EXAMINING THE § 271(E)(1) SAFE HARBOR OF THE HATCH-WAXMAN ACT: A LEGISLATIVE PROPOSAL GRANTING MANDATORY POST-MARKETING EXCEPTIONS*

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INTRODUCTION

Almost eighty percent of the pharmaceutical prescriptions in the United States are for generic drugs, which cost approximately eighty to eighty-five percent less than their branded equivalents. Enhancing consumer access to these affordable generic medicines is therefore a key congressional objective, as the Hatch-Waxman Act demonstrates. The Hatch-Waxman Act established a safe harbor to promote expedited generic drug development by granting generic entrants an exception to patent infringement when their experimental uses of patented drugs relate closely to regulatory approval. To maintain the continued FDA approval of their drugs, generic drug companies often conduct comparative post-marketing studies involving the patented drug equivalents. Thus, express protection of costly FDA-mandated studies to monitor generic drugs after they are sold to the public will aid the congressional goals of incentivizing generic drug development. The Supreme Court has continued to expand the safe harbor scope, aligning with these aims. In the most recent rulings on the § 271(e)(1) safe harbor for post-marketing uses, the closely-divided Federal Circuit issued contradictory opinions in Classen Immunotherapies, Inc. v. Biogen Idec and Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc. Classen denied safe harbor to post-marketing...

5 See Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661 (1990) (expanding the safe harbor to include medical devices); Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193 (2005) (expanding the safe harbor to include preclinical studies).
6 See Classen Immunotherapies, Inc. v. Biogen Idec, 659 F.3d 1057 (Fed. Cir. 2011); Momenta,
uses, while *Momenta* subsequently granted safe harbor for post-marketing studies mandated by the FDA, when the studies were required for continued approval of the generic manufacturer’s novel pharmaceutical.\(^7\)

Following the conflicting readings of the research use exception in *Classen* and *Momenta*, Congress should enact a statute limiting the safe harbor to explicitly allow only non-commercial, FDA-mandated post-marketing activity. This legislative solution will provide advance notice to generic companies seeking to patent medical inventions with federal regulatory agencies. Instead of confronting ambiguous Federal Circuit directions regarding the scope of permissible post-marketing uses, generic companies will be able to follow an express legislative framework. Once their generic therapeutics are marketed, the proposed statute will continue to promote generic drug development by enabling systemic post-marketing studies. Through these methods, the proposed statute aims to advance the primary congressional purposes behind § 271(e)(1), namely early and continuous generic marketing.

This Note analyzes Congressional intent behind § 271(e)(1) of the Hatch-Waxman Act, the goals for advancing early marketing of generic drugs, and the ongoing dispute over generic research activities permissible under the § 271(e)(1) safe harbor, and concludes by proposing a legislative solution to address the division. Part I of this Note provides an overview of the drug approval process and mechanisms for expediting generic drug approval within the Hatch-Waxman Act, including incentives for challenging the validity of patents held by pioneer, branded entrants through the § 355(j) revisions to the Act and through the experimental use exception in § 271(e)(1) of the Act. Part II examines litigation that analyzes the § 271(e)(1) safe harbor scope, and concludes by raising the need for a legislative proposal to clarify recent Federal Circuit disputes regarding specific post-marketing uses allowed by the safe harbor. Part III addresses the Federal Circuit conflict by suggesting a statute which expressly restricts post-marketing tests solely to studies mandated for continued FDA approval.


A. The Pharmaceutical Drug Development Process

Pharmaceutical drugs pass through an extensive development process before obtaining marketing approval from the Food and Drug

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\(^6\) 686 F.3d at 1358–59.

\(^7\) *Classen*, 659 F.3d at 1059; *Momenta*, 686 F.3d at 1358–59.
Administration ("FDA"), the chief regulatory agency of pharmaceuticals in the United States. Pharmaceutical drugs are divided into two categories: branded and generic. Branded, pioneer drugmakers must complete the entire drug development process, whereas generic drugmakers do not conduct the compound screening, preclinical trials, and clinical trials required for branded drugmakers and instead enter the drug development process at the drug application step. The drug development process comprises two main stages: 1) compound screening and 2) the FDA approval process. During the compound screening stage, pharmaceutical companies examine large numbers of compounds to identify active compounds that meet baseline efficacy and safety requirements for development into potential therapeutic leads. During the FDA approval process, pharmaceutical companies conduct preclinical and clinical trials to demonstrate the safety and efficacy of their drug candidates. Stage two begins with preclinical studies, where the drug candidate is first tested in the lab and representative animal species. This stage is essential for gaining marketing approval from the FDA. The branded entrant submits an Investigational New Drug ("IND") application to the FDA for its novel drug, which proceeds onto clinical trials once the IND demonstrates that preclinical trials pass specified thresholds for safety and potency.

Before a novel drug is approved, three phases of clinical trials must be conducted, where the therapeutic effects of medicines are tested in human subjects. Phase I tests the impact of the medicine in a small group of people to identify primary adverse effects while Phase II studies the effectiveness in larger groups of human subjects, and Phase

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10 Id.

11 JP Hughes et al., Principles of Early Drug Discovery, 162 BRIT. J. PHARMACOLOGY 1239, 1239–40, Fig. 1 (2011) (depicting the two main stages of drug development: 1. Compound screening, which comprises basic research, lead discovery), and 2. the FDA approval process, which comprises preclinical development, clinical development, and FDA filing).

12 Id. at 1239, Fig. 1, 1242–43, Table 1 (depicting the compound screening stage as the examination of a large number of compounds to identify active compounds with the desired safety and efficacy profiles for further development as drug candidates).


14 The FDA’s Drug Review Process: Ensuring Drugs Are Safe and Effective, supra note 8 (stating that the FDA requires preclinical studies of drug candidates in animals before clinical trials in humans).

15 See id.

16 Id.

III, the most expensive and lengthy phase, collects information to confirm the drug’s safety and efficacy in human subjects. After the drug candidate demonstrates sufficient efficacy in the clinical trials of Phases I–III, the drug candidate then proceeds onto the novel drug application filing process.

Following clinical trials, the branded manufacturer files a New Drug Application (“NDA”) to propose its drug for FDA approval. In contrast, generic drug manufacturers file Abbreviated New Drug Applications (“ANDA”), meaning that these manufacturers are not required to prepare novel safety and efficacy data for their drug candidates. Rather than having to conduct the preclinical studies and clinical trials discussed above, generic manufacturers only need to demonstrate that their generic drug has the same active ingredient, route of administration, dosage form, and strength as its branded counterpart, so that the generic entrant may use the safety and efficacy data of the bioequivalent drug generated by the branded manufacturer.

Once the FDA approves the new drug application, for both NDA’s and ANDA’s, the novel pharmaceutical enters Phase IV, which includes several post-marketing research categories. Phase IV demands consistent monitoring of the new drug’s effects, even after the FDA approves use of the pharmaceutical drug in humans, to confirm the drug’s safety and effectiveness over long periods of use. Accordingly, mandatory Phase IV research studies are also termed post-marketing studies. Phase IV research comprises three main categories: mandatory post-marketing commitments required by the FDA (“PMC”); commercial, optional drug company PMC’s which support continued drug development, and non-commercial, voluntary third party PMC’s conducted by independent researchers.

