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The Weakening of Pharmaceutical Method Patents: The Federal Circuit Addresses the 'FDA Conundrum'

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The US Food and Drug Administration (FDA) has strict requirements for generic drugs. These requirements may prevent a generic manufacturer from altering a drug product to unequivocally avoid patent infringement, and may also require a generic manufacturer to use a patented method for quality control purposes. These situations are called the 'FDA conundrum.' While Congress and the FDA desire to have generic drugs enter the market as soon as possible, the requirements FDA imposes raise issues of patent infringement that often take years to resolve. The Federal Circuit addressed these issues in the year 2012, in three separate cases: *Momenta* v *Amphastar*, *AstraZeneca* v *Apotex*, and *Bayer Schering Pharma AG* v *Lupin*.

Keywords: Hatch-Waxman, safe harbor, label, prescribing information, FDA, injunction, ANDA, submission, bioequivalence, sameness, Federal Circuit, Supreme Court

Generic drug companies face a conundrum today. For certain complicated drugs (such as proteins and polysaccharides), the US Food and Drug Administration (FDA) requires testing every drug batch to be marketed by a test method it has found acceptable. This testing is performed to ensure that the generic drug has the same active ingredient as the brand name company's drug. If the FDA has only found one test method acceptable, however, all generic manufacturers may be required to use that test. Historically, when the test method was patented, a generic manufacturer faced the choice of (i) using the test method and being charged with patent infringement, or (ii) developing and validating an alternative test method with FDA, which is time consuming, expensive, and an unpredictable process.

Another instance where the FDA conundrum exists is the labeling of generic drugs. The label (prescribing information) for a generic drug must typically include the same information as that for the brand name drug. This requirement is to ensure that physicians and patients are provided all the safety and efficacy information for the generic drug. This requirement, however, in some instances, makes it nearly impossible for a generic manufacturer to remove information from the label which refers to patented uses. Since enactment of the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act; or commonly the generic drug act),[1] courts have struggled with whether the inclusion of references to a patented use in a drug label constitutes patent infringement. For example, does the filing of an abbreviated new drug application (ANDA) infringe a patent covering treatment of cancer, where the Clinical Pharmacology section of the label reports clinical trials showing the drug is effective in the treatment of cancer, even when the generic is only seeking approval for a different use?

The US Court of Appeals for the Federal Circuit (Federal Circuit) in 2012 directly addressed the FDA conundrum in three cases, resulting in a weakening of certain method of use patents.

The Safe Harbor Conundrum

Momenta Pharmaceuticals v Amphastar Pharmaceuticals

In *Momenta Pharmaceuticals* v *Amphastar Pharmaceuticals*,[2] the Federal Circuit vacated a preliminary injunction that barred Amphastar Pharmaceuticals from marketing its generic Enoxaparin (Levenox®). In doing so, the court found that the district court, in granting the injunction, 'applied an unduly narrow interpretation of the Hatch-Waxman safe harbor.' The Federal Circuit held that the safe harbor (35 U.S.C. § 271(e)(1))[3] is not limited

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to activities reasonably related to development of information submitted in an ANDA to the FDA. Instead, the court wrote, Congress intended the safe harbor provision to be broader, encompassing any activity reasonably related to the development and submission of information under any US federal law that regulates the manufacture, use, or sale of drugs or veterinary biological products, including post-ANDA compliance testing. Thus, as long as an allegedly infringing use of another's invention is for uses reasonably related to the development and submission of information required under any US federal law that regulates generic drug or biosimilar products, such use is not an act of infringement.

By way of background, FDA laws and regulations impose requirements on ANDA applicants to submit certain information related to their ANDA product prior to receiving FDA marketing approval. In particular, an applicant must show (i) the labeling for the drug for which the ANDA is sought is the same as the approved labeling for the listed drug; (ii) the generic drug, its route of administration, dosage form, and strength are the same as the listed drug, or supply such information respecting any differences as FDA may require; and (iii) the generic drug is bioequivalent to the listed drug; and also (iv) supply information regarding the status of any *Orange Book*-listed patents on the approved drug.[4] Applicants must provide information about its chemical processes, manufacturing and controls, batch formulation and records, descriptions of facilities, specifications and testing, packaging, and stability. After market approval, ANDA applicants must collect and report to the FDA information about adverse events, good manufacturing practices, batch records, and other information specified by the FDA as part of the marketing approval.[5] The *Momenta* case involved maintaining batch records after ANDA approval.

