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Setting Sail for Safe Harbor:

Is the use of “research tools” eligible for Safe Harbor protection under 35 U.S.C. § 271(e)(1)?

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Outline

- What are “research tools”?
- General background of § 271(e)(1)
- Established case law
- Recent cases
- Points for discussion

What are "research tools"?

- Short answer: tools or techniques that scientists use in the laboratory
- Long answer: research tools "encompass [the] full range of 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 definition of research tools)

https://sharing.nih.gov/other-sharing-policies/research-tools-policy

What are "research tools"?

- To determine whether a resource is a research tool in the context of the NIH Research Tools Policy, funding recipients should consider whether:
  - The resource is primarily a tool for discovery rather than an FDA-approved product or an integral component of such a product;
  - The resource is a broad, enabling invention that will be useful to many other users, rather than a project or product-specific resource; and
  - The resource is readily useable or distributable as a tool, as opposed to an instance where private sector involvement is either a necessary means or the most expedient means for developing or distributing the resource.

https://sharing.nih.gov/other-sharing-policies/research-tools-policy

General Background

- In *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984), the court found that Bolar infringed when it used Roche's patented drug compound prior to expiration of the Roche's patent on the compound, to prepare FDA submission to enable Bolar to market its own version of the drug after the Roche patent expired

- This decision delayed Bolar's introduction and allowed the Roche to maintain market exclusivity long after patent expired due to FDA approval process for the generic

- This delayed the initial research and development, which leads to further delays in the process of entering the market (seeking FDA approval, etc.)

35 U.S.C. § 271(e)(1)

- (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 (…) 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.

Purpose of 35 U.S.C. § 271(e)(1)

- Referred to as a “safe harbor” provision
- Allows companies to perform research on patented drugs in advance of patent expiration so long as the experiments are “reasonably related” to securing regulatory approval
- Without the safe harbor provision, a patent holder would effectively obtain patent term extension because companies could not begin testing required for the FDA approval until expiration of the patent

General Background

- Competition is a good thing for the market because it can increase quality of products and keep prices lower
- In pharmaceuticals, the cost and risk to enter the market are higher
- Innovation between potential competitors seeking FDA regulatory approval must be incentivized and protected simultaneously

Established case law

1. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990)
2. *Merck KGaA v. Integra Lifesciences I, Ltd*., 545 U.S. 193 (2005)
3. *Proveris Sci. Corp. v. Innovasystems, Inc.*, 536 F.3d 1256 (Fed. Cir. 2008)

Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661 (1990)

- Eli Lilly filed an action against Medtronic claiming that Medtronic's testing and marketing of an implantable cardiac defibrillator (*i.e.*, a medical device) infringes its two related patents
- Medtronic argued that its activities were "reasonably related to the development and submission of information under" the Federal Food, Drug, and Cosmetic Act (FDCA), and thus exempt from a finding of infringement under 271(e)(1)

Holding

- § 271(e)(1) refers to the entirety of any Act, including the FDCA, at least some of whose provisions regulate drugs, rather than (as Eli Lilly contends) to only those individual provisions of federal law that regulate drugs.
- § 271(e)(1) supports Medtronic's interpretation
- Eli Lilly's interpretation of § 271(e)(1) would allow the patentee of a medical device or other FDCA-regulated nondrug product to obtain the advantage of § 201's patent-term extension without suffering the disadvantage of § 202's noninfringement provision

Holding

- What is a “patented invention”?
  - the phrase 'patented invention' in section 271(e)(1) includes all products listed in section 156(f) as producing a 'perfect "product" fit' between the two provisions
    - section 156(f) is related to patent-term extension for patents relating to certain products that were subject to lengthy regulatory delays and could not be marketed prior to regulatory approval, and listed the products eligible for extensions as including a drug products or any medical device, food additive, or color additive subject to regulation under the FDCA
  - A “patented invention” includes drugs, but also medical devices, food additives and color additives

- “In 1984, the Court of Appeals for the Federal Circuit decided that the manufacture, use, or sale of a patented invention during the term of the patent constituted an act of infringement, see *§ 271(a)*, even if it was for the sole purpose of conducting tests and developing information necessary to apply for regulatory approval. See *Roche Products, Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858*, cert. denied, *469 U.S. 856, 105 S. Ct. 183, 83 L. Ed. 2d 117 (1984)*.
- Since that activity could not be commenced by those who planned to compete with the patentee until expiration of the entire patent term, the patentee's de facto monopoly would continue for an often substantial period until regulatory approval was obtained. In other words, the combined effect of the patent law and the premarket regulatory approval requirement was to create an effective extension of the patent term.”

Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 669-70 (1990).

Scope of § 271(e)(1)

- § 271(e)(1) states, in part, "…solely for *uses reasonably related* to the development and submission of information under a Federal law.."
- What is the scope of "reasonably related"?
- Answered in *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005)
  - How far back in the drug development process the competitor can perform otherwise-infringing experiments without incurring liability for patent infringement?

Background of *Merck*

- Integra owns a series of patents related to peptides (“RGD peptides”)
- Scripps researchers found that some RGD peptides could be used to effectively block the cell receptor that controls blood vessel growth
- Some of the peptides were potentially valuable for the inhibition of solid tumor growth
- Merck entered into an agreement with Scripps to identify possible drug candidates.
- Led to the discovery of a promising cancer drug, RGD Peptide 121974
- Integra offered Merck a license to the RGD peptide patents, but negotiations failed
- Integra sued Merck for patent infringement
- Merck raised the affirmative defense that the experiments were protected under the safe harbor provision in § 271(e)(1)

At the CAFC…

- CAFC holding: Merck infringed Integra's patents and § 271(e)(1) did not exempt Merck from infringing the RGD peptide patents
- Reasoning: Merck's early work was preclinical and "only general biomedical research," particularly the development of a number of lead candidates simultaneously, only one of which was ultimately selected
- Merck's activities were not "reasonably related" to generating data for regulatory approval, and were not exempt from infringement liability

At the USSC…

- CAFC reversed

- " § 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 under the FDCA," (emphasis in original) and that "[t]his necessarily includes preclinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process."

- § 271(e)(1) applies to preclinical *in vitro* and *in vivo* studies intended to obtain information on the pharmacological, toxicological, pharmacokinetic, and biological qualities of the drug

What was not addressed by *Merck*?

- Application of the *Merck* holding to “research tool” patents
- “Research tools” are generally defined as devices, compounds, and methods that are used in drug development but are not themselves drugs
  - *E.g.*, devices such as protein synthesizers, cell surface receptors of disease pathways that will be used to identify antibodies or small molecule drugs, or particular methods of high throughput screening, etc.

What was not addressed by *Merck*?

- Does § 271(e)(1) immunize the manufacture, marketing, or sale of a device (*i.e.*, a research tool) used in the development of FDA submissions, but is not itself subject to the FDA approval process?
  - Answered by *Proveris Sci. Corp. v. Innovasystems, Inc.*, 536 F.3d 1256 (Fed. Cir. 2008)

Background on *Proveris*

- Proveris owned a patent directed to an apparatus for characterizing aerosol sprays used in various drug delivery devices (i.e., nasal spray pumps and inhalers; shown on right)
- Innova makes and sells a device known as Optical Spray Analyzer ("OSA“)
  - OSA itself is ***not*** subject to FDA approval, but is used in connection with FDA regulatory submissions for measuring physical parameters of aerosol sprays used in nasal spray drug delivery devices
- Proveris sued Innova for infringement

