Review Article

FDA PERSPECTIVE OF ANDA CERTIFICATION PROCESS AND CASE STUDIES ON PARAGRAPH-IV CERTIFICATION

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ABSTRACT

The evolution of pharmaceutical competition since Congress passed the Hatch-Waxman Act in 1984 raises questions about whether the act's intended balance of incentives for cost savings and continued innovation has been achieved. Generic drug usage and challenges to brand-name drugs' patents have increased markedly, resulting in greatly increased cost savings but also potentially reduced incentives for innovators. Key catalysts for this were legal and regulatory changes that awarded 180-day exclusivity rights for first-filing generic firms not only on the basis of a court victory, but also through a settlement with the patent owner. The new regulatory environment induced significant behavioral changes, including racing by generic firms to challenge patents for large-selling drugs in an environment where more patents are filed by branded firms. Increased generic challenges to different types of patent claims are linked to reduced market exclusivity periods for branded drugs, based on regression analyses and litigation outcomes. Settlements that allow entry prior to patent expiry are a prevalent litigation outcome given the risks of an unfavorable court decision that can adversely affect a company's market valuation. Congress should review whether Hatch-Waxman is achieving its intended purpose of balancing incentives for generics and innovation. This topic remains an important issue for further research, particularly given different public policies governing patent challenges for biosimilars and biologics compared with those for generic drugs and new chemical entities.

Keywords: FDA, ANDA, Hatch-Waxman Act, Orange Book, Patent infringement, Paragraph-IV Certification.

The Certification Procedure

The Drug Price Competition and Patent Term Restoration Act of 1984, otherwise known as the Hatch-Waxman Act, has been quite successful in increasing the availability of generic drugs to consumers. By 1996, forty-three percent of the prescription drugs sold in the United States were generic compared to just nineteen percent in 1984. Despite the Act's overall success in promoting increased availability of generic drugs, the Act's provisions relating to patent certification actually delay approval of generic drugs.

Through the abbreviated new drug application ("ANDA") process, a party may obtain FDA approval of generic drugs without clinical trials if the drug is a bioequivalent of a drug previously granted NDA approval. ANDA approval requires that an applicant make a patent certification with respect to each patent issued by the United States Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or claims a use of such listed drug for which the applicant is seeking approval...."[1] Certification requires the ANDA applicant to state that: (1) the NDA holder submitted no patent to the FDA; (2) any patent submitted has expired; (3) the date the applicable patent expires; or (4) that "the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the abbreviated application is submitted."[2]

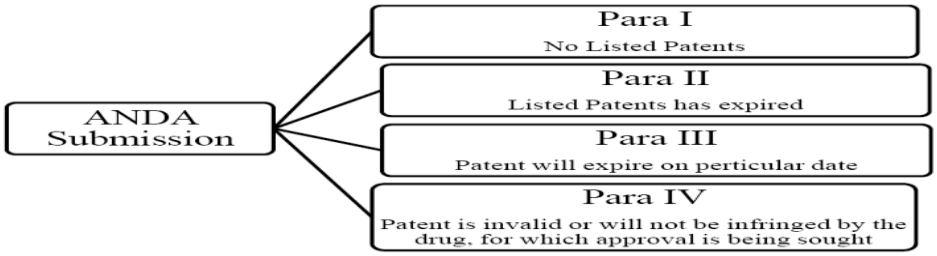

Fig. 1: Parts of ANDA Submission

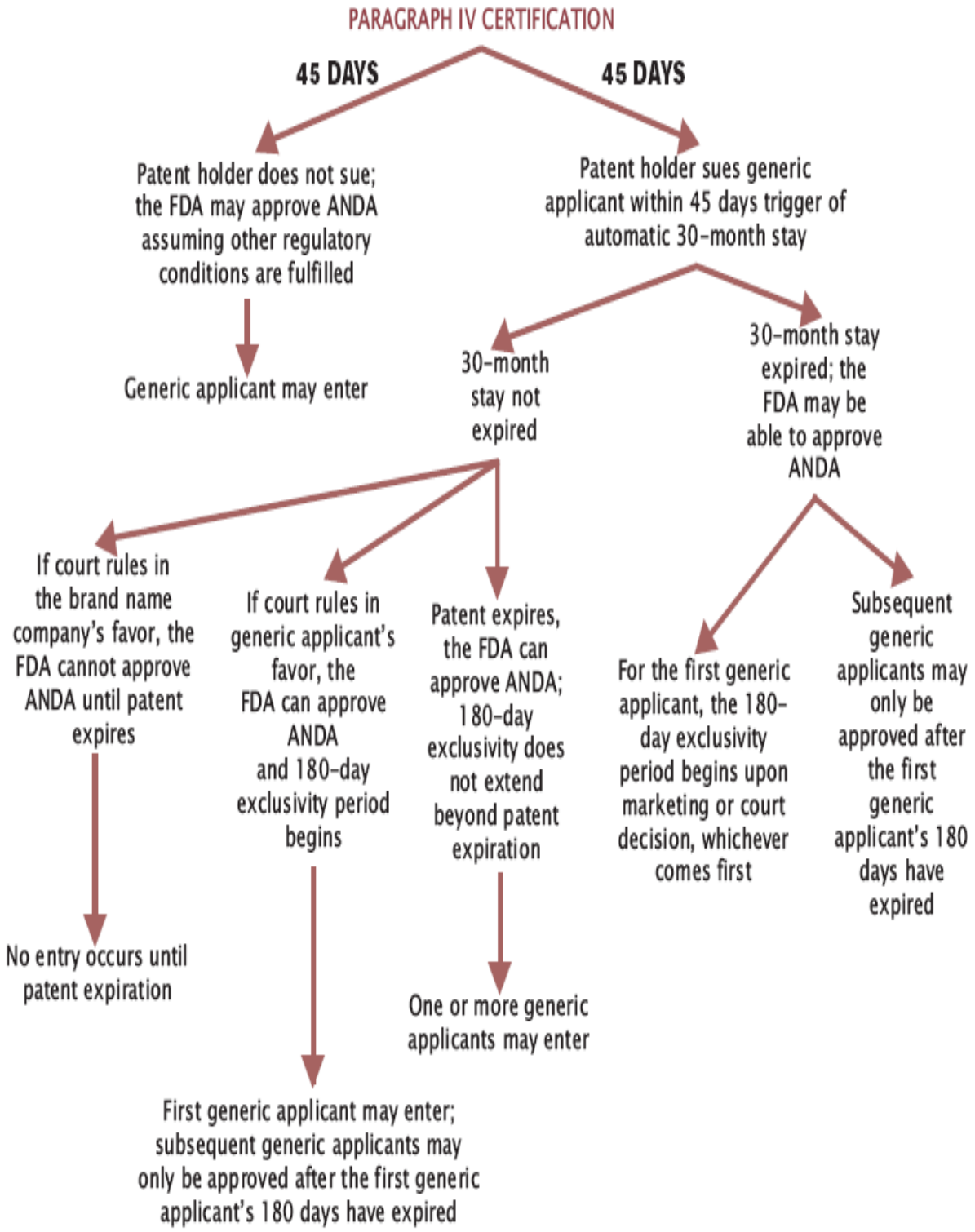

Fig. 2: Paragraph-IV Certification

Comparing the ANDA Stay Provision with Preliminary Injunction Practice

The scope of exclusivity granted by the FDA's thirty month stay provision under 21 C.F.R. 314.107(b)(3)(i)(A) has the same effect as a preliminary injunction because the provision prevents the ANDA applicant from producing, selling, or using its applied for drug product until a trial decision is made in the ANDA applicant's favor. Because of the statute has a similar result to a preliminary injunction, it is useful to compare the differences in how these to results are obtained.

