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Sarah J. Chickos*


The Safe Harbor provision of the Patent Act of 19841 (also know as the "Hatch-Waxman Act" or "the Act") provides an exemption for patent infringement for those uses of patented inventions that are reasonably related to the development and submission of information under the federal laws regulating drugs and medical devices.2 The Safe Harbor provision is a critical "port in the storm," allowing companies to use patented inventions in the service of obtaining regulatory approval for drugs and medical devices. Courts have been fleshing out the boundaries of this exemption since 1984, and these decisions provide valuable guidance for companies seeking to bring new drugs and devices to market and advance the healthcare field. This article aims to survey these decisions to determine the scope and extent of this exemption and how litigants can best establish this exemption for their activities.

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2. 35 U.S.C. § 271(e)(1) provides "[i]t shall not be an act of infringement to make, use, offer to sell, or sell . . . 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."
Congress enacted the Hatch-Waxman Act in 1984 to reconcile the goals of the patent statutes with the realities of obtaining regulatory approval for drugs and medical devices. Obtaining regulatory approval to market drugs and devices took so long that it was causing "distortions" of the terms of the relevant patents. These distortions occurred at both the beginning and end of patent terms. At the beginning of a patent term, obtaining regulatory approval to market a drug or device took significantly longer than the time it took to obtain a patent, so that much of the patent term had run before a company was able to actually market the drug. Thus, companies launching a new drug or device had little of the patent term left to sell that drug or device. At the end of the patent term, an unintended extension of the patent term occurred because competitor companies, including generic companies, had to wait until the patent term had expired before beginning to test and develop the drug or device covered by the patent. This amounted to an extension of the monopoly by the patent holder.

Congress addressed the unintended effects of regulatory activity via the Hatch-Waxman Act. In § 202 of the Act, Congress provided a "Safe Harbor" against patent infringement by creating 35 U.S.C. § 271(e)(1). Section 271(e)(1) allows competitors of the patent holder to comply with regulatory laws and bring their products to market sooner than was possible before the passage of the Act. Congress wanted to encourage both innovation and competition. Indeed, Congress declared that one of the purposes of the Act was to encourage both innovation and the ability to bring new drug products to market more quickly while still upholding patent rights. Section 201 of the Act addressed the distortion at the early end of the patent term caused by the patentee being unable to market his invention while seeking regulatory approval by creating a new statutory provision, codified at 35 U.S.C. § 156. Section 156 provides a patent term extension for patented inventions that are subject to lengthy regulatory approval processes.

II. OVERALL TEST: MERCK V. KGAA V. INTEGRA LIFESCIENCES I, LTD.

The Supreme Court has interpreted § 271(e)(1) broadly so that this exemption "extends to all uses of patented inventions that are reasonably related to the development and submission of any information under the Federal Food Drug and Cosmetic Act." The overall test is an objective one.


that asks whether a drugmaker has a reasonable basis for believing that a patented product may work and uses the product in research that, if successful, would be appropriate to include in a submission to the Food and Drug Administration (FDA). If such a reasonable basis exists, then the Safe Harbor protection applies to the use of the patented technology research.\textsuperscript{5}

Provided this objective reasonable basis test is met, a broad spectrum of activities can be undertaken.

On each occasion that it has interpreted it, the Supreme Court has declined to limit the scope of the § 271(e)(1) Safe Harbor Exemption. In \textit{Eli Lilly v. Medtronic Inc.},\textsuperscript{6} the Court declined to limit the exemption from infringement to activities generating submissions under the particular statutory provisions that regulate drugs.\textsuperscript{7} In \textit{Merck KGaA v. Integra Lifesciences I, Ltd.}, the Supreme Court expressly rejected any restriction on the Safe Harbor exemption limiting it to preclinical data relating to the safety of a drug in humans.\textsuperscript{8} Instead, the Court reemphasized that the reasonable relation language of § 271(e)(1) applied to all uses of patented inventions and the submission of any information under the FDCA, regardless of the development phase in which it was generated.\textsuperscript{9}

\section*{III. Activities "Reasonably Related to the Development and Submission of Information"}

Much of the case law has focused on determining, on a factual basis, which activities are reasonably related to the development and submission of information to the FDA.\textsuperscript{10} There are various stages to the activities conducted to obtain regulatory approval. The Food, Drug, and Cosmetic Act

\begin{itemize}
\item \textit{Merck}, 545 U.S. at 202; see 21 C.F.R. § 312.23(a)(5) (2007).
\item \textit{Id}.
\item \textit{Merck}, 545 U.S. at 203.
\item \textit{Id}. at 205-06.
\end{itemize}
(FDCA), is "a Federal law which regulates the manufacture, use, or sale of drugs." The FDCA separates new drug development into general stages, each of which requires the submission of certain research data to the FDA. In the pre-clinical stage, an investigational new drug application (IND) is submitted to obtain authorization to conduct tests in humans (clinical trials). The FDCA, in § 355(i)(1)(A), states that the IND must contain information about "preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing." In the clinical stage, approval to market the new drug is sought in a New Drug Application (NDA). The NDA must describe all clinical studies and preclinical studies relating to a drug's efficacy, toxicity, and pharmacology to demonstrate that the drug is both safe and effective. However, the requirements for information do not cease after approval to market the new drug has been obtained, and additional information must be submitted to the FDA in the post-approval stage regarding an approved drug's performance, especially regarding safety.

