The Role of Regulatory Agencies and Intellectual Property: Part I

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The patent and regulatory regimes of different agencies of the federal government are not always in agreement, and although the concept of the “unified executive” holds that the executive branch speaks with one voice, that is not always the case.¹ Some agencies, like the Food and Drug Administration, tend toward cooperation with government patent policies, whereas others, notably the Federal Trade Commission, are often at odds with the Patent Office, the patent system, or both. These skirmishes, when they arise, eventually come before federal courts and ultimately the Supreme Court, where balancing the differing policy objectives, as well as the will of Congress as embodied in its statutes, is subject to the vagaries of the politics of how the issues are framed by the courts, and the judges’ and justices’ own predilections and prejudices. Examples of these situations were prevalent in 2013 and the circumstances surrounding them illustrative of the tensions inherent between the various federal agencies.

THE EXTENT OF THE “SAFE HARBOR” UNDER THE HATCH–WAXMAN ACT

Section 202 of the Drug Price Competition and Patent Term Restoration Act of 1984² provides as follows:

It shall not be an act of infringement to make, use or sell a patented invention . . . solely for uses reasonably related to the development and sub-

mission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

This law (and corresponding patent term restoration codified under 35 U.S.C. §156) was an attempt by Congress to provide a balance between the interests of the pharmaceutical industry and generic drug manufacturers: On the one hand, patent-owning pharmaceutical companies had their patent term shortened by delays in regulatory approval required for marketing drugs protected by patents.³ On the other

¹See, for example, the refusal of the legal branch of the Patent and Trademark Office to sign onto the government’s brief in *Association for Molecular Pathology v. Myriad Genetics, Inc.* See Brief for the United States as Amicus Curiae in Support of Neither Party, *U.S.P.T.O. v. Myriad Genetics, Inc.* (2010) (No. 2010-1406).

²Public Law No. 98-417, 98 Stat. 1585 (1984) (codified in pertinent part as 35 U.S.C. §271(e)(1)) (hereinafter the Hatch–Waxman Act).

³Competitive drug companies are motivated by both U.S. and foreign patent laws to file patent applications as soon as possible, which is generally shortly after discovery or early in the development of novel drugs, synthetic methods, and

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hand, generic drug companies had been precluded from performing the testing needed to obtain Food and Drug Administration (FDA) approval of generic counterparts of branded drugs, because these activities had been deemed infringing under the Federal Circuit's decision in *Roche Products, Inc. v. Bolar Pharmaceutical Co.* (733 F.2d 858) (Fed. Cir.), (*cert. denied*, 469 U.S. 756) (1984).⁴

For the past 30 years, the scope and extent of the "safe harbor" provided by the statute has been the subject of litigation and judicial interpretation. For example, based on its construction of the statutory language (and devoid of taking recourse to the legislative history or purported rationale behind the statute), the Supreme Court extended the scope of the safe harbor to include medical devices in *Eli Lilly & Co. v. Medtronic, Inc.* (496 U.S. 661, 676) (1990).⁵

other patentable inventions. At the same time, federal regulatory approval for drug products is lengthy, frequently much lengthier than the time the U.S. Patent and Trademark Office takes to examine and issue a patent, and is generally not even initiated until well into the patent procurement process and frequently not until long after a patent has issued. Because the time it takes to obtain a patent is often much shorter than the time required to obtain FDA approval, the useful life of the patent (i.e., the time period during the pendency of a patent when the patented drug can be commercially marketed) is shortened. Although one enterprising company pursued the legislative remedy of a private bill to extend patent term for the artificial sweetener aspartame, the industry generally suffered this lost patent term without remedy.

⁴Generic companies that seek to commercialize a patented drug must await expiration of another's patent before entering the marketplace. Before selling a drug, however, the generic drug company must obtain FDA approval, which requires making and using the patented drug to demonstrate, for example, bioequivalence, safety, and the ability to make commercial-scale quantities. Generic drug companies were thus faced with a dilemma. The generic company must make and use a patented drug, synthetic method, or other patented invention to fulfill the requirements for FDA approval. If it waited until the patent expired to fulfill FDA requirements, it would not obtain approval for several years after patent expiry, delaying its entry into the marketplace and de facto extending the patentee's term. Making and using a patented drug, synthetic method, or other patented invention prior to patent term expiration (to obtain FDA approval before the patent expired) constituted infringement prior to enactment of the Hatch–Waxman Act.

⁵Thereafter, the Federal Circuit developed a "two part" test for deciding whether the safe harbor applies: whether the activities at issue would constitute infringement absent the

A more significant expansion of the boundaries of the safe harbor occurred in the *Merck KGaA v. Integra Lifesciences I, Ltd.* (545 U.S. 193, 207) (2005) case,⁶ in which the court considered the extent to which activities that occur during drug development (i.e., significantly prior to FDA regulatory submissions occur) should be subject to the safe harbor. The Supreme Court reversed district court and Federal Circuit⁷ decisions that these activities did not

safe harbor and whether the activities are "reasonably related" to developing and submitting information under a federal law regulating drugs. Thereafter, courts have found that almost any activity short of commercial sale will fall within the scope of the safe harbor. See Noonan et al. (2003).