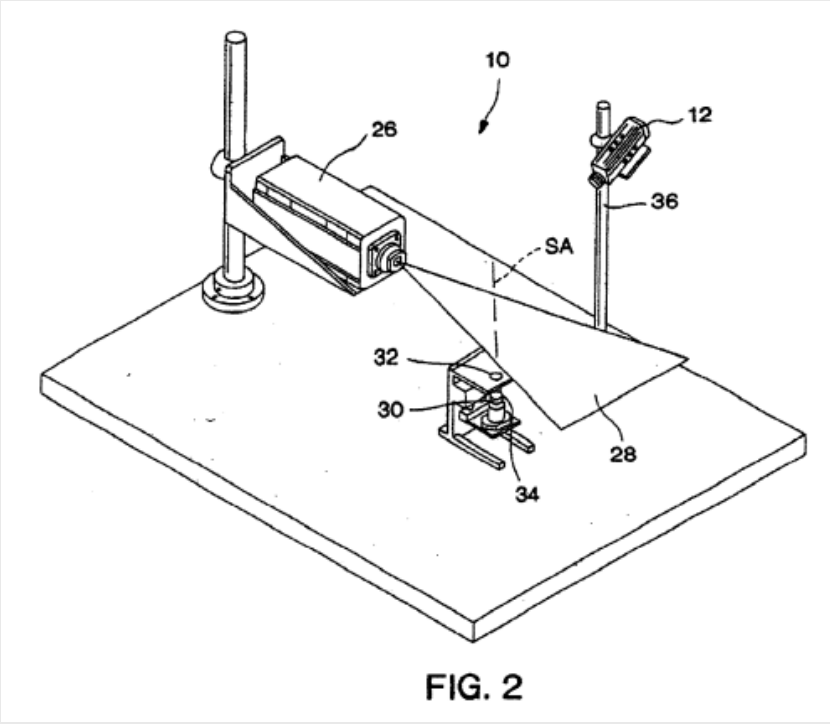


FIG. 2

Arguments

- Innova used the Safe Harbor affirmative defense and argued that safe harbor provision should not be limited to exclude research tools - assuming its OSA device is a research tool –based on *Merck*

- Proveris argued that the scope of § 271(e)(1) does not include patents on equipment that may be used in a pharmaceutical laboratory or for manufacturing, such as microscopes, analytical balances, and computers, therefore Innova's OSA device is not "reasonably related" to FDA submissions because Innova's infringement is not for purposes of its own FDA-related research, but rather for commercial sale to third parties engaged in such research

Holding

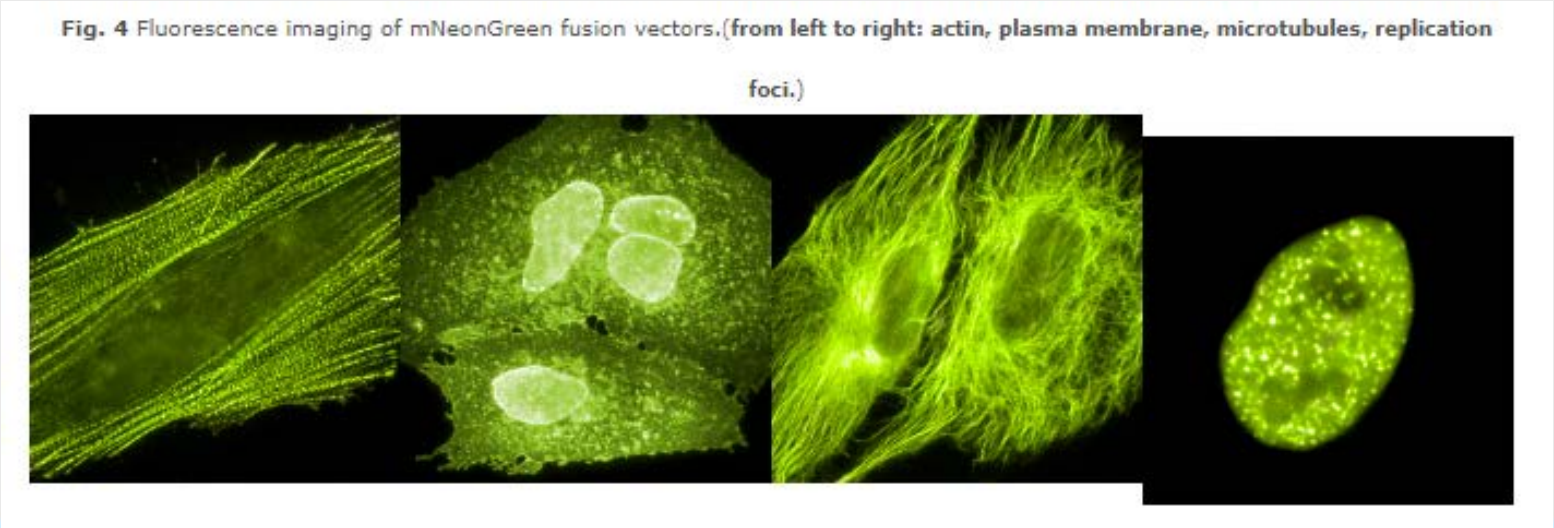
- Safe harbor provision does not apply because neither the patented product nor the accused product require FDA approval
  - Neither are the type of products Hatch-Waxman Act intended to protect

Recent decisions

1. *Allele Biotechnology & Pharm., Inc. v. Pfizer, Inc.* (S.D. Cal. May 4, 2021)
2. *Allele Biotechnology & Pharm., Inc. v. Regeneron Pharm., Inc.*, (S.D.N.Y 2020)
3. Regenxbio Inc. v. Sarepta Therapeutics, Inc. (D. Del. Jan. 4, 2022)

Allele Biotechnology & Pharm., Inc. v. Pfizer, Inc., No. 20-cv-01958-H-AGS, 2021 U.S. Dist. LEXIS 85347 (S.D. Cal. May 4, 2021)

