



Patent Infringement or Smooth Research Sailing?

*A look at § 271(e)(1) Infringement
Safe Harbor in light of recent court decisions*

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Jeffrey I. D. Lewis
Cecilia Copperman



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Speakers



Jeffrey Lewis

Partner, Registered Patent Attorney

New York
Foley Hoag

212.812.0304
jjdLewis@foleyhoag.com

- Former American Intellectual Property Law Association (AIPLA) President
- Former AIPPI-US President
- Current AIPPI worldwide Amicus chair
- NYIPLA Amicus Brief Committee



Cecilia Copperman

Associate

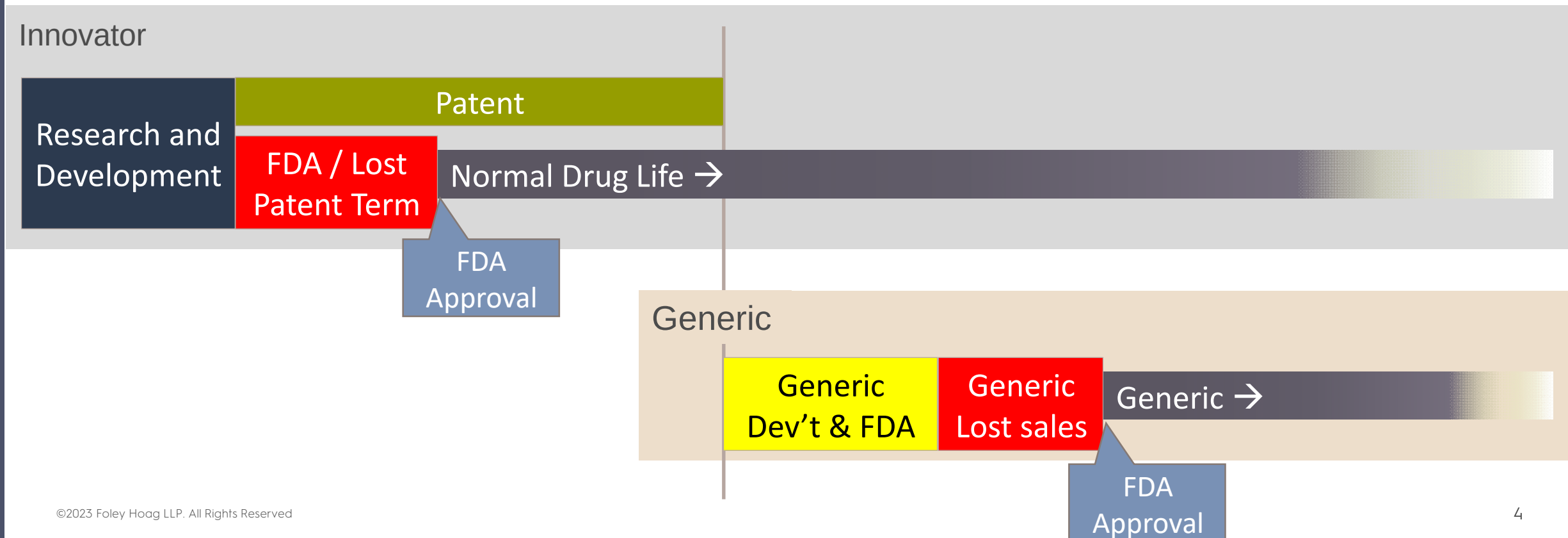
New York
Foley Hoag

212.812.0435
ccopperman@foleyhoag.com

- Patent litigation, trade secret and copyright associate
- Published author of PLOS One journal article and two Genetic Testing and Biomarker articles

Before Hatch-Waxman/ANDA

- Drug Amendments of 1962 substantially increased time required for development and approval of a pioneer new drug.
 - Approval of equivalent to approved drug → at least two years



Roche Prods. v. Bolar Pharm. Co. 733 F.2d 858 (Fed. Cir. 1984)

