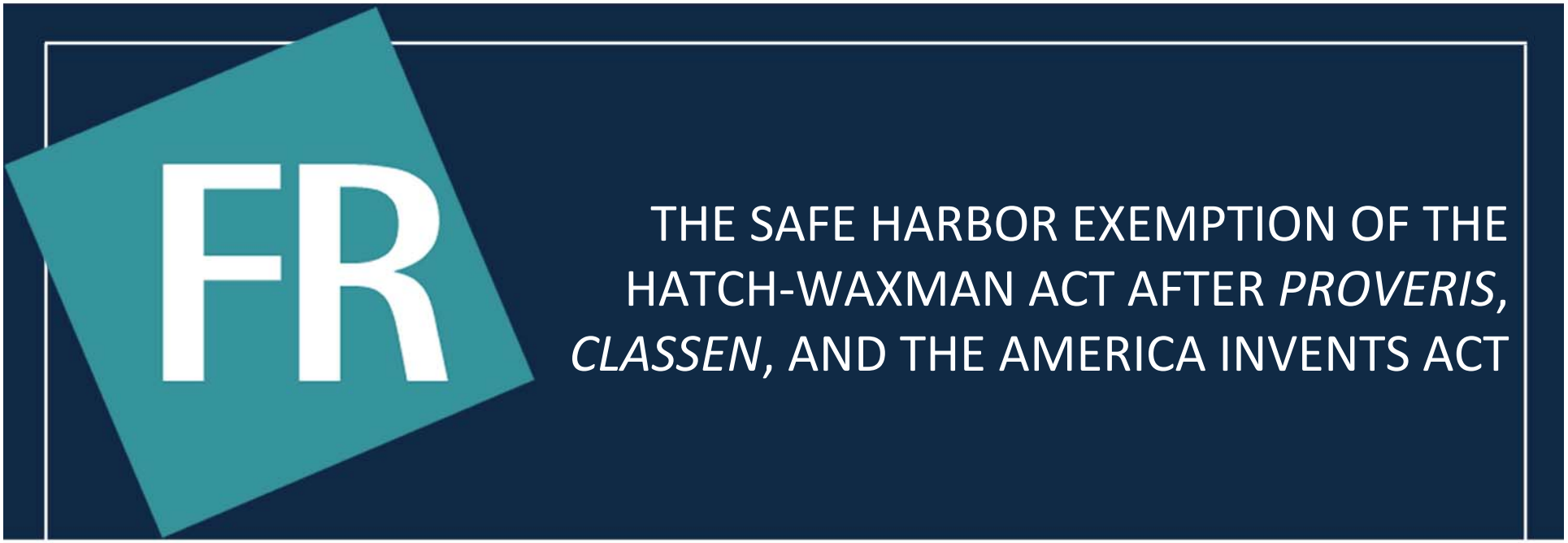
NEW JERSEY INTELLECTUAL PROPERTY LAW ASSOCIATION
25TH ANNUAL PHARMACEUTICAL/CHEMICAL UPDATE



THE SAFE HARBOR EXEMPTION OF THE HATCH-WAXMAN ACT AFTER *PROVERIS*, *CLASSEN*, AND THE AMERICA INVENTS ACT

BRIAN D. COGGIO
SENIOR PRINCIPAL

December 7, 2011

FISH & RICHARDSON

PATENT INFRINGEMENT

Title 35, U.S.C § 271(a) reads:

[W]hoever without authority **makes, uses, offers to sell**, or **sells** any **patented invention**, within the United States or **imports** into the United
States any patented invention during the term of the patent therefore, infringes the patent.

Title 35, U.S.C. § 271(e) (1) 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.

SAFE HARBOR PROVISION

Purpose of the section was to permit "limited amount of testing" so generic companies could establish bioequivalence. Thus, the nature of the interference with the rights of a patentee is "not substantial." (legislative history).

The term "patented invention" is used consistently in § 271(a) and in § 271(e)(1).

EU has so-called *Bolar* exemption, which differs from country-to-country. Does not include research tool patents. All countries (not the U.S.) have general research exemption.

PATENT TERM RESTORATION

35 U.S.C. § 156(a), part of the Hatch-Waxman Act, allows an extension of the patent term to compensate the patentee for the time (or at least a portion of it) that the product, *e.g.,* the FDA "approved product," was subject to regulatory review before commercial marketing or use was authorized.

Unlike § 271(e) (1), which covers "**patented inventions**," § 156(a) only covers product patents (including all types of medical devices), patents covering the use of an approved product, or patented methods for manufacturing an approved product. This distinction between § 271(e)(1) and § 156(a) played a significant role in the *Proveris* decision on research tools.