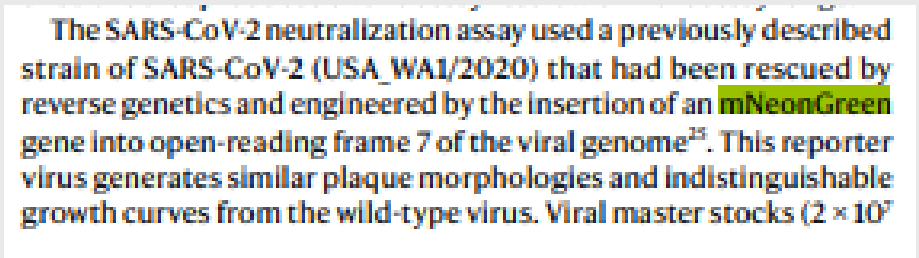
- Allele markets mNeonGreen as “a new high performance monomeric yellow-green fluorescent protein” and “is the brightest monomeric green or yellow fluorescent protein to date, and is an excellent fusion tag for traditional imaging as well as stochastic single-molecule super resolution imaging.”



https://reagents.allelebiotech.com/mneongreen-1/

Background

- mNeonGreen is covered by Allele's patent (US 10,221,221)
- use of mNeonGreen does not require FDA approval
- Pfizer and BioNTech analyze patient samples using an mNeonGreen neutralization assay to evaluate COVID-19 neutralizing antibody levels as mentioned in a Nature publication:



The SARS-CoV-2 neutralization assay used a previously described strain of SARS-CoV-2 (USA_WA1/2020) that had been rescued by reverse genetics and engineered by the insertion of an mNeonGreen gene into open-reading frame 7 of the viral genome[25]. This reporter virus generates similar plaque morphologies and indistinguishable growth curves from the wild-type virus. Viral master stocks (2×10^7

Mulligan, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adult, *Nature*, Vol. 586, August 12, 2020.

Background

- Neither Pfizer nor BioNTech are a licensee of Allele

- Allele sued Pfizer for infringement asserting that "*Defendants have used and continue to use mNeonGreen to research, develop, and test their SARS-CoV-2 vaccine candidates.*"

Arguments

- In their Motion to Dismiss, Pfizer asserted the affirmative defense that their allegedly infringing conduct is immune from patent infringement under section 271(e)(1) because their activities “were undertaken in order to develop information for submission to the FDA pursuant to federal law regulating the manufacture, use, or sale of drugs, and, thus, all of the infringement allegations are encompassed by the safe harbor provision in section 271(e)(1).”

Arguments

- Pfizer's argument that research tools are *not* exempted from the section 271(e)(1) safe harbor was based on *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990).

- Pfizer argued that in *Eli Lilly*, the Supreme Court explained that the term "patented invention" in section 271(e)(1) covers all inventions

Arguments

- Allele argued that Pfizer's MTD should be denied because:
  - (1) the safe harbor provision does not apply to "research tools" that are used in the development of FDA regulatory submissions, but are not themselves subject to FDA premarket approval based on *Proveris*; and
  - (2) even if it could apply, the determination of whether the infringement at issue is covered by the safe harbor provision is a "fact-sensitive inquiry inappropriate for resolution at the motion to dismiss stage"

MTD denied

- Here, the court disagreed with Pfizer's interpretation in view *Proveris*, where the CAFC held that the device claimed in the patent at issue was not a "patented invention" for purposes of section 271(e)(1) because it "was not subject to the premarket approval required by the FDCA."
- "Defendants have failed to demonstrate that the invention claimed in the '221 Patent is a "patented invention" for the purposes of section 271(e)(1)"

Current Status of Allele v. Pfizer

- Allele dismissed with prejudice in January 2022
- As of October 2022, neither Pfizer nor BioNTech are listed as active licensees of mNeonGreen (https://reagents.allelebiotech.com/fluorescent-protein-active-licenses/)

***Allele Biotechnology & Pharm., Inc. v. Regeneron Pharm., Inc.*, Case No. 7:20-cv-08255 (S.D.N.Y 2020)**

- Allele filed a similar suit for patent infringement against Regeneron for use of mNeonGreen covered by US Patent No. 10,221,221
- Regeneron does not have, and has never had, a license to use mNeonGreen, but has multiple published articles authored by Regeneron researchers, which use mNeonGreen
- Allele asserted that Regeneron used mNeonGreen to test its coronavirus antibody cocktail, REGEN-COV, in neutralization assays