A patent holder seeking a preliminary injunction against an alleged infringer must demonstrate "(1) a reasonable likelihood of success on the merits; (2) irreparable harm if an injunction is not granted; (3) a balance of hardships tipping in its favor; and (4) the injunction's favorable impact on the public interest."[3] The factors taken individually are not dispositive; instead, a district court in its discretion "must weigh and measure each factor against the other factors and against the form and magnitude of the relief requested.[4] Showing the first two factors, likelihood of success and irreparable harm, are essential if a preliminary in-junction is to be granted.[5] The preliminary injunction should not issue if the alleged infringer raises an infringement or invalidity defense that the plaintiff cannot prove "lacks substantial merit."[6] For example, if the defense puts forth evidence of invalidity insufficient to prove invalidity on summary judgment yet "presents a serious challenge to validity" to be assessed at trial, the preliminary injunction will not be granted.[7]

In contrast to the requirements for issuance of a preliminary injunction, the FDA's thirty-month stay provision under 21 C.F.R.314.107 takes effect regardless of likelihood of success or irreparable harm. If a NDA holder files suit, the ANDA applicant's entry into the market is delayed for thirty months or until the ANDA applicant receives a favorable verdict even where the NDA holder has a very small chance of success on the merits of the suit. The ANDA applicant's barrier to entry remains absolute even where the ANDA holder presents powerful defenses that either tend to show non-infringement or presents serious challenges to validity of the NDA holder's patents. Further, the stay provision is effective even though the only harm of ANDA approval to the NDA holder may be monetary so that no threat of irreparable harm exists.

NDA holders gain a scope of protection on their patents allowing immediate injunctions against competition even if the patents are likely to be found invalid or to narrow to cover the ANDA applicant's product. No other patent holders enjoy this broadened scope of preliminary protection. Instead, other patent holders must seek preliminary injunctions that are available only when the relevant patent is likely to be found valid and where infringement is likely. Without being able to make these showings, the patent holder can only seek damages after the fact of infringement and cannot prevent the competitor from making, using, or selling the patented product during the lengthy trial process.

Tactical Use of the Thirty-Month Stay Provision

Because the thirty-month stay provision takes effect automatically, NDA holders have a very significant incentive to file suit against ANDA applicants even where the merits of the case are weak. Additionally, the power of the thirty-month stay provision provides incentive for NDA holders to list as many patents as possible in the Orange Book in order to ensure that competitors will need to make a paragraph IV certification even after a primary patent covering the NDA product has expired. The practice of prosecuting and listing secondary patents is referred to as "evergreening" or "trip wire" listing of patents.[8]

The incentive of NDA holders to list as many patents in the Orange Book as possible ("land mine" patents) exacerbates thirty-month stay provision problems. Regulations allow "drug substance (ingredient) patents, drug product (formulation and composition) patents, and method of use patents" to be listed in the Orange Book.[9] Thus, pharmaceutical companies often list "unapproved uses, special crystalline forms of the active ingredient, specific formulations, tablet shape or other subject matter."[10] A patent on narrow subject matter such as a special crystalline form or tablet shape would not cover an ANDA applicant's proposed use of the same drug unless the applicant was using the exact same special form or shape.[11] Nonetheless, if an ANDA applicant certifies against these narrow patents, the NDA holder may sue the ANDA applicant to trigger the thirty-month stay provision.

The Limited Options Available to ANDA Applicants

An ANDA applicant who wants to avoid the thirty-month stay provision and faces patents listed in the Orange Book which do not cover the NDA drug itself but instead cover narrow forms of the drug or irrelevant uses for the drug (unapproved uses) has a very limited number of undesirable legal options available to it. The applicant either must argue to the FDA or to a court that paragraph IV certification

should not be required or must certify against all the patents listed in the Orange Book and hope to have the inevitable lawsuit by the NDA holder dismissed on the merits as soon as possible to end the thirty-month stay.

The ANDA regulations require that certifications be made only against patents “which claims the reference [Orange Book] listed drug or that claims a use of such listed drug."[12] To “claim" the drug, according to the patent law definition of “claim," a patent's claim section would have to include every element directed at the drug and no other elements. For example, a patent having claims that include elements of the drug and elements of packaging does not “claim" the drug.[13] The code suggests that the term “drug" includes only drug products (dosage forms) and drug substances (active ingredients).[14]

In cases where a patent's claimed elements include more than dosage form or active ingredient (for example, the patent may include packaging elements or crystalline form elements irrelevant to the active ingredient), an ANDA applicant might be able to convince the FDA or a court that it does not need to certify against patents even though they are listed in the Orange book because the patents “claim" more than the drug, not the drug itself. Alternatively, the ANDA applicant may argue that the patents should be removed from the Orange Book because the patent does not claim the drug, and that once removed, the patents need not be certified against. Each of these approaches presents difficulties.

FDA regulation interpretations indicate that, in the FDA's view, an ANDA applicant must certify against every patent listed in the Orange Book. The FDA has “determined that `Congress intended that an ANDA applicant need only consult the Orange Book to determine the existence of an applicable patent claiming the listed drug or use of the listed drug."[15] The FDA has explained that “the Orange Book `provides notice to potential ANDA applicants of the patents which may protect the pioneer drug product, thus allowing them to provide appropriate certification under... the act.'"

The FDA's view is supported by the regulations' mechanism for challenging disputed patent.[16] Existence of a formal procedure for disputing an Orange Book listing implies that third parties would have a reason, such as required certification, to dispute a listing. The FDA statements quoted by the Abbott court combined with the formal procedure for ANDA applicants to challenge the relevancy of information listed in the Orange Book indicates that the FDA is likely to interpret the code as requiring certification against all patents listed under a drug in the Orange Book.

The FDA's stance on the issue is critical if an ANDA applicant hopes to receive approval without an extended delay due to a court challenge of the FDA's position. A suit challenging the FDA's requirement that a certain Orange Book patent be certified against could itself take thirty months to resolve, thus being useless in preventing delay. Further, if an ANDA applicant argued in court that it need not certify against a patent listed in the Orange Book, the FDA's stance carries substantial weight because “an agency's construction of a statute it is charged with enforcing is entitled to deference if it is reasonable and not in conflict with the expressed intent of Congress."[17]

Because the FDA is likely to rule that an ANDA applicant must provide certification against any patent listed in the Orange Book without evaluating whether or not the listed patent claims the drug or drug product, an ANDA applicant may wish to remove a patent from the Orange Book before refusing to certify against the patent. The Supreme Court in dicta stated that “ANDA's and paper NDA's are required to contain one of the four certifications with respect to each patent named in the pioneer drug application" thus implying that no certification needs to be made against patents not included in the Orange Book.[18] Further, the FDA's interpretation states that an ANDA applicant should only need to consult the Orange Book in determining what certifications are necessary.[19]

Unfortunately for ANDA applicants, it is rather difficult to have a patent removed from the Orange Book. The regulations allow ANDA applicants to dispute “the accuracy or relevance of patent information."[20] Under this regulation, a party disputing a patent listing must inform the FDA of its grounds of disagreement with the patent's inclusion. The FDA then requests the NDA holder to withdraw or amend its patent information. If the NDA holder refuses, the Orange Book remains unchanged and the ANDA applicant must certify against every listed patent. Since the regulation puts NDA patent listing entirely at the control of the NDA holder, the procedure provides no hope of relief for ANDA applicants who feel a patent is listed improperly.