⁶Integra sued Merck for infringement of several patents relating to a tripeptide segment of fibronectin having the sequence Arg-Gly-Asp (the RGD peptide), which promotes cell adhesion to substrates in culture and in vivo by interacting with the cell surface receptor $\alpha_v\beta_3$. Merck partnered with The Scripps Research Institute, where a scientist had discovered that blocking the $\alpha_v\beta_3$ receptor inhibited angiogenesis (the process of generating new blood vessels), an effect thought to provide an effective means for eliminating tumor growth and for treating a variety of other diseases. The Merck–Scripps agreement contemplated a research and development program to bring a cyclic peptide $\alpha_v\beta_3$ receptor inhibitor discovered by Scripps or a derivative thereof to clinical trials and through FDA approval. Toward this end, additional Scripps research led to two derivatives of interest, and Scripps scientists conducted several in vivo and in vitro experiments "to evaluate the specificity, efficacy, and toxicity [of the compounds] for various diseases, to explain the mechanism by which these drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans." These experiments included histopathology, toxicology, circulation, diffusion, and half-life of the peptides in the bloodstream and examined the proper mode of administration for optimum therapeutic effect. Learning of the Scripps–Merck agreement, Integra contacted Merck and offered a license under its patents, which Merck ultimately declined. Integra sued for patent infringement, and Merck asserted §271(e)(1) as a defense. The district court held that the Scripps–Merck activity did not fall under the §271(e)(1) exemption, and the Federal Circuit affirmed. *Integra Lifesciences I, Ltd. v. Merck KGaA* (331 F.3d 860, 872) (Fed. Cir. 2003), (*vacated*, 545 U.S. 193, 125 S. Ct. 2372, 162 L. Ed. 2d 160) (2005).

⁷The Federal Circuit referred to the House committee's characterization of the activities permitted by the infringement exemption as "a limited amount of testing so that generic manufacturers can establish the bioequivalency of a generic substitute." *Id.* at 865 (quoting H.R. Rep. No. 857, at 8, reprinted in 1984 U.S.C.A.N. at 2692). The court also considered important the committee's characterization of exempt activity as interfering with the patentee's rights in a de minimis, rather than substantial, way. By the plain language of its terms the statute limits the exemption to activities conducted "solely for purposes reasonably related

fall within the scope of the safe harbor, based on the court's construction of the statutory language.⁸ The court found no statutory basis for making a distinction between preclinical and clinical activities, holding that the plain wording of the statute made it "apparent" that the exemption "extends to all uses of patented inventions that are reasonably related to the development and submission of *any* information under the [Food, Drug and Cosmetic Act]" (*Merck KGaA v. Integra Lifesciences I, Ltd.* (545 U.S. 193, 202) (2005)). The court asserted, "[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 have been included."⁹ As construed by the court, whether any particular activity falls within the §271(e)(1) safe harbor will depend on the reasonableness of the relationship between the infringing activity and the development of information for submission to the FDA. Thus, every activity using a patented

compound will have been done (in retrospect) "with the intent to develop a particular drug."

The effects of this expansion on the scope of the safe harbor are evident in the Federal Circuit's decision in the *Integra* case on remand (*Integra Lifesciences I, Ltd. v. Merck KGaA* (496 F.3d 1334) (Fed. Cir. 2007)). According to the appellate court, the proper line of demarcation is the "discovery that a cyclic RGD peptide inhibited angiogenesis."¹⁰ This knowledge provides a bright line that distinguishes "research" or "discovery," which may not fall within the exemption, from experiments directed toward "efficacy, mechanism of action, pharmacology, or pharmacokinetics," which do.¹¹ Consequently, it is difficult to envision any research activities that would not fall within the scope of the safe harbor as now judicially construed.

One possible exception is for patents on research tools¹²; both the Supreme Court and the Federal Circuit have expressly refused to consider whether the safe harbor extends to such patents. The continued uncertainty over whether

to the development and submission of information under Federal law." *Id.* The court reasoned that the term "reasonably related" tied the exempt activities to the submission of information to the FDA. The court opined that although infringing activities need not directly produce data that is submitted to the FDA to enjoy the safe harbor of §271(e)(1), such activities "strain[] the relationship to the central purpose of the safe harbor." *Id.* at 866. Accordingly, the court commended the district court for confining the exemption to activity that "would contribute (relatively directly)" to information the FDA considers for drug approval. *Id.* at 867. To further define the scope of "reasonably related," the court referred back to the purpose of the Hatch–Waxman Act, which was, in part, to facilitate the immediate entry into the market upon patent expiration of generic versions of patented drugs already in the market. Viewed in this context, the court held that the term "reasonably related" does not embrace all activity in the research and development chain simply because they may lead to an FDA approval process. In particular, the court stated: "[t]he FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval." *Id.* at 866. "The safe harbor does not reach any exploratory research that may rationally form a predicate for future FDA clinical tests." *Id.* at 867. To view it otherwise, the court held, would ignore the language of §271(e)(1) and its context in the 1984 act. *Id.*

⁸And without regard for the legislative history or purported congressional purpose for the law, both of which were the grounds for the contrary decisions below.

⁹*Id.*

¹⁰*Id.* at 1347.

¹¹These experiments included $\alpha_v\beta_3$ receptor binding assay (efficacy); angiogenesis chick chorioallantoic membrane (CAM) assay (efficacy, mechanism of action, and pharmacokinetics); angio-matrigel tests (efficacy and mechanism of action); cell adhesion assay (efficacy); chemotaxis assay (efficacy and mechanism of action); chick embryo pharmacokinetics assay (pharmacokinetics); fluorescence-activated cell sorting (FACS) analysis (mechanism of action and efficacy); rabbit pharmacokinetics assay (pharmacokinetics); tumor growth in severe combined immunodeficiency (SCID) mouse (efficacy, mechanism of action, and pharmacology); tumor growth nude mouse assay (efficacy, pharmacology, pharmacokinetics, and mechanism of action); mice retina vacuole assay (efficacy, mechanism, pharmacology, and pharmacokinetics); rabbit cornea assay (pharmacokinetics and efficacy); mouse retina IF vasculogenesis assays (pharmacokinetics); rabbit arthritis experiments (efficacy, pharmacology, pharmacokinetics, safety, and mechanism of action); mice arthritis experiments (efficacy); and chick CAM tumor growth with melanoma cells (efficacy and mechanism of action).