The Federal Circuit's *Momenta* decision follows two court decisions interpreting the scope of the safe harbor, *Merck KGAA* v *Integra Lifesciences*[6] and *Classen Immunotherapies* v *Biogen IDEC*,[7] each of which took different views of the safe harbor provision. Those cases, and now *Momenta*, describe the Congress' intent to promote lower prices and availability of drugs by creating a category of activities related to the manufacture, use, or sale of drugs or veterinary biological products excluded from infringement liability, even where infringement would otherwise be clear.

The potential impact of the Federal Circuit's *Momenta* decision on regulated generic drug and biologically similar technology companies is significant. Such companies must establish, as part of their FDA submissions, the bioequivalence of their products to a specified standard, and they are often required to maintain test results of batches made after FDA approval. That testing may be covered by another's patents, such as those covering methods adopted by the FDA as a standard test method (by, for example, when the FDA adopts the method in the US Pharmacopeia). Use of such patented methods would, under *Momenta*, be covered by the safe harbor and excluded from infringement liability. As *Momenta* stated on its website after the Federal Circuit's opinion, the *Momenta* decision 'could render numerous method, composition, and packaging patents completely worthless.'[8]

Momenta Pharmaceuticals appealed to the US Supreme Court in February 2013, arguing in its petition for *writ of certiorari* that the Federal Circuit's *Momenta* decision is irreconcilable with previous Federal Circuit decisions because the safe harbor may or may not apply to the same set of circumstances, depending on which standard is applied. In June 2013, the Supreme Court denied the petition.

Background

The *Momenta* case involved Enoxaparin (Lovenox®), which is approved by the FDA for preventing blood clots.[9] The drug is a low molecular weight version of heparin (LMWH), a naturally occurring polysaccharide. Heparin molecules can differ in the length of the polysaccharide chain, and in the component disaccharide units and the corresponding distribution of disaccharide unit sequences in the polysaccharide chains. For that reason, the FDA issued criteria or 'standards for identity' to assist ANDA applicants demonstrate their 'generic enoxaparin has the 'same' active ingredient as Lovenox.' In particular, to be 'enoxaparin,' as defined in the US Pharmacopeia (USP), a marketed generic drug product must be shown to contain between 15 and 25 percent of a 1, 6-anhydro derivative, which is determined according to a specific test involving HPLC analysis of a depolymerized enoxaparin sodium solution by a mixture of heparinases.[10]

Momenta developed and patented a method involving digestion of an enoxaparin sample with a

heparin-degrading enzyme, followed by the use of a separation method to detect the presence of the non-naturally occurring sugar resulting from a B-eliminative cleavage. The signal corresponding to the non-naturally occurring sugar can be used to analyse the test sample based on a comparison with the above-mentioned USP reference. Momenta was awarded US Patent 7,575,886 ('886 patent) for its method. Claims 6, 16, and 53 of the '886 patent describe how to analyse a sample of enoxaparin to ensure its conformity to the USP monograph standard.

In July 2010, after receiving FDA approval of its ANDA, Momenta (in collaboration with Sandoz Inc) launched its generic Enoxaparin. On 19 September 2011, Amphastar, which was the first ANDA filer for a generic version of Enoxaparin, also received FDA approval. Momenta sued Amphastar two days later. In its complaint, Momenta asserted that Amphastar 'included in their process for manufacturing batches of enoxaparin sodium ... a method for determining that a defined percentage of the oligosaccharide chains that make up enoxaparin include ... a non-naturally occurring sugar that includes a 1, 6-anhydro ring structure, which method infringes the '886 patent.' Momenta contended that the testing was necessary because the 'FDA requires a generic manufacture to include in its manufacturing process the analysis of each batch of its enoxaparin drug substance to confirm that ... [it] includes a 1, 6-anhydro ring structure.'

In its defense, Amphastar argued the safe harbor provision, 35 U.S.C. § 271(e)(1) (shown below), exempted its laboratory testing activities from infringement.