Within the first category, the FDA requires that drug manufacturers continue to systematically monitor use of marketed drugs

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19 Id.
20 See How Drugs Are Developed and Approved, supra note 13.
23 Id.
24 Id.
26 FAQ, ClinicalTrials.gov—Clinical Trial Phases, supra note 17.
28 ESSENTIALS OF CLINICAL RESEARCH, supra note 25, at 76.
in patients to produce data on the drugs’ safety, efficacy and optimal
conditions for usage.\textsuperscript{29} For example, the FDA may require branded drug
manufacturers to report adverse effects that were not observed in the
pre-approval clinical studies.\textsuperscript{30} Mandatory PMC’s often include drug-
drug interaction studies,\textsuperscript{31} research on novel pill or intravenous drug
formulation, and studies of the drug’s effect within specific populations
to demonstrate the drug’s safety and efficacy.\textsuperscript{32} For continued ANDA
approval of their generic versions of branded drugs, generic drug
companies also use data generated by branded manufacturers.\textsuperscript{33} In short,
the FDA demands Phase IV post-marketing studies to assuage consumer
safety concerns, to ensure that currently marketed drugs distributed in
mass quantities to the public continue to meet minimum FDA standards
for quality.\textsuperscript{34}

The optional drug company PMC category is primarily
commercial; branded drug companies initiate optional PMC’s in support
of a promotional and marketing strategy.\textsuperscript{35} Here, the branded
manufacturers start these studies to demonstrate their drug’s
affordability to differentiate it from competitors while promoting the
drug to medical professionals.\textsuperscript{36} As a result, these marketing fringe costs
can be high for drug manufacturers.\textsuperscript{37} The second Phase IV category is
distinguished from the first by its commercial and optional nature.
Whereas the first category is FDA-mandated, in the second category,
branded drug manufacturers often begin PMC’s to support aggressive
marketing campaigns for selling its novel pharmaceutical to physicians
and other medical professionals.\textsuperscript{38} The branded drug manufacturer aims
to benefit from increased sales as a result of its voluntary, commercial
Phase IV post-marketing activities.\textsuperscript{39}

The third Phase IV category features voluntary post-approval

\begin{thebibliography}{99}
\bibitem{29} Morris, supra note 27, at 255.
\bibitem{30} See Postmarketing Requirements and Commitments: Introduction, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketing PhaseIVCommitments, (last updated Feb. 8, 2012) (stating that FDA-mandated post-marketing studies may require the identification of unexpected, serious risk resulting from use of the drug, as indicated by available data); see Steenburg, supra note 27, at 300, n.43.
\bibitem{32} ESSENTIALS OF CLINICAL RESEARCH, supra note 25, at 75, Table 5.3 (listing FDA-mandated post-marketing study examples, including studies of drug-drug interactions, formulation advancement, and special populations comprising the elderly or children).
\bibitem{33} See Momenta Pharm., Inc. v. Amphastar Pharm., Inc., 686 F.3d 1348, 1358 (Fed. Cir. 2012); see Abbreviated New Drug Application (ANDA): Generics, supra note 4.
\bibitem{34} See Postmarketing Requirements and Commitments: Introduction, supra note 30.
\bibitem{35} Steenburg, supra note 27, at 371–72.
\bibitem{36} Id.
\bibitem{37} Morris, supra note 27, at 255.
\bibitem{38} Steenburg, supra note 27, at 371–72.
\bibitem{39} Id.
\end{thebibliography}
studies of branded drugs executed by independent researchers. Also considered to be post-marketing, this category of Phase IV research is similarly non-mandatory, but it is conducted by a third party, rather than the branded drug manufacturer. Like the FDA-mandated research, independent studies do not have explicit commercial goals. Independent scientific research on branded drugs generally lacks a commercial motive as drug manufacturers do not monitor independent researchers; instead, the research studies are usually supervised by governmental science boards. When adverse drug effects are uncovered during Phase IV studies, the FDA reevaluates its decision to approve the drug and updates the labels of the drug in question. The following section explores the federal statutory provisions for expediting the drug approval and development process outlined above.

B. Background of the 35 U.S.C. § 271(e)(1) Research Use Exception


Recognizing the competing interests of branded pharmaceutical companies and generic pharmaceutical companies in the FDA approval process, Representative Henry Waxman and Senator Orrin Hatch drafted the Hatch-Waxman Act of 1984 to balance these opposing goals. The Act aimed to simultaneously increase the availability of lower cost generic drugs while providing increased incentives for pharmaceutical research and development, in the hope that generic pharmaceutical companies could quickly market affordable medicines to the public.

To win congressional approval of the bill, the sponsors had to include two complementary statutory provisions, sections 201 and 202, each serving the interests of the competing constituencies. Section

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40 ESSENTIALS OF CLINICAL RESEARCH, supra note 25, at 76.
41 Id. at 79.
42 See id. at 79, 202 (stating that the investigator dictates the research study’s objective and purpose).
43 See id. at 76, 151–52 (stating that supervision of independent observational studies is not affiliated with the pharmaceutical company).
46 Also known as the Drug Price Competition and Patent Term Restoration Act of 1984. Id. at 1424.
47 Kotze, supra note 45, at 1424 (describing the history and purpose of the Hatch-Waxman Act); Morris, supra note 27, at 247–48.
201, enacted as 35 U.S.C. § 156, aimed to protect the interests of branded manufacturers by reducing the harm from “front end distortion,” the loss of patent protection during the beginning of the patent period, which results from marketing prohibitions on branded pharmaceutical products during regulatory review.\footnote{Id. at 112, 114 (“[S]ection 201 was intended to eliminate front end distortion—whereby a patent began to run while a product was still undergoing regulatory review and could not be sold by the manufacturer.”).} With the intent of remedying this regulatory delay, section 201 was created to provide patent term extensions for branded drug manufacturers.\footnote{Id. at 112.} Meanwhile, section 202, amending § 271(e)(1) of the Hatch-Waxman Act,\footnote{See id. (stating that Section 202 amended § 271(e)(1) of the Hatch-Waxman Act).} reduces “back end distortion,” the de facto patent term extension created when generic competitors experience a delay while bringing their products to market, since they cannot test branded drugs during the patent term.\footnote{Id.; see also id. at 114 (defining back end distortion as an unintended patent extension where competitors cannot use patented invention in tests for regulatory approval).} In short, § 271(e)(1) was added to shield generic drug companies when their activities merely involve tests of branded drug equivalents closely tied to the regulatory approval process,\footnote{Id. at 114.} thereby expediting generic drug approval.

The ANDA, the separate new drug application specifically designed for generic manufacturers, further maximizes the efficiency of the generic drug approval process.\footnote{See Abbreviated New Drug Application (ANDA): Generics, supra note 4.} 21 U.S.C. 355(j) codified the Hatch-Waxman Act revisions that established ANDA’s.\footnote{See Kotze, supra note 45, at 1430 n.64.} An ANDA limits the patent monopoly branded manufacturers hold over their novel pharmaceuticals, since generic manufacturers face a lower burden of proof for demonstrating bioequivalence, safety, and potency of their products.\footnote{See id. at 1430–31.} In the ANDA, generic entrants only need to demonstrate that their generic versions have the same active ingredient and general pharmacokinetics of the branded drug, rather than having to perform safety and potency tests already conducted by the senior, branded manufacturer, as would be required in a branded new drug application.\footnote{See 21 U.S.C. § 355(j)(2)(A)(iv) (2012).} Practically speaking, this means that the generic manufacturer simply must prove its generic drug has the same active ingredient, route of administration, dosage form, strength, and labeling as the branded counterpart.\footnote{See 21 U.S.C. § 355(j)(2)(A)(ii)-(v) (2012).} The ANDA allows generic manufacturers with limited resources to bring generic drugs to the market more quickly.
35 U.S.C. § 271 identifies various types of patent infringement, defined as the unauthorized use of a competitor’s patented invention. Congress created two provisions within the Hatch-Waxman Act to encourage generic entrants to challenge branded patents: 1) incentives for successful Paragraph IV infringement challenges, and 2) the § 271(e)(1) safe harbor for generic infringers. As for the first provision, the Hatch-Waxman Act creates benefits for generic drug manufacturers when they file Paragraph IV certifications in their ANDA’s, which state that the branded patent is invalid under patent law or that their drug does not infringe the branded equivalent. For example, section 355(j) incentivizes generic entrants when they successfully question the patent validity of branded drugs by filing successful Paragraph IV ANDA challenges. These successful Paragraph IV challenges grant generic drug plaintiffs a 180-day exclusivity advantage over other generic companies when their invalidity claims succeed, so that the successful generic plaintiffs gain a 180-day hold on the FDA approval of generic, bioequivalent competitors.


