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The patent laws specify requirements for patent infringement in 35 U.S.C. § 271. Section 271(e)(1), however, removes liability for certain uses of patented inventions that would otherwise infringe, so long as those uses are reasonably related to developing and submitting information for regulatory purposes. Recent court decisions have interpreted this statutory safe harbor to include methods and tools that can be used in research or manufacturing—inventions for which no regulatory approval is being sought. One fact informing the analysis is whether those uses result in data that must be submitted to the Food and Drug Administration, but a blurred line separates exempt and infringing uses of some inventions.

Finding the Line Separating Infringement and Exempt Uses: Enforcing Biotechnology Patents in View of 35 U.S.C. § 271(e)(1)



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For nearly a decade, companies involved in basic biotechnology research could rely on guidance from the Supreme Court in *Merck KGaA v. Integra Lifesciences*,[1] which considered the scope of the 35 U.S.C. § 271(e)(1) statutory safe harbor. The statute states that:

> [i]t 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.[2]

In *Integra*, the patented invention was an ''RGD peptide,'' referring to the single letter designation for the three amino acids arginine-glycine-aspartic acid.[3] RGD peptides were known to promote cell adhesion. The crux of the issue in *Integra* was that while the RGD pep-

[1] *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005).

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[2] 35 U.S.C. § 271(e)(1).
[3] *Integra*, 545 U.S. at 197.

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tides could be used as pure research tools, those chemicals could also be used to develop therapies for patients. Experimental data relating to the latter use, but not the former, presumably would be submitted to the Food and Drug Administration.

Merck collaborated with academic researchers in the late 1980s to mid-1990s, discovering that RGD peptides could be used to block tumor vascularization by disrupting angiogenesis, the process for forming new blood vessels. Merck's academic partner—the Scripps Research Institute—tested RGD peptides that Merck manufactured as potential drug candidates.[4] Experiments tested three derivative RGD peptides to evaluate efficacy and specificity as angiogenesis inhibitors. Animal model studies also evaluated the peptide derivatives' mechanism of action and pharmacokinetics. Finally, other Scripps-run experiments used the RGD peptide derivatives as controls to identify other potential angiogenic inhibitors, including monoclonal antibodies and synthetic molecules that mimicked RGD peptide function.[5] Based on the results of those various projects, Merck started a formal project to obtain regulatory approval of a lead compound in 1996, and began clinical trials in 1998.[6]

The patent holder, Integra Lifesciences, filed a patent infringement lawsuit the same year that Merck initiated its formal regulatory program. At trial, the court found that Merck and Scripps had infringed the asserted patents, despite defendants' assertion that the Section 271(e)(1) safe harbor exempted their activities from infringement.[7] The Federal Circuit agreed that the safe harbor did not apply to the Merck-sponsored work at Scripps because those studies were not clinical tests to generate data to submit to the FDA, but ''only general biomedical research to identify new pharmaceutical compounds.''[8]

The Supreme Court disagreed. ''Basic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce, is surely not 'reasonably related to the development and submission of information' to the FDA.''[9] But experimentation on drugs that are not ultimately the subject of an FDA submission, or use of patented compounds in experiments that are not ultimately submitted to the FDA, are not ''categorically exclude[d]'' from the protections of Section 271(e)(1).[10] ''At least where a drugmaker has a reasonable basis for believing that a patented compound may work, through a particular biological process to produce a particular physiological effect, and uses that compound in research that, if successful, would be appropriate to include in a submission to the FDA,'' that use is safe harbored.[11]

Different Outcome for Pure Research Tool?

In *Integra*, the accused infringer eventually sought approval for the patented research tool. Would the result have been different if the patented invention was a pure research tool, and not the subject of a submission to the FDA? The Federal Circuit has considered this question twice since *Integra*, but has reached different conclusions.