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention…solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

The District Court Decision[11]

Under US law, a court must weigh four factors before issuing a preliminary injunction, including whether the person who moved for the injunction has sufficiently established 'a reasonable likelihood of success on the merits.' In the present case, to prove a likelihood of success on the merits, Momenta had to prove that Amphastar infringed the '866 patent.

The district court acknowledged that Amphastar's use of Momenta's patented method was for the purpose of developing information to submit to the FDA, but nevertheless concluded that the safe harbor does not apply to Amphastar's post-ANDA submission testing, relying primarily on the legislative history of the safe harbor provision and the Federal Circuit's decision in *Classen Immunotherapies Inc* v *Biogen IDEC*, 659 F.3d 1057 (Fed. Cir. 2011). In *Classen*, the Federal Circuit found that the activities of Biogen and GlaxoSmithKline 'in providing vaccines, in advising on immunization schedules, and in reporting any adverse vaccine effects to the FDA' was not 'reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products,' and therefore the safe harbor provision did not exempt Biogen and GlaxoSmithKline from infringement liability. On that basis, the district court granted Momenta a temporary restraining order to prevent generic entry from Amphastar, then granted Momenta a preliminary injunction on the basis that Amphastar's quality control batch testing, required by the FDA, infringed the '886 patent.

The Federal Circuit's Analysis of the Safe Harbor Provision

After a hearing following Amphastar's appeal, the Federal Circuit stayed, then vacated the preliminary injunction following a comprehensive analysis of the applicable statutory language, 35 U.S.C. § 271(e)(1). In its analysis of the Hatch-Waxman Act,[12] the Federal Circuit found that the Act set up a statutory system to 'balance the need to stimulate innovation against the goal of furthering the public interest.'[13] This balance, the court wrote, is embodied, in part, in the so-called safe harbor provision of the statute.

The Federal Circuit also found that 'Congress could not have been clearer in its choice of words.' That is, as long as the use of the patented invention is solely for uses 'reasonably related' to developing and submitting information pursuant to 'a Federal law' regulating the manufacture, use, or sale of drugs, it is not 'an act of infringement.' And while the Hatch-Waxman safe harbor provision was enacted in the context of the then-novel ANDA approval process, the statutory language does not refer to the portion of the Federal Food, Drug, and Cosmetic Act describing the ANDA requirements, e.g., 21 U.S.C. § 355(j).

Instead, the Federal Circuit concluded, Congress used broader language that 'unambiguously applies to submissions under any federal law,' as long as the law 'regulates the manufacture, use, or sale of drugs.'

Thus, the scope of the Hatch-Waxman safe harbor does not only encompass activities reasonably related to development of information submitted in an ANDA to the FDA. As long as the allegedly infringing use is 'for uses reasonably related' to the development and submission of information, it is not an act of infringement, regardless of where that submission requirement resides in the law.

Addressing the district court's reliance on *Classen*, the Federal Circuit wrote that the *Classen* panel found that § 271(e)(1) 'does not apply to information that may be routinely reported to the FDA, long after marketing approval has been obtained.' In particular, the Federal Circuit found that studies conducted by a vaccine license holder according to patented methods were not insulated by the safe harbor because the studies did not facilitate marketing a generic drug by 'expedit[ing] development of information for regulatory approval.' Accordingly, the scope of the safe harbor provision does not extend to 'information that may be routinely reported to the FDA, long after marketing approval has been obtained.'

The Federal Circuit's Analysis of Amphastar's Activities

The Federal Circuit considered whether Amphastar's testing activities, including creating documents concerning its batch analysis of Enoxaparin, were related to a 'submission of information [to the FDA]' under § 271(e)(1), even though such documents were not actually submitted to the FDA but instead were retained by Amphastar.

FDA regulations require that all records associated with a produced batch of drugs, including Amphastar's batch records for its generic Enoxaparin, 'be retained for at least 1 year after the expiration date of the batch.'[14] Under those rules, such retained records 'shall be readily available for authorized inspection' by the FDA at any time.[15]

The Federal Circuit concluded that, as a generic drug manufacturer under an ANDA, Amphastar cannot sell a batch of its Enoxaparin unless it has established that the strength and quality of the batch is consistent with applicable FDA standards. Although FDA's document retention rules do not explicitly impose a duty to affirmatively submit such records to the FDA, the Federal Circuit concluded that the requirement to 'maintain records' for FDA inspection satisfies the requirement that the use of Momenta's method claims to generate such records 'is reasonably related to the development and submission of information to the FDA.' In fact, the Federal Circuit noted that Momenta and Amphastar did not dispute that the records are produced to develop and submit to the FDA proof that Amphastar's products comply with a Federal law.