¹²The National Institutes of Health has defined "research tools" as "tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines." *Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice*, 64 Fed. Reg. 72090, 72092 n.1 (Dec. 23, 1999).

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activities using research tools is illustrated in a lawsuit filed by St. Jude's Children's Research Hospital, Inc. against Novartis Pharmaceuticals Corp.¹³; the case is too early in its development to provoke anything more than the possibility that the Federal Circuit and, quite likely, the Supreme Court will provide further guidance on the scope of patent protection for research tools.

Another aspect of the scope of the Hatch–Waxman safe harbor is the activities that occur *after* approval, specifically activities related to postapproval surveillance.¹⁴ This question and the Federal Circuit's answer(s) to it have revealed sharply divided opinions from at least two members of the court. This situation is reflected in how the court decided two cases on the question: *Classen Immunotherapies, Inc. v. Biogen IDEC* (659 F.3d 1057) (Fed. Cir. 2011),¹⁵ in which Chief Judge Rader and Judge Newman formed a majority (Judge Moore, dissenting) rejecting extension of the safe harbor to after-approval activities; and *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.* (686 F.3d 1348, 1361) (Fed. Cir. 2012), (*cert. denied*, 133 S. Ct. 2854) (U.S. 2013), in which Judge Moore joined by Judge Dyk (Chief Judge Rader, dissenting) held that the safe harbor did

extend to such activities. In the *Classen* case, the activities of the defendants, Biogen and Glaxo-SmithKline (GSK), constituted postapproval studies to determine whether immunizations with hepatitis B and *Haemophilus influenzae* vaccines increased the incidence of type 1 diabetes, as well as an allegation that Biogen induced infringement by GSK by “providing instructions and/or recommendations on a proper immunization schedule for vaccines” (*Classen Immunotherapies, Inc.* (659 F.3d at 1070)). *Classen* argued that the §271(e)(1) safe harbor was limited to *preapproval* activities, and the majority agreed, based on the legislative history of the Hatch–Waxman Act.¹⁶ Further, the majority found no change in this analysis based on the Supreme Court's decision in *Merck KGaA v. Integra Lifesciences I, Ltd.*¹⁷

Judge Moore's dissent on this issue relies on dicta from the court's *Merck* decision (insofar as the court was not considering the issue of postapproval activities), and that the court has mandated a broad reading of the statute.¹⁸ However, the dissent also distinguished postap-

¹⁶ Assaying the legislative history and the purported purposes of the Hatch–Waxman Act, the opinion states that the safe harbor only applies to preapproval activities (which the Biogen and GSK actions clearly were not):

§271(e)(1) provides an exception to the law of infringement in order to expedite development of information for regulatory approval of generic counterparts of patented products. The statute does not apply to information that may be routinely reported to the FDA, long after marketing approval has been obtained. *Id.*

¹⁷ The majority found that the court's *Merck* decision was directed toward (and limited to) “preclinical research, whether or not ultimately included in a submission to the Food and Drug Administration, [that] is exempted from infringement by §271(e)(1) ‘as long as there is a reasonable basis for believing that the experiments will produce the types of information that are relevant to an IND [Investigational New Drug application] or NDA [New Drug Application].’” *Id.* at 1071–72 (quoting *Merck KGaA v. Integra Lifesciences I, Ltd.* (545 U.S. 193, 208) (2005)). Because the accused actions by Biogen and GSK were “not related to producing information for an IND or NDA,” the majority concluded that §271(e)(1) does not provide a safe harbor under the *Merck* precedent. *Id.* at 1072.

¹⁸ In doing so, Judge Moore focused on the several times the *Merck* opinion emphasized that the statute provided a safe harbor against infringement liability for “*all*” activities related to submitting information under “*any*” federal law regulating “the manufacture, use, or distribution of drugs.” *Id.* at 1083 (Moore, J., dissenting). For Judge Moore, this

¹³ Complaint for Patent Infringement, *St. Jude's Children's Research Hospital, Inc. v. Novartis Pharmaceuticals* (No. 2:13-cv-02802) (W.D. Tenn. Oct. 11, 2013). The grounds for St. Jude's infringement allegations are activities by Novartis “to research, develop, and evaluate small molecule tyrosine kinase inhibitors, including, but not limited to, LDK378.” *Id.* at 2. Those activities include, according to the complaint, making or using “ALK nucleic acids, proteins, polypeptides, and/or antibodies in a manner that infringes” U.S. Patent Nos. 5,529,925; 5,770,421; and 6,696,548. *Id.* at 3.

¹⁴ The importance of such activities is illustrated by several recent cases of postapproval safety issues, including the fentanyl diet drugs and cyclooxygenase-2 inhibitors Vioxx® and Celebrex®.