Patent infringement arises during ANDA filings when the generic manufacturer uses pharmacokinetic data of the bioequivalent patented drug in the ANDA. Within the Hatch-Waxman Act, § 271(e)(1) is a second means of encouraging generic challenges to branded patents. Section 271(e)(1) creates a statutory safe harbor for limited types of infringing experimental activity, when the activity is conducted to gain regulatory approval. While § 271 bars most uses of patented products without the patent holder’s consent, the safe harbor amendment in § 271(e)(1) grants protection for generic infringers of pharmaceutical

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60 Paragraph Four Explained, PARAGRAPHER FOUR REP. http://www.paragraphfour.com/explained/process.html (last visited Mar. 7, 2013); Kotze, supra note 45, at 1431–32 (stating that both the generic use safe harbor and the ANDA provisions encourage generic companies to challenge patented products).
61 Id.
64 Rainey & Schoenhard, supra note 59 (citing an abbreviated new drug application, ANDA, as one major example of artificial patent infringement, as exemplified in Eli Lilly & Co. v. Medtronic, Inc.) (last visited Sept. 21, 2013).
patents when the infringing use relates closely to research purposes.66

Legislators hoped to promote early marketing of generic pharmaceuticals with this generic research exception.67 In particular, Congress intended to limit the patent monopoly of branded manufacturers by complementing section 201 of the Hatch-Waxman Act with section 202, which included the safe harbor exception for generic manufacturers of pharmaceuticals and medical devices.68 Section 271(e)(1) protects infringing activities under the research exception when they reasonably relate to the regulatory approval of drugs:

It shall not be an act of infringement to make, use, offer to sell, or sell... a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) 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... 69

Before the statutory revision, the use of experimental data created by branded manufacturers was considered infringing activity.70 However, the revision created a safe harbor provision that lowers the barriers to early generic marketing in two main ways: 1) expediting generic market entry and 2) lowering the burden for demonstrating drug bioequivalence.71 As to the first, 35 U.S.C. § 271(e)(1) hastens market entry for generic drugs, by allowing generic companies to use regulatory data generated by branded pharmaceutical manufacturers in their ANDA’s. This makes it easier to enter the generic market, since the production of drug safety and efficacy data is expensive and time-consuming.72 Under § 271(e)(1), generic manufacturers no longer need to produce their own, often expensive, safety and efficacy studies for FDA regulatory approval. In short, § 271(e)(1) grants generic manufacturers an exception for uses of research produced by branded

66 See Kotze, supra note 45, at 1431.
68 See Bloch, supra note 48, at 111, n.1.
70 See Roche Prods., Inc. v. Bolar Pharm. Co., 733 F.2d 858 (Fed. Cir. 1984) (holding that generic manufacturers cannot use patented active compounds to produce data used for FDA approval of its own generic version of the drug).
71 See Morris, supra note 27, at 262–63.
72 See id.
entrants, when the studies are used for FDA submissions.\textsuperscript{73} Pioneer drug manufacturers can no longer receive extended patent monopolies on their branded drugs, the side effect formerly created by the regulatory delay for generic entry.\textsuperscript{74} Since generic entrants previously needed to generate the same detailed tests of drug potency and safety as their branded counterparts, while constrained by fewer financial resources, without section 271(e)(1) generic approval was significantly delayed.

As a counterpart to the safe harbor, § 271(e)(2) explicitly does not protect an application for federal regulatory approval for a patented drug’s bioequivalent when the application employs the patented drug in anticipation of a “commercial manufacture, use, or sale” of the infringing drug:

\begin{quote}
It shall be an \textit{act of infringement} to submit . . . an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent . . . \textit{if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.}\textsuperscript{75}
\end{quote}

Section 271(e)(2) establishes that commercial uses employed during ANDA’s do not qualify for the research protection of § 271(e)(1).\textsuperscript{76} Read literally, the statute appears to suggest that post-marketing activities with commercial motivations might be entirely excluded under § 271(e)(2), but the increasingly broad judicial interpretations of § 271(e)(1) provide room for a more lucid, novel legislative approach to post-marketing studies that might include commercial potential.\textsuperscript{77}

3. The Legislative History of the Hatch-Waxman Act

Courts have turned to the legislative history of the Hatch-Waxman Act to define the scope of expansive § 271(e)(1) protection for activities reasonably related to the regulatory approval process.\textsuperscript{78} The courts are divided on the particular federal regulatory processes that are protected, since § 271(e)(1) protects what might otherwise be considered infringement during submissions for the regulatory approval of

\begin{itemize}
  \item \textsuperscript{73} 35 U.S.C. § 271(e)(1).
  \item \textsuperscript{74} See Kotze, supra note 45.
  \item \textsuperscript{75} 35 U.S.C. § 271(e)(2) (2012) (emphasis added).
  \item \textsuperscript{76} See id.
  \item \textsuperscript{78} See Classen Immunotherapies, Inc. v. Biogen Idec (Classen), 659 F.3d 1057, 1071 (Fed. Cir. 2011); see also Momenta, 686 F.3d at 1354–57.
\end{itemize}
pharmaceuticals.\textsuperscript{79} In addition, the inclusion of medical devices and FDA-mandated post-approval studies under the safe harbor were issues for interpretation in cases involving § 271(e)(1).\textsuperscript{80}

The legislative history of the Hatch-Waxman Act provides further insight into the source of the divergent § 271(e)(1) interpretations. As the 1984 House Committee on Energy and Commerce Report stated, the Act aims to increase the availability of affordable generic drugs and reduce the regulatory delay for generic entrants.\textsuperscript{81} However, narrow court readings of the research exception cited this House Report for allowing experiments that use patented drugs only when the activity does not pose an adverse economic impact on the branded manufacturer’s patent monopoly.\textsuperscript{82} Under this restricted view of permissible uses, generic experimentation would be allowed only in preparation of commercial sales that begin after the branded patent expires.\textsuperscript{83} Moreover, the House Report’s language permitting generic experimental use during the final year of the branded patent’s life is cited in support of a narrow interpretation allowing generic manufacturers to only conduct bioequivalence tests.\textsuperscript{84} As a result of ambiguous language within the legislative history, the scope of the safe harbor likely faces continued litigation in the Supreme Court, the Federal Circuit and the lower courts.\textsuperscript{85}

The split in authority over the scope of the safe harbor exception centers on two issues: 1) the protection of product categories\textsuperscript{86} and 2)
the protection of pre-marketing and post-marketing uses. On the issue of product categories, a broad interpretation of the safe harbor might protect all products encompassed in the Food, Drug, and Cosmetic Act ("FDCA"), including cosmetics and medical devices, while a narrower reading might protect only pharmaceuticals and veterinary biological products, as a literal reading of the statute would dictate. As for the second issue, the proposed inclusion of post-marketing studies drives additional litigation, especially since some courts mistakenly view all post-marketing research as profit-driven. However, generic post-marketing research is more nuanced. Some post-marketing studies are voluntary, promotional activities, specifically designed to generate additional revenue for the pharmaceutical company. Other post-marketing studies might even be conducted by independent, third-party researchers with no financial interest in the commercial success of the generic manufacturer. Meanwhile, the FDA and other federal regulatory agencies mandate a significant number of post-marketing studies. These mandatory, ongoing research activities help promote early generic marketing of essential medical inventions, a primary Congressional goal driving the passage of the research use exception. The following section examines key Supreme Court and Federal Circuit cases that analyze the scope of § 271(e)(1) protection.

II. AN ANALYSIS OF LITIGATION SURROUNDING OTHERWISE INFRINGING ACTIVITY ENCOMPASSED BY THE 35 U.S.C. § 271(e)(1) SAFE HARBOR

As mentioned earlier, the use of a patented invention without a formal agreement, for example, a licensing agreement, constitutes patent infringement. In the pharmaceutical arena, when the infringing use is primarily research based, the Hatch-Waxman Act creates a research exception through 35 U.S.C. § 271(e)(1) for otherwise infringing activity that "reasonably relate[s] to the development and submission of information" for the approval of the FDA and other

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87 See Momenta, 686 F.3d 1348 (Fed. Cir. 2012) (debating the inclusion of specific post-marketing studies in the research use exception); Classen, 659 F.3d 1057.
88 See Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661 (1990) (debating the inclusion of medical devices under the safe harbor, as the text of the safe harbor only expressly identifies protected uses of drug research used in submissions for federal regulatory approval).
89 Bloch, supra note 48, at 112.
90 See Classen, 659 F.3d at 1070.
91 See Steenburg, supra note 27, at 371–72.
92 ESSENTIALS OF CLINICAL RESEARCH, supra note 25, at 76.
93 See Morris, supra note 27, at 255.
94 See H.R. REP. NO. 98-857, supra note 2, at 14–15 (stating that one purpose of the Hatch-Waxman Act is to limit the regulatory delay for companies that require federal pre-marketing approval).
95 See Rainey & Schoenhard, supra note 59.
Before and after the passage of the statutory research exception, the Federal Circuit has taken a range of approaches while choosing whether to allow specific exceptions to infringements involving experimental use. Meanwhile, the Supreme Court has broadened the safe harbor scope in consecutive cases. The Supreme Court, in 1990, moved toward a generous reading of the § 271(e)(1) exception with the Eli Lilly & Co. v. Medtronic, Inc. decision. In 2005, in Merck KGaA v. Integra Lifesciences I, Ltd., the Court also granted a broad research exception for most activity reasonably relating to FDA approval, including preclinical studies. Subsequently, the Federal Circuit addressed permissible post-marketing uses in two contentious cases: Classen Immunotherapies, Inc. v. Biogen Idec, in 2011, which appeared to exclude all post-marketing activity, and Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc., in 2012, which granted exceptions for FDA-mandated post-marketing tests, thereby generating confusion as to the scope of post-marketing studies allowed under the safe harbor.