The regulatory framework governing medical devices is different than that of drugs, and the specific regulatory requirements depend on how the medical device is classified. Medical devices are classified in three categories based on the risk posed by their use. Devices that do not "present a potential unreasonable risk of illness or injury" and do not purport to be used for sustaining human life are designated Class I medical devices. Class I medical devices are subject to minimal regulation through "general controls." Potentially more harmful devices are designated Class II devices and although they may be marketed without advance approval, Class II devices are subject to federal performance

15. See 21 C.F.R. §§ 314.80(c)(2), 314.98, 600.80(c) (2007).
17. Id. § 360c(a)(1)(A).
18. Id.
A device that "presents a potential unreasonable risk of illness or injury" or that is "purported or represented to be for a use in sustaining human life or for a use which is of substantial importance in preventing impairment of human health" is designated a Class III medical device. Class III medical devices require pre-market approval or must meet performance standards before they can be shipped in interstate commerce for use in human subjects. An Investigational Device Exemption (IDE) may be obtained from the FDA, however, to allow for investigational use pursuant to an FDA-approved protocol. Clinical trials and experiments can be conducted with an IDE in order to generate the data necessary to obtain FDA approval for the Class III medical device. Similar to an IND in the case of drugs, an application for the IDE generally proposes an investigational plan for clinical testing of the device with a written protocol demonstrating the scientific soundness of the investigation. Thus, in the case of both drugs and medical devices, there are various stages of regulatory approval, each with its own data requirements.

A. Protected Activities: Reasonable Basis for Belief?

In Merck KGaA v. Integra Lifesciences I, Ltd., the Supreme Court addressed the issue of whether preclinical studies qualified for the § 271(e)(1) exemption from patent infringement. The Court held that the use of patented compounds in preclinical studies is protected under the Safe Harbor exemption provided that there is a reasonable basis for belief that the experiments will produce the types of information relevant to a submission to the FDA. In Merck, Integra Lifesciences I, Ltd. and the Burnham Institute sued Merck KGaA for infringement and inducement of infringement of five patents related to the tripeptide sequence Arg-Gly-Asp (the "RGD peptide") during angiogenesis research. Early research using

19. Id. § 360c(a)(1)(B).

20. Id. § 360c(a)(1)(C).


22. See id. §§ 812.3, 912.25.


24. Id.

25. Id. at 197.
an RGD peptide succeeded in reversing tumor growth in chicken embryos. This led to RGD peptides being tested both *in vitro* and *in vivo*. The RGD peptides were tested for efficacy, specificity, and toxicity as angiogenesis inhibitors, and their mechanism of action and pharmacokinetics were studied to determine which peptides were suitable drug candidates. Upon determination of a suitable candidate, the test results were to be included in an application for an IND from the FDA. The district court found that these research activities were not protected by § 271(e)(1) and the Court of Appeals for the Federal Circuit affirmed on the ground that the research was "not clinical testing to supply information to the FDA but only general biomedical research to identify new pharmaceutical compounds."

The Supreme Court granted certiorari specifically to review the Federal Circuit Court of Appeals's construction of § 271(e)(1).

The Supreme Court stated, at the outset of its opinion, that the statutory text made it apparent that § 271(e)(1)'s exemption extended to all uses of patented inventions that are reasonably related to the development of *any* information under the FDCA. The Court then referenced the *Eli Lilly* decision in which the Court declined to limit § 271(e)(1) exemption to portions of statute that regulate drugs. The Court explained that "[t]here is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included." The Court also rejected respondents' arguments that the only preclinical data of interest to the FDA are that which pertain to the safety of the drug in humans, not the drug's efficacy, mechanism of action, and pharmacokinetics data.

The Supreme Court's analysis in *Merck* demonstrates how FDA requirements and guidelines are often central to a court's determination of whether an activity qualifies for the § 271(e)(1) Safe Harbor exemption from infringement. The Court focused on the process of drug development and the requirements for data submission at each phase of the process. The

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26. *Id.* at 201 (quoting *Merck KGaA v. Integra Lifesciences I, Ltd.*, 331 F.3d 860, 866 (Fed. Cir. 2003)).

27. *Id.* at 202.


29. *Id.*

30. *Id.* at 203.
Court pointed to the FDA’s requirement that an IND application include summaries of the drug’s pharmacological, toxicological, pharmacokinetic, and biological aspects in animals. The source of these data is usually preclinical in vitro and in vivo studies. Additional reasoning for the Court came from an FDA directive that an IND must provide sufficient information to allow a detailed risk-benefit analysis to be made, the source of which is also usually preclinical in vitro and in vivo studies.

1. Experimentation on Drugs That Are Not Ultimately the Subject of An FDA Submission Are Not Excluded From Exemption

The Supreme Court described § 271(e)(1) as providing a researcher with a wide berth for experimentation and failure and explained that

at least where a drug maker 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 under . . . Federal law.

In articulating the reasonable basis test in Merck, the Supreme Court was cognizant of the realities of new drug development and the process of trial and error. The Court appreciated that, in most cases, those involved with developing a drug had no way of knowing whether new drug candidates would ultimately be successful and understood that the fear of failed experimentation would be a disincentive for researchers to experiment. In laying out the reasonable basis test the Court particularly pointed out that


The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans.

Id.