- Bolar began efforts **prior to patent expiration**
 - Patent covered brand drug active ingredient.
- Roche sued for infringement
 - Granted TRO after discovery began.
 - Bolar admitted it intended to immediately begin testing for FDA approval
- District court denied a permanent injunction
 - Bolar **did not infringe**.
 - Bolar's use of the patented compound = **experimental and *de minimis***
- Federal Circuit reversed: **Bolar infringed Roche's patent.**

Roche v. Bolar: Limited Experimental Use Exception

- Experimental use exception is “truly narrow”
 - Tests, demonstrations, and experiments that are consistent with legitimate business of accused infringer are not covered by exception.
- **No new exception** to allow FDA required drug testing
 - **Bolar’s Argument**: FDA increased time for approval.
 Patent terms *effectively extended* by preventing generics from taking steps towards FDA approval until patent expires.

Generic
Lost sales

➔

Extra Patent
Term
 - “Simply because a later enacted statute affects in some way an earlier enacted statute is poor reason to ask us to rewrite the earlier statute. Repeals by implication are not favored.”
 - “Where Congress has the clear power to enact legislation, our role is only to interpret and apply that legislation. It is not our job to apply laws that have not yet been written.” (internal quotations omitted)

Hatch-Waxman Act's *Two* Goals

Hatch-Waxman Act was designed to **respond to two regulatory (FDA) “distortions”**:

- **Reduced** effective **patent life** caused by the **FDA premarket approval process**; and
- **Generic** manufacturer **cannot begin** FDA related regulatory work during **patent term**

FDA / Lost
Patent Term

Generic Lost
sales

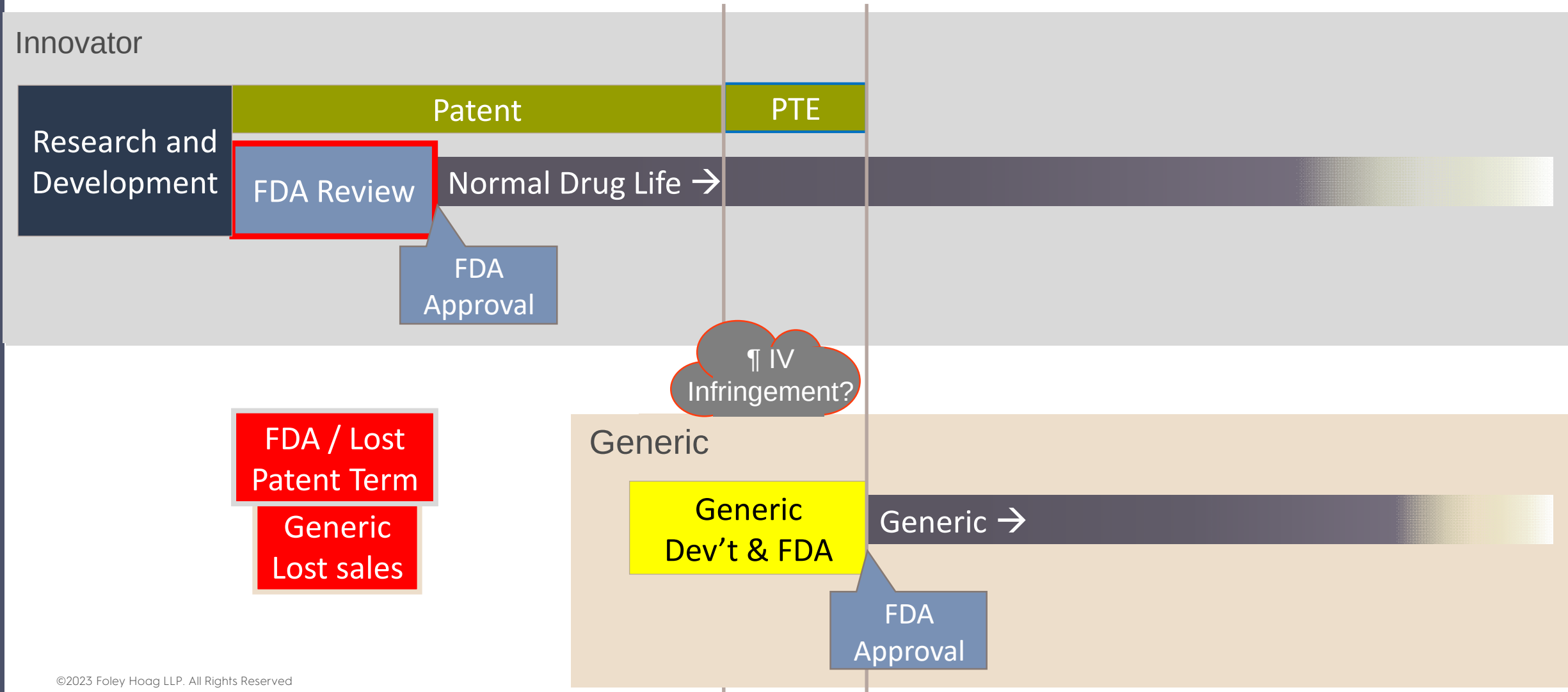
Drug Price Competition and Patent Term Restoration Act of 1984