In *Proveris Scientific Corp. v. Innovasystems, Inc.*, the patent holder's infringement claims covered use of a drug development tool, an Optical Spray Analyzer (''OSA'') that measures the characteristics of nasal spray from a drug delivery device.[12] While the OSA, itself, was not subject to regulatory approval, Innova's customers used the device in connection with regulatory approval activities for various drugs.[13] The district court excluded Innova's reliance on the Section 271(e)(1) safe harbor as a matter of law, and a jury found infringement.[14] On appeal, the Federal Circuit agreed that Section 271(e)(1) did not apply to Innova's conduct. The Federal Circuit reasoned that the Hatch-Waxman Act included the safe harbor to eliminate a distortion in the term of patents covering drugs by allowing generic manufacturers to practice a patent before expiration to seek premarket approval from the FDA.[15] Because Innova's accused product was not subject to premarket approval, Innova was not entitled to benefit from the safe harbor exemption.[16]

Four years later, the Federal Circuit decided *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.*, which blurred the line between what is—and is not—a ''patented invention'' within the ambit of Section 271(e)(1).[17] In *Momenta*, patented manufacturing methods had been used during the manufacture of blood clot medication. The Federal Circuit reversed the district court's grant of a preliminary injunction, reasoning that Momenta was unlikely to succeed on its infringement claim. The court held that Momenta's competitor Amphastar's post-market approval activities fell within the scope of 35 U.S.C. § 271(e)(1).[18] The rationale? The plain language of the statute indicates that ''*all uses*'' of patented inventions are exempt from infringement when they are ''reasonably related to the development and submission of any information'' to the FDA.

After *Momenta*, information need not actually be submitted to the FDA, but only be of the type that is appropriate to include in a submission.[19] The FDA required Amphastar to conduct tests to determine the identity and strength of the active ingredients in each of its commercial batches, *and* to maintain records of

[4] *Integra,* 545 U.S. at 197-198.
[5] *Integra,* 545 U.S. at 198-199.
[6] *Integra,* 545 U.S. at 199.
[7] *Integra,* 545 U.S. at 200-201.
[8] *Integra,* 545 U.S. at 201.
[9] *Integra,* 545 U.S. at 205-206.
[10] *Integra,* 545 U.S. at 206.
[11] *Integra,* 545 U.S. at 207.

[12] *Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1259 (Fed. Cir. 2008).
[13] *Proveris*, 536 F.3d at 1259.
[14] *Proveris*, 536 F.3d at 1259.
[15] *Proveris*, 536 F.3d at 1265.
[16] *Proveris*, 536 F.3d at 1265.
[17] *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.*, 686 F.3d 1348 (Fed. Cir. 2012). *Momenta* came on the heels of the Federal Circuit's *Classen Immunotherapies* decision, in which the invention was a method of optimizing immunization schedules. *Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057 at 1060-1061 (Fed. Cir. 2011). In that case, the Federal Circuit determined that the safe harbor does not apply to information that may be routinely reported to the FDA, long after marketing approval has been obtained. *Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057 at 1070 (Fed. Cir. 2011).
[18] *Momenta*, 686 F.3d at 1348.
[19] *Momenta*, 686 F.3d at 1357.

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those tests for inspection for at least a year after the batch expiration date. Those requirements, according to the Federal Circuit, triggered the statutory safe harbor.

Momenta argued, to no avail, that its specific inventive methods were entirely optional.[20] Although the FDA requires batch testing, the agency permits a variety of testing methods to be used, and does not demand the particular method recited by Momenta's claims. Regardless, the activities Amphastar carried out to satisfy FDA requirements were exempt under the safe harbor.[21]

Momenta therefore expanded the scope of 35 U.S.C. § 271(e)(1) to reach methods that *could* be used to develop information relevant to FDA submissions or requirements. What about methods and tools at the other end of the drug development spectrum that do not generate information directly related to regulatory approval? The U.S. Solicitor General has expressed doubt, stating that ''it is unclear'' whether the provision applies to patented research methods.[22] Although the statutory language ''on its face encompasses '*any* patented invention,' '' the Solicitor General cited *Merck*, noting that the Supreme Court specifically reserved the question of whether the exemption was ''intended to shield drug makers from claims of infringement concerning patented research tools,'' which are, themselves, employed to generate useful information.[23]

Uncertainty for Biotechnology Patent Holders

Together, *Merck* and *Momenta* create some uncertainty for patent holders in the biotechnology space, and district courts face the formidable prospect of navigating what oftentimes are fine distinctions.