A. Before the § 271(e)(1) Safe Harbor: The Narrow View of the Research Use Exception

When generic drug companies use patented safety tests produced by branded drug manufacturers in their own ANDA’s, litigation often results. The branded drug manufacturer may bring suit for infringement when a generic drug manufacturer files an ANDA using the branded entrant’s data. In 1984, before the institution of the § 271(e)(1) research exception, Roche Products, Inc. v. Bolar Pharmaceutical Co. categorically held that generic manufacturers could not use patented active compounds to produce their own studies in the FDA approval process. Roche barred generic manufacturers from using studies of patented, branded pharmaceuticals in their FDA applications for the generic bioequivalent counterparts. However, the

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98 See Eli Lilly, 496 U.S. at 665–66 (protecting infringing studies of medical devices as well as drugs).
99 Integra, 545 U.S. at 203.
100 See Alfred B. Engelberg, Special Patent Provisions for Pharmaceuticals: Have They Outlived Their Usefulness?, 39 IDEA 389, 401–02 (1999); Morris, supra note 27, at 264 (stating that an “artificial” act of infringement “leads to controversy when an ANDA with Paragraph IV certification is filed).
passage of § 271(e)(1) reversed the broad, categorical denial of generic research protection in *Roche*. In a gesture benefitting generic drug companies, § 271(e)(1) directly granted generic manufacturers permission to use data generated by branded manufacturers when their activities were closely tied to federal regulatory approval. Subsequently, however, the Federal Circuit produced contradictory interpretations while attempting to determine the proper degree of reasonable relation to regulatory approval for permissible research activities.

B. Moving Toward a Broader Reading of the § 271(e)(1) Safe Harbor

As the first major test of the research exception in the Federal Circuit, *Warner-Lambert Co. v. Apotex Corp.* reaffirmed § 271(e)(1), upholding the experimental use exception for otherwise infringing activity by generic manufacturers. After *Warner-Lambert*, the issue of acceptable types of generic drug manufacturer infringement, where a generic manufacturer files an ANDA using the branded drug manufacturer’s regulatory approval data, continued to be unsettled in the Federal Circuit. The Supreme Court and the Federal Circuit have diverged while interpreting the scope of permissible generic infringing activities.

The Supreme Court’s opinions have continued the successive expansion of the safe harbor’s scope. In *Eli Lilly*, the owner of a ventricular defibrillation device patent sought to enjoin a competitor from conducting research with its patented invention for regulatory approval under the FDCA. The *Eli Lilly* Court considered the structure of the Hatch-Waxman Act, which ultimately led them to take a generous view of the § 271(e)(1) safe harbor, holding that the safe harbor also protected uses of medical devices.

The Court found that § 271(e)(1) does not merely protect otherwise infringing tests that employ branded drugs, but also protects analogous uses of non-pharmaceuticals,
like medical devices, so long as the research is conducted for FDCA regulatory approval.\textsuperscript{113} Although the statutory language of § 271(e)(1) explicitly protects only research for purposes closely related to regulatory approval of drug manufacture and use, including inventions under “Federal law which regulates the manufacture, use, or sale of drugs,”\textsuperscript{114} the court focused on the public policies underlying the construction of the Hatch-Waxman Act.\textsuperscript{115}

To arrive at its conclusion, the \textit{Eli Lilly} Court analyzed 35 U.S.C. § 156, the Hatch-Waxman Act’s expansive benefits for branded entrants, in comparison with the Act’s concessions to generic entrants, including the § 271(e)(1) research use exception,\textsuperscript{116} finding that the Act sought to strike a measured balance of interests.\textsuperscript{117} The \textit{Eli Lilly} Court recognized that the safe harbor protection awarded to generic drug manufacturers was just as applicable to generic \textit{medical device} manufacturers; in uses related to regulatory approval, the Court found that the protection of § 271(e)(1) extended to “all inventions” and was not limited to “drug-related inventions alone.”\textsuperscript{118} Ultimately, the \textit{Eli Lilly} Court decided that allowing branded \textit{medical device} manufacturers, providers of inventions regulated by the FDCA, to benefit from the patent term extension, while denying the corresponding safe harbor benefits to their generic counterparts would upset the Hatch-Waxman Act’s complementary design.\textsuperscript{119} As a result, the Court granted broad § 271(e)(1) protection, allowing generic manufacturers to test branded medical devices during the regulatory delay, when they were related to medical device regulation governed by the FDCA.\textsuperscript{120}

In 2005, in \textit{Merck KGaA v. Integra Lifesciences I, Ltd.}, the Supreme Court continued to expand its interpretation of the § 271(e)(1) research use safe harbor by holding that generic competitors could use patented drugs in preclinical tests when the tests might produce information relevant to an NDA, moving even closer to the inclusion of post-marketing studies.\textsuperscript{121} There, the owner of a patented peptide with pharmaceutical potential sued a competing research institution, Scripps, for infringement.\textsuperscript{122} Scripps used tests of the peptide’s “efficacy, specificity, and toxicity” as a benchmark to evaluate the pharmaceutical

\textsuperscript{113} \textit{Id.} at 678.
\textsuperscript{114} § 271(e)(1).
\textsuperscript{115} \textit{Id.} at 665–74, 680 (emphasis added).
\textsuperscript{116} \textit{Id.}
\textsuperscript{118} \textit{Eli Lilly}, 496 U.S. at 665–66.
\textsuperscript{119} \textit{Id.} at 661.
\textsuperscript{120} See \textit{id.} at 665–66 (stating that § 271(e)(1) protects “all inventions, not just drug-related inventions alone”).
\textsuperscript{121} See McMinn, \textit{supra} note 83, at 235; \textit{Merck KGaA v. Integra Lifesciences I, Ltd.}, 545 U.S. 193, 207 (2005).
\textsuperscript{122} \textit{Integra}, 545 U.S. at 197–200.
potential of its own related peptide. In essence, Scripps, in preparing its novel peptide as a drug candidate, used the patented peptide for general comparison, but did not submit an NDA actually including the infringing tests.

The Court held that § 271(e)(1) protected all uses of patented inventions in manners “reasonably related to the development and submission of information” submitted for FDA approval and employed for further drug development. Thus, the infringing actions fell within the safe harbor because the infringer merely used the patented peptide as a research benchmark, since the subject of its NDA was a related peptide and not the bioequivalent version of the patented peptide. Despite the indirect link between the preclinical infringing tests and the subsequent FDA submission, the Court believed that the § 271(e)(1) safe harbor should be construed generously. Here, the Court concluded that the safe harbor protected the infringer’s preclinical tests of the drug’s “efficacy, mechanism of action, pharmacokinetics, and pharmacology,” and thus should be considered reasonably related to information submitted for regulatory approval. The Court held that such tests were permissible uses, and did not find the distinction between preclinical and clinical research as paramount to the decision for inclusion under the research exception.

The Court concluded that the infringing tests were closely related to an FDA submission, since preclinical research on a drug candidate’s pharmacokinetic effects, like those conducted by Scripps, often lead to an application for a related drug. In supporting its decision, the Integra Court noted that the § 271(e)(1) research exception does not categorically exclude experiments on drugs that do not ultimately become the subject of FDA NDA’s. The Court’s expansive reading of “reasonably related” broadened the protective reach of § 271(e)(1), paving the way for flexible interpretations of research “reasonably related” to FDA submissions. This broad interpretation places

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123 Id. at 198–99.
124 See id.
125 Id. at 202.
126 See id. at 198–99; 205–08.
127 Id. at 206 (stating that § 271(e)(1) provides broad protection for the use of patented drugs related to FDA regulatory approval).
128 Id. at 203.
129 Id. at 193.
130 Id. at 202–03 (finding that preclinical studies are also reasonably related to FDA regulatory approval, and subsequently protected by § 271(e)(1)).
131 See id. at 207–08 (protecting an infringer’s preclinical, pharmacokinetic studies under § 271(e)(1), when the infringer reasonably believes the drug candidate may become the subject of an FDA drug application).
132 Id. at 205–06.
133 See id. at 206–07 (stating that § 271(e)(1) “leaves adequate room for experimentation … on the road to regulatory approval,” and the reasonable relation requirement is met when the
preclinical research featuring drug candidates with commercial potential squarely under the research protection of § 271(e)(1), when the research is likely create information used in a drug’s FDA application. As in Eli Lilly, the Integra Court continued to advance a broad interpretation of § 271(e)(1).