Patent Term
Extensions

Safe Harbor
Protection

“New” Act of
Infringement

Effect of Hatch-Waxman/ANDA



Safe Harbor Protection

35 U.S.C. § 271(e)(1):

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*** (other than a new animal drug or veterinary biological product ... which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) 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.

Legislative History

“The information which can be developed under this provision is the type which is required to obtain approval of the drug. ...

The purpose ... is to establish that experimentation with a patented drug product, when the purpose is to prepare for commercial activity which will begin after a valid patent expires, is not a patent infringement..”

H.R. Rep. No. 98-857(I), at 15, 45 (1984), *reprinted* 1984 U.S.C.C.A.N. 2647, 2648 quoted in *Momenta Pharm., Inc. v. Teva Pharm. USA Inc.*, 809 F.3d 610 (Fed. Cir. 2015) (“*Momenta II*”).

Eli Lilly v. Medtronic

“... submission of information under a Federal law which regulates the manufacture, use, or sale of **drugs or veterinary biological products**.”

- Implantable Cardiac Defibrillators (Class III medical device)
- **HELD**:
 - Provisions for (i) **Patent Term Extensions (“PTE”)** and (ii) **Safe Harbor** “are meant generally to be complementary.”
 - PTE extends to:
 - A. “ingredient of a new drug, antibiotic drug, or human biological product,” and
 - B. “Any medical device, food additive, or color additive subject to regulation under the Federal Food, Drug, and Cosmetic Act.”

496 U.S. 661 (1990)

Safe Harbor Protection – *Eli Lilly*

35 U.S.C. § 271(e)(1):

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“The phrase ‘patented invention’ in § 271(e)(1) is defined to include all inventions, not drug-related inventions alone.” at 665

“...***petitioner*** interprets the statutory phrase, to refer only to those individual provisions of federal law that regulate drugs, whereas ***respondent*** interprets it to refer to the entirety of any Act ... at least some of whose provisions regulate drugs.” at 665-66 ✓

Eli Lilly – Not Literally

“... submission of information under a Federal law which regulates the manufacture, use, or sale of **drugs or veterinary biological products**.”

- “[T]here may be some *relatively rare situations* in which a **patentee will obtain the advantage of the [] extension but not suffer the disadvantage of the [] noninfringement [safe harbor] provision, and others in which he will suffer the disadvantage without the benefit.**” 496 U.S. at 671-72.

“No interpretation we have been able to imagine **can transform §271(e)(1) into an elegant piece of statutory draftsmanship**. To construe it as the Court of Appeals decided, one must posit a good deal of legislative imprecision; but to construe it as petitioner would, one must posit that and an implausible substantive intent as well.”

Scalia, J.:

“The text is the law, and it is the text that must be observed.”

Safe Harbor Protection

35 U.S.C. § 271(e)(1):

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 (other than a new animal drug or veterinary biological product ... which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques)*** 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.