¹⁵ There were three patents in suit: U.S. Patent Nos. 5,723,283; 6,420,139; and 6,638,739, which were subject to challenge on patent eligibility grounds (not discussed here). *Id.* at 1060. The claims were directed generally to methods for reducing the “incidence, prevalence, frequency or severity” of chronic immune-mediated disorders produced attendant upon immunizing children with a variety of immunizations, as well as methods for immunizing children in ways that minimized the frequency of such disorders. *Id.* at 1061.

proval activities that do not fall within the safe harbor, specifically where “[defendants] are not required by law or regulation to perform such post-approval vaccinations in order to generate data,” which are thus not “reasonably related to the development and submission of data to the FDA and therefore do *not* fall within § 271(e)(1)’s safe harbor exception.”¹⁹

Reversing roles in the *Amphastar* case,²⁰ Judge Moore’s majority opinion held that the postapproval activities in this case properly fell within the safe harbor of §271(e)(1).²¹ The case involved Momenta’s claims to methods for analyzing heparin and specifically low-molecular-weight heparins such as enoxaparin.²² Judge Moore’s opinion characterized Momenta’s complaint as alleging that Amphastar infringed its patent by complying with FDA requirements

interpretation includes activities related to *postapproval* activities, such as monitoring drugs to detect adverse event. *Id.* ¹⁹*Id.* at 1084.

²⁰The case involved a district court grant of a preliminary injunction to Momenta in litigation between two Abbreviated NDA (ANDA) filers. Momenta entered the marketplace after ANDA litigation with the patent holder, Aventis, over Lovenox (enoxaparin), a specific formulation of heparin. As explained in the opinion, heparin (unlike most drugs) is not “a single defined molecule” but rather a heterogeneous mixture of molecules that differ in “the length of the polysaccharide chain” and the “component disaccharide units and the corresponding distribution of disaccharide unit sequences in the polysaccharide chains.” *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.* (686 F.3d 1348, 1349) (Fed. Cir. 2012), (*cert. denied*, 133 S. Ct. 2854) (U.S. 2013). This affects its molecular weight distribution as well as the distribution of uronic acid moieties. Enoxaparin is the result of fragmentation of native heparin into a “diverse set” of oligosaccharides. *Id.* at 1350. Accordingly, FDA approval for ANDA filers required five “criteria” or “standards of identity” to be met, including “[e]quivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species” identified by specific enzymatic treatment and physical/chemical analyses of the drug product, including separation and spectroscopy. *Id.* (quoting FDA Letter to Aventis Pharmaceuticals, Inc., July 23, 2010, FDA Docket No. FDA-2003-P-0273 (FDA Letter), J.A. 295). Although Amphastar filed its ANDA first, Momenta was first to market. *Id.* at 1351.

²¹Factual differences between this and the *Classen* case provided the context (or pretext) for the majority to assert that it was not violating *stare decisis* by coming to a conclusion diametrically opposite to the decision of the court in *Classen*.

²²As contained in U.S. Patent No. 7,575,866 assigned to Momenta.

for testing its enoxaparin product as part of the quality control necessary for making this drug.²³ This characterization determined the majority’s analysis, because the district court had rejected the defendant’s attempt to avail itself of the statutory safe harbor because the infringing activity occurred after Amphastar received regulatory approval, and the court interpreted the statute to be limited to otherwise infringing acts that were performed to obtain approval (while acknowledging that the information was, ultimately, submitted to the FDA). This was an error,²⁴ according to Judge Moore, because, using the “plain meaning” of the statutory language, Amphastar’s activities were entitled to safe harbor protection.²⁵ This interpre-

²³*Id.* at 1352.

²⁴Importantly, Momenta relied in its appellate arguments on the Federal Circuit’s decision in *Classen Immunotherapies, Inc. v. Biogen IDEC*, which under analogous circumstances held that postapproval activity does *not* fall within the §271(e)(1) safe harbor. See *supra* note 113 and accompanying text. In addition, Momenta argued that the FDA did not specifically require tests falling within the scope of the ’886 patent to be performed, and noninfringing alternatives existed. *Momenta Pharmaceuticals, Inc.* (686 F.3d at 1359).

²⁵In the majority’s view, resort to the legislative history was unnecessary if the “plain meaning” of the statutory language was clear. *Id.* at 1355. Indeed, the panel majority deems any such recourse to the legislative history to be improper, quoting *Robinson v. Shell Oil Co.* (519 U.S. 337, 340) (1997), for the proposition that the “inquiry must cease if the statutory language is unambiguous and ‘the statutory scheme is coherent and consistent.’” *Id.* at 1354. Selectively quoting from portions of the legislative history, the opinion notes that the statute was enacted to “balance the need to stimulate innovation against the goal of furthering the public interest.” H.R. Rep. No. 98-857, pt. 2, at 2714 (Aug. 1, 1984). In citing the statute, the majority highlighted the clause reading that the safe harbor was “solely for uses reasonably related to the development and submission of information under a Federal law.” *Id.* And this is the end of it, for the majority: “Congress could not have been clearer in its choice of words,” and thus “any activity” included acts taken after approval (provided that there was information submitted under a federal law). *Id.* Moreover, for the majority it is significant that Congress did not limit (expressly) the scope of the safe harbor to the Food, Drug and Cosmetic Act but “broadly” included within the scope of the safe harbor “any federal law” that “regulates the manufacture, use, or sale of drugs.” This interpretation is consistent with the majority’s parsing of the rest of the statute, citing portions of the provision that do specifically reference the Food, Drug and Cosmetic Act (referring to “animal drug or veterinary biological product[s]” and by reciting in §271(e)(2) the specific provisions of the act relating to submission of an ANDA). *Id.* at 1355.