33. Id. at 203-04.

34. Id. at 207.
"[p]roperly construed, § 271(e)(1) leaves adequate space for experimentation and failure on the road to regulatory approval."\(^{35}\)

2. **Use of Patented Compounds in Experiments That Are Not Ultimately Submitted to the FDA Are Not Excluded From the Safe Harbor**

The experiment with the drug does not have to ultimately be submitted to the FDA, provided that the researcher has a reasonable basis to believe that the experiment could produce information relevant to a regulatory submission under federal law.\(^{36}\) As such, testing conducted during the clinical stage does not have to be submitted to a regulatory agency to qualify for Safe Harbor protection. Safety testing is one of several types of tests that courts have determined to be protected by the Safe Harbor exemption even when the results are never submitted to the FDA. In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*,\(^{37}\) Amgen brought an infringement action based on several of its patents covering a recombinant form of erythropoietin (EPO). Pyrogens are fever-inducing agents that are often considered to be impurities. The FDA requires that biological pharmaceuticals undergo purity tests to detect the presence of pyrogens. Hoechst had performed two kinds of purity tests for pyrogens on its EPO product, a Limulus Amebocyte Lysate (LAL) test and a test in which the EPO was injected into rabbits.\(^{38}\) Hoechst submitted the LAL purity test results to the FDA but never submitted the rabbit pyrogen tests. Amgen argued that LAL test was not reasonably related to FDA approval and was conducted to satisfy European regulatory requirements.\(^{39}\) Hoechst replied that, while not reported to the FDA, the results of the rabbit pyrogen tests were conducted to confirm the purity and safety of their EPO product for use in clinical trials, which would be submitted to the FDA.\(^{40}\) The *Amgen* court held that the rabbit pyrogen tests were reasonably related to the approval process and that any suggestion

\(^{35}\) *Id.*

\(^{36}\) *Id.*


\(^{38}\) *Id.*

\(^{39}\) *Id.*

\(^{40}\) *Id.* at 110.
that Hoechst had other purposes in conducting the rabbit pyrogen tests was irrelevant.\(^{41}\)

3. **Provision of Raw Materials Protected by Safe Harbor**

The provision of raw materials to a company so that it may in turn prepare its Abbreviated New Drug Application (ANDA) is protected from infringement under the Safe Harbor exemption.\(^{42}\) In *Ortho-McNeil Pharmaceuticals, Inc. v. Mylan Laboratories, Inc.*, Ortho-McNeil made a motion to amend its complaint of patent infringement against Mylan Laboratories in order to add inducement of patent infringement claims against raw material suppliers Quimica and Betachem.\(^{43}\) The only allegation in the proposed Amended Complaint was that Quimica and Betachem provided Mylan with the raw materials for its ANDA preparations.\(^{44}\) The court determined that this activity was excepted from infringement by §271(e)(1) and denied Ortho-McNeil's motion.\(^{45}\)

4. "**Commercial Reasons**" and "**Alternate Purposes**" Do Not Preclude Coverage for Uses Reasonably Related to Obtaining FDA Approval

Uses that are related to FDA approval can be conducted for purposes other than, or in addition to, obtaining FDA approval. Examples of such uses include animal testing, human clinical trials, and chemical composition analysis.\(^{46}\) Ulterior motives or alternate purposes do not preclude application of the Safe Harbor exemption.\(^{47}\) Indeed, once the use is determined to be qualified for the §271(e)(1) exemption, courts have

\(^{41}\) *Id.*


\(^{43}\) *Id.* at 547.

\(^{44}\) *Id.* at 549.

\(^{45}\) *Id.*


\(^{47}\) *Id.*
regarded the defendant's intent or the underlying purpose of the activity as "statutorily irrelevant."\textsuperscript{48}

\textit{a. Trade Shows}

In \textit{Telectronics Pacing Systems, Inc. v. Ventritex, Inc.},\textsuperscript{49} Ventritex demonstrated its defibrillator to some non-physicians at medical conferences. Telectronics alleged the demonstrations were not reasonably related to FDA approval, and Ventritex replied that all of its demonstrations had been set up to procure clinical investigators.\textsuperscript{50} The Federal Circuit found that such demonstrations constitute a protected use that is reasonably related to obtaining FDA approval because device sponsors are required to select qualified investigators and provide them with the information necessary to conduct clinical testing.\textsuperscript{51} The court dismissed as unimportant the fact that some non-physicians had seen the device at the conferences on the ground that such an occurrence is unable to detract from the conclusion that the uses satisfied the requirements of § 271(e)(1).\textsuperscript{52} The court found it significant that Telectronics admitted that the demonstrations did not constitute a sale or an offer to sell.\textsuperscript{53}

Similarly, in \textit{Intermedics, Inc. v. Ventritex Co.},\textsuperscript{54} the Federal Circuit reaffirmed that trade show displays that are used to obtain necessary information for clinical testing are exempt under § 271(e)(1). Ventritex demonstrated an implantable defibrillator at trade shows even after Ventritex had procured all of the clinical investigators that it needed.\textsuperscript{55} The Federal Circuit found it significant that Telectronics admitted that the demonstrations did not constitute a sale or an offer to sell.

\textsuperscript{48} \textit{Id.} at 108.

\textsuperscript{49} \textit{Telectronics Pacing Sys., Inc. v. Ventritex, Inc.,} 982 F.2d 1520, 1521 (Fed. Cir. 1992).

\textsuperscript{50} \textit{Id.} at 1522-23.