“All of the products eligible for a patent term extension [] are subject to [Safe Harbor], since all of them ... are subject to premarket approval under various provisions of the FDCA And the products subject to premarket approval ... that are not made eligible for a patent term extension [] -- new animal drugs and veterinary biological products -- are excluded from [the Safe Harbor] as well.”

Eli Lilly v. Medtronic

Class II Medical Device – Safe Harbor?

- Class II Medical Device (sterilization apparatus)
 - No FDA approval Delays
 - Fed. Cir.: Broad reading of *Medtronic*:
 - SCOTUS did not distinguish between medical devices/classes
 - ALL medical devices subject to Safe Harbor
 - ◆ Statutory symmetry of “distortions” would indicate otherwise.
- Safe Harbor to **Class II** plasma sterilizer.



Class I: No unreasonable risks, minimal regulations/controls.

Class II: Potentially harmful; federal performance regulations (may be marketed without advance approval).

Class III: Potential unreasonable risk of illness or injury; possible use ← *Medtronic* supporting or sustaining human life or substantial importance preventing impairment.

AbTox Inc. v. Exitron Corp., 122 F.3d 1019, 1029-30 (Fed. Cir. 1997)

Class I Medical Device – Safe Harbor?

- Optical Spray Analyzer (inhaler testing);
not “Medical Device”
- Device **used for FDA submissions** but ***not subject to FDA approval*** so ***not a Safe Harbor “patented invention”***
 - “[Defendant’s] OSA device ... face[d] **no regulatory barriers** to market entry upon patent expiration.”
 - Proveris is **not a patentee who would have been faced with a reduction of effective patent life caused by the FDA approval process** ... [T]he invention ... is not subject to the premarket approval required by the FDCA.

No
Distortions

Proveris Sci. Corp. v. Innovasystems, Inc., 536 F.3d 1256 (Fed. Cir. 2008)



Class I: No unreasonable risks, minimal regulations/controls.

Class II: Potentially harmful; federal performance regulations (may be marketed without advance approval). ← *AbTox*

Class III: Potential unreasonable risk of illness or injury; possible use supporting or sustaining human life or substantial importance preventing impairment. ← *Medtronic*

Proveris (Class I) versus Abtox (Class II)

Proveris 536 F.3d at 1263:

In **Abtox**, “[f]aced with a tension between the Supreme Court’s broader holding in *Eli Lilly* that ‘patented invention’ means ‘all [PTE] inventions’... and the Court’s narrower focus on statutory symmetry between the two provisions, we adopted the broader holding that the phrase ‘patented invention’ of [the §271(e)(1) Safe Harbor] includes any medical device, regardless of its eligibility for patent term extension ...”

-  **Class I: No unreasonable risks, minimal regulations/controls.** ← *Proveris*
-  **Class II: Potentially harmful; federal performance regulations (may be marketed without advance approval).** ← *AbTox*
-  **Class III: Potential unreasonable risk of illness or injury; possible use supporting or sustaining human life or substantial importance preventing impairment.** ← *Medtronic*

Allele Biotech: Proveris versus Abtox

“**Abtox** was issued prior to **Proveris**. ... [T]he full sentence in *Abtox* reads: ‘the Supreme Court commands that statutory symmetry is preferable but not required.’ Moreover, *Abtox* appears to be distinguishable from *Proveris* and the present case.

Although the patented invention at issue in *Abtox* was not covered by section 156(f) because it was a Class II medical device, ... the patented invention in **Abtox** was **still subject to a FDA ‘abbreviated approval process.’**

In contrast, here, it is alleged that the patented invention is not ‘subject to review ...’ As such, the Court does not find Defendants’ reliance on *Abtox* persuasive.”

Allele Biotech. v. Pfizer, 2021 U.S. Dist. LEXIS 85347 (S.D. Cal. May 4, 2021)

Pending case: *Allele Biotech*.