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tation was also consistent with the Supreme Court's expansive reading of the statute with regard to the extent of the safe harbor.²⁶ And whether or not Amphastar actually submitted the results of its postapproval testing to the FDA was irrelevant, in the majority's view.²⁷ Finally, the existence of noninfringing alternatives neither mandated nor motivated a decision in *Momenta's* favor.

Judge Rader wrote a vigorous dissent to the panel majority's opinion in *Momenta v. Amphastar*, disagreeing with the panel majority's interpretation that the safe harbor embodied in 35 U.S.C. §271(e)(1) extended to postapproval activities.²⁸ His analysis is predicated

on the statute *not* being "plainly comprehensible,"²⁹ justifying his resort to the legislative history (which his dissent extensively discusses).³⁰ The danger, according to the chief, is that the majority's disregard for the legislative history creates a distortion stemming from reading out the word "solely" from the safe harbor requirements. Consequently:

This new interpretation would allow almost all activity by pharmaceutical companies to constitute "submission" and therefore justify a free license to trespass. The FDA can inspect records of any drug manufacturer and seller. See 21 U.S.C. § 374. Thus, the drug manufacturer need only make a record, which could potentially be inspected by the FDA, and then any activity could satisfy this new meaning of "submission."³¹

²⁶The panel majority cites two specific instances in which the Supreme Court ruled on the meaning of §271(e)(1) in a manner consistent with its interpretation: *Eli Lilly & Co. v. Medtronic, Inc.* (496 U.S. 661, 666) (1990) and *Merck KGaA v. Integra Lifesciences I, Ltd.* (545 U.S. 193, 202) (2005). *Id.* at 1355–56.

²⁷The panel majority rejected *Momenta's* contention that the process and quality control information obtained by Amphastar's infringement was not submitted to the FDA but was retained by defendants; these "batch records" must be maintained "for at least one year after expiration of the batch" of generic enoxaparin and must be "readily available for authorized inspection" by the FDA. *Id.* at 1357. "The fact that the FDA does not in most cases actually inspect the records" does nothing to change the majority's view that the records are produced using the infringing method for producing information that the agency could demand to see. *Id.* The information obtained from infringing *Momenta's* patents was necessary for Amphastar to continue to sell enoxaparin (and failure to do so could cause FDA to "suspend" or revoke Amphastar's ANDA approval." *Id.* at 1358. Accordingly, the opinion states that "[w]e therefore hold that post-approval studies that are 'reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs' fall within the scope of the § 271(e)(1) safe harbor." *Id.* at 1359.

²⁸The dissent is premised on the limited scope of the safe harbor, based on the chief judge's understanding of the fundamental right to exclude embodied in the patent statute and the limited exception to that right granted under §271(e)(1). See *id.* at 1362 (Rader, J., dissenting) ("Thus, exceptions to the traditional property remedy amount to a get-out-of-jail-free card for the trespasser. Accordingly, such exceptions must occur only sparingly with awareness that this license allows the wrongdoer free reign to continue trespassing.") That limited scope is the result of a balance, expressly struck by Congress, between the recompense to patentees who lost patent term during regulatory review (comprising the patent term extension provisions of 35 U.S.C. §156 et seq.) and the benefits to the public by legislative override of *Roche Products, Inc. v. Bolar Pharma-*

ceutical Co. (733 F.2d 858, 861) (Fed. Cir. 1984) (preventing any infringing activity prior to patent expiration including activities required by the FDA or other government agencies for approval of drugs).

²⁹*Momenta Pharmaceuticals, Inc.* (686 F.3d at 1362) (Rader, J., dissenting). The chief judge based this conclusion on the Supreme Court's decision in *Eli Lilly & Co. v. Medtronic, Inc.* (496 U.S. 661, 669) (1990). This judicial recognition that the statute is not eminently clear justifies the chief's resort to the legislative history (because, after all, the same language of the patent statute cannot be "not plainly comprehensible" some of the time and have a "plain meaning" at other times).

³⁰*Id.* at 1362–67. The point of this historical exercise was to make the case that "§ 271(e)(1) won approval because it was limited in time, quantity, and type: [f]irst, as to time, § 271(e)(1) only applies to pre-marketing approval; [s]econd, as to quantity and type, § 271(e)(1) only applies to experimentation—and therefore would have limited impact on the patentee's exclusivity during the life of the patent." *Id.* at 1365 (internal citations omitted) (emphasis in original). Importantly, "the authors made clear that section 271(e)(1) would not apply to commercial sales, i.e., the 'infringing' product would not enter the market until after the patent's life," according to the dissent. *Id.* at 1366 (citing H.R. Rep. No. 98-857, pt. 1, at 45 (1984) ("This section *does not permit the commercial sale* of a patented drug by the party using the drug to develop such information, but it does permit the commercial sale of research quantities of active ingredients to such party.")) (emphasis added).