\textsuperscript{51} \textit{Id.} at 1523 (stating information was provided pursuant to 21 C.F.R. § 812.40 (1989)).

\textsuperscript{52} \textit{Id.}

\textsuperscript{53} \textit{Id.}


\textsuperscript{55} \textit{Id.}
Circuit recognized that it was unforeseeable how much data the FDA would require for submission during the approval process, so efforts to continue finding potential clinical investigators well into the approval process did not negate the demonstrations’ qualifications for the § 271(e)(1) exemption.\textsuperscript{56} The court noted that Intermedics did not contest the trial court’s finding that there were no implantable defibrillator sales.

The Federal Circuit reaffirmed that displays at trade shows to obtain necessary clinical testing information are exempt under § 271(e)(1) in Chartex International PLC v. M.D. Personal Products Corp.\textsuperscript{57} In Chartex, M.D. Personal Products Corporation (MDPP) made three trade show displays of its medical device, a female condom.\textsuperscript{58} The court noted that the record contained no evidence that MDPP made or solicited any sales of its female condom.\textsuperscript{59} Chartex’s failure to dispute the district court’s finding to this effect was also mentioned in the court’s opinion.\textsuperscript{60} As such, the lack of any sales activity at trade show demonstrations is a persuasive factor in § 271(e)(1) exemption determinations.

\textit{b. Consumer Surveys}

In Chartex, the Federal Circuit also addressed the issue of whether consumer surveys were exempt activity under § 271(e)(1).\textsuperscript{61} MDPP had conducted three consumer studies in the form of focus groups, color tests, and interviews, and MDPP subsequently used the information they provided in designing the female condom.\textsuperscript{62} MDPP proceeded with clinical testing on the condom that was designed from the consumer survey information and then submitted the testing data to the FDA.\textsuperscript{63} The Federal Circuit concluded

\textsuperscript{56} Id.
\textsuperscript{58} Id.
\textsuperscript{59} Id.
\textsuperscript{60} Id. at *2.
\textsuperscript{61} Id. at *3.
\textsuperscript{62} Id.
that the MDPP's consumer studies were exempt under § 271(e)(1) because they were directed at developing information required for FDA approval.64

c. Commercial Scale Production

Experiments can actually be conducted specifically for commercial reasons, and any information that they produce can still be submitted to the FDA.65 Indeed, even activities not traditionally associated with obtaining regulatory approval, such as increased product production and scale-ups of offending products, are protected under the Safe Harbor exemption if they are reasonably related to obtaining regulatory approval.66

An example of increased product production is found in NeoRX Corp. v. Immunomedics, Inc.67 NeoRX sued Immunomedics to enforce its patent to processes and products for radiolabeling proteins that detect and treat cancer.68 Although Immunomedics had increased production of ImmuRAID, the District Court of New Jersey held that Immunomedics’ stockpiling of ImmuRAID-CEA for sale was reasonably related to the FDA approval process.69 In focusing on the FDA’s requirements, the district court highlighted that it is an FDA requirement that an applicant provide evidence it can manufacture the product on a commercial scale.70

The court reasoned that the FDA’s knowledge of the scale-up production plans, coupled with the unpredictability of the FDA’s information demands, made the increased production plans reasonably related to the development and submission of information to the FDA.71 In reaching the determination that the FDA was aware of Immunomedics’ scale-up production plans, the court looked at the minutes of a meeting between the FDA and

64. Id.


68. Id.

69. Id.

70. Id.

71. Id.
Immunomedics. Those minutes revealed that the parties discussed the scale-up, as well as a manufacturing report submitted to the FDA that discussed production increases and scale-up plans. In reaching its holding, the court acknowledged the unforeseeability of the amount of data the FDA will ultimately require, referencing the Federal Circuit’s *Intermedics* decision recognizing this uncertainty.

*Amgen, Inc. v. Hoechst Marion Roussel, Inc.* provides another example of commercial scale production. Hoechst Marion Roussel had produced at least four commercial scale production batches of the allegedly infringing product, GA-EPO. The court pointed to the FDA requirement “that a manufacturer demonstrate the consistency of its manufacturing process by producing three consecutive batches within certain tolerances of a standard reference.” The court held the production of the batches fell within the § 271(e)(1) exemption and dismissed the fact that the batches were never submitted to the FDA to satisfy the consistency requirement.

d. **Collateral Use of Data**

Once data have been submitted to the FDA, the subsequent use of the same data is not an infringing act. For example, in *NeoRX Corp. v. Immunomedics, Inc.*, Immunomedics submitted foreign clinical data to a European regulatory body to obtain a European Product Marketing Authorization after submitting the foreign clinical data to the FDA. The

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72. *Id.* at 207 n.4.