- Fluorescent protein (**mNeonGreen**) = biological tag to test, research, develop vaccine
- Pfizer moved to dismiss under **Safe Harbor**:
 - **Accused acts** “were undertaken in order **to develop information for submission to the FDA** pursuant to federal law ...”
- Court denied motion to dismiss:
 - *Eli Lilly* describes Safe Harbor as including “all inventions” (496 U.S. at 665)
 - Fed. Cir. in *Proveris* and *Momenta* **explained not every “patented invention” is a Safe Harbor patented invention.** (**12-13)
 - *Abtox* (1) pre-*Proveris*; and (2) abbreviated FDA approval.
 - **mNeonGreen is not subject to FDA review.**

Pending Case: *Regenxbio Inc. v. Sarepta Therapeutics*

- Cultured host cells used to make/develop recombinant adeno-associated virus ("rAAV") gene therapy products.
 - **Gene therapy product requires FDA approval, but cultured host cells do not.**
- Sarepta moved to dismiss: Safe Harbor because uses solely related to future FDA Biologics License Application to the FDA
- Dist. Ct.: denied motion to dismiss
 - ***Proveris***: because “the patented product at issue is not subject to FDA premarket approval, it is not a ‘patented invention’ under the [Safe Harbor].”
 - rAAV requires FDA approval; **host cells do not**
 - Unapproved cells are not a Safe Harbor “patented invention.”
 - No “distortion” (effective patent life): Sarepta can use cells at patent expiration.

Regenxbio Inc. v. Sarepta Therapeutics, 2022 U.S. Dist. LEXIS 1945 (D. Del. Jan. 4, 2022)

PSN III., LLC v. Abbott Labs

- Molecular cloning / expression of G-protein coupled receptors in the SIP family.
 - **Abbott used the receptors to screen potential drug candidates.**
- Court denied summary judgment because not a 271(e)(1) “patented invention.”
 - Under *Proveris*, **receptors are not Safe Harbor “patented invention”** within the meaning of the statute **because do not require regulatory approval.**

“Defendants were **not infringing** on the ... **receptors** in order to obtain FDA approval to introduce a generic receptor **to compete in the marketplace when the patent on those receptors expired.** They were using a patented invention to develop their own patentable product.”
 - *Merck* does not stand for broad principal that “*any* use of a patented invention to gather information to submit to the FDA is protected.”

2011 U.S. Dist. LEXIS 108055 (N.D. Ill. 2011)

Safe Harbor “Patented Invention”– How Used?

35 U.S.C. § 271(e)(1):

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Section 271(e)(1) "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, 1070 (Fed. Cir. 2011).

Merck KGaA v. Integra Lifesciences I Ltd. – Background

- Merck **preclinical** work with two potential drug candidates; only one submitted to FDA.
- **Fed. Cir.**: Safe Harbor did not apply because the work was *not clinical testing to supply information to the FDA*, but only **general biomedical research to identify new compounds**.
- Integra argued Safe Harbor does *not* include “preclinical studies related to a drug’s efficacy, mechanism of action, pharmacokinetics, and pharmacology.”
- **Sup. Ct.**: accused **activity** was **protected by Safe Harbor**

545 U.S. 193 (2005)

Merck : Exemption “provides a wide berth”

- Applies to “**all uses of patented inventions** that are reasonably related to the development and **submission of any information under the FDCA**. This necessarily **includes preclinical studies of patent compounds** that are appropriate for submission the FDA regulatory process.”

“FDA requires that applicants include in an IND summaries of the **pharmacological, toxicological, pharmacokinetic and biological qualities** of the drug in animals ... Such information necessarily includes preclinical studies ...”

“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 research intends to induce, is surely **not ‘reasonably related to the development and submission of information’ to the FDA.**”

- “It does not follow ... that § 271(e)(1)'s exemption from infringement categorically *excludes* either (1) **experimentation on drugs** that are not ultimately the subject of an FDA submission or (2) ... experiments that are not ultimately submitted to the FDA. Under certain conditions, we think the exemption is sufficiently broad to protect the use of patented compounds in both situations.” (545 U.S. at 205-06.)