Moreover, Amphastar's activities, the Federal Circuit found, were not 'routine submissions' to the FDA, as in *Classen*. Instead, Amphastar's activities involved developing information required to be maintained by the FDA for approval. Failure to comply with the testing and result retention requirements under FDA rules could result in suspension or revocation of Amphastar's ANDA approval to market its generic Enoxaparin. Also, the rules require Amphastar to test its batches as a condition for the drug's approval and release into commerce, which the Federal Circuit found was a predicate to Amphastar's ability to market the ANDA-approved drug to the public. Thus, the Federal Circuit concluded, Amphastar's activities were not 'routine.'

The Federal Circuit rejected Momenta's argument that the safe harbor does not apply to Amphastar's activities because Amphastar could have used alternative, FDA-endorsed, non-infringing test methods. The language of the safe harbor, the court concluded, does not mandate the use of existing non-infringing alternative methods. That is, just because the FDA might accept the use of other, non-patented, test methods for the development and submission of information does not preclude a company from relying on the safe harbor. Rather, the express language of the safe harbor provision provides that a company like Amphastar is free to use an otherwise patented means to develop the necessary information demanded by a federal law.

Finally, the Federal Circuit concluded that because Amphastar's testing activities were carried out to 'satisfy the FDA's requirements' and thus fell within the scope of the safe harbor, Momenta had not established a likelihood of success on its claim of infringement, and thus no injunction could stand.

Federal Circuit Denies Momenta's Petition for Rehearing

In November 2012, the Federal Circuit denied Momenta's request for a rehearing *en banc* to reconsider the three-judge panel opinion. In response,

Momenta stated that it would file a petition for certiorari, and ask the Supreme Court to review the matter, arguing that the Federal Circuit decision 'finds no support in the statutory text of the safe harbor provision of the patent law, or in Supreme Court precedent, and a final decision upholding this case could have wide-ranging, negative effects on drug development.'

Supreme Court Appeal[16]

In its petition for *writ of certiorari* to the Supreme Court filed in February 2013, Momenta framed the legal issue as whether the use of a patented invention after FDA marketing approval, in connection with manufacturing a drug for commercial sale, where the FDA requires a record of that manufacturing activity be maintained, is exempt from liability for patent infringement under Section 271(e)(1). Momenta argued that the *Classen* and *Momenta* decisions are irreconcilable, because had the Federal Circuit applied the standard articulated in *Classen*, Amphastar's use of Momenta's patented invention would not have been exempted from infringement under the safe harbor.

Momenta also argued that the Federal Circuit's decision is inconsistent with *Merck* v *Integra*, despite the Supreme Court stating in that opinion that the safe harbor provides a wide berth for the use of patented drugs in activities related to the federal regulatory process. In fact, the Supreme Court held in *Merck* that 'preclinical research, whether or not ultimately included in a submission to the Food and Drug Administration, 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].' Momenta argued that *Merck* limits the § 271(e)(1) safe harbor to pre-FDA approval activities.

Post Momenta

Because the Supreme Court denied Momenta's *writ*, some of the uncertainty surrounding the scope of the Hatch-Waxman safe harbor remains unresolved. As a result, many patents covering laboratory methods used in the pharmaceutical and biotechnology fields, where such methods are used in connection with non-routine submission (or retention for later inspection) of information required by the FDA, will in fact have far less value than they did prior to *Momenta*. Thus, companies that engage in marketing generic drugs and biosimilars in the US might consider the impact of *Momenta* on on-going and future research and development activities, and their internal patent strategies. It may no longer be assumed, post *Momenta*, that a company can assert patents covering newly-developed methods for testing formulations and substances for bioequivalence or biosimilarity, related to seeking initial and on-going FDA marketing approval.