A district court may however issue a declaratory judgment that a NDA holder must remove a patent from the Orange Book.[21] In Ben Venue Laboratories, Inc. v. Novartis Pharmaceutical Corp., the court gave the FDA's listing of a patent some deference since the FDA has rejected patents in the past.[22] However, the Court held that an Orange Book listing creates no presumption that the patent is listed correctly because the FDA lacks resources and expertise to properly review submitted patents. Therefore, an ANDA

applicant could perhaps avoid the thirty-month stay provision by challenging, in court, a patent's inclusion in the Orange Book. However, lawsuits are often lengthy processes, and a lawsuit challenging an Orange Book listing could delay ANDA approval almost as much, or perhaps even more, than the thirty-month stay provision.

Strategies involving refusal to certify or removal of a patent from the Orange Book rely on the argument that the patents do not claim the NDA approved drug or use. If the patents claim legitimate variants of the drug or drug use, there is no way an ANDA applicant can argue that they need not certify against these patents even if the patents claim variants which are not useful or are irrelevant to ANDA applicant's proposed product.

If an ANDA applicant is unable to reasonably argue that it need not certify against a NDA holder's patent or is unwilling to go through what may be a lengthy court battle to have a patent removed from the Orange book, the only option is to certify against the NDA holder's patent, wait for the NDA holder's lawsuit to trigger the thirty-month stay provision, and try to get the lawsuit dismissed as quickly as possible. The problem with this situation is that the stay provision acts like a preliminary injunction entered against the ANDA applicant regardless of the merits of the NDA holder's case or of the lack of irreparable harm the NDA holder would suffer.[23] To avoid the injunction, the ANDA applicant must obtain dismissal by showing that the NDA holder's suit could not be successful even if all facts are favorable to the NDA holder, where under a normal preliminary injunction standard the NDA holder would have the burden of showing a likelihood of the suit's success on the merits.

Incentives of Patent Law

Exclusive rights granted for the originator of an invention or creative work, intellectual property rights, are well recognized in the modern laws of nearly every nation.[24] In fact, the Constitution specifically allows Congress “to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."[25] The primary question when formulating intellectual property regimes is, “How much exclusivity should be granted and for what period of time?"

A number of principle philosophical foundations for privileging intellectual property rights exist. The foundations can help inform policy makers on what extent of intellectual property rights should be granted. Specifically, the ANDA thirty-month stay provision can be evaluated on the basis of how well the provision furthers the goals addressed by these philosophical foundations.

Economic Analysis

The United States patent law regime, according to most courts, is primarily concerned with providing an economic incentive for invention. The U.S. Supreme Court has stated that, “The patent monopoly was not designed to secure to the inventor his natural right in his discoveries. Rather, it was a reward, an inducement, to bring forth new knowledge."[26] People are more likely to invent new products if they get an award in the form of the exclusive right to sell the product because the exclusive right to sell often translates into the ability to charge significant royalties for the invention compared to the price that would be charged if competition existed.

The ability of the patent law to encourage development of knowledge through incentives must be weighed against the harm caused by the “patent monopoly."[27] Ultimately, the inventor's royalty results in higher prices for consumers of the invention and perhaps a reduced output of production of the invention.[28] Higher cost and lower output of the invention may mean that the public resorts to inefficient alternatives or in some cases goes without the utility the invention would provide, and thus, the public utility may not be maximized.

Applying a utilitarian or economic standard to drug patents is an especially delicate balance. Obviously, for utilitarian and humanitarian reasons, the development of promising new drugs should remain a very high priority, and the government should maximize incentives for developing these new drugs. On the other hand, the costs of one inventor maintaining a monopoly on a drug are also quite high. Patient demand for a very needed drug is relatively inelastic, so the royalty on a drug monopoly can be very costly to consumers.

The ANDA thirty-month stay provision is problematic from an economic or utilitarian perspective for several reasons. First, an NDA holder may sue an applicant based on any patent listed in the Orange Book for which it can make even the most strained argument for infringement. Many of these patents cover “unapproved uses, special crystalline forms of the active ingredient, specific formulations, tablet

shape or other subject matter"[29] which may or may not be truly useful or practical in a real world setting.[30] For drugs, efficacy in a laboratory experiment is sufficient to meet the utility requirement of patent law[31] even though efficacy in a laboratory experiment certainly does not mean the drug would be useful in a wide variety of human patients or could possibly be made commercially viable.

Thus, the thirty-month stay provision extends the patent monopoly on a drug sold by the NDA holder while potentially only encouraging the NDA holder to prosecute and file suit on patents that disclose inventions that really do not help society at all. In these cases, the stay provision clearly is not supported by an economic or utility maximizing approach to patent law since the provision does nothing to encourage useful drug development while society suffers all the costs of the patent monopoly.

Secondly, the thirty-month stay provision encourages drug companies to file suit against an ANDA applicant based on unsustainably broad interpretations of their patent claims.

Third, the thirty-month stay provision does not particularly encourage patents on the core commercial drug invention but instead encourages the practice of listing “evergreening" and “trip wire" patents.[32] In order to promote maximum utility and economic efficiency in society, it would be far better to encourage development on useful core drug inventions instead of encouraging drug companies to spend resources devising and identifying non-useful sub-inventions that may act as “trip wire" patents.

A fourth problem with the thirty-month stay provision from an economic or utility maximizing perspective is that it encourages drug company emphasis on profits through patents in general. One problem with patents is that their power to encourage invention is limited by the ability of consumers to pay monopoly rents. The patent system works very well in encouraging development of drugs that benefit, no matter how slightly, the part of the population that can afford monopoly rents (Viagra and Rogaine are examples). The patent law does very little to encourage development of drugs that will help people who cannot afford to pay for drugs even where the benefit for society as a whole is potentially very large (drugs to treat AIDs and malaria in the impoverished African nations for example).

The most economically efficient system would encourage that drugs be developed that will help society the most for the minimum research costs, rather than encouraging development of drugs that help the wealthy segment of the population slightly at greater research expense. To reach greater efficiency than the patent system allows, the public could, for example, divert funds from monopoly rents paid to patent holders toward direct government subsidies for drug researchers developing drugs which attack the most devastating diseases that effect the greatest number of people.

The thirty-month stay provision enhances the value of patents in a vague way by allowing the patent to be used to significantly delay ANDA approval regardless of whether the patent actually covers the ANDA drug as long as some argument for infringement can be made. By enhancing the value of patents, the stay provision encourages drug companies to focus on the kind of drugs that are made most valuable by patents, namely those drugs which are marketable to people have the money to pay monopoly rents. Since drugs that provide slight utility to wealthy people are not necessarily the drugs that provide maximum utility to the human population as a whole, the thirty-month stay provision, and patent law for new drugs generally, is not necessarily an efficient means for providing incentives for drug invention.

A fifth problem with the thirty-month stay provision is that any gains it may provide to a company are too unpredictable and speculative to be substantial incentive for research and development. The drug company's primary patent on a new drug protects the company's monopoly on the NDA product for at least twenty years from the date the patent is filed. “Evergreening" or “trip wire" patents which might trigger the thirty month stay of ANDA approval would not have value until after the primary patent which prevents others from manufacturing and selling the drug has expired.

During the twenty-year life of the primary patent, a better drug or treatment technology could potentially be developed thus making the potentiality of a thirty-month stay of competing ANDAs worthless. The thirty-month stay provision could be rescinded or reinterpreted not to be triggered upon suits based on “trip wire" patents again making the stay provision worthless. After twenty years, there may be no need to exclude ANDA competitors as it could be that no significant competitor exists.

Since, ex ante, a drug company or inventor is likely to consider the potential gains from the thirty-month stay provision merely speculative rather than significant, the stay provision provides very little incentive for new drug manufacture. The stay provision is thus economically inefficient since it not likely to provide the public with the benefit of new drugs even though the public pays the full price of the thirty-month patent monopoly whenever a company triggers the stay provision.