75. *Id.*

76. *Id.*

77. *Id.*


court held that the submission of the data to the European regulatory body was not an infringing act.\(^8\)

In *Telectronics*, Ventritex presented clinical trial data at a cardiology conference, informed investors, analysts, and the press about the progress of clinical trials, and discussed the clinical trials in written private fundraising communications.\(^8\) The Federal Circuit rejected Teletronic’s argument that the disclosure of clinical trial data to persons other than the FDA somehow revoked the § 271(e)(1) exemption for the underlying clinical trials.\(^8\) The Federal Circuit flatly stated that § 271(e)(1) provided for no such possibility.\(^8\) Furthermore, a coordinated effort to obtain regulatory approval in the United States and foreign countries can be conducted using the same package of data and clinical studies and the § 271(e)(1) exemption will still apply to the appropriate activities.\(^8\)

5. **Protection Available After Approval**

The protection of the § 271(e)(1) Safe Harbor exemption continues to be available to qualifying activity once regulatory approval has been obtained. Repeatedly, courts have held that the § 271(e)(1) exemption applies when the reasonably related test is met, even if a drug has been approved by the FDA and is already on the market.\(^8\)

In *Classen Immunotherapies, Inc. v. Biogen IDEC*, defendant Biogen IDEC conducted a study to evaluate possible associations between the timing of vaccinations against Hepatitis B and Haemophilus influenza and the risk of developing Type 1 diabetes.\(^8\) The United States District Court for the District of Maryland cited the Supreme Court’s decision in *Merck* and held that participation in a study evaluating risks associated with various

\(^8\) Id.

\(^8\) *Telectronics*, 982 F.2d at 1523.

\(^8\) Id. at 1524.

\(^8\) Id.


\(^8\) Id. at 455.
Navigating the Safe Harbor

vaccine schedules were protected activities under the § 271(e)(1) exemption because they were reasonably related to the development and submission of information required under the Federal Food, Drug, and Cosmetic Act. The court specifically noted that the FDA collects vaccine data from vaccine manufacturers after their vaccines have been approved and pointed to provisions of the Code of Federal Regulations requiring annual progress reports of postmarketing studies and reports of postmarketing adverse reactions to vaccinations.

6. Exporting Product Does Not Constitute Infringement

It is worth noting that the exporting or shipping abroad of a product is not an infringing activity, not by virtue of any exemption under § 271(e)(1), but because it does not constitute infringement under § 271(a) in the first place. Similarly, receiving, storing, or shipping products are also not "uses" and therefore do not amount to infringements.

B. Unprotected Activities

1. Purely Commercial and Promotional Use in the United States or Abroad Is Not Covered by the Safe Harbor Exemption

Sales in the United States or abroad that are purely for profit and are without a regulatory information generating purpose have been determined to be unprotected by the Safe Harbor exemption from infringement. The Safe Harbor exemption is available for activities that are necessary to obtain

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87. Id. at 456.

88. Id. at 455; see also 21 C.F.R. § 601.70 (2005) (requiring annual progress reports of postmarketing studies); 21 C.F.R. § 600.80 (requiring postmarket reports of adverse experiences).


regulatory approval in the United States; however, courts have found that this exemption does not apply to activities conducted in pursuit of obtaining regulatory approval in foreign countries, absent a reasonable relation to United States regulatory approval. Thus, in NeoRX Corp. v. Immunomedics, Inc., the manufacture and shipping abroad of infringing products for labeling proteins was not protected under the Safe Harbor exemption when it was only for the purpose of obtaining foreign regulatory approval.92

On the other hand, manufacture and shipping abroad has been found to be protected when it can generate information that may be useful in obtaining FDA approval. Specifically, manufacture and shipping abroad has been protected when it is done for the purpose of evaluating an alternative manufacturing process. In Amgen, Inc. v. Hoechst Marion Roussel, Inc., Amgen brought an infringement action based on several of its patents covering a recombinant form of erythropoietin (EPO).93 Hoechst had made and exported a quantity of EPO to a Japanese affiliate for use as a standard reference in studies being conducted to evaluate an alternative manufacturing process.94 Amgen argued that this activity was not reasonably related to FDA approval because the alternative manufacturing process was not the process for which FDA approval was sought and no approval had even been sought for the alternative manufacturing process.95 Hoechst replied to this argument with the assertion that the Japanese study is one of several efforts to improve its manufacturing process and FDA approval will not be sought on these alternative manufacturing processes until the FDA has approved the current process.96 The court in Amgen held that Hoechst's activities were protected by the Safe Harbor exemption, regardless of whether Hoechst had sought FDA approval on the alternative manufacturing process at the time.97 The court particularly noted that "the FDA guidelines contemplate the use of a reference standard sample from one manufacturing process to evaluate the effects of alterations in that


94. Id.

95. Id.

96. Id.

97. Id.
process.\textsuperscript{98} Thus, the nature of the information that can be produced in carrying out the activity is central to any analysis of whether manufacture and shipping abroad falls under the ambit of the Safe Harbor exemption.

2. \textit{Limits of the Safe Harbor: Insufficient Evidence}

Since the Supreme Court's 2005 \textit{Merck} decision, courts have addressed situations where the limits of the Safe Harbor exemption were at issue.\textsuperscript{99} In \textit{Third Wave Technologies, Inc. v. Stratagene Corp.}, the Western District of Wisconsin held that in the absence of defendant's straightforward assertion that past testing of products was performed in order to develop or submit information to the FDA, the mere assertion that FDA approval was motivation for past testing was insufficient evidence to establish a Safe Harbor exemption.\textsuperscript{100} The court explained that the statement of defendant's CEO that its testing was driven in part by the desire to eventually expand the utility of the products and submit products using the platform for FDA approval was also insufficient in light of the CEO's admission that defendant was only in the start up phase for pursuing the diagnostics market for this product.\textsuperscript{101} Thus, defendants have some evidence to establish the § 271(e)(1) defense from patent infringement. According to the \textit{Third Wave} court, it is not sufficient just to claim that testing or experimentation is part of a future desire to expand into a market requiring regulatory approval; defendants must also be prepared to show a concrete relationship between its past activities and its future intent to seek regulatory approval.\textsuperscript{102} Defendants cannot just invoke the Safe Harbor exemption defense to protect themselves from an assertion of patent infringement. The court emphasized the need for evidence that would show a more concrete relationship between past testing and the future intent to seek FDA approval.\textsuperscript{103}

\textsuperscript{98} \textit{Amgen, Inc.}, 3 F. Supp. 2d at 109; see Ctr. for Biologics Evaluation & Research & Ctr. for Drug Evaluation & Research, FDA Guidance Concerning Demonstration of Comparability of Human Biological Prods. 3-6 (1994).