The FDA Labelling Conundrum

AstraZeneca v *Apotex* and *Bayer Schering Pharma AG* v *Lupin*

The two cases — *AstraZeneca* v *Apotex* and *Bayer Schering Pharma AG* v *Lupin* — address issues of whether parts of the drug label (and other facts) can be used for determining patent infringement in connection with filing an ANDA. Before discussing those cases, a brief summary of how method of treatment patents are handled under the Hatch-Waxman Act is helpful.

Brand name companies are required to submit information to FDA for patents which cover the approved drug substance (active pharmaceutical ingredient), drug product, or method of use. The FDA publishes this patent information in a database known as the Orange Book. For each method of use patent, the brand name company proposes a 'use code' to be associated with it. The use code indicates the patented use.

If a generic manufacturer desires to market a generic version of a brand name product before a patent listed in the Orange Book has expired, the generic manufacturer may submit what is known as a Paragraph IV certification and notify the brand name company of its basis for believing that the patent is not infringed or invalid. Under the Hatch-Waxman Act (in particular, 35 U.S.C. §271(e)(2)), the filing of an ANDA creates an artificial act of infringement. If the brand name company files a lawsuit within 45 days of the notice letter, FDA approval of the generic manufacturer's ANDA is stayed, typically for up to 30 or 42 months (referred to as a '30 month stay').

A generic manufacturer can avoid submitting a paragraph IV certification and the possibility of a 30 month stay with respect to a method of use patent by removing the patented indication (i.e., method of use) from the generic's proposed label, and submitting a

statement (known as a section (viii) statement) averring that the ANDA excludes all uses claimed in the patent. There is no requirement for the generic manufacturer to notify the brand name company regarding a section viii statement.

AstraZenenca* v *Apotex

In *AstraZeneca* v *Apotex*[17], Apotex filed an ANDA for the drug rosuvastatin. Rosuvastatin (Crestor®) was approved by FDA for four indications: (1) treatment of heterozygous familial hypercholesterolemia (HeFH) in pediatric patients, (2) preventative use in high-risk patients with elevated C-reactive protein (CRP), (3) treatment of hypertriglyceridemia, and (4) treatment of homozygous familial hypercholesterolemia (HoFH).

AstraZeneca listed two patents in the Orange Book which, according to the use codes associated with them, are directed to only two of the approved indications (HeFH and elevated CRP). Apotex removed the patented indications from their proposed labels and submitted section (viii) statements with respect to the two patents. AstraZeneca, nonetheless, sued Apotex asserting that if the generic drugs were approved, the generic drugs would be prescribed and administered to treat the patented indications, and that Apotex would be inducing infringement of the patents. AstraZeneca also argued that FDA might in the future require Apotex to amend its ANDA to include the patented indications.

The district court dismissed AstraZeneca's infringement claims, ruling that it lacked subject matter jurisdiction as Apotex's ANDA did not refer to the patented indications and therefore could not induce infringement of the patents. According to the district court, the Hatch-Waxman Act 'creates in the ANDA context a limited and artificial cause of action where none would otherwise exist, so that in such cases a district court's jurisdiction turns on whether a plaintiff asserts a valid claim under [the statutes, 35 U.S.C. §271(e)(2)].' The court also held that AstraZeneca's claims were unripe to the extent that they relied on possible future labeling changes.

The Federal Circuit affirmed the dismissal of the lawsuit but on different grounds. First, subject matter jurisdiction for the case was found to exist. According to the Federal Circuit, subject matter jurisdiction is established when an ANDA is filed, irrespective of the merits of the lawsuit. The Federal Circuit pointed out that 'the requirements for jurisdiction in the district courts are met once a patent owner alleges that another's filing of an ANDA infringes its patent under §271(e)(2), and this threshold jurisdictional determination does not depend on the ultimate merits of the claims.'[17] As an ANDA was filed here, the court had jurisdiction to determine the merits of the action.