There more efficient possibilities for encouraging research and development of new drugs rather than allowing new drug applicants to block ANDA applications based on patents which would not meet a preliminary injunction standard. One possibility, mentioned above, is that the public's payments toward patent monopoly rents could be shifted towards direct research for the most needed drugs. In this scenario, the thirty-month stay provision would decrease in importance as drug patents in general decrease in importance to drug companies.

Another possibility is an accelerated FDA review of new drug applications. Accelerated review of FDA new drug applications could greatly increase profits by allowing the NDA holder's product to get to market more quickly. Accelerated review is worth more to companies, and is thus a better incentive, than future delay of competition in the marketplace through the thirty-month stay provision. The value from future delay of competition may be several years away and thus any gains must be discounted against the time value of money.[33]

Legal Professionalism

If suits are being brought merely to trigger the thirty-month stay provision rather than on the merits of the case, the question arises: may lawyers ethically participate in this kind of litigation? The American Bar Association's Model Rules of Professional Conduct states: A lawyer shall not bring or defend a proceeding, or assert or controvert an issue therein, unless there is a basis for doing so that is not frivolous, which includes a good faith argument for an extension, modification or reversal of existing law. The annotations to the code go on to state that an advocate has a duty not to abuse legal procedure, but that the law is “not always clear and is never static."

The “not frivolous" standard of conduct is rather vague. A suit brought in order to trigger the thirty month stay provision clearly serves the client's substantive purpose of delaying a competitor's entry into the marketplace. The suit however may be considered frivolous “if it is found, beyond doubt and under any arguable legal or factual construction, that the substance of the claim would not entitle the claimant to relief." Since the facts of the patent cases triggering the thirty-month stay provision are often not in dispute, the question of frivolousness depends on the likelihood of relief under any arguable legal construction. While an experienced patent attorney may know full well that a case has zero chance on the merits,[34] a trial judge unfamiliar with patent law may not recognize that no arguable construction could make the NDA holder's case winnable. Thus, it seems unlikely that a lawyer would be sanctioned for filing a lawsuit to trigger the thirty-month stay provision as long as some tortured legal argument can be made.

The individual's personal sense of professional responsibility might however preclude him or her from filing suits that they feel are meritless. How an individual attorney proceeds is likely to depend on their view of their role as a professional. Are lawyers obligated to pursue the client's interests in every permissible manner? Or do lawyers have a greater obligation to present the court only with meritorious arguments that will advance justice and the state of the law?

Antitrust Limitations

Because a lawsuit brought in order to trigger the thirty-month stay provision is brought in order to maintain a monopoly, antitrust law is implicated. The FTC has filed complaints against NDA holders who conspire with an ANDA applicant to prevent generic products from reaching the marketplace.[35] In reaching a settlement with Abbott Laboratories and Geneva Pharmaceuticals Inc., the FTC required the companies to stipulate that they will not enter contracts where an ANDA applicant agrees with a NDA holder not to waive or transfer exclusivity rights or produce a generic product. The settlement also requires any agreement during pending patent litigation involving payment of ANDA applicants by NDA holders to prevent production of generic drugs be approved by the court.

The FTC's enforcement actions are attacking situations similar to those that arose in In re Cardizem CD Antitrust Litigation.[36] In this case, the court held that drug companies could be liable for violation of the Sherman Act because of agreements where a NDA holder pays an ANDA applicant not to market a generic product, even if the agreement is incidental to a patent suit. Even if agreements between NDA holders and ANDA applicants are likely to give rise to significant antitrust issues as in In re Cardizem CD Antitrust Litigation, it is far less likely that the single act of an individual NDA holder suing a ANDA applicant implicates antitrust law. Noerr-Pennington doctrine generally gives antitrust immunity parties who engage in legitimate government petitioning activity even if some injury to competition results directly or indirectly.[37] The Noerr-Pennington doctrine has extended antitrust immunity to “non-sham, pre-litigation threats of suit, demand letters, and communications about pending suits."[38]

This extension combined with an immunity extended to an antitrust defendant's refusal to settle[39] makes clear that invoking litigation itself is immune from antitrust liability even if there are anticompetitive results. Noerr acknowledged however that petitions to the government are not immune when they are merely a "sham."[40] To determine if litigation is a sham, it must be "objectively baseless in the sense that no reasonable litigant could realistically expect success on the merits.[41] Secondly, in a sham litigation, "the baseless suit conceals an attempt to interfere directly with the business relationships of a competitor."

The first prong in proving antitrust violation through sham litigation may be difficult, for many excluded generic drug manufacturers to prove when formulating an antitrust claim. Specific facts supporting an objectively baseless claim must be alleged.[42] In *In re Cardizem*, the State Law Plaintiffs alleged sufficient facts to state a claim by asserting that the generic manufacturer provided samples of the product to the NDA holder, Hoechst, for them to evaluate and confirm no infringement and that Hoechst prosecuted and listed in the Orange Book a second patent which has no significant change or improvement to the original product but instead was prosecuted and listed for the purposes of initiating litigation and triggering the thirty-month stay provision. In other words, the "trip wire" patents recommended by Terry Mahn[43] could give rise to antitrust liability if they are sought for the sole purpose of triggering the thirty-month ANDA stay provision.

CASE STUDIES ON PARA-IV CERTIFICATION

- Cases resolved by ***Settlement***.
- ***Non-infringement*** where the ANDA holder wins over the NDA holder.
- ***Infringement*** cases (may be ***direct / indirect***) where the NDA holder wins over the ANDA holder (also may include ***inducement of infringement***).
- ***Preliminary injunction*** cases – to restrain a party from going ahead with a course of conduct until the case has been decided.
- Cases where a ***30-Month Stay*** is granted.
- Cases where a ***Patent Term Extension*** is granted.
- ***Invalidity*** cases.
- Cases where the federal circuit ***Upholds Patents and Affirms Non-Infrigement.***

Case Study I: Federal Circuit Vacates Preliminary Injunction in Metformin Case *: Sciele Pharma v. Lupin*

In a precedential decision , the Federal Circuit vacated a preliminary injunction that had been entered against Lupin in the ANDA litigation over Lupin's generic version of FORTAMET (metformin extended-release tablets). This is the second preliminary injunction against Lupin that the Federal Circuit has vacated in the litigation.

The U.S. District Court for the District of Delware entered the first preliminary injunction against Lupin in December 2011. The Federal Circuit vacated the injunction on February 6, 2012, because the "district court's order imposing the preliminary injunction failed to even address Lupin's obviousness arguments." On remand shortly therafter, the district court again entered a preliminary injunction against Lupin. Lupin then moved for a stay, which the district court denied. Lupin appealed again to the Federal Circuit, which ordered expedited briefing, held oral arguments on April 18, 2012, and, later the same day, granted Lupin's request to stay the second preliminary injunction.

Lupin argued in the appeal that the presumption of validity should not apply because the PTO erroneously granted the asserted claims of the patent-in-suit, U.S. Patent No. 6,866,866. Sciele argued, on the other hand, that there should be a heightened presumption of validity because the prior art references relied upon by Lupin (Cheng and Timmins) were before the PTO during prosecution. The Federal Circuit explained that, while new evidence not considered by the PTO "may carry more weight than evidence previously considered," the burden of proof required to prove invalidity, clear and convincing evidence, never changes:

The burden does not suddenly change to something higher--"extremely clear and convincing evidence" or "crystal clear and convincing evidence"--simply because the prior art references [relied on to prove invalidity] were considered by the PTO. In short, there is no heightened or added burden that applies to invalidity defenses that are based upon references that were before the Patent Office. The burden is always the same, clear and convincing evidence.