³¹*Id.* at 1367. Applying this reasoning, Amphastar's activities are antithetical to the congressional intent according to the dissent because these activities are not "preapproval" because they occur after Amphastar has obtained FDA approval; are not "limited because Amphastar uses *Momenta's* invention on a continuous basis in the manufacture of each commercial batch and during the life of *Momenta's* patent"; and are not "experimental because Amphastar uses *Momenta's* invention in manufacturing each commercial batch of its product for contemporaneous sale on the market (in com-

On remand (*Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.* (Civ.A. 11-11681-NMG, 2013 WL 3816712, at *6) (D. Mass. July 19, 2013)), the U.S. District Court for the District of Massachusetts granted a summary judgment motion of noninfringement in favor of Amphastar. In doing so, the court rejected Momenta's arguments that included the following: that the FDA did not mandate the use of its patented test, and therefore its use by Amphastar was entirely voluntary; that the required record-keeping was not a "submission," and therefore fell outside the statute; or that the use of this information during manufacturing was for commercial purposes, and therefore not "solely" for uses related to satisfying federal law.³²

The Supreme Court has declined to grant certiorari (on the safe harbor issue) in both *Classen* (*GlaxoSmithKline v. Classen Immunotherapies, Inc.* (133 S. Ct. 973) (2013)) and *Momenta* (*Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.* (133 S. Ct. 2854) (2013)). The discord within the Federal Circuit and entry of final judgment against Momenta may change the court's calculus. On the evidence of their earlier jurisprudence it is likely that, should the court address the issue, its ruling will be closer to Judge Moore's opinion than Judge Rader's and thus the scope of the safe harbor even further expanded.

GENETIC DIAGNOSTIC TESTING

Both the Federal Trade Commission (FTC)³³ and the FDA³⁴ have voiced concerns over di-

rect-to-consumer (DTC) genetic diagnostic testing services, which arose as the result of the Human Genome Project.³⁵ That effort, which culminated in the complete elucidation of the human genetic sequence (see Lander et al. 2001), was followed by several further efforts to identify genetic variants associated with disease or the propensity for disease.³⁶ These agencies, and several commentators (Lea et al. 2005), voiced concern over consumers having access to their genetic data, based in large part on the generally incomplete understanding of the degree to which a particular genetic variant was determinant of an individual developing a disease (see Hogarth et al. 2008). Of even more concern were instances in which a particular variant was definitively associated with disease, particularly incurable diseases like Huntington's chorea (see Wexler 1996), because of the possibility that a diagnosis, even a correct diagnosis, required a physician, genetic counselor, or both to intervene and interpret the significance of the test results and identify possible treatment options (as palliative as they may be in such instances) (www.cancer.gov/cancertopics/pdq/genetics/risk-assessment-and-counseling/HealthProfessional/page5). Moreover, identifying agency authority posed a problem: The FTC certainly had the authority to regulate such testing but not the agency expertise,³⁷ and the FDA arguably did not have the statutory authority to intervene; indeed, a great deal of clinical laboratory testing was not regulated by the agency but rather under the Clinical Laboratory

merce) to obtain profits and to compete with Momenta." *Id.* at 1368 (emphasis in original).

³²*Id.* at *3. The U.S. District Court for the Southern District of New York also used the Federal Circuit's *Momenta* decision to dismiss ANDA litigation for failure to state a claim, in Opinion and Order at 13, *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.* (No. 09 Civ. 10112) (S.D.N.Y. July 16, 2013).

³³See "FTC facts for consumers: At-home genetic tests: A healthy dose of skepticism may be the best prescription" (2006), http://oba.od.nih.gov/sites/default/files/DTC_Consumer_Alert_Jul06.pdf.

³⁴See "Direct-to-consumer genetic testing and the consequences to the public before the Subcommittee on Over-

sight and Investigations, House Committee on Energy and Commerce" (2010) (Statement of J. Shuren, Director, Center for Devices and Radiologic Health), www.fda.gov/newsevents/testimony/ucm219925.htm.

³⁵See "All about the Human Genome Project (HGP)," www.genome.gov/10001772.

³⁶See "International HapMap Project," <http://hapmap.ncbi.nlm.nih.gov/abouthapmap.html>.

³⁷For example, the 23andMe website contains (marketing) language extolling the virtues of its testing for disease prevention and mitigation, but also carries the disclaimer that the results are "not designed to diagnose, prevent, or treat any condition or disease or to ascertain the state of your health and ... are intended for research, informational, and educational purposes only." 23andMe Terms of Service, 23andMe.com, <http://blog.23andme.com/terms-of-service/>.

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Improvement Amendments of 1988 (CLIA).³⁸

Recently, the best known of the DTC genetic testing services, personal genomics company 23andMe, received a warning letter demanding that the company stop selling its Personal Genomic Services (PGS) product without obtaining FDA approval. The letter characterized the PGS product of being a “medical device” falling within the scope of §201(h) of the Food, Drug and Cosmetic Act (21 U.S.C. §321(h)) and thus requiring FDA approval prior to marketing (something 23andMe has failed to obtain).³⁹ The agency’s letter set out as particular concerns inclusion of the *BRCA* genes in the company’s tests, as well as testing related to genetically based, individualized reactions to warfarin, clopidogrel, and 5-fluorouracil “because of the potential health consequences that could result from false positive or false negative assessments for high-risk indications such as these.” At issue is patients undergoing unnecessary prophylaxis or “self-managing” their drug dosing depending on their personal genetic proclivities, in ways that are best done under a doctor’s supervision. The genetic information provided by 23andMe’s PGS product could be misinterpreted

ed or provide patients with misunderstood, incorrect, or misleading information, according to the agency’s letter.

The agency noted that the company had submitted an application under §510(k) for “several of these indications” but that 23andMe has “failed to address the issues described during previous interactions with the Agency,” including specifically requests for additional information sent in September and November 2012.⁴⁰ As a consequence, 23andMe’s applications have been considered by the agency to be withdrawn, meaning there are currently pending no applications for the PGS product as required by law. The FDA letter further warns the company that it must “immediately discontinue marketing the PGS until such time as it receives FDA marketing authorization for the device.”⁴¹

There have been two immediate responses to the FDA’s warning letter. First, a petition⁴² has been published on the “We the People” por-

³⁸Administered by the Centers for Medicare and Medicaid Services (CMS).