\textsuperscript{100} Third Wave Techs., 381 F. Supp. 2d at 913.

\textsuperscript{101} \textit{Id.}

\textsuperscript{102} \textit{Id.}

\textsuperscript{103} \textit{Id.}
The *Third Wave* decision highlights the benefits of having business development plans and other documentation about particular markets that a company's products could be launched in. Companies can more easily establish this defense by maintaining records of business plans, business development plans, and marketing research as they relate to the penetration of a desired market subject to regulation. This type of documentation could be useful in establishing a concrete relationship between past activities and a company's future intent to penetrate a market in which its product would be subject to regulation. Additional helpful documentation would include records of past activities in order to more clearly explain the relationship. The *Third Wave* court appeared uncomfortable with defendant CEO's stated desire to enter a market that was expressed during the litigation process as the only evidence presented. Proper record keeping would provide adequate documentation preceding litigation with which a court would be more comfortable.

IV. "[A] PATENTED INVENTION"

A. Medical Devices: *Eli Lilly v. Medtronic Inc.*

In *Eli Lilly*, the Supreme Court broadly held that the term "patented invention" as used in § 271(e)(1) includes all inventions, not just drug-related inventions.104 In this case, *Eli Lilly* owned patents of ventricular defibrillation devices and sued to enjoin Medtronic from testing and marketing a ventricular defibrillation device.105 Medtronic asserted that its activities were exempt from infringement under § 271(e)(1) because it was trying to develop and submit information to the government to obtain premarketing approval for the device under § 515 of the FDCA. Medtronic argued that the phrase "a Federal law which regulates the manufacture, use, or sale of drugs" referred to the entirety of any Act, including the FDCA, whose provisions regulate drugs and other devices, rather than those individual provisions of federal law that only regulate drugs, as *Eli Lilly* argued.106 The district court concluded that § 271(e)(1) did not apply to medical devices and found that Medtronic infringed *Eli Lilly*’s patents. The Court of Appeals for the Federal Circuit reversed on the basis that Medtronic's activities were undertaken to obtain regulatory approval under


105. *Id.* at 661.

106. *Id.*
the FDCA and were exempt from a finding of infringement under § 271(e)(1).\(^\text{107}\)

The Supreme Court looked to the statutory language and reasoned that the word “law” was most likely being used in its broader sense.\(^\text{108}\) The phrase “a Federal law which regulates the manufacture, use, or sale of drugs” more naturally refers to a statutory scheme in its entirety, as opposed to a single provision.\(^\text{109}\) Likewise, the phrase “the development and submission of information under a Federal law” suggests that actions are taken in compliance with an overall regulatory scheme.\(^\text{110}\) Also persuasive to the Court was that the immediately preceeding § 201 of the 1984 Act used the phrase “the provision” when it meant to refer to particular provisions of the law rather than an entire Act.\(^\text{111}\) The Court, recognizing the ambiguity in the phrase “a Federal law which regulates the manufacture, use, or sale of drugs,” held that § 271(e)(1) exempts from infringement the use of patented inventions, including medical devices, that are reasonably related to obtaining approval under the FDCA.\(^\text{112}\)

Since the Supreme Court decided *Eli Lilly*, the Federal Circuit has reiterated that the § 271(e)(1) exemption applies to all patented inventions and is not limited to those patented inventions listed in § 156 of the Hatch-Waxman Act.\(^\text{113}\) The Federal Circuit has applied the Supreme Court’s *Eli Lilly* holding in *Chartex International PLC v. M.D. Personal Products Corp.*\(^\text{114}\) and *Abtox, Inc. v. Exitron Corp.*\(^\text{115}\) in concluding that both Class I and Class II medical devices are among the patented inventions encompassed by the FDCA. In *Abtox*, the medical device at issue was a

\(^{107}\) *Id.*

\(^{108}\) *Id.* at 667.

\(^{109}\) *Id.* at 666.


\(^{111}\) *Id.*

\(^{112}\) *Id.* at 661.


\(^{115}\) *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997).
The patentee sought to distinguish the holding in **Eli Lilly** on the basis that the defibrillation device at issue was a Class III medical device, whereas the plasma sterilizer at issue was a Class II medical device. The patentee emphasized the more involved regulatory requirements for Class III devices, but the Federal Circuit rejected this distinction and applied the broad holding in **Eli Lilly** to exempt the use of the plasma sterilizer from infringement under § 271(e)(1). Likewise, in **Chartex**, the Federal Circuit held that M.D. Personal Products’ female condom was a medical device that the § 271(e)(1) exemption applied pursuant to the Supreme Court’s holding in **Eli Lilly**. The female condom at issue in **Chartex** was a Class I medical device.