AstraZeneca, however, failed to state a viable claim of patent infringement. AstraZeneca argued that the filing of an ANDA is an act of infringement of any method of use patents. The statute provides that the filing of ANDA 'for a drug claimed in a patent or the use of which is claimed in a patent' is an act of infringement. Specifically, AstraZeneca argued that the ANDA was for 'a drug', rosuvastatin, 'the use of which is claimed in a patent.' The Federal Circuit construed the term 'the use' to mean the use listed in the ANDA. [17] Rejecting AstraZeneca's argument, the Federal Circuit held that '[i]nfringement of method claims under §271(e)(2) requires filing an ANDA wherein at least one 'use' listed in the ANDA is claimed in a patent.'[17] 'Thus, an ANDA seeking to market a drug not covered by a composition patent for unpatented methods of treatment cannot infringe under §271(e)(2).'[17]

AstraZeneca also argued that '[s]ection viii statements and restricted generic labeling ignore market realities because even if a generic drug is formally approved only for unpatented uses, pharmacists and doctors will nonetheless substitute the generic for all indications once it becomes available.' The court found this unpersuasive as it would (i) vitiate the statutory language permitting section viii statements, and (ii) permit brand name companies to maintain *de facto* indefinite exclusivity over a drug by obtaining serial method of use patents and wielding them as swords against generic manufacturers.

The court also found AstraZeneca's assertion regarding possible future off-label use as too speculative and therefore insufficient to establish infringement prior to marketing by the generic manufacturers.

As Apotex was not seeking FDA approval for the patented indications, the filing of its ANDA did not infringe the patents under §271(e)(2).

This decision may prevent future lawsuits against generic manufacturers only seeking FDA approval for indications not patented.

Bayer Schering Pharma AG* v *Lupin

In *Bayer Schering Pharma AG* v *Lupin*[18], generic manufacturers filed ANDAs seeking approval to market Bayer's Yasmin® product, an oral contraceptive. Bayer asserted a patent claiming a method of simultaneously achieving a gestagenic (or contraceptive) effect, anti-androgenic effect, and an anti-aldosterone effect in a female patient in need of all three effects by administering dihydrospirorenone, one of the active ingredients in Yasmin. According to the 'indications and usage' section of the Yasmin label, Yasmin is approved to prevent pregnancy.

The district court dismissed the lawsuit for failure to state a claim for patent infringement. Because the patent required three simultaneous uses and FDA had approved Yasmin for only one use (i.e., prevention of pregnancy), the court found that a claim for patent infringement could not be established based on the ANDA alone as required by §271(e)(2).

On appeal, Bayer argued that FDA had approved the use of Yasmin for all three effects. First, Bayer argued that FDA's listing of the patent in the Orange Book was evidence that the product was approved for all three uses. Second, Bayer argued that the label refers to all three indications — the contraceptive effect in the indications and usage section of the label, and the anti-androgenic and anti-aldosterone effects in the clinical pharmacology section of the label. Third, Bayer argued that the marketing materials for Yasmin, which referred to all three effects, were approved by FDA.

The Federal Circuit was not persuaded by any of these arguments. According to the Court, an ANDA constitutes infringement under §271(e)(2) 'only if the [ANDA seeks] approval for the use protected by the … patent, i.e., for the combination of a gestagenic effect, an anti-androgenic effect, and an anti-aldosterone effect in patients needing that combination of effects.' As the generics' ANDAs were substantially identical to Bayer's NDA for Yasmin, the uses for which the ANDAs seek FDA approval are the same as that approved for Yasmin. Therefore, whether Yasmin has been approved by FDA to achieve the combination of all three effects claimed in the patent determines whether the ANDAs constitute infringement under §271(e)(2).

The listing of Orange Book patents is handled as a clerical matter by the FDA. The FDA does not evaluate the substance of a patent to determine whether the patent is properly listed by a brand name company. Consequently, the listing of the patent in the Orange Book is not evidence that the patent covers the approved uses of the product.

Furthermore, FDA regulations state that approved uses for a drug only appear in the indications and usage section of the label, and that uses 'must not be implied or suggested' by other sections of the label, such as the clinical pharmacology section 21 C.F.R. §201.57(c)(2)(iv) (The Court did note that approved dosage regimens and methods of administration are provided in the dosage and administration section of the label). The uses listed in the indications and usage sections are those for which FDA has found the drug safe and effective. Yasmin's label only shows that FDA found the drug safe and effective for preventing pregnancy.

FDA regulations also require the label to provide a summary of the essential scientific information for the safe and effective use of the drug [21 C.F.R. §201.56(a)(1)]. The Yasmin label does not provide physicians with such a summary for the anti-androgenic and anti-aldosterone effects. This is further evidence that FDA did not approve Yasmin for these two indications.