INTERPRETATION OF THE SAFE HARBOR

In *Merck KGaA v. Integra Life Sciences*, 545 U.S. 193 (2005), *vacated*, 331 F.3d 860 (Fed. Cir. 2003), *remanded*, 496 F.3d 1334 (Fed. Cir. 2007), the Supreme Court stated:

> [W]e think it apparent from the statutory text that § 271(e)(1)'s exemption from infringement extends to ***all*** uses of patented inventions that are reasonably related to the development and submission of ***any*** information to the [FDA]. This necessarily includes preclinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process.

545 U.S. at 203 (emphasis on "any" in original).

INTERPRETATION OF THE SAFE HARBOR

As to the "reasonably related" requirement, the Supreme Court stated:

> 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 the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is "reasonably related" to the "development and submission of information [to the FDA]." 545 U.S. at 207 (emphasis added).

Knowledge of “particular biological process” is not required. Also, an actual FDA submission is not required.

INTERPRETATION OF THE SAFE HARBOR

[The exemption] necessarily includes **preclinical** studies of patented compounds that are appropriate for submission to the FDA in the regulatory process. 545 U.S. at 202.

* * *

[T]he FDA requires that applicants include in an IND summaries of the pharmacological, toxicological, **pharmacokinetic, and biological qualities of the drug** in animals. . . . The primary (and, in some cases, only) way in which a drugmaker may obtain such information is through preclinical **in vitro** and **in vivo** studies. *Id*. at 203.

Potentially exempt uses (14 uses) are itemized by the Federal Circuit in the *Merck* decision on remand. All were found protected by the safe harbor.

EXPERIMENTAL USE: *CLASSEN v. BIOGEN*

In *Roche Prods. Inc. v. Bolar Pharmaceuticals Co.,* 733 F.2d 858 (Fed. Cir. 1984), the Federal Circuit held that the use of a patented drug for tests ***prior*** to patent expiration to obtain FDA approval to market a generic substitute was infringement and not an experimental use.

The experimental use defense to a charge of patent infringement is "very narrow" and "strictly limited." *Madey v. Duke University*, 307 F.2d 1351, 1361-62 (Fed. Cir. 2002).

"[U]se does not qualify for the experimental use defense when it … has definite, cognizable, and not insubstantial commercial purposes." *Id.* at 1362. The "use is disqualified … if it has the slightest commercial complication" or if it is "in keeping with the legitimate business of the alleged infringer." *Id. See also Monsanto Co. v. E.I. Dupont de Nemours & Co.*, 2010 U.S. Dist. LEXIS 77877, * 32 - *35 (E.D. Mo. 2010) (genetically-modified soybean and corn seed products).

EXPERIMENTAL USE: *CLASSEN v. BIOGEN*

In *Classen Immunotherapies, Inc. v. Biogen Idec,* 659 F.3d 1057 (Fed. Cir. 2011), the Federal Circuit discussed the scope of the experimental use defense.

[T]he subject matter of patents may be investigated and verified and elaborated; the [patent's] technological/scientific contribution to knowledge is not insulated from analysis, study and experimentation [until the patent expires].

* * *

Such use of the information in the patent is not a violation of the patent, whereas "the making of a machine for use, with a design to use it for profit, was an infringement of the patent right." (citation omitted).

In general, the alleged infringing conduct related to reporting vaccine relationships to the FDA.

TIMING OF SAFE HARBOR PROTECTION: *CLASSEN v. BIOGEN*

The safe harbor is "limited" to pre-approval activities, *i.e.,* conduct directly relevant to obtaining FDA approval. In *Classen v. Biogen,* the Federal Circuit stated:

The statute does not apply to information that may be ***routinely*** reported to the FDA, long after marketing approval has been
obtained. (emphasis added).

If defendants had been required to conduct post-approval studies and report the results to the FDA, the conduct may have been protected. *See* dissenting opinion of Judge Moore, where she states that § 271(e)(1) is not limited to the pre-approval process. *See also Wesley Jessen Corp. v. Bauch & Lomb, Inc.* 235 F. Supp. 2d 371 (D. Del. 2002) (post-approval testing required by FDA was within the safe harbor).

Research conducted after an FDA submission will be examined carefully to ascertain if it relates to "marketing" or changes to an NDA/BLA. *Amgen, Inc. v. ITC,* 519 F.3d 1343, 1349-50 (Fed. Cir. 2008).