Before *Momenta*, for example, a court in the Northern District of Illinois, in *PSN Illinois, LLC v. Abbott Labs.*,[24] addressed a dispute between Abbott Laboratories and a patent holder with claims on cloning and expressing certain G-protein coupled receptors. Abbott had used the claimed inventions, including primers and cell lines, as tools to identify potential drug candidates.[25] Although Abbott did not commercialize any of the drugs, it had submitted data regarding the candidates to the FDA. Concluding that the safe harbor does not apply to patented inventions that are not, themselves, subject to regulatory approval,[26] the court concluded that the safe harbor did not shield Abbott from liability since the ''patented invention'' that Abbott used only covered the research tools used to identify drug candidates.[27]

A court in the Southern District of California considered whether the safe harbor applied in a case involving antisense technology and methods of inhibiting the expression of genes implicated in the development of certain cancers.[28]

Patentee Isis Pharmaceuticals accused Santaris Pharma's drug development platform that is used for developing RNA-targeted therapies. Santaris filed for summary judgment on the basis that its activities were protected by the Section 271(e)(1) safe harbor. Santaris argued that its antisense technology is used only after a therapeutic target has already been identified to generate a library of candidates tailored to that particular target. If its pharmaceutical partner wishes to obtain FDA approval for any of the drug candidates, then the data Santaris generated in the design and development process is available for submission.[29]

The district court found that the record was insufficient to determine whether *all* of Santaris' activities could be exempt under the safe harbor. Relying on the Federal Circuit's opinion on remand in *Integra*, the district court in *Santaris* noted that ''the variety of experimental activity that may apply to any specific biologic or physiologic investigation reinforces the fact-dependency of the inquiry.''[30] The court found that a fact dispute existed as to when the accused infringing platform was used: once a therapeutic target was identified or at other times in the discovery process.

Last December, Santaris again moved for summary judgment of noninfringement based on the safe harbor provision.[31] Isis' allegations include infringement based on Santaris' offering its antisense technology for sale, evident in publicly-announced agreements with Pfizer, Enzon Pharmaceuticals, Shire and GlaxoSmithKline.[32] Santaris argued that its activities are within the safe harbor because the terms of the agreements require one or both parties to design and develop drugs, and to generate data that will be used to support FDA approval of promising drugs.[33] Isis disagreed, arguing that disputes of material fact existed as to whether the collaboration agreements were, at the time of execution, ''reasonably related'' to the type of information that is submitted to the FDA.[34] Isis also argued that its invention is not a ''patented invention'' within the meaning of Section 271(e)(1).

The district court agreed with Isis, relying on language in *Integra* to distinguish between exempt uses of an invention and basic scientific research. The court focused on the preliminary nature of the experiments

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[20] *Momenta*, 686 F.3d at 1353.

[21] *Momenta*, 686 F.3d at 1357.

[22] *GlaxoSmithKline v. Classen Immunotherapies, Inc.,* No. 11-1078, Brief for the United States as Amicus Curiae (Dec. 13, 2012) at 10, 19, 21. Although the Supreme Court declined requests for certiorari in *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.*, 133 S. Ct. 2854 (2013) and *GlaxoSmithKline v. Classen Immunotherapies, Inc.*, 133 S. Ct. 973 (2013), it allowed amicus briefing by the Solicitor General.

[23] *GlaxoSmithKline v. Classen Immunotherapies, Inc.,* No. 11-1078, Brief for the United States as Amicus Curiae (Dec. 13, 2012) at 21 (citing *Integra*, 545 U.S. at 205 n.7).

[24] *PSN Illinois, LLC v. Abbott Labs.*, No. 09-cv-5879, 2011 U.S. Dist. LEXIS 108055 (N.D. Ill. Sept. 20, 2011)

[25] *PSN Illinois, LLC*, 2011 U.S. Dist. LEXIS 108055 at *3-6.

[26] *PSN Illinois, LLC*, 2011 U.S. Dist. LEXIS 108055 at *15-18.

[27] *PSN Illinois, LLC*, 2011 U.S. Dist. LEXIS 108055 at *18. PSN and Abbott settled before the case was tried. *PSN Illinois, LLC v. Abbott Labs.*, No. 09-cv-5879 (D.I. 351).

[28] *Isis Pharmaceuticals, Inc. v. Santaris Pharma A/S Corp.*, No. 11-cv-02214, 2012 U.S. Dist. LEXIS 134107 (S.D. Cal. Sept. 18, 2012).

[29] *Isis Pharmaceuticals, Inc.*, 2012 U.S. Dist. LEXIS 134107 at *12.

[30] *Isis Pharmaceuticals, Inc.*, 2012 U.S. Dist. LEXIS 134107 at *13.

[31] *Isis Pharmaceuticals, Inc. v. Santaris Pharma A/S Corp.*, No. 11-cv-02214, 2014 U.S. Dist. LEXIS 26148 (S.D. Cal. Feb. 27, 2014) (''*Isis II*'').