The Federal Circuit next addressed the merits of Lupin's invalidity argument, i.e., that the asserted claims of the '866 patent are invalid as obvious over Cheng and Timmins. The asserted claims are directed to

controlled-release dosage forms of metformin providing a mean time to maximum plasma concentration (T_{max}) of between 5.5 and 7.5 hours. According to the Federal Circuit, Cheng discloses all of the limitations of the asserted claims except for the T_{max} range of 5.5 to 7.5 hours (instead disclosing a T_{max} of 8-12 hours). In addition, while Timmins discloses a *median* T_{max} and not the claimed *mean* T_{max}, Timmins, according to the Federal Circuit, "also provides the raw data from which one skilled in the art could compute the range of possible mean T_{max} values." According to the court, "based on this data, one skilled in the art would understand that the mean T_{max} in Timmins must fall between 4.67 and 6.33 hours." Thus, according to the court, Timmins "teaches one skilled in the art to lower the T_{max} of Cheng." This, in the Federal Circuit's view, was sufficient to raise a substantial question of validity that should have precluded a preliminary injunction.

To buttress its findings on the issue of obviousness, the Federal Circuit cited statements that the patentee made during prosecution in support of *enablement*:

During prosecution the applicant indicated "that one skilled in the art would be able to manipulate the processes and formulations of the [prior art] by other methods to obtain the claimed pharmacokinetic parameters of the present invention by routine experimentation. While [Sciele] argued, and the district court seemed to accept, that this statement applies only to enablement, we are hard pressed to understand this distinction. Coupled with the motivation to lower the T_{max}, as disclosed in Timmins, the applicant's characterization of the predictability and skill in the art during prosecution provides further evidence that it would have been a routine and obvious design choice to make an extended-release dosage form with a lower T_{max}.

Quoting *KSR*, the Federal Circuit concluded, "After all, 'if a person of ordinary skill can implement a predictable variation, section 103 likely bars its patentability.'"

Accordingly, the court vacated the preliminary injunction and remanded the case to the district court for further proceedings.

Watson Pharmaceuticals Inc. acquired Andrx in 2006 for about $1.9 billion, resulting in the merger of the pharmaceutical companies' patent portfolios. Japan-based pharmaceutical manufacturer Shionogi & Co. Ltd. acquired Sciele in October. Hence the issue was resolved by settlement.

Case Study II: *Ranbaxy and Pfizer settle Lipitor litigation worldwide*

Ranbaxy Laboratories Limited (Ranbaxy), announced that it has entered into an agreement with Pfizer Inc. to settle most of the patent litigation worldwide involving Atorvastatin (Lipitor), the world's most-prescribed cholesterol-lowering medicine. This decision will allow for an earlier introduction of a generic formulation that will benefit patients and many healthcare systems throughout the world. Lipitor is the world's largest selling drug with worldwide sales in 2007 of $12.7 billion. The agreement pertains solely to Ranbaxy and its affiliates and does not cover legal challenges to the Lipitor patents involving other generic manufacturers. However, as Ranbaxy was the first generic challenger to the listed Lipitor patents, it retains the right to the marketing exclusivity of 180 days in the United States. Under the terms of the agreement, Ranbaxy will have a license to sell generic versions of Atorvastatin and the fixed-dose combination of Atorvastatin-Amlodipine besylate in the United States effective Nov. 30, 2011.

Ranbaxy will also have a license to sell Atorvastatin on varying dates in an additional 7 countries, including: Canada, Belgium, Netherlands, Germany, Sweden, Italy and Australia. Ranbaxy and Pfizer have also resolved their disputes regarding Atorvastatin in Malaysia, Brunei, Peru and Vietnam.

In addition, the lawsuits between Pfizer and Ranbaxy regarding Atorvastatin will be dismissed in select countries and the lawsuits between Pfizer and Ranbaxy regarding the fixed dose combination product containing Atorvastatin and amlodipine will be dismissed in the U.S. and Ranbaxy will no longer contest the validity of Pfizer's patents in such countries. Such patent challenges by Ranbaxy regarding Lipitor have been underway innumerous markets since 2003. The Atorvastatin patents involved in this agreement are the basic compound patent, which expired in the United States in 2010; the enantiomer patent, which expired in the United States in 2011; and various process and crystalline form patents, which expired in 2016 and 2017; and the combination patent for fixed-dose combination product which expires in 2018.

The agreement also covers the fixed-dose combination of Atorvastatin-Amlodipine besylate, a fixed-dose combination product indicated for patients suffering from both high blood pressure and high levels of cholesterol. The patent for the fixed-dose combination expires in 2018. The settlement also resolves additional patent litigation between the companies involving the branded drugs Accupril (in the U.S.) and Viagra (in Ecuador) and all patent litigation with Ranbaxy relating to generic formulation of Quinapril

hydrochloride in the United States and Sildenafil in Ecuador. Litigation between Ranbaxy and Pfizer relating to Lipitor will continue in five other European countries — Finland, Spain, Portugal, Denmark and Romania.

Case Study III: *Mylan Wins Omeprazole Patent Litigation against Astrazenneca*

Mylan Laboratories Inc. announced that the United States District Court for the Southern District of New York has ruled that Mylan's 10 mg and 20 mg omeprazole delayed-release capsules, which are the generic versions of AstraZeneca LP's Prilosec (R), do not infringe patents (4,786,505 and 4,853,230) asserted against it by AstraZeneca. The Court also found that omeprazole products from Apotex and Impax do infringe the same patents asserted against Mylan. Mylan launched its omeprazole products on August 4, 2003 despite the patent infringement litigation, which at the time was unprecedented in the generic pharmaceutical industry.

A determination of infringement requires a two-step analysis. First the court determines the scope and meaning of the patent claims asserted, and then the properly construed claims are compared to the allegedly infringing device. A finding is 'clearly erroneous' when although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed.

The court primarily rested its conclusion on its finding that Astra failed to prove the presence of carbonates in Mylan's product (which is responsible for the drug stability by creating micro p^H of not less than 7 around the particles of omeprazole or other labile compound).

Case Study IV: *Mylan Infringed Cephalon Painkiller Patents, Judge Says*

A Delaware federal judge on Monday ruled that Mylan Pharmaceuticals Inc. infringed three patents for Cephalon Inc.'s cancer painkiller drug Fentora, saying the former company's proposed generic version of the drug includes components cover by the patents. U.S. District Judge Sue Robinson said in a order that Mylan infringed U.S. Patent Numbers 6,200,604; 6,974,590; and 8,119,158, through its attempts to market a generic version of Fentora. Judge Robinson also found that the 158 patent and another related patent, U.S. Patent Number 8,092,832, are valid. The patents, which Cima Inc. owns and licenses exclusively to.

Direct infringement requires a party to perform each and every step or element of a claimed method or product. To establish, indirect infringement, a patent owner has available two theories: active inducement of infringement and contributory infringement. To establish active inducement of infringement a patent owner must show that an accused infringer "knew or should have known[its] actions would induce actual infringements". To establish contributory infringement, a patent owner must show that an accused infringer sells "a compound of a patented invention knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial non-infringing use".

Cephalon asserts indirect infringement of its patents by arguing that the citric acid and sodium bicarbonate components of Mylan's ANDA products satisfy the court's construction "at laest one compound that evolve gas by means of an effervescent reaction is present in an amount sufficient to increase the rate and/or extent of absorption of an orally administerable medicament across the oral mucosa. The amount is greater than the required for disintegration and does not include the p^H-adjusting substance separately claimed". Hence Cephalon through various experiments proved that an effervescent reaction do occur in the saliva and points to Mylan's development path to argue that the amount of effervescence in the ANDA products increase the rate and extent of fentanyl absorption.