Examples of patented inventions that have been determined to be covered by the § 271(e)(1) exemption by courts include a drug containing an adhesive transdermal patch, an implantable cardiac defibrillator, a plasma sterilizing medical device, the active ingredient in an anti-ulcer medication, an oral contraceptive, a hormone that stimulates red blood cell growth, a product for labeling proteins to detect and treat cancer, a

116. Id.

117. Id.

118. Id.


120. Id.


123. **Abtox, Inc. v. Exitron Corp.**, 122 F.3d 1019 (Fed. Cir. 1997).


female condom,\textsuperscript{128} a perfluorocarbon used in retinal surgery,\textsuperscript{129} and diagnostic equipment for determining the presence and concentration of bacteria in blood.\textsuperscript{130}

### B. Research Tools

The Supreme Court addressed § 271(e)(1) again fifteen years later in its \textit{Merck} decision. The Court specifically refrained from expressing a view about whether research tools were exempt from infringement under § 271(e)(1).\textsuperscript{131} The Court noted that the Federal Circuit Court of Appeals had supported its narrower construction of § 271(e)(1) on the basis that the narrower construction protected patentees of research tool patents.\textsuperscript{132} Since the Supreme Court rejected this narrower construction and refused to express an opinion about the exemption of research tools under § 271(e)(1), there remains considerable doubt about whether research tools are exempt under § 271(e)(1).

However, at least one court has held that research tools are patented inventions that can be exempt from infringement by virtue of § 271(e)(1).\textsuperscript{133} Classen Immunotherapies (Classen) holds patents on methods of identifying and commercializing new uses of existing drugs.\textsuperscript{134} Elan Pharmaceuticals (Elan) conducted a study that determined that food impacted significantly the bioavailability of Skelaxin, a muscle reactant.\textsuperscript{135} Elan included the study

\begin{itemize}
  \item \textsuperscript{127} NeoRX Corp. v. Immunomedics, Inc., 877 F. Supp. 202 (D.N.J. 1994).
  \item \textsuperscript{129} Infinitech, Inc. v. Vitrophage, Inc., 842 F. Supp. 332 (N.D. Ill. 1994).
  \item \textsuperscript{130} Baxter Diagnostics Inc. v. AVL Scientific Corp., 798 F. Supp. 612 (C.D. Cal. 1992).
  \item \textsuperscript{131} Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 205 (2005).
  \item \textsuperscript{132} \textit{Id.}
  \item \textsuperscript{133} Classen Immunotherapies, Inc. v. King Pharms., Inc., 466 F. Supp. 2d 621 (D. Md. 2006).
  \item \textsuperscript{134} \textit{Id.} at 623.
  \item \textsuperscript{135} \textit{Id.} at 624.
\end{itemize}
findings in a labeling supplement to its own NDA for Skelaxin that it submitted to the FDA, and the FDA approved Elan's amendments to the Skelaxin product label. In a Citizen's Petition that was ultimately granted, Elan also requested that the FDA require Skelaxin ANDA applicants to submit fed (studies conducted with patient taking Skelaxin with food) and fasted (studies conducted with patients taking Skelaxin without food) studies to the FDA. Classen sued Elan for infringement based on Elan's study and the application of the study to identify and commercialize a new use for Skelaxin. Elan argued that even if its conduct fell within the scope of Classen's patents, its actions were exempt from patent infringement under § 271(e)(1) because it had submitted the results of its study to the FDA. In rendering its opinion, the district court pointed to the Supreme Court's broad interpretation of § 271(e)(1) in Merck and quoted the Court's language when it stated that "there is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included." The district court determined that since the results of the study were submitted to the FDA in Elan's Citizen's Petition and labeling supplement to its Skelaxin NDA, and because § 271(e)(1) made no exclusions based on the particular submission in which information was submitted to the FDA, Elan's activities were reasonably related to the submission of information under the FDCA and § 271(e)(1) therefore protected them from infringement. The court noted that the Supreme Court had declined to rule on whether the use of research tools was protected under § 271(e)(1). The court then held that the Classen process could be considered to be a research tool and extending the Safe Harbor to cover the use of these tools was warranted by both the language in Merck and a plain reading of the statute.

136. Id.

137. Id.

138. Id.


140. Id. at 625 (citing Merck KGaA v. Integra Lifesciences I. Ltd., 545 U.S. 193, 202 (2005)).

141. Id. at 625.

142. Id.
V. "[A] Federal Law Which Regulates the Manufacture, Use, or Sale of Drugs"

In *Eli Lilly*, the Supreme Court interpreted the phrase "a Federal law which regulates the manufacture, use or sale of drugs" to refer to an entire statutory scheme of regulation and not just to single sections or subsections related to drugs or veterinary biological products."\(^{143}\)

In *Merck*,\(^{144}\) the Supreme Court indicated that the Federal Food Drug and Cosmetic Act (FDCA) is "a Federal law which regulates the manufacture, use, or sale of drugs."\(^{145}\) The Court also indicated that while the FDCA is such a federal law, it is not necessarily the only one.\(^{146}\)

VI. Application of the Case Law

The federal regulatory law and its requirements and guidelines are the touchstone for the courts when determining the applicability of the Safe Harbor to particular circumstances. Courts frequently refer to the requirements or guidelines of the regulations to determine whether activity is reasonably related to obtaining regulatory approval.