PRIOR USE DEFENSE: 35 U.S.C. § 273

The burden of proof by clear and convincing evidence is on the party asserting the defense.

A person shall be entitled to a defense under § 282(b) with respect to subject matter consisting of a process, or consisting of a machine, manufacture, or composition of matter used in a manufacturing or other commercial process that would otherwise infringe a claimed invention….

Defendant must have acted in good faith and commercially used the subject matter in the United States.

The commercial use by defendant must have occurred at least 1 year before the earlier of: (A) the effective filing date of the claimed invention, or (B) the date when the invention was disclosed to the public in a manner that qualified for an exception from prior art under § 102(b).

PRIOR USE DEFENSE: 35 U.S.C. § 273

Prior use must not have been derived from the patentee.

Prior use is domestic in scope and is limited to the product-specific use giving rise to the defense.

Preliminary regulatory review is a prior use such that pharmaceutical company having a product in premarket regulatory review may rely on such activity to establish a defense.

Use by non-profit lab qualifies as a prior use, but defense may be asserted only for continued and non-commercial use by and in the laboratory.

Prior use defense is personal and can be asserted only by person who performed, directed or controlled or is controlled by or under common control of the person relying on the defense.

PRIOR USE DEFENSE: 35 U.S.C. § 273

Only if entire business to which the defense relates is transferred to another entity can the defense be asserted.

University Exception –

Person cannot assert defense if the claimed invention was made, owned or subject to assignment to an institution of higher education or technology transfer organization.

The above exception does not apply if any of the activities required to reduce the claimed invention to practice were undertaken using funds provided by the Federal Government.

For a frivolous assertion of this defense, "court **shall** find the case exceptional…"

Applies to all patents granted from September 16, 2011.

RESEARCH TOOL PATENTS

In the original *Merck v. Integra* decision, Judge Rader opined:

> [E]xpansion of § 271(e)(1) to include the Scripps Merck activities would effectively vitiate the exclusive rights of patentees owning **biotechnology tool patents** …. Thus, exaggerating § 271(e)(1) out of context would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions. **Needless to say, the 1984 Act was meant … not to deprive entire categories of inventions of patent protection.** 331 F.3d at 867.

An assay is a representative example of a research tool.

RESEARCH TOOL PATENTS

Judge Rader concluded:

> According to the [NIH], **research tools** are defined to be "tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines." [NIH Guidelines]. The dissent asserts that Integra's patented RGD peptides are not research tools, but simply new compositions having certain uses…. **The dissent does not explain why one of those "certain uses" cannot embrace use of an RGD peptide as a laboratory tool to facilitate the identification of a new therapeutic.** *Id*. at 872 n.4.
>
> The "use" of a patented invention is a factor in determining if the patent is a research tool patent.

RESEARCH TOOL PATENTS

In *Merck v. Integra*, Judge Rader, on remand, opined:

> [T]he '734 patent covers a purified cell receptor, in the words of the patent, the '734 patent is "[a] method of isolating cell surface receptors utilizing a short peptide sequence bound to an affinity column." … Purified cell receptors operate in a laboratory to determine compounds that will bind to it **(and thus may be useful as drugs).** Many pharmaceutical drugs work by binding to receptors on the surface of certain human cells. Therefore, a laboratory needs methods to study the binding process and to choose drug candidates. **These purified cell receptors do not operate as "patented compounds" for FDA approval themselves, but rather as experimental targets to test for attachment characteristics ….** As such, this method of isolating cell surface receptors is only a tool to ***conduct research on biological and chemical systems***. *Id.* at 1351.

PROVERIS SCIENTIFIC CORP. v. INNOVASYSTEMS, INC., 536 F.3d 1256 (Fed. Cir. 2008)

Patent covered system and apparatus for characterizing aerosol sprays used in testing drug delivery systems. The apparatus was not subject to FDA approval. Innovasystems sold patented instruments to three companies for the sole use of gathering information for FDA submission. District court found safe harbor did not apply.

Proveris argued that safe harbor does not apply to research tool patents because: (1) such patents can not be extended under § 156(a), and (2) Innovasystems did not itself gather the data for FDA submission and, therefore, § 271(e)(1) does not apply.

Innovasystems argued that: (1) § 271(e)(1) applies to all "patented inventions" without limitation, and (2) "sales" from third parties (*e.g.,* Innovasystems) are contemplated because "sales" are specifically exempted in the statute. Thus, the safe harbor exemption is not limited to the organizations that themselves gather data for FDA submission.

The second issue was never decided.