Merck KGaA v. Integra Lifesciences, 545 U.S. 193 (2005)

Merck: Info in INDs and NDAs

- “Congress **did not limit** §271(e)(1)’s safe harbor to the development of information for **inclusion in a submission to the FDA**; nor did it create an exemption applicable only to the research relevant to filing an **ANDA for approval of a generic drug**. Rather, **it exempted from infringement all uses of patent compounds** ‘reasonably related’ to the process of developing information for submission under *any* federal law regulating the manufacture, use, or distribution of drugs.” (citing *Eli Lilly*)
- “Properly construed, §271(e)(1) leaves adequate space for experimentation and failure on the road to regulatory approval: 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’ ...”
- “We thus agree with the [amicus brief by the] Government that the use of patented compounds in preclinical studies is protected under §271(e)(1) **as long as there is a reasonable basis for believing that the experiments will produce ‘the types of information that are relevant to an IND or NDA.’**”

Changing Momentum: *Momenta I*

Momenta I

- Method patent directed to a set of manufacturing control processes that ensure that each product batch meets quality standards.
- District Court: Preliminary Injunction
- Fed. Cir. reversed preliminary injunction.
 - **Activity protected under Safe Harbor** because **required to maintain FDA approval** and not routine.
 - Remanded to district court.

Momenta Pharm., Inc. v. Amphastar Pharm., Inc., 686 F.3d 1348 (Fed. Cir. 2012) (“*Momenta I*”)

Momenta II

- Dist. Ct.: Summary Judgment of Non-Infringement
- Fed. Cir.: Reversed; held **not exempt under Safe Harbor**:
 - Have “the **benefit of additional briefing** in the current appeals, which reflects the **full district court record** developed by all parties after the preliminary injunction phase.”
 - Batch info generated routinely (i.e., habitually, regularly, and repeatedly); recorded and retained per regulations.
 - Contrast with non-routine submissions that may occur both pre- and post-approval, such as the submission of investigational new drug applications ("INDs"), new drug applications ("NDAs"), supplemental NDAs, or other post-approval research results.
 - **Not “reasonably related** to development and submission of information” to FDA.

How Was Claimed Invention Used?

Nevro Corp.:

“The use of the [accused] systems in patients that have participated in the [clinical] trial **fits within the safe harbor provision** of 35 U.S.C. § 271(e), **even after the patients have completed their participation in the trial.** ... The FDA specifically approved a trial plan that allowed participants to continue to receive treatment after results were collected. And international standards for medical research require trial sponsors allow participants to access studied treatments even after the trial's conclusion. ... ”

Nevro Corp. v. Boston Sci. Corp., 2018 U.S. Dist. LEXIS 220403 at *13 (N.D. Cal. 2018)(citations omitted)

Edwards Lifesciences:

Importing systems protected under **Safe Harbor** for

- (i) **display** at medical conference **recruiting** doctors for **clinical study** even if devices not actually used, and
- (ii) **pre-clinical studies** even if data not ultimately submitted to FDA.

Ultimate commercial purpose not test – look at objective acts

Edwards Lifesciences Corp. v. Meril Life Scis. Pvt., 2020 U.S. Dist. LEXIS 192337 (N.D. Cal. 2020)

How Used: *Amgen Inc. v. Hospira*

- Methods of manufacture can be considered patented inventions.
- Jury:
 - 7 of 21 Accused drug substance batches entitled to **Safe Harbor**.
 - ◆ 2 = qualifying process to make the drug and alternate equipment
 - ◆ 5 = mandatory pre-approval inspection by the FDA.
 - 14 of 21 batches infringe
 - ◆ Testing (biosimilarity, stability, process verification, etc.).
 - Expert: manufacture not necessary for FDA approval.
 - Expert: stability tests “not required”; for post-approval commitment.
 - Documents: Hospira’s materials to serve as commercial inventory.
- Affirmed:
 - *Merely* submitting to FDA does NOT equal the Safe Harbor. (n.3, citing *Momenta*)

Jury:

Factual
questions

Burden of
proof

Were acts
“... solely
for uses
reasonably
related ...”?

Amgen Inc. v. Hospira, 944 F.3d 1327 (Fed. Cir. 2019)