A. Relate to FDA Requirements and Guidelines

Courts generally agree that the Safe Harbor exemption is an affirmative defense that defendants raise by asserting that their activities are exempt from patent infringement under § 271(e)(1).\(^{147}\) As an affirmative defense, the § 271(e)(1) exemption must be asserted by the defendant.\(^{148}\) This provides those seeking regulatory approval with the opportunity to take

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145. *Id.* at 195.

146. *Id.* at 193.

147. *See Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1272 (N.D. Cal. 1991) (indicating that the § 271(e)(1) exemption is an affirmative defense); *Ventrassist Pty, Ltd. v. Heartware, Inc.*, 377 F. Supp. 2d 1278, 1286 (S.D. Fla. 2005) (concluding that defendant raised an affirmative defense by asserting its activities were exempt from patent infringement under § 271(e)(1)).

helpful steps before litigation arises that will make a Safe Harbor defense easier to establish.

A Safe Harbor defense can be better prepared through regular contemporaneous documentation of an activity's relation to FDA information submission requirements and guidelines. It is important first to be aware of the FDA guidelines and requirements, so that any activities can be related to them in documentation. Records of this documentation should be maintained. It is common practice during litigation for a patentee to question the sincerity of defendant's assertions that activities are reasonably related to the development and submission of regulatory information. Documentation that is contemporaneous with the activity will assist the defendant in rebutting a patentee's challenge of sincerity. Since such documentation is created before litigation arises, it is helpful evidence that courts appear to be comfortable using in determining that an activity is protected under § 271(e)(1).

For demonstrations at trade shows, care should be taken to document that no sales or offers for sale occurred at the trade show. In determinations that demonstrations at trade shows are exempt from patent infringement, the absence of sales activity is a factor favoring exemption that courts rely on.149

With respect to products or processes that could be characterized as research tools, it may be worthwhile to characterize these products or processes as drugs or medical devices, or processes involving the same in this documentation. This may serve to support a characterization during litigation that would be more certain to receive the benefit of Safe Harbor protection. Such a characterization would also serve to take maximum advantage of the Supreme Court's holding in Merck, regardless of how a court ultimately classifies the products or processes at issue in litigation.150

B. Maximize Information Generation

Business planning should include being cognizant of the information generating the potential of particular activities. As the cases have held, the purpose of the activity does not preclude application of the Safe Harbor exemption, and the generation of relevant information is very helpful in establishing the Safe Harbor defense.151

149. See supra text accompanying notes 49-61.


Efforts should be made to maximize the information generated by activities conducted during drug development. Thus, business development plans can memorialize desires to enter markets in which regulatory approval will be required. Market surveys can also document these business intentions. These surveys can serve as helpful antecedent evidence of plans to seek regulatory approval in markets where such approval is necessary to sell products. Such evidence could be helpful in situations like *Third Wave*, where a defendant who is still in the early stages of pursuing an FDA regulated market needs to establish that past activity was performed in order to develop or submit information to the FDA.\textsuperscript{152}

Although the process of obtaining regulatory approval can be uncertain, the uncertainty does provide some advantages to those seeking regulatory approval, including the fact that courts are aware of the uncertainty surrounding the FDA’s data requirements. As the Federal Circuit noted in *Intermedics, Inc. v. Ventritex Co.*, “it is unforeseeable how much data FDA will require Ventritex to submit during the approval process.”\textsuperscript{153} Drug and product developers can engage in a variety of activities without the fear of infringement liability when these activities are generating information relevant to the regulatory approval process.

\begin{enumerate}
\item \textbf{C. Submit Information to the FDA}
\end{enumerate}

The actual submission of data generated by an activity to the FDA during the regulatory process is very persuasive to courts when making Safe Harbor determinations. Given that the purpose of the \textsection 271(e)(1) exemption is to exempt activities from infringement involved in the process of gaining regulatory approval, and data submission is the mode by which regulatory approval is obtained, this is obviously a powerful factor. The fact that data were actually submitted to the FDA is often determinative of the \textsection 271(e)(1) exemption for a court.\textsuperscript{154}

\begin{enumerate}
\item \textbf{D. Keep FDA Informed}
\end{enumerate}

Making the FDA aware of the activity is another helpful step to take from an evidentiary standpoint in establishing a Safe Harbor defense. Efforts

\begin{footnotes}


\end{footnotes}
should be made to keep the FDA informed of activities that are taking place. Communications with the FDA should be memorialized in writing. In the NeoRX decision, the court found it persuasive that the FDA was fully aware of Immunomedics' scale-up production plans in holding that Immunomedics' production of ImmunoRAID-CEA was reasonably related to the FDA approval process. 155

VII. CONCLUSION

In the twenty-three years since the Hatch-Waxman Act was enacted, the courts have applied the § 271(e)(1) in many different factual situations. In analyzing the various factual patterns and submitted evidence in cases where the Safe Harbor exemption applies, the data requirements of the FDA regulations have emerged as a factor of great importance. If information is generated that is relevant to the regulatory process or that is submitted to the FDA, many activities will fall within the ambit of the Safe Harbor exemption. Additionally, the unforeseeability of the amount of information required by the FDA during the regulatory approval process can work as an advantage for those seeking the Safe Harbor's protection. Thus, tailoring activities to meet FDA requirements for information, generating, and documenting relevant information from activities, and submitting information to the FDA are optimal ways to avail an activity of the Safe Harbor's protection. As the cases have shown, these simple and systematic steps taken before and during an activity can be enormously helpful in establishing a Safe Harbor defense.