[32] *Isis II*, 2014 U.S. Dist. LEXIS 26148 at **7-10.

[33] *Isis II*, 2014 U.S. Dist. LEXIS 26148 at **13-14.

[34] *Isis II*, 2014 U.S. Dist. LEXIS 26148 at *14.

contemplated by the agreements. At the time the agreements were executed, Santaris' partners had identified few—if any—of the targets that Santaris would later attempt to modify using its antisense platform. The compounds also were unknown, as the very purpose of the agreements was for Santaris to develop a library of compounds for each target. Thus, unlike the *Integra* case, Santaris had *no* knowledge whether any of the antisense compounds it would go on to develop would affect a particular biological process, or have a particular physiological effect.[35] Relying on *Proveris*, the court further found a factual dispute as to whether Isis's patented methods and compounds are themselves subject to FDA approval, so as to qualify for exemption under § 271(e)(1).[36]

In contrast to the decisions in *Isis* and *PSN*, a district court in the Southern District of New York has broadly interpreted ''patented invention'' in the context of Section 271(e)(1), concluding that it is *not* limited to inventions for which regulatory approval must be obtained.[37] In a case against Mylan and other defendants, Teva asserted patents relating to polypeptide markers that can be used to calibrate the chromatographic columns used to measure the molecular weight of the active ingredient in Copaxone.[38] Like the Optical Spray Analyzer device in *Proveris*, the polypeptide markers are not subject to regulatory approval, but instead, are used to generate data that then are submitted to the FDA.[39]

On defendants' motion, the court determined that the accused activities were within the safe harbor and dismissed the case.[40] In reaching its conclusion, the district court noted ''striking similarities'' with *Momenta* and determined that the ''elective use'' of patented technology is exempt from infringement, so long as it ''serves to produce information required under a federal law.''[41] The court also supported its conclusion by citing to *Merck*, under which ''the safe harbor provides a wide berth for the use of patented products in activities related to the federal regulatory process.''[42]

Rejecting Teva's arguments, the court held that the Federal Circuit's decision in *Proveris* did not dictate a different result. Unlike the case before it, the court characterized the accused infringers in *Proveris* as engaging in ''blatant commercial use'' of the asserted claims, and were not, themselves, ''engaged in development and submission of information'' to the FDA.[43] In the court's view, the issue in *Proveris* was not simply whether the ''patented invention'' was subject to regulatory approval, but whether the party using the invention was the same party that was gathering information for the purposes of submission.

Conclusion

Going forward, a patent holder with claims reading on research methods or tools will want to take care to articulate infringement theories directed to the accused infringer's earliest uses of the invention. Under *Integra*, the safe harbor exemption should not apply to the early stages of discovery and development, before the accused infringer has identified a particular compound, or developed an understanding of how a compound may affect ''a particular biological process to produce a particular physiological effect.'' Patent holders also will want to be cognizant that some jurisdictions (but not others) have distinguished between inventions for which regulatory approval must be obtained, and those that are simply used as tools.

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[35] *Isis II*, 2014 U.S. Dist. LEXIS 26148 at *35.

[36] *Isis II*, 2014 U.S. Dist. LEXIS 26148 at **37-38.

[37] *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, No. 09-cv-10112, 2013 U.S. Dist. LEXIS 99121 (S.D.N.Y. July 15, 2013).

[38] *Teva Pharmaceuticals USA, Inc.*, 2013 U.S. Dist. LEXIS 99121 at *5-6. Copaxone consists of synthetic polypeptides that are injected to modulate the immune response in patients with Multiple Sclerosis. Daily Med, *Copaxone (glatiramer acetate)injection* (http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=837).

[39] *Teva Pharmaceuticals USA, Inc.*, 2013 U.S. Dist. LEXIS 99121 at *5-6.

[40] *Teva Pharmaceuticals USA, Inc.*, 2013 U.S. Dist. LEXIS 99121 at *26.

[41] *Teva Pharmaceuticals USA, Inc.*, 2013 U.S. Dist. LEXIS 99121 at *19.

[42] *Teva Pharmaceuticals USA, Inc.*, 2013 U.S. Dist. LEXIS 99121 at *26.

[43] *Teva Pharmaceuticals USA, Inc.*, 2013 U.S. Dist. LEXIS 99121 at *23.

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