Case Study V: Federal Circuit Affirms Summary Judgment of No DOE Infringement in CENESTIN Case *Duramed Pharms., Inc. v. Paddock Labs., Inc.*,

CENESTIN is a conjugated estrogen pharmaceutical composition used to reduce the symptoms of menopause. The Federal Circuit affirmed that Paddock's generic version of CENESTIN would not infringe U.S. Patent No. 5,908,638, directed to conjugated estrogen compositions, under the Doctrine of Equivalents.

Claim 1 of the '638 patent recites:

A pharmaceutical composition in a solid, unit dosage form capable of oral administration for the hormonal treatment of pre-menopausal, menopausal and post-menopausal disorders in a woman comprising: conjugated estrogens coated onto one or more organic excipients forming a powdered

conjugated estrogen composition where said composition is substantially free of inorganic excipients and further comprises about 30-70% gel-forming organic excipient and about 30-70% non-gel forming organic excipient by weight and having less than about 2.5% free water by weight and greater than 2.5% total water wherein said solid unit dosage form is coated with a moisture barrier coating comprising ethylcellulose.

In 2008, Paddock filed an ANDA for a generic version of CENESTIN, after which Duramed filed suit for infringement of the '638 patent. Duramed asserted infringement of independent claim 1 and dependent claims 4 and 6-8 under the doctrine of equivalents only.

In an opinion , District Judge Sand (S.D.N.Y.) concluded on summary judgment that the four asserted claims were not infringed under the doctrine of equivalents due to prosecution history estoppel. During prosecution, claim 1 originally recited a conjugated estrogen pharmaceutical composition "coated with a moisture barrier coating" (MBC). Original dependent claim 7 limited "said moisture barrier coating" to one that "comprises ethylcellulose." After initially rejecting both claims as obvious, the examiner later advised that he would allow the application if Duramed amended claim 1 to include the limitations of claim 7. In response, Duramed amended claim 1 to recite pharmaceutical compositions with "a moisture barrier coating comprising ethylcellulose."

Judge Sand concluded that the amendment adding the ethylcellulose limitation was substantially related to patentability and narrowed the claim scope, thus triggering the *Festo* presumption that Duramed had surrendered all territory between the original and amended claim scope (i.e., between "coated with a moisture barrier coating" and coated with a moisture barrier coating "comprising ethylcellulose"). Judge Sand also concluded that Duramed had failed to rebut the *Festo* presumption based on an argument of the unforeseeability of the use of polyvinyl alcohol (PVA) MBC, used in Paddock's proposed generic product and marketed as Opadry AMB. Judge Sand concluded that PVA MBCs were foreseeable at the time of Duramed's narrowing amendment (December 1998) because, among other things: (1) a Colorcon PCT application published in January 1996 described PVA as "a moisture barrier coating for pharmaceutical tablets and the like"; (2) pre-September 1996 invoices existed for the sale (by Colorcon) of Opadry AMB; and (3) a 1976 patent to Groppenbächer disclosed the use of PVA in moisture-tight tablets.

In affirming, the Federal Circuit noted that Duramed could rebut the presumption of prosecution history estoppel by showing that the alleged equivalent would have been unforeseeable at the time of the amendment and was thus beyond a fair interpretation of what was surrendered. Duramed argued that the district court applied the wrong legal test for foreseeability, and that an equivalent is not foreseeable unless it was understood by one of ordinary skill to be suitable for use in the invention as originally claimed. But the Federal Circuit rejected Duramed's arguments.

Duramed argued that fore seeability requires that PVA must have been known as an MBC for moisture-sensitive pharmaceutical compounds, like the claimed conjugated estrogens. Relying on *Schwarz Pharma, Inc. v. Paddock Labs., Inc.*, 504 F.3d 1371, 1377 (Fed. Cir. 2007), the Federal Circuit stated that when the language of the original and issued claims begins with the words "[a] pharmaceutical composition," that language (and not merely the specifically-claimed constituent ingredient (here, conjugated estrogens)) defines the field of the invention for purposes of determining foreseeability. Accordingly, PVA MBCs need only to have been known in the field of pharmaceutical compositions, as of the time of Duramed's narrowing amendment. Because the Colorcon PCT discloses PVA MBCs, including Opadry AMB, in the field of pharmaceutical compositions, such PVA MBCs were "known in the field of the invention," and thus foreseeable. Thus, the Federal Circuit held that the Colorcon PCT established foreseeability as a matter of law.

The Federal Circuit also explained that "foreseeability does not require . . . precise evidence of suitability. . . . Foreseeability does not require flawless perfection to create an estoppel." Thus, the Federal Circuit rejected Duramed's arguments that the Colorcon PCT did not establish foreseeability due to its inclusion of (1) technical drawbacks, and (2) conclusory statements, rather than test data showing precise characteristics or precise suitability.

Case Study VI: Federal Circuit Sidesteps Interesting Questions of Jurisdiction Under 271(e)(2) and Inducement of Infringement in Ropivacaine Case *Abraxis Bioscience v. Navinta*

In 2006, Navinta filed an ANDA for a generic version of Naropin (ropivacaine), a drug indicated for use in surgical anasthesia and acute pain management. At the time, there was only one patent listed for ropivacaine in the Orange Book, U.S. Patent No. 4,870,086, which claims an optically pure isomer of

ropivacaine hydrochloride monohydrate. Navinta's ANDA included a paragraph IV certification to the '086 patent.

Shortly after receiving Navinta's notice of paragraph IV certification to the '086 patent, Abraxis sued Navinta under 35 USC 271(e)(2), alleging infringement not only of the '086 patent, but also of U.S. Patent Nos. 5,670,524 and 5,834,489(the "method patents"), which are directed to methods of using low concentrations of ropivacaine for the treatment of pain. Although the '524 and '489 patents issued years earlier, they were not listed in the Orange Book at the time Navinta filed its ANDA.

Navinta filed a motion to dismiss Abraxis's claims regarding the method patents, arguing that because the method patents were not listed in the Orange Book, Navinta did not file paragraph IV certifications on them, and therefore there was no basis for suit under section 271(e)(2). The district court, however, denied Navinta's motion to dismiss, concluding that suit under 271(e)(2) was proper notwithstanding that the method patents weren't listed in the Orange Book.

Navinta appealed this ruling to the Federal Circuit, arguing that jurisdiction under section 271(e)(2) is proper only when an ANDA filer has made a paragraph IV certification, and citing several cases from the Supreme Court and Federal Circuit that allegedly "held that section 271(e)(2) requires a paragraph IV certification." In response, Abraxis argued that the alleged "holdings" cited by Navinta were actually mere dicta, and that neither the Supreme Court nor Federal Circuit has ever directly answered whether a paragraph IV certification is a prerequisite to suit under 271(e)(2).

Some number of months after the district court denied Navinta's motion to dismiss for lack of jurisdiction under section 271(e)(2), Navinta filed a second motion to dismiss, this time alleging that Abraxis lacked standing to sue because, due to a break in the chain of title, Abraxis did not own the patents-in-suit at the time that it filed the Complaint. The district court, however, again denied Navinta's motion, finding that although there was a break in the chain of title to the patents, the "intent" of the various assigning entities was sufficient to imply a *nunc pro tunc* (retroactively to correct an earlier ruling) assignment based on the relationship between the corporate entities. Having denied Navinta's second motion to dismiss, the case proceeded to trial.

