.¹⁴ The *Bristol* decision was important because it confirmed that drug companies could conduct virtually all research, starting from synthesis of potential new

¹¹ *Amgen Inc., v. Hoechst Marion Roussel Inc.* 3 F. Supp. 2d, 104 (D. Mass. 1998).

¹² *Id.*

¹³ *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 C 8833, 2001 WL 1512597 (S. D.N.Y. 2001).

¹⁴ Here, the court was utilizing the test enunciated in the *Intermedics* decision, *supra*.

drug candidates, through the initial testing of the same, and continuing on through preclinical and clinical testing (but not commercialization), within the safe harbor provision of the Act.

The above court decisions, and other similar decisions, represented a continuing trend toward a broad interpretation of the safe harbor provision.

One Hole After Another...

The tide has now turned, and the trend is reversing. Companies may no longer be entitled to pursue a broad range of protected activities under the safe harbor provision in view of recent court decisions.

In the first of these decisions, the Court of Appeals for the Federal Circuit considered whether the use of patented free electron laser equipment fell within a common law “exception” for patent infringement liability for uses that are solely for research, academic or experimental purposes. The court held that the common law experimental use defense is very narrow and limited to actions performed for amusement, to satisfy idle curiosity, or for strict philosophical inquiry, and clearly did not immunize patent use in furtherance of an alleged infringer’s legitimate business.¹⁵ Although statutory safe harbor provision was not applicable to that case, the court’s decision was instructive for the future.

More recently, on June 6, 2003, that court held that there was no right to conduct discovery-based research, either under the common law research exemption or the statutory immunity provided by the safe harbor provision.¹⁶ This case concerned research on which Scripps and Merck collaborated concerning certain peptide components of fibronectin. In this research, various RCD peptides were synthesized and studied, eventually leading to the filing of an Investigatory New Drug application (IND)

¹⁵ *Madley v. Duke University*, 307 F. 3d 1351 (Fed. Cir. 2002).

¹⁶ *Integra v. Merck*, 331 F.3d 860 (Fed. Cir. 2003).

with FDA. Integra sued Merck for infringement of its patents relating to the RCD peptide. After noting that it had previously held that the safe harbor provision permitted pre-market approval activity conducted for the *sole* purpose of sales after patent expiration¹⁷, the court further noted that it had not considered whether the safe harbor reaches back down the chain of experimentation to embrace development and identification of new drugs (which are subject to FDA approval). The court found that it did not.

The court took a narrow view of the exemption and took the view that the term “solely” in the statutory language constrains the inquiry concerning activities in question. The court noted that the express objective of the 1984 Act was to facilitate safety and effectiveness testing required of generic companies prior to patent expiration on a pioneer drug so that the generic is available immediately upon patent expiration. Accordingly, the court held that the exemption could not extend at all beyond uses reasonably related to the development and submission of information for FDA’s safety and effectiveness approval processes, and certainly not to globally embrace all experimental activity that at some point might lead to an FDA submission (including the exploratory research conducted by Merck).

Does this mean that no pre-marketing testing will be deemed to fall within the safe harbor provision, except for safety and efficacy testing by generic companies? What about testing to determine whether the generic product falls within a patent claim? Weren’t the patent laws intended to allow the subject matter in patents to be studied so that it could be improved upon, designed around, etc.? What about the advancement of technology intended as the quid pro quo for patent protection? Does this mean that the study of patented compositions for the creation of new knowledge and products is no longer permissible by third parties prior to patent expiration? Certainly as of now the Court of Appeals for the Federal Circuit has deemed pre-clinical screening testing for new drug candidates utilizing third party patented drugs, as well as the use of patented

¹⁷ Citing its decision in *Hoeschst-Roussel Pharms., Inc. v. Lehman*, 109 F. 3d 756 (Fed. Cir. 1997).

research tools and screening methods, to fall outside the safe harbor exemption.

Hold onto your seats, everyone. These issues have yet to be settled. Merck has petitioned the Supreme Court for a writ of certiorari in the *Integra* case. In the meantime, generic companies need not worry too much, as long as they don't go astray from bioequivalency testing. The safe harbor provision was meant for them, and bioequivalence testing for ANDA and branded generic submissions still appear to be safe. However, testing which might be conducted by generics for patent clearance purposes may no longer be safe. Further, those start-up companies desiring to utilize patented pharmaceuticals to find a new, improved drug product take note – there may be a hole in your safety net!

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