PROVERIS v. INNOVASYSTEMS

Discussing *Eli Lilly*, the Federal Circuit states that interpreting the phrase "patented invention" in § 271(e)(1) to include all products in § 156(f) (patent term extension) produced a "perfect fit" between the two sections. 536 F.3d at 1262. But *Lilly* was not discussing the term "patented inventions," but the term "drugs." Moreover, in *Abtox v. Exitron*, 122 F.3d 1019 (Fed. Cir. 1997), the Federal Circuit held that Class II medical devices – not subject to patent term extension – were still within "patented invention" of § 271(e)(1). Therefore, all medical devices are covered. So not a "perfect fit."

Also, in *Lilly*, the Supreme Court indicated that the phrase "patented invention" in § 271(e)(1) covered all inventions. *See also Chartex v. MD Personal Prod. Corp.*, 5 F.3d 1505 (Fed. Cir. 1993) (Court will not read limitations from § 156(a) into § 271(e)(1)). But it did!

PROVERIS v. INNOVASYSTEMS

Two distortions corrected by the Hatch-Waxman Act: First distortion deals with reduction of patent life caused by FDA premarket approval. Second deals with *de facto* extension of effective patent life at the end of the term. Accordingly, the Federal Circuit, second distortion is "relevant" to case.

> Innova's OSA device is not subject to FDA premarket approval…. In short, Innova is not a party seeking FDA approval for a product in order to enter the market to compete with patentees. **Because the OSA device is not subject to FDA premarket approval, and therefore faces no regulatory barriers to market entry before patent expiration, Innova is not a party who, prior to the enactment of the Hatch-Waxman Act, could be said to have been adversely affected by [the distortion rectified by § 271(e)(1)]**… Put another way, insofar as its OSA device is concerned, Innova is not within the category of entities for whom the safe harbor provision was designed to provide relief. *Id*. at 1265.

The alleged infringing device must be subject to FDA pre-market approval. *In Proveris*, product was not, and therefore no delay before marketing. *Contra Monsanto Co. v. E. I. Du Pont De* Nemours & *Co., supra* at *31-32 (pre-market approval not required for § 271(e)(1) to apply).

PROVERIS v. INNOVASYSTEMS

As to the other distortion – Proveris is not a patentee who would have been affected by a loss in its patent life because its patent was not subject to FDA premarket approval process. *Id.* at 1265-66. Thus, Proveris is not a party who, prior to Hatch-Waxman Act, would have been adversely affected by the this distortion. Citing *Eli Lilly*, the Federal Circuit held that the Proveris patent was not subject to an extension under § 156(a) and therefore is not a "patented invention" under §271(e)(1). No delay in FDA approval to patentee.

The patent-at-issue must be subject to an extension under § 156(a).

Do both prongs ("distortions") need to be satisfied before the safe harbor applies?

HYPOTHETICAL: USE OF A MONOCLONAL ANTIBODY AS A TOOL

Antibodies are subject to pre-marketing approval if used as a therapeutic.

Would the use of a patented antibody in a pre-clinical test for some other drug be within the safe harbor? **It is being used as a research tool.**

But patent is the type of patent that is extendable **AND**, if someone developed antibody as a drug, FDA pre-market approval would be necessary. So both, prongs are theoretically satisfied. Safe harbor?

What about patents with two sets of claims – one "product oriented" and one "tool oriented"? Safe harbor? Arguments both ways. Since no FDA approval is needed for its "tool" use, possibly no safe harbor exemption in view of Rader's comments. But the patent is, at least hypothetically, a "patented invention" within § 271(e)(1) because it is extendable under § 156(a). But only limited protection afforded by patent is extendable.

ANTIBODIES

Immunization of animals with antigen X to generate antibodies.

Anti-X antibodies, because of this technology, will be generated, each of which "may" have the desired properties to a greater or lesser extent. The researcher therefore has "a reasonable basis for believing" that **each** antibody may work. *Merck*, 545 U.S. at 203. Accordingly, safe harbor protection is quite possible.

Further research is permissible:

> Even at late stages in the development of a new drug, scientific testing is a process of trial and error…. Properly construed, § 271(e)(1) leaves adequate space for experimentation and failure in the road to regulatory approval. *Merck,* 545 U.S. at 206-07.

The selection of the final antibody candidate is similar to "the selection of a suitable species from a patented genus [which] is apparently the situation which the Supreme Court placed within the § 271(e)(1) exemption." *Merck*, 496 F.3d at 1352 (Rader, J., concurring in part/dissenting in part).

Thank You!

Brian D. Coggio
Coggio@fr.com
(212) 641-2336