In August, after a seven-day bench trial, the district court issued its opinion on the merits. The court found direct and indirect infringement of the '086 composition patent, and indirect infringement of the '524 and '489 method patents. Pursuant to its findings of infringement of the method patents, the district court ordered that the effective date of approval of Navinta's ANDA product be no earlier than September 14, 2014, the expiration date of the method patents.

The district court's findings that Navinta would induce infringement of the method patents are the most interesting, because while the method patents are limited to the use of a low concentration of ropivacaine for the treatment of acute pain, Navinta had amended its ANDA not to seek approval of the low concentration of ropivacaine and, pursuant to section viii, had "carved out" the acute pain indication from its proposed ANDA product labeling. The district court, however, concluded that Navinta "knows or should know that practicioners will use its ANDA products at diluted concentrations for pain management." Furthermore, despite Navinta's section viii labeling carve-out, the district court concluded:

Navinta's Package Insert Labeling is sufficient to establish Navinta's encouragement of direct infringement of the '524 and '489 patents: (1) Navinta's Labeling specifically encourages infringement by including multiple references to use of the ANDA Products in labor and delivery, which is an acute pain management application that is only FDA-approved at [low] concentrations and by epidural administration; (2) Navinta's Labeling specifically encourages infringement by including statements referring practicioners to medical practice texts and references, which would instruct practicioners to use ropivacaine at concentrations of 0.2% or below for pain management; (3) Navinta's Labeling specifically encourages infringement by encouraging the use of the ANDA Products at the lowest possible concentrations for pain management issues.

Navinta appealed these findings. Navinta argued in its appeal brief that the district court erred "because there was insufficient evidence that Navinta will actively encourage infringement or that Navinta possesses specific intent to encourage infringement," as required under the Federal Circuit's *en banc* decision in *DSU Medical v. JMS*. Navinta argued: "In holding Navinta responsible for uses of its ANDA product that are not mentioned or suggested in its labeling, the district court converted indirect infringement into a strict liability offense where Navinta was held responsible for possible downstream uses that it did nothing to encourage." In support, Navinta cited the Federal Circuit's two off-label use decisions of 2003: *Warner-Lambert v. Apotex* and*Allergan v. Alcon*. In those cases, the Federal Circuit

concluded that the ANDA filers were not liable for inducement of infringement of patents claiming off-label uses.

The Federal Circuit issued its decision on the appeal. Unfortunately, however, it based its decision on the least interesting of the three issues that Navinta appealed. The Federal Circuit concluded that due to a break in the chain of title, Abraxis did not own the patents-in-suit when it filed the Complaint, and Abraxis therefore lacked standing. Accordingly, the Federal Circuit reversed and vacated the district court's denial of Abraxis's second motion to dismiss, and remanded with instructions for the district court to dismiss Abraxis's complaint without prejudice.

Case Study VII: *District Court Finds Inducement of Infringement in Doxercalciferol Case*

The U.S. District Court for the District of Delaware found in favor of Genzyme and against ANDA applicants Roxane, Sandoz, and Anchen in the paragraph IV litigation concerning HECTOROL (doxercalciferol), Genzyme's drug for the treatment of secondaryhyperparathyroidism (SHPT) in patients with end-stage renal disease (ESRD). The court ruled that defendants' ANDA products would induce infringement of claims 7 of U.S. Patent No. 5,602,116; that claim 7 is entitled to a 1988 priority date; and that claim 7 is not invalid as "inoperative" or obvious. This post focuses on the inducement issue.

Claim 7 of the '116 patent is directed to:

A method for lowering or maintaining lowered serum parathyroid hormone [PTH] in patients suffering from hyperparathyroidism secondary to end stage renal disease, comprising: administering to said patients an effective amount of [doxercalciferol] to lower and maintain lowered serum parathyroid hormone levels.

After a *Markman* hearing, the court construed the term "effective amount of doxercalciferol to lower and maintain lowered serum parathyroid hormone levels" to mean "an amount of doxercalciferol sufficient to lower and maintain lowered blood concentrations of PTH with a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol to achieve the same level of PTH suppression."

After concluding that claim 7 would be directly infringed by the defendants' ANDA products (a predicate to finding inducement of infringement), the court addressed whether the defendants have the required intent to induce infringement. The key issue here was whether the defendants intend to induce infringement of claim 7 notwithstanding that their proposed labeling says nothing about the incidence of hypercalcemia resulting from doxercalciferol relative to the incidence resulting from calcitriol or alfacalcidol. The court thus concluded:

With respect to the specific intent element of inducement, the court concludes that the plaintiffs have sufficiently shown that the defendants "knew or should have known their actions would induce actual infringements." In this case, all defendants filed ANDAs with the FDA seeking approval to market a doxercalciferol product that would be sold accompanied by information instructing physicians and medical professionals to administer doxercalciferol according to the method explained in claim 7 for treating SHPT in patients with ESRD. This FDA-approved indication is the same use set forth in claim 7 of the patent-in-suit . . . .

The court concludes that, based on the clinical trials and literature available, the defendants knew or should have known that doxercalciferol has been shown to lower and maintain lowered PTH levels with a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol at the same level of PTH suppression. Thus, the court concludes that the defendants, in submitting their ANDAs, knew or should have known that their proposed products would induce actual infringement of claim 7. The court finds this level of intent sufficient for inducement purposes.

Case Study VIII: Federal Circuit Affirms Dismissal of Bayer's Inducement Claims in Yasmin Case *Bayer Schering Pharma et al. v. Lupin et al.*,

The Federal Circuit affirmed a district court decision dismissing Bayer's patent infringement claims against Watson, Sandoz and Lupin because their ANDAs did not seek approval for the patented use. At issue, according to the majority opinion, was whether the FDA approved certain uses of Yasmin (drospirenone/ethinyl estradiol) that were not mentioned in the "Indications and Usage" section of the drug label.

Bayer's U.S. Patent No. 5,569,652 is a method-of-use patent listed in the Orange Book for Yasmin, a product approved "for the prevention of pregnancy in women who elect to use an oral contraceptive" (according to the Indications and Usage section of the Yasmin label). The '652 patent claims a method of simultaneously achieving a contraceptive effect, an anti-androgenic effect (which can be useful for treating acne), and an anti-mineralocorticoid effect (which can be useful for reducing excess water

retention). After Watson, Sandoz and Lupin submitted ANDAs with paragraph IV certifications to the '652 patent, Bayer filed suit against the ANDA applicants under 35 U.S.C. § 271(e)(2), alleging that their generic versions of Yasmin would induce infringement of the '652 patent.

In the district court, Watson and Sandoz moved for judgment of non infringement on the pleadings under Fed. R. Civ. P. 12(c), arguing that their ANDAs related to the use of of generic Yasmin only for oral contraception and not for the combination of uses claimed in the '652 patent. The district court granted their motions, holding that "because the FDA had not given approval for the use of the drug that was claimed in the '652 patent, Bayer could not state a claim for patent infringement."

On appeal, Bayer argued that the FDA did approve the use of the drug for all three effects because in the Clinical Pharmacology section of the drug label, which is identical to the proposed label in each ANDA, there was information regarding the use of the drug for all three effects. While the Federal Circuit acknowledged that the description of the effects in the label demonstrated that the FDA was aware that Yasmin could cause those effects, the court did not agree that the presence of the information anywhere in the label was sufficient evidence to show that the FDA approved Yasmin to achieve the combination of the three effects claimed in the '652 patent.

According to the Federal Circuit, "The FDA labeling regulation, 21 C.F.R. § 201.57, makes clear that the FDA has not approved the use of Yasmin to produce the pharmacological effects that are listed in the Clinical Pharmacology section of the label." The court stated that approved uses are listed in the Indications and Usage section of the label and indications or uses "must not be implied or suggested in other sections of the labeling if not included in [the Indications and Usage] section." Moreover:

The reference in the Clinical Pharmacology section of the label to the anti-mineralocorticoid and anti-androgenic activity of drospirenone is certainly not a direct indication of an appropriate use for Yasmin, and even if it could be considered an "implied or suggested" indication of an appropriate use, the regulation expressly states that such implied or suggested uses do not constitute approved uses.