FDA's acceptance of marketing materials does not indicate its approval of a use not otherwise indicated in the label. Additionally, description of anti-androgenic and anti-aldosterone effects is qualified. The discussion of the anti-aldosterone effect in the marketing materials is qualified by a warning regarding the potential for hyperkalemia in high-risk patients. The anti-androgenic effect was only observed in preclinical studies (animal studies).

The Court therefore found that FDA had not approved Yasmin for all three uses. Bayer acknowledged that the patent only covers all three uses of the drug simultaneously, and does not cover its use for contraception alone. As Lupin was only seeking approval for contraception, its product was not found to infringe the patent.

One of the three judges (Judge Newman) on the Federal Circuit panel that heard this case dissented. According to Judge Newman, 'the portion of the FDA label in which a product's properties are described is irrelevant to whether the patent is infringed by sale or use of the product.'[18] The FDA concluded that the drug was safe and effective for use as recommended by the Yasmin label. Thus, according to Judge Newman, FDA must have reviewed the safety and efficacy of Yasmin for its

anti-androgenic and anti-aldosterone effects. Bayer also provided evidence that physicians prescribe Yasmin as an oral contraceptive with the intent to produce the two other pharmacological effects. Finally, Judge Newman argued that the label does not need to specifically authorize physicians to prescribe Yasmin to provide all three effects. Rather, Bayer only needs to establish that Lupin's label would induce patient's to use the drug for all three effects.

Conclusion

The FDA conundrum, while substantially diminished by these cases, still exists. One open issue is whether a patent directed to a sub-population of the intended population to be treated by a drug can be infringed by filing of an ANDA. Drug companies and the courts will likely continue to struggle with the FDA conundrum in the future.

References

1 Drug Price Competition and Patent Term Restoration Act of 1984, 98 Stat. 1585; 21 USC § 355(j)(2)(A).

2 *Momenta Pharmaceuticals* v *Amphastar Pharmaceuticals*, 686 F. 3d 1348 (Fed. Cir. 2012).

3 35 U.S.C. § 271(e)(1) (2013) ('It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (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 or veterinary biological products.').

4 Federal Food, Drug, and Cosmetics Act, § 505(j)(2)(A).

5 21 C.F.R. § 314.98 (Postmarketing Reports) (2003).

6 *Merck KGAA* v *Integra Lifesciences*, 545 U.S. 193 (2005) (explaining that the statutory § 271(e)(1)'s exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of any information under the FDCA, which 'necessarily includes preclinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process.').

7 *Classen Immunotherapies* v *Biogen IDEC*, 659 F.3d 1057 (Fed. Cir. 2011) (holding that the 271(e)(1) safe-harbor provision is limited to activities conducted to obtain pre-marketing approval of generic counterparts of patented inventions, and that 271(e)(1) does not apply to information that may be routinely reported to the FDA, long after marketing approval has been obtained.); *cert. denied* (*Classen Immunotherapies* v *Biogen IDEC*, slip. op. No. 11-1078 (2013).

8 Petition for writ of certiorari, filed by Momenta Pharmaceuticals, 21 February 2013.

9 Lovenox® prescribing information, http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020164s080lbl.pdf (16 May 2013).

10 See FDA response to Citizen's Petition, 23 July 2010, at 3; http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM220083.pdf (16 May 2013).

11 *Momenta Pharmaceuticals* v *Amphastar Pharmaceuticals*, 882 F. Supp. 2d 184 (D. Mass 2011).

12 Drug Price Competition and Patent Term Restoration Act of 1984, 98 Stat. 1585; 21 USC § 355(j)(2)(A).

13 US House of Representatives Report 98-857, pt. 2, at 2714 (1 August 1984).

14 21 C.F.R. § 211.180(a) (General Requirements – retention of batch records) (2003).

15 21 C.F.R. § 211.180(c) (General Requirements – availability for inspection) (2003).

16 Petition for Writ of Certiorari, No. 12-1033 (21 February 2013).

17 *AstraZeneca* v *Apotex*, 669 F.3d 1370, 1377-78 (Fed. Cir. 2012).

18 *Bayer Schering Pharma AG* v *Lupin*, 676 F.3d 1316, 1328 (Fed. Cir. 2012).