³⁹The agency warning letter provided its rationale for determining that the company’s PGS product is a device within the meaning of the statute, saying that it “is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body.” Letter from Alberto Gutierrez, Director, Office of In Vitro Diagnostics and Radiological Health, Center for Devices and Radiological Health, to Ann Wojcicki (Nov. 22, 2013) (Doc. No. GEN1300666), www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm. The letter cited the company’s website for touting the product as providing “health reports on 254 diseases and conditions,” which include “carrier status” (for the genetic predisposition of particular diseases), “health risks” and “drug response[s].” *Id.* Also noted in the letter are 23andMe’s claims that its PGS product can be used as “[a] first step in prevention” wherein users can “take steps toward mitigating” diseases like diabetes, coronary artery disease, and breast cancer (including Myriad’s *BRCA* genes). *Id.* And the letter evinced the agency’s frustration at the company’s apparent recalcitrance in obtaining approval, stating that “[m]ost of these uses have not been classified and thus require premarket approval or de novo classification, as FDA has explained to you on numerous occasions.” *Id.*

⁴⁰*Id.* In this regard, the warning letter asserts that “FDA has spent significant time evaluating the intended uses of the PGS to determine whether certain uses might be appropriately classified into class II, thus requiring only 510(k) clearance or de novo classification and not PMA approval, and we have proposed modifications to the device’s labeling that could mitigate risks and render certain intended uses appropriate for de novo classification. Further, we provided ample detailed feedback to 23andMe regarding the types of data it needs to submit for the intended uses of the PGS. As part of our interactions with you, including more than 14 face-to-face and teleconference meetings, hundreds of email exchanges, and dozens of written communications, we provided you with specific feedback on study protocols and clinical and analytical validation requirements, discussed potential classifications and regulatory pathways (including reasonable submission timelines), provided statistical advice, and discussed potential risk mitigation strategies.” *Id.*

⁴¹*Id.* According to the agency, “The PGS is in class III under section 513(f) of the FD&C Act, 21 U.S.C. 360c(f). Because there is no approved application for premarket approval in effect pursuant to section 515(a) of the FD&C Act, 21 U.S.C. 360e(a), or an approved application for an investigational device exemption (IDE) under section 520(g) of the FD&C Act, 21 U.S.C. 360j(g), the PGS is adulterated under section 501(f)(1)(B) of the FD&C Act, 21 U.S.C. 351(f)(1)(B). Additionally, the PGS is misbranded under section 502(o) of the Act, 21 U.S.C. § 352(o), because notice or other information respecting the device was not provided to FDA as required by section 510(k) of the Act, 21 U.S.C. § 360(k).” *Id.*

⁴²The text of the petition read as follows:

We, the healthcare consumers of America, demand that we maintain access to genomics testing services like

tion of the White House website by a group of self-titled healthcare consumers, calling for the Obama administration to overrule the FDA and permit 23andMe to continue to market the company's PGS product. The petition alleges that the FDA "grossly overstates the risks associated with 23andMe's assessments. Statements such as those suggesting that dangers like false positives may 'lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening, or other morbidity-inducing actions' are outrageous and patently false" and "[r]isks associated with services like 23andMe's are understood by private consumers, while the benefits of these services (such as early diagnoses for chronic diseases) are significant. The price of over-regulation is lengthy delays in potentially life-saving medical innovations."⁴³

The second response to the FDA's warning letter was a class action lawsuit, filed in the U.S. District Court for the Southern District of California (No. 13-cv-2847H; complaint). The action was brought on behalf of Lisa Casey, "an individual" in the class, and on behalf of "tens or hundreds of thousands of women" who may have used the PGS testing service.⁴⁴ The complaint⁴⁵ patterns most of its allegations⁴⁶ from

23andMe's, which serve as a 100% privately purchased complement to government-regulated healthcare.

⁴³The petition had a deadline of December 25, 2013, to amass 100,000 signatures, a goal it did not achieve. If it had, "White House staff [would] review it, ensure it's sent to the appropriate policy experts, and issue an official response."

⁴⁴Representing the class plaintiffs is Mark Ankorn of the Ankorn law firm, whose website characterizes the practice as "fighting for consumers since 1993."

⁴⁵The complaint alleges that 23andMe "falsely and misleadingly advertises their Saliva Collection Kit/Personal Genome Service ('PGS') as providing 'health reports on 240+ conditions and traits,' 'drug response,' 'carrier status,' among other things," despite the fact that "there is no analytic or clinical validation of the PGS for its advertised uses." Complaint at 1–2, *Casey v. 23andMe, Inc.* (No. 13-cv-2847) (S.D. Cal. Nov. 27, 2013).