The Federal Circuit further remarked that the FDA regulation requires that "the label provide a summary of essential scientific information needed for the safe and effective use of the drug" and the Yasmin label does not provide this type of summary regarding the anti-androgenic and anti-mineralocorticoid effects. The court found this to be further evidence that the FDA did not approve Yasmin to treat those effects.

The court continued: the fact that certain of the effects of a drug are described in the Clinical Pharmacology section of the label does not mean that the FDA has approved the use of the drug to produce those effects; it only ensures that physicians are aware of the full range of the drug's pharmacological effects (especially those that might be considered adverse effects) when prescribing the drug for a purpose set forth in the Indications and Usage section and under the conditions described in other parts of the label.

The court concluded that the FDA did not approve the Yasmin for its anti-androgenic and anti-mineralocorticoid effects because the FDA did not find Yasmin to be safe and effective to cause those effects and the recognition of such safety and efficacy is absent from the Yasmin label. The court held that since the FDA did not approve Yasmin for the method of use claimed in the '652 patent and the defendants' ANDAs sought to market the generic form solely for contraceptive use, the defendants could not induce infringement of the '652 patent.

In dissent, Judge Newman found the majority's ruling to be in error because "the portion of the FDA label in which a product's properties are described is irrelevant to whether the patent is infringed. . . ." Instead, in her view, "the infringement inquiry is whether the generic counterpart, when used in accordance with its proposed ANDA authorization, would infringe the patent."

Case Study IX: *Preliminary Injunction Ordered in POZEN Treximet Patent Litigation*

POZEN Inc. announced that the U.S. District Court for the Eastern District of Texas has granted a preliminary injunction ordering Par Pharmaceutical Inc. not to make, use, sell, offer to sell, or import into the United States a generic version of sumatriptan/naproxen sodium that competes with Treximet(R) (sumatriptan and naproxen sodium) sold by GlaxoSmithKline in the United States under an exclusive license from the Company.

The order was entered in connection with the patent infringement lawsuit pending among the Company and Par, AlphaPharm Pty Ltd., Teva Pharmaceuticals USA, Inc., and Dr. Reddy's Laboratories, Inc. relating to the submission to the U.S. Food and Drug Administration (FDA) of Abbreviated New Drug Applications by the four generic companies and the generic companies' plans to market sumatriptan and

naproxen sodium products pursuant to such ANDAs, which the Company contends infringe three of its patents covering Treximet.

Teva was dismissed without prejudice from the consolidated litigation in April 2010. The case against the other three defendants was tried before Judge Leonard Davis in the Eastern District of Texas on October 12-15, 2010. The case against the other three defendants was tried before Judge Leonard Davis in the Eastern District of Texas on October 12-15, 2010. A decision is pending in the case. The injunction will remain in effect until a final decision is issued in the pending patent litigation. The Company continues to believe that its patents covering Treximet are valid and enforceable, and that these beliefs will be upheld by the Court.

The district court ruled U.S. Patent Nos. 6,060,499 and 6,586,458 to be valid, enforceable and infringed by the three defendants. A third patent, U.S. Patent No. 7,332,183 covering the Treximet formulation was held to be valid, enforceable and infringed by Par and DRL. The '183 patent was not asserted against Alphapharm.

The district court also ordered that defendant's ANDAs not be approved by FDA until, with respect to Par and DRL, at least the expiration of '183 patent on February 2,2025, and with respect to Alphapharm, the expiration of '499 and '458 patents on August 14,2017. Each of the above dates may be extended by six months if the FDA grants GSK's petition for pediatric exclusivity.

Case Study X: Federal Circuit Vacates Preliminary Injunction Entered Against Mylan in Doxycycline Case *Warner Chilcott Labs. v. Mylan Pharms. Inc.*,

The Federal Circuit vacated a preliminary injunction against Mylan because the district court "relied on disputed facts in granting the preliminary injunction without holding an evidentiary hearing, and failed to make any findings as to Mylan's invalidity defense."

In this case, involving Mylan's ANDA for a generic version of DORYX (doxycycline hyclate), Warner Chilcott sued Mylan for infringement of U.S. Patent No.6,958,161, directed to a tablet formulation of doxycycline. In August 2011, just one month before the 30-month stay would expire, Warner Chilcott filed a motion for a temporary restraining order and preliminary injunction against Mylan. The district court heard arguments from counsel, but did not conduct an evidentiary hearing and did not hear live testimony from any of the witnesses. The district court granted the preliminary injunction, but "did not address Mylan's arguments that the '161 Patent is invalid because of anticipation or obviousness, though it did acknowledge that those claims had been asserted." The Federal Circuit granted Mylan's request for expedited briefing and heard oral arguments on November 22, 2011.

At the outset of its analysis, the Federal Circuit cited the four well-known requirements for a preliminary injunction, as established by the Supreme Court, and noted that a preliminary injunction "is an extraordinary remedy never awarded as of right." The court then cited its own precedent as establishing that when an accused infringer has challenged the validity of a patent in response to a motion for a preliminary injunction, "the trial court first must weigh the evidence both for and against validity that is available at this preliminary stage in the proceedings." The Federal Circuit found:

In this case, the district court abused its discretion in two ways. The court: (1) failed to hold an evidentiary hearing despite acknowledging that the decision turned on disputed factual issues; and (2) did not weigh the evidence or make any findings as to Mylan's invalidity challenge.

Interestingly, while the Federal Circuit vacated the preliminary injunction, it suggested that a temporary restraining order might be appropriate.

Case Study XI: "Defective" Complaint Triggers 30-Month Stay *Endo Pharmaceuticals v. Mylan*,

The U.S. District Court for the District of Delaware granted leave to Endo Pharmaceuticals to file an amended complaint to correct a defective initial complaint. In doing so, the court found that Endo's first complaint, while defective, properly triggered a statutory thirty-month stay.

On January 28, 2011, Endo received a Paragraph IV notice letter from Mylan concerning generic LIDODERM (lidocaine patch 5%) and asserting that U.S. Patent No. 5,741,510 is invalid or not infringed. According to Endo, LecTec Corp. (not Endo) was the owner of the '510 patent at the time. On March 14, 2011, Endo filed a complaint alleging that (1) Mylan failed to comply with the statutory requirements because it failed to notify the patent owner, LecTec (Count 1); and (2) "if the court determines now or at a future date that Mylan has complied with its obligations under the Hatch-Waxman Act to provide valid notice" then Endo pleads in the alternative that Mylan infringed the '510 patent by submitting its ANDA (Count 2).

In an order dated March 30, 2012, in response to a motion to dismiss from Mylan, the court dismissed Endo's complaint because: (1) Endo lacked standing to challenge Mylan's compliance with the statutory notice provisions; and (2) the court could not reach the infringement claim of Count 2 because Endo phrased Count 2 to be conditioned on a determination concerning Count 1.

Endo moved for leave to amend its initial complaint, arguing that the conditional language in Count 2 of the complaint was a technical defect in pleading. In its opinion Monday, granting Endo's motion, the court found that Endo did not unreasonably delay in filing its motion and that Mylan would not suffer undue prejudice as a result of the amended complaint.

In addition, the court rejected Mylan's argument that the amended complaint could not relate back to the initial complaint under Fed. R. Civ. P. 15(c). Mylan had argued that the statutory 45-day time period to