C. The Federal Circuit’s Narrow Interpretation of § 271(e)(1)

In the 2011 decision of Classen Immunotherapies, Inc. v. Biogen Idec, the Federal Circuit barred the protection of a generic company’s post-marketing uses of an immunization method developed by the patent holder, in a narrow interpretation of the § 271(e)(1) exception. In a divided opinion, the court declined to extend protection to a generic drug manufacturer’s routine, voluntary studies following FDA approval of a patented immunization method, which evaluated the link between children’s vaccinations and the risk of developing immune disorders.

To rationalize the exclusion of the infringer’s post-marketing studies on adverse side effects of vaccination from § 271(e)(1) protection, the majority emphasized the voluntary nature of the post-approval reports. The court reiterated the need to restrict the research use exception to pre-marketing approval activities and highlighted the commercial nature of post-marketing studies, given the primary legislative purpose behind the research use exception, expediting generic regulatory approval. Since the Classen court stated that the research exception was confined to purely non-commercial purposes, and the post-approval studies were linked to commercial activity, they were found to be indisputably beyond the scope of the research exception. The Classen court found that the Integra holding supported its reasoning, emphasizing the non-commercial impact of the infringer’s permissible, voluntary post-approval studies in Integra. The court further distinguished Integra on its facts by noting that the preclinical research protected in Integra would likely lead to an NDA closely linked to the drug candidate under investigation, whereas the post-approval activities barred in Classen would not lead to an

“drugmaker has a reasonable basis for believing a patented compound may work ... to produce a particular physiological effect, and uses the compound in research” that would likely result in an FDA submission).

134 Id.
135 Classen Immunotherapies, Inc. v. Biogen Idec, 659 F.3d 1057, 1057 (Fed. Cir. 2011).
136 Id. at 1070.
137 Id. at 1070–71.
138 Id.
139 Id. at 1070–72 (stating that the research use exception did not apply to activity conducted after FDA marketing approval, by further arguing that the infringer’s activity was not research used to produce a new drug application, and beyond the exception’s scope).
140 See id. at 1071–72.
application for drug approval. The majority cited the legislative record, including the 1984 House Report discussed in the legislative history section above, as foundation for its opinion that only premarketing research is protected for establishing the bioequivalence of a generic drug to its branded equivalent. The Classen dissent, however, persuasively pointed out that the inclusion of premarketing research does not exclude postmarketing research from § 271(e)(1) protection. Since the statutory language of § 271(e)(1) protects all uses reasonably related to regulatory approval, as emphasized in Integra, the post-marketing research of the infringer in Classen would meet this definition if mandated by the FDA. Accordingly, the Classen dissent convincingly articulated that the majority followed an erroneously narrow reading of § 271(e)(1) when it limited the safe harbor to pre-marketing uses.

Not only did the majority err in its exclusion of post-marketing research from § 271(e)(1) protection, the majority also incorrectly focused on the commercial nature of protected research. Uses of patented research following FDA approval, termed post-marketing activity, can range from voluntary, promotional marketing activities to additional FDA-mandated studies to ensure continued safety and efficacy of the approved pharmaceutical. Thus, the Classen majority ignored the other post-marketing activities, and concentrated primarily on the commercial potential of the generic manufacturer’s vaccine studies. Since all post-marketing activities are potentially commercial in nature, the majority in Classen reintroduced ambiguity for the protection of post-marketing uses, where Integra had already presented a clear approach. This is problematic because after drug approval, the generic manufacturer must conduct systemic monitoring of the approved drug to continue to market the drug.

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141 See id. (stating that the infringer’s research activities did not lead to data used in a new drug application, meaning § 271(e)(1) protection would not apply).
142 Id. at 1071 (citing the House Report as support for protecting premarketing research under the proposed § 271(e)(1) exception).
143 Id. at 1071 (stating the infringing generic manufacturer’s activities were not premarketing, and therefore not protected by § 271(e)(1)).
144 Id. at 1082–83 (Moore, J., dissenting) (stating that the inclusion of premarketing activity under § 271(e)(1) does not restrict § 271(e)(1) protection to premarketing uses alone).
146 See Classen, 659 F.3d at 1083–84 (Moore, J., dissenting).
147 See id.
148 Id. (stating that the reasonable relation test focuses on the close relationship between the protected activity and FDA regulatory requirements, and not the activity’s commercial or non-commercial purpose).
149 Postmarketing Surveillance Programs, supra note 44.
150 ESSENTIALS OF CLINICAL RESEARCH, supra note 25, at 75–76.
151 See Classen, at 1070–72.
152 FAQ, ClinicalTrials.gov, supra note 26.
monitoring is linked to commercial sales, but the § 271(e)(1) scope should not depend on the commercial nature of the post-marketing studies. Instead, whether or not the research is FDA-mandated should be the litmus indicator for what constitutes permissible post-marketing research.

D. Returning to a Broad Interpretation of § 271(e)(1): Granting Post-Marketing Uses

Only a year after Classen, the Federal Circuit reversed course on Classen’s holding in Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc., the most recent Federal Circuit ruling on the issue of the § 271(e)(1) research use exception for the otherwise infringing activities of generic manufacturers.153 The Momenta court extended the safe harbor to include FDA-mandated post-marketing uses,154 mirroring the Supreme Court’s expansive views of the research exception.155

In Momenta, the invention at issue was enoxaparin, an anti-blood clotting agent.156 Previous pharmaceutical cases involving § 271(e)(1) featured traditional small molecule drugs,157 but the drug in Momenta was not a small molecule, and instead comprised a complex combination of sugars of varying sizes.158 While the drug manufacturer Amphastar filed an ANDA on the generic drug first, Momenta, a competing generic manufacturer of the same drug, was the first to market this generic drug and held a patent on the method for analyzing the complex drug.159

Because bioequivalence analysis of the drug under contention was extremely difficult,160 the infringer Amphastar used the method of its

154 Id. at 1356–57, 1359–61.
156 Id. at 1349.
159 Momenta, 686 F.3d at 1351; Wilson, supra note 158.
160 Momenta, 686 F.3d at 1362 (Rader, J., dissenting) (citing the difficulty of the patented procedure for bioequivalence analysis).
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competitor, Momenta, to verify bioequivalence of the two pharmaceuticals in order to meet FDA standards after approval.161 Subsequently, Momenta sued the competing generic drug manufacturer, Amphastar, for unauthorized use of its patented analytical method during the competitor’s NDA filing.162 The alleged infringement was necessary to fulfill FDA requirements for continued marketing of Amphastar’s own drug following its ANDA filing.163 Thus, Momenta directly raised the issue of whether the § 271(e)(1) safe harbor should also encompass mandatory post-marketing studies, an issue Classen left open in rejecting protection for optional post-marketing activities.164

Momenta interpreted § 271(e)(1) broadly, as the Supreme Court had in Integra and Eli Lilly.165 In contrast to the preclinical experiments that would likely have become part of the NDA in Integra, which were closely related to the initial FDA approval of a generic drug, the infringing activities in Momenta were vital for continued FDA approval of the infringer’s generic drug, so that both were closely tied to an eventual submission for FDA approval.166 Therefore, the Momenta experiments also fit within the statutory requirement of 271(e)(1) that they be “reasonably related” to submission for federal regulatory approval.”167

In Momenta, the infringing activity was a mandatory part of the FDA approval process, fitting the statutory requirement of “reasonably related” to submissions for federal regulatory approval, meaning the court found that the infringer’s post-marketing tests must be protected in its reading of § 271(e)(1).168 Here, the tests for determining bioequivalence to the branded pharmaceutical were essential for continued approval of the infringer’s drug, so that the § 271(e)(1) safe harbor also protected these infringing uses of the patented bioequivalence tests.169

Despite the post-marketing nature of the infringing research, the Momenta court distinguished Amphastar’s post-marketing commitments as monitoring tests for producing safety and efficacy data mandatory for receiving continued FDA approval.170 The court found that the plain language of § 271(e)(1) does not distinguish between post-approval and

161 Id. at 1349–52, 1358.
162 Id. at 1351–52.
163 Id. at 1358.
164 See id. at 1353, 1357–59.
165 See id. at 1355-57, 1358–59.
166 See id. at 1356–59.
167 See id.
168 Id. at 1356–57, 1359–61.
169 Id. at 1359 (stating that the FDA requires generic drug manufacturers to carry out tests after drug approval to confirm that every batch of the drug has a composition identical to that of the branded drug).
170 Id. at 1358–59.
pre-approval activity, and confirmed that the holding in *Classen* did not foreclose post-approval activity from protection. The court specifically emphasized that the § 271(e)(1) safe harbor protects testing after the drug’s FDA approval, finding that the infringer’s tests are included even when the infringing activity is “carried out after approval” according to FDA regulations, to ensure the bioequivalence of the infringer’s generic drugs sold commercially.