⁴⁶The suit alleges liability under the California Business and Professional Code §§ 17200 as an "unlawful, unfair or deceptive business act or practice and unfair, deceptive, untrue or misleading advertising" (Count 1: the "unfair" and "fraudulent" prongs; Count 2: the "unlawful" prong) and §§ 17500 ("false and misleading advertising"; Count 3); the California Civil Code §§ 1750 and 1770 (Count 4); breach of warranty of merchantability and fitness for a particular pur-

the assertions in the FDA's warning letter, including these:

- To date, 23andMe has failed to provide adequate information to support a determination that the PGS is substantially equivalent to a legally marketed predicate for any of the uses for which you are marketing it; no other submission for the PGS device that you are marketing has been provided under section 510(k) of the [Food, Drug, and Cosmetic] Act, 21 U.S.C. § 360(k).⁴⁷
- The risk of serious injury or death is known to be high when patients are either non-complaint or not properly dosed; combined with the risk that a direct-to-consumer test result may be used by a patient to self-manage, serious concerns are raised if test results are not adequately understood by patients or if incorrect test results are reported.⁴⁸

The complaint recites several examples of 23andMe's advertising that it characterizes as "[material] representations" class action plaintiffs allege are fraudulent⁴⁹ and that "Defendant

pose (Count 5); unjust enrichment (Count 6); "deceit by concealment" under California Civil Code §§ 1709 and 1710 (Count 7); and negligent misrepresentation (Count 8). *Id.* at 11, 13, 16, 19, 22–24.

⁴⁷*Id.* at 6.

⁴⁸*Id.*

⁴⁹*Id.* These include the following:

- "Learn hundreds of things about your health. Using your DNA information, 23andMe helps you know more about your health so you can take an active role in managing it. With reports on over 240+ health conditions and traits, here are a few of the things you'll learn about you."
- "Plan for the future. Find out if your children are at risk for inherited conditions, so you can plan for the health of your family."
- "Living well starts with knowing your DNA."
- "Health tools—Document your family health history, track inherited conditions, and share the knowledge."
- "Drug response—Arm your doctor with information on how you might respond to certain medications."
- "Below are a few examples [diabetes, arthritis, coronary heart disease, breast cancer, plavix, lactose intolerance] where we can help you learn more. And when you know more, you can make better lifestyle choices, look out for common conditions and take steps toward mitigating serious diseases."

(www.23andme.com/health/ Accessed 11/26/13). *Id.* at 4.

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uses the information it collects from the DNA tests consumers pay to take to generate databases and statistical information that it then markets to other sources and the scientific community in general, even though the test results are meaningless.”⁵⁰ These actions have injured both the named plaintiff and the class,⁵¹ according to the complaint, which asks the court to enjoin 23andMe’s advertising and to provide “full restitution” to class members (estimated as being at least \$5 million).⁵²

The agency’s actions (not to mention the civil liability that may arise in the class action lawsuit) raise interesting questions on the future of genetic testing, particularly under circumstances where the Supreme Court has raised significant barriers to obtaining patent protection for these types of testing. In such an environment there may be a much lower impetus for disclosing the “natural law” correlations between disease propensity and genetic variability, because once that disclosure is made, it cannot be retracted. If patent exclusivity is not possible, there could easily arise a “tragedy of the commons,” where no company is motivated to undertake the type of efforts demanded by the agency of 23andMe just to have those efforts coopted by its competitors. In this situation, the agency may be required to permit applicants to keep substantial portions of their submissions confidential and be satisfied by a showing that the correlation between a particular genetic variant and a particular disease is sufficiently robust to justify approval. And even that arrangement is problematic, as most confidentiality provisions in applications for government approval can be overcome on notice to the

proprietor that a member of the public has filed a Freedom of Information Act request. It is hard to discern instances in which there would not be intense political pressure to rescind confidentiality for genetic testing regarding a medical disease or condition, with that propensity increasing with increased reliability of the test and incidence of the disease or condition. Of course, the agency cannot disclose what it does not know, so perhaps (and against the tendencies of governments and particularly science-based government agencies like the FDA) approval could be obtained without disclosing the identities of the genes involved in the testing. The perpetual nature of this state of nondisclosure is such that even if the agency were willing to permit nondisclosure for a time, it is unlikely that it would agree to less than a reasonable term (e.g., 20 years from the date the application was submitted for approval). Thus, it could be that in such a round about way agency action could achieve what the patent system has always provided, but perhaps in a form less amenable to meddling from the court.

CONCLUSIONS

This intersection of intellectual property and regulatory agency review is focused in large part in the life sciences area, particularly regarding healthcare and drugs and diagnostic methods. This is perhaps as it should be: Although consumer protection in other areas is important, commentators and scholars have recognized that it is in the life sciences area where patents have the most impact on commercialization. Some of that has to do with the differences in development costs and obsolescence timelines in different industries. A drug can cost \$1 billion to bring to market but has a long time to obsolescence; indeed, drug and other life sciences patents are frequently most valuable in the last few years of their term (which is one reason Myriad Genetics continues to sue alleged infringers of its cancer-testing patents). Computer and other high-tech inventions have much shorter timelines

⁵⁰*Id.* at 2.

⁵¹The complaint defines the class as “[a]ll persons in any of the 50 United States and District of Columbia who purchased a 23andMe Saliva Collection Kit and Personal Genome Service within the Class Period.” *Id.* at 8. The complaint also alleges facts relating to numerosity of class members, typicality (of the named plaintiff), and commonality and predominance of “[w]ell-defined, common legal or factual questions [that] affect all class members.” *Id.* at 9.

⁵²*Id.* at 21. Plaintiffs also demand a jury trial, punitive damages, costs of suit and pre- and postjudgment interest. *Id.* at 25.

(would you want to use a phone from 1995?) and lower development costs (perhaps as little as a bright 17-year-old working on a computer in his garage). These differences have been translated into political differences between life sciences companies that need patents for investment and high-tech companies that fight “patent wars” over cell phone technology on the business pages of the *Wall Street Journal*. Irrevocably these political differences are played out in the courts and by regulatory agencies (backed by the Department of Justice) and explain at least in part the interactions set forth here.

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