Arguments

- Allele argued that mNeonGreen is a “research tool” and is not the type of invention covered by the safe harbor
    - Argued that Regeneron’s use of mNeonGreen is commercial in nature and has been undertaken in the development and production of commercial products

Arguments

- Regeneron argued that their conduct was protected by the "safe harbor" provision of 35 U.S.C. § 271(e)(1)
  - Based on *Eli Lilly*, Regeneron argued that as long as a party is using a "patented invention"—which the *Eli Lilly* "defined to include all inventions"—in a manner "reasonably related" to the development and submission of information to the FDA, it is protected by the safe harbor
  - According to Regeneron, "The proper analysis is not whether mNeonGreen is a "research tool," a term not found in the statute, but whether Regeneron's alleged use was for purposes "reasonably related" to generating information for submission to the FDA.

Arguments

- Regeneron argues that since Allele relies on the NIH's definition of "research tools," peptides as used in this case also fit the definition of research tools.

- As defined, "research tools" include "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."

- But, there is no bright line rule regarding whether "research tools" are not implicitly listed as a category covered under the safe harbor

Arguments

- Regeneron compared to *Teva Pharms. USA, Inc. v. Sandoz Inc.*, 2013 WL 3732867 (S.D.N.Y. July 16, 2013)
- In *Teva*, the district court concluded that the safe harbor applied to the use of patented laboratory "markers" to characterize a drug in generating data for the FDA, even though the markers were not themselves drug products and did not require FDA approval.
  - In *Teva,* the court distinguished from *Proveris* noting that the Federal Circuit only declined to apply the safe harbor because the defendant was not itself generating data for FDA submission or seeking FDA approval. Here, unlike *Proveris*, Regeneron was developing a drug product.

Current Status of Allele v. Regeneron

- Regeneron's MTD was denied in March 2022
  - judge noted that Allele's argument that Regeneron may have also used the protein in testing for other purposes like quality control, but could not come to a conclusion based on the current record
- Matter is still on-going

Regenxbio Inc. v. Sarepta Therapeutics, Inc., Civil Action No. 20-1226-RGA, 2022 U.S. Dist. LEXIS 1945 (D. Del. Jan. 4, 2022)

- Regenxbio and University of Pennsylvania own the 10,526,617 ("the '617 patent")
  - The '617 patent is directed to a "cultured host cell containing a recombinant nucleic acid molecule"
  - The patented cultured host cells do not require FDA regulatory approval

- Sarepta uses the patented cultured host cells covered by the Regenxbio ‘627 patent to develop a gene therapy product (their SRP-9001)
  - SRP-9001 is currently in clinical development
  - SRP-9001 requires FDA regulatory approval for marketing

Arguments

- Sarepta argues that their activities fall within the protections of 35 U.S.C. § 271(e)(1) because the activities were solely related to the development and future submission of a Biologics License Application to the FDA under the Federal Public Health Service Act and are thus protected
  - Tries relying on *Teva*

Holding

- Sarepta is not using the patented cultured host cells to obtain FDA approval to introduce generic cultured host cells to compete in the marketplace when the '617 patent expires.
- Sarepta is using the patented cells to develop *its own patentable product*.
- Sarepta can begin using the patented host cells immediately upon expiration of the patent because the cells are not subject to any FDA regulatory approval process. Thus, Regenxbio will not receive any effective patent term extension.

- Sarepta's MTD **denied**

Discussion

- Types of patented “research tools” or methods used in vaccine R&D –
  - vectors, formulations comprising specific mRNA sequences for new virus strains, etc.
  - mass producing mRNA (such as by using plasmid), inducing immune response, purifying mRNA, etc.
- Research tools used during R&D do not automatically qualify for safe harbor protection
  - May turn on specific facts to be useful

- Allele cases: fluorescent proteins are “research tools” and are not the type of invention covered by the safe harbor provision
- Sarepta raises a “marketplace” issue
  - Should it depend on what market the patented product is in?

Discussion

- What is the best way to limit the risk of potential infringement (or ensure applicability of Safe Harbor protection)?
  - License for research tools that are more unique to the R&D
  - Are there alternatives to the components that would not require a license?
  - Consider what are the patented tools/methods being used for:
    - Quality?
    - Generating a new product for FDA approval?
    - Another purpose?
  - What is the market for the patented research tool vs. the target market for the result of the R&D? Are they the same market or different markets?

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Thank you for your attention!