Thus, *Momenta* included post-marketing research by generic manufacturers under the umbrella of § 271(e)(1) protection, despite its link to commercial activity.

Although the majority relied on legislative history in reaching its decision, finding its broad interpretation of § 271(e)(1) closely aligns with Congress’ goals of promoting expedited generic approval, Judge Rader, who had written the *Classen* opinion, dissented here, also applying the legislative history, to protest the inclusion of commercial, post-marketing infringing research within the reach of § 271(e)(1). Relying on House Reports and Congressional testimony, Judge Rader emphasized that infringement is only protected by § 271(e)(1) when the infringing activity would be used for applications for FDA approval. An approach strongly favoring the intellectual property rights of pioneer manufacturers was the foundation for Judge Rader’s dissent.

Judge Rader’s dissent argued that the court’s decision to include post-marketing activities was granting generic manufacturers a “free license to trespass” on the patent rights of the branded manufacturer, which he feared would allow the infringer to profit commercially from its post-marketing infringement. His textual argument was based on the legislative history preceding the passage of § 271(e)(1) of the Hatch-Waxman Act, finding that the court’s decision would ignore the legislative intent behind § 271(e)(1) to promote expedient generic

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171 Id.
172 Id. at 1359.
173 See id. at 1358–59.
174 Id. at 1354–57.
175 See *Classen Immunotherapies, Inc. v. Biogen Idec*, 659 F.3d 1057 (Fed. Cir. 2011).
176 *Momenta*, 686 F.3d at 1362 (Rader, J., dissenting).
177 Id. (Rader, J., dissenting) (suggesting that the legislative history of the Act, including “2 House reports, 25 statements and letters … and many pages of Congressional testimony” supports his limited reading of the § 271(e)(1) safe harbor).
178 Id. at 1361–62.
179 Id. at 1367 (Rader, J., dissenting).
180 Id. at 1366 (Rader, J., dissenting).
181 Id. at 1365–66 (Rader, J., dissenting) (describing how the authors of § 271(e)(1) intended for the Hatch-Waxman Act’s protections to be limited, stating that the § 271(e)(1) authors forbade the protection of post-approval activities including the “commercial sale of a patented drug” by the junior manufacturer, while allowing the junior manufacturer to purchase the patented drug in research quantities alone).
approval alone.\textsuperscript{182} As read in isolation, on its face, the legislative history might appear to limit the safe harbor reach to pre-marketing uses alone. However, as the Classen dissent\textsuperscript{183} and the Momenta majority more persuasively emphasized,\textsuperscript{184} the explicit protection of research preceding FDA approval does not exclude post-approval studies from protection.\textsuperscript{185} Indeed, Judge Rader’s dire prediction, that protecting infringing post-approval activity along with pre-approval studies would erode the patent system, has not yet materialized.

Moreover, the majority’s broad reading of the research use exception more convincingly articulated the legislative intent, by creating fewer barriers for generic market entry and continued marketing of the generic drug,\textsuperscript{186} aligning with the policy goals for early generic marketing cited in \textit{Eli Lilly}.\textsuperscript{187} Although the infringer may profit through commercial sales of its drug while conducting FDA-mandated tests to ensure the bioequivalence of its generic drug, post-marketing uses actually constitute a complex range of activities carried out under varied motives.\textsuperscript{188} While some post-marketing research is strictly optional, for example, marketing activities for educating and selling the generic drug to medical professionals, the type of post-marketing studies the court aimed to protect in \textit{Momenta} is mandated by the FDA.\textsuperscript{189} Voluntary post-marketing promotional activities are the types of profitable studies Judge Rader hoped to eliminate with his restricted view of the § 271(e)(1) umbrella.\textsuperscript{190} In contrast, tests to ensure the bioequivalence of each subsequent batch of generic drugs align with the general legislative goals of expanding access to generic medications. Ensuring the safety and effectiveness of generic pharmaceuticals marketed to the public is a vital component of the drug approval process.\textsuperscript{191}

\textsuperscript{182} \textit{Id.} at 1367–68 (Rader, J., dissenting).
\textsuperscript{183} \textit{Id.} at 1367–68 (Rader, J., dissenting).
\textsuperscript{184} \textit{Id.} at 1367–68 (Rader, J., dissenting).
\textsuperscript{185} \textit{Id.} at 1367–68 (Rader, J., dissenting).
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\textsuperscript{190} \textit{Id.} at 1367–68 (Rader, J., dissenting).
\textsuperscript{191} \textit{Id.} at 1367–68 (Rader, J., dissenting).
In addition, the novel drug formulation at issue in *Momenta* creates additional questions surrounding the scope of the research use exception. Since a growing proportion of pharmaceuticals are now complex mixtures, like the polysaccharide combination in *Momenta*, or biologics,192 the analysis of similar, modern drug formulations will likely be similarly complex. Thus, like the post-marketing studies observed in *Momenta*,193 the infringing use of a competitor’s analytical method to verify bioequivalence for continued FDA approval is a likely possibility. As a consequence, the identification of permissible post-marketing uses within the safe harbor becomes even more relevant.

As demonstrated by the Court’s shift in opinion regarding the protection of post-marketing research between *Classen* and *Momenta*,194 these decisions do not reflect the final word on the matter. Legislators must provide explicit guidance to generic manufacturers, to enable Congressional goals of expediting generic marketing and continuing to bring affordable pharmaceuticals to consumers. In order to avoid future uncertainty and ambiguity, the scope of post-marketing uses under the § 271(e)(1) safe harbor should not be left to judicial interpretation, but should instead be resolved through legislation.


As illustrated in *Eli Lilly & Co. v. Medtronic, Inc.* and *Merck KGaA v. Integra Lifesciences I, Ltd.*, the Supreme Court has held § 271 (e)(1) to protect premarketing, otherwise infringing research conducted by generic manufacturers when the activities were mandated by the FDA as part of the FDA approval process.195 *Eli Lilly* initiated the expansion of the § 271(e)(1) research exception by granting an exemption for medical devices, as well as all medical inventions included in the FDCA, although the exact wording of § 271(e)(1) only protected pharmaceuticals.196 The *Integra* Court found it necessary to expand the safe harbor scope to include preclinical studies,197 in order to effectuate the Congressional intent of promoting rapid generic

192 See Carmichael, supra note 157 (stating that over one-third of pharmaceuticals in development are now biologics).
193 See *Momenta*, at 686 F.3d at 1358–59.
194 *Compare* *Classen Immunotherapies, Inc. v. Biogen Idec*, 659 F.3d 1057, 1070 (Fed. Cir. 2011) (declining to extend protection to post-marketing research entirely) with *Momenta*, 686 F.3d at 1358–59 (granting safe harbor for otherwise infringing, FDA-mandated post-marketing uses).
196 *Integra*, 545 U.S. at 203.
marketing advanced by *Eli Lilly*.\textsuperscript{198}

In the Federal Circuit, the *Classen* court denied protection to optional post-marketing activities, only to have the *Momenta* court reverse course, and again expand protection to include post-approval activities required for continued FDA approval.\textsuperscript{199} As an exception to the general trend toward an expansive approach to the § 271(e)(1) safe harbor, the *Classen* court denied protection to optional post-marketing activities.\textsuperscript{200} As the prospect of future interpretive shifts would create continued instability, a legislative proposal would be the best solution for setting out the permissible post-marketing uses. With statutory resolution, instead of guessing whether particular tests of branded counterpart drugs would be protected, generic manufacturers can concentrate on their primary goal—innovation of generic medical products and bringing these generic products to market—the outcome Congress had envisioned when enacting the section 271(e)(1) research use exception.\textsuperscript{201}

Explicitly limiting the safe harbor’s scope to mandatory post-marketing studies would promote the spirit of the legislative intent underpinning section 271(e)(1) of the Hatch-Waxman Act. Since Congress originally intended to hasten the generic drug approval process,\textsuperscript{202} protecting FDA-mandated post-marketing activity aligns neatly with these legislative goals. Section 271(e)(1) should protect non-commercial, preclinical research activity by allowing generic manufacturers to use research generated by branded manufacturers in ANDA’s for generic drugs. Moreover, post-marketing studies required for the continued FDA approval of generic drugs should be protected, since these mandatory tests are closely linked to faster marketing of generic pharmaceuticals. The Federal Circuit rulings of *Classen* and *Momenta* each supply a component for the proposed statutory resolution.

**A. The Federal Circuit’s Contribution: Protection for Mandatory Post-Marketing Activity**

In the Federal Circuit, the recent *Classen* and *Momenta* decisions present conflicting interpretations of the § 271(e)(1) protection for post-marketing activity.\textsuperscript{203} Where *Momenta* continued to extend the inclusive

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\textsuperscript{198} See *Eli Lilly*, 496 U.S. at 661–66.
\textsuperscript{199} Compare *Classen*, 659 F.3d at 1070 (declining to extend protection to post-marketing research entirely) with *Momenta*, 686 F.3d at 1358–59 (granting safe harbor for otherwise infringing, FDA-mandated post-marketing uses).
\textsuperscript{200} *Classen*, 659 F.3d at 1057.
\textsuperscript{202} Id.
\textsuperscript{203} Compare *Classen*, 659 F.3d at 1070 (declining to extend protection to post-marketing research entirely) with *Momenta*, 686 F.3d at 1358–59 (granting safe harbor for otherwise infringing,
progression set forth in *Eli Lilly* and *Integra* by additionally protecting post-marketing activity, *Classen* restricted the safe harbor to activities required for regulatory approval, without distinguishing between pre-marketing and post-marketing studies.\(^{204}\) Although on its face, *Classen* appears to narrow the exception’s scope, *Classen* supports the proposed legislative solution. Although *Classen* denied protection for the optional reports of adverse effects, it nonetheless granted limited § 271(e)(1) protection for FDA-mandated post-marketing studies.\(^{205}\) A feasible legislative compromise would also incorporate the holding in *Classen*, so that only mandatory post-marketing studies necessary for continued regulatory approval would be included in the research use exception.

Expedit ed generic approval was the policy rationale driving the majority opinion in *Classen* as well as in *Momenta*.\(^{206}\) The proposed statute, which limits the protection of post-marketing studies to those required for continued regulatory approval aligns with the policy behind *Classen*. By accounting for Judge Rader’s strong opposition to the protection of post-marketing activity with commercial potential,\(^ {207}\) the proposed statute would address his concerns.

In his emphasis on pre-marketing status as a primary requirement for protective inclusion,\(^ {208}\) Judge Rader mistakenly grouped the wide range of post-marketing uses into a single, purely commercial category. However, profit is not the sole factor behind all post-marketing studies—the FDA and other regulatory agencies mandate certain post-marketing tests to ensure the safety of drugs currently on the market.\(^ {209}\) When generic manufacturers are required to report adverse effects of their marketed drugs to the FDA in order to receive continued approval for their pharmaceuticals, their reporting does not produce commercial benefits for the manufacturer.\(^ {210}\) In fact, the FDA must update drug labeling to warn medical professionals of adverse drug effects, or even reevaluate its decision to continue to market the pharmaceutical in question; thus, the generic entrant generally will not directly profit from the continued submission of information required for FDA drug approval.\(^ {211}\) In contrast, voluntary post-marketing activities could involve marketing or promotional campaigns to introduce physicians to the new generic drug. Profit drives these post-marketing activities, so

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\(^{204}\) See id.

\(^{205}\) *Classen*, 659 F.3d at 1070–71.

\(^{206}\) *Id.* at 1070; *Momenta Pharms.*, Inc. v. Amphastar Pharms., Inc., 686 F.3d 1348, 1358–59 (Fed. Cir. 2012).

\(^{207}\) See *Momenta*, 686 F.3d at 1365–66 (Rader, J., dissenting).

\(^{208}\) See *Classen*, 659 F.3d at 1070.

\(^{209}\) See *Postmarketing Surveillance Programs*, supra note 44.

\(^{210}\) *Id.*

\(^{211}\) See *id.*
unlike FDA-mandated studies, voluntary promotional campaigns should not be protected by § 271(e)(1), which was created to promote the rapid development of generic medical inventions.

Since promotional post-marketing activities would not promote expedited generic approval or aid the continued approval of generic drugs and medical devices, § 271(e)(1) should not protect these activities when they are fueled solely by profit. The Classen majority incorrectly painted all voluntary post-marketing uses as profit-driven.\(^{212}\) Profit is not the sole driving force behind the voluntary systemic monitoring of adverse reactions to marketed generic drugs. For example, the drug manufacturer might be motivated to release notice of adverse effects out of genuine concern for the health of potentially affected consumers, along with fears that reports of adverse effects from alternate sources would slash its profit. The Classen dissent therefore articulates the more appropriate interpretation by recognizing the different types of permissible post-marketing activities.

1. The Classen Dissent and Majority: Both Post-Marketing and Pre-Marketing Activity Merit Inclusion

The Classen dissent properly pointed out an error in the Classen majority’s decision: although the Supreme Court chose to allow pre-marketing studies in Eli Lilly and Integra, this inclusion does not automatically exclude post-marketing activities.\(^{213}\) Additionally, the dissent found that the plain language of § 271(e)(1) does not restrict protection to pre-marketing research.\(^{214}\) For these reasons, it concluded that the absence of post-marketing infringement in cases addressed by the Supreme Court did not automatically imply that post-marketing uses would not be protected.

Meanwhile, the Classen majority also protected post-marketing research, but only when the studies are mandatory.\(^{215}\) However, the Classen assumption that voluntary post-marketing activities are influenced by the prospect of profit was incorrect. However, some post-marketing studies are profit-based,\(^{216}\) and the Classen concerns for the commercial potential of voluntary post-marketing uses can also be taken into account. Therefore, a proposed statute that would explicitly allow only post-marketing activity under § 271(e)(1) when the tests are mandatory for regulatory approval is a logical way of incorporating these considerations. Permissible post-marketing research must be

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\(^{212}\) See Classen, at 1070–72.

\(^{213}\) See id. at 1083 (Moore, J., dissenting) (finding that “[n]owhere does the statute limit the safe harbor to pre-approval uses,” and concluding that the safe harbor also protects information relating to “post-approval” research).

\(^{214}\) Id. at 1084.

\(^{215}\) See id. at 1070.

\(^{216}\) See Steenburg, supra note 27, at 371–72.
closely tied to FDA regulatory approval; for example, FDA-mandated studies employing the branded drug to test adverse reactions between drugs, research to create novel drug delivery systems, and tests of the drug within special segments of the population would all qualify. Making mandatory studies into a threshold test would reduce suspicion of commercial motives. Restricting the safe harbor scope to mandatory post-marketing uses confines the exception to its purported goals of early generic marketing, at least on first glance.

If the main legislative purpose of rapid generic drug development were truly taken into consideration,\textsuperscript{217} both voluntary and mandatory reports of adverse effects alike would promote these goals. However, to avoid further strife over the intended motivations behind certain categories of post-marketing activities, an ideal statute would only allow post-marketing research required for regulatory approval. The discussion of permissible mandatory post-marketing activities under § 271(e)(1) leads to \textit{Momenta}.

\textbf{C. The Addition of Momenta: Direct Inclusion of Post-Marketing Activities: Examples of Permissible and Impermissible Post-Marketing Uses}

\textit{Momenta} reiterated the safe harbor protection of post-marketing uses.\textsuperscript{218} In \textit{Momenta}, the infringer used its competitor’s bioequivalence tests to verify the identity of its drug.\textsuperscript{219} With the advent of biologic pharmaceuticals, pharmaceuticals comprising complex mixtures, like the drug in \textit{Momenta},\textsuperscript{220} clarification of the post-marketing scope of the safe harbor will become increasingly important. Given the difficulty in analyzing biologics, a generic competitor’s use of an established analytical method for confirming bioequivalence would avoid unnecessary duplicative effort. Protecting the use of an established bioequivalence test under the safe harbor will foster early and continued availability of the generic drug, closely aligning with the legislative goals of § 271(e)(1).\textsuperscript{221} These tests form an especially crucial part of the mandatory systemic reports to the FDA because evidence that the drug was adulterated or otherwise compromised may force the FDA to issue consumer warnings or retract drug approval altogether.\textsuperscript{222} If generic entrants were forced to develop their own bioequivalence tests, a back end distortion would arise. The generic entrant would experience a

\textsuperscript{218} Momenta Pharm., Inc. v. Amphastar Pharm., Inc., 686 F.3d 1348, 1358–59 (Fed. Cir. 2012).
\textsuperscript{219} \textit{Id}. at 1349–52, 1358.
\textsuperscript{220} \textit{Id}. at 1349.
\textsuperscript{222} See Postmarketing Surveillance Programs, supra note 44 (stating that adverse drug effects uncovered through systemic post-marketing surveillance programs may prompt the FDA to issue consumer warnings via health professionals or retract marketing of the drug altogether).
regulatory delay for continued marketing of its generic drugs, given the difficulty of creating an accurate bioequivalence test, which grants the senior manufacturer a de facto term patent extension.

In addition, the Momenta majority observed that, as a matter of statutory interpretation, § 271(e)(1) does not restrict the safe harbor to pre-approval studies.\(^\text{223}\) The Momenta majority aptly reasoned that § 271(e)(1) cannot be limited to specific types of pre-approval applications, since the § 271(e)(1) safe harbor text expressly applies to all submissions reasonably related to federal regulatory approval, rather than the particular types of submissions that § 271(e)(2) dictates.\(^\text{224}\) So, the proposed legislative solution would incorporate the conclusion in Momenta by expressly allowing post-marketing studies.

Only post-marketing studies mandated by the FDA and other federal regulatory agencies for continued drug approval, including the bioequivalence tests of Momenta, would be protected by a novel statutory proposal. This legislative solution will defer to the FDA-mandated post-marketing surveillance guidelines for newly approved drugs,\(^\text{225}\) expressly permitting post-marketing tests that examine adverse pharmaceutical effects.

The FDA research mandates provide an ideal starting point for statutory guidelines for dictating permissible post-marketing surveillance activities within the proposed legislation.\(^\text{226}\) Section 271(e)(1) should only allow post-marketing research when the FDA mandates such investigations for analyzing adverse effects potentially caused by the drug, including studies of precursors to the adverse effects. The FDA has distinct databases to track the post-market testing requirements for approved drugs\(^\text{227}\) and medical devices.\(^\text{228}\) As an initial matter, the FDA divides post-marketing requirements into various categories which are based on the legislation mandating each particular study, including the assessment of serious, previously known drug-related risks, the assessment of signals related to use of the drug, and the identification of unexpected serious risks of the drug.\(^\text{229}\) The Food and

\(^{223}\) *Momenta*, 686 F.3d at 1354–55 (stating that Congress would have expressly limited the statutory exception to specific submissions of applications for approval under the Food, Drug, and Cosmetic Act, for example ANDA applications, if Congress had this intent in mind).

\(^{224}\) *Id.*

\(^{225}\) *Postmarketing Requirements and Commitments: Introduction*, supra note 30.

\(^{226}\) *Id.*


Drug Administration Amendments Act of 2007 ("FDAAA") details the most recent FDA requirements for post-marketing studies, which primarily provide for further analysis of a marketed drug’s serious adverse effects.230 Meanwhile, the FDA separates the post-marketing requirements for medical devices in a similar manner, by medical specialty and manufacturer, and tracks the status of the studies involving each invention.231 The legislative proposal will incorporate the FDA’s scheme of dividing post-marketing requirements into two categories: 1) pharmaceutical drugs for human use and 2) medical devices. The types of FDA-mandated studies granted safe harbor would also derive from the post-marketing requirements set out in the FDA databases.232 For example, the statute proposed here would establish protection for post-marketing studies required for the ongoing FDA regulation of pharmaceuticals.233 Meanwhile, in discussing permissible post-marketing activities involving medical devices, the proposed statute would similarly create an express research exception granting safe harbor to FDA-mandated tests for continued approval. In both sections, the statute would generally adhere to the FDA databases detailing specific examples of permissible, mandatory testing for pharmaceuticals and medical devices. Voluntary reports to the FDA citing adverse effects from vaccine schedules following marketing approval would be impermissible.234 Protected studies would encompass trials required to demonstrate a drug’s clinical safety and efficacy, and studies mandated to analyze serious known effects and potential adverse effects of the novel pharmaceutical.235

A statute expressly limiting permissible post-marketing activities to research uses mandated by the FDA for ongoing regulatory approval will clarify the ambiguous interpretations of the research use exception in *Momenta* and *Classen*. This proposed statute consolidates the components of *Eli Lilly*, *Integra*, *Classen*, and *Momenta* into a guideline that provides easy guidance for generic manufacturers. This way, generic manufacturers will understand which post-marketing infringing activities are permissible under the safe harbor. When generic manufacturers choose to employ patented bioequivalence tests or

230 Id.
231 *Post-Approval Studies, Medical Devices*, supra note 228.
232 See *Postmarket Requirements and Commitments*, supra note 227; *Post-Approval Studies: Medical Devices*, supra note 228.
233 *Postmarket Requirements and Commitments*, supra note 227; *Post-Approval Studies: Medical Devices*, supra note 228.
235 *See Postmarketing Requirements and Commitments: Introduction*, supra note 30 (citing examples of potential post-marketing studies under the Food and Drug Administration Amendments Act).
medical invention for additional studies not required by the FDA, these uses will be unprotected.

Moreover, this legislative solution addresses the property concerns of Judge Rader in his dissenting Momenta opinion.\textsuperscript{236} Although generic manufacturers will be able to use patented methods while testing their own pharmaceuticals, the statute restricts the increasingly wide scope of the safe harbor in Momenta. This legislative proposal bars optional activities, by accounting for concerns that allowing optional post-marketing activities would contradict the primary legislative intent for the research use exception (expedited generic approval), and the possibility that such activities might even derive from a commercial motive.\textsuperscript{237} Thus, the proposed legislation recognizes and directly addresses the property concerns cited by Judge Rader in his Federal Circuit Classen opinion.\textsuperscript{238}

**CONCLUSION**

The Federal Circuit decisions of Classen and Momenta set out conflicting permissible post-marketing uses,\textsuperscript{239} plaguing the manufacturers of modern generic drugs. Without a clear legislative solution providing statutory protection for mandatory post-marketing tests by generic manufacturers, serious obstacles to generic post-marketing tests will persist. Given the ambiguous scope of permissible post-marketing activities after Momenta,\textsuperscript{240} generic manufacturers face unnecessary hurdles after bringing their generic versions of essential drugs to market. With limited resources and the inability to use data previously produced by pioneer entrants, generic entrants will likely face litigation without express statutory guidance establishing protection for limited types of mandatory post-marketing activity. For example, in Momenta, the generic manufacturer of an essential blood clot medication used a patented bioequivalence method for FDA-mandated post-marketing submissions, only to confront litigation during ongoing drug development,\textsuperscript{241} delaying its mission of bringing affordable generic therapeutics to consumers.

In many instances, use of the branded manufacturers’ research is necessary in post-market comparison studies.\textsuperscript{242} A proposed statute will

\textsuperscript{236} See Classen, 659 F.3d at 1366–67 (Rader, J., dissenting).
\textsuperscript{237} See id.
\textsuperscript{238} See id. at 1365–67 (Rader, J., dissenting).
\textsuperscript{239} Compare Classen, 659 F.3d 1070 (declining to extend protection to post-marketing research entirely) with Momenta, 686 F.3d at 1358–59 (granting safe harbor for otherwise infringing, FDA-mandated post-marketing uses).
\textsuperscript{240} Id.
\textsuperscript{241} Momenta Pharm., Inc. v. Amphastar Pharm., Inc., 686 F.3d 1348, 1351–52 (Fed. Cir. 2012)
\textsuperscript{242} Facts About Generic Drugs, supra note 1 (describing bioequivalence comparison studies of generic and branded drugs).
allow generic manufacturers to use data from branded manufacturers in limited post-marketing research settings in order to satisfy FDA requirements for continued marketing of their generic pharmaceuticals and medical devices. The legislative solution will advance early and continuous marketing of generic therapeutics, the intended congressional motive for enacting the research use exception.\textsuperscript{243} Thus, in light of the concerns highlighted previously in Part II, in a world of increasingly complex medications, Congress should elucidate the interpretation of the § 271(e)(1) research exception and enact legislation limiting the research exception solely to FDA-mandated, non-commercial post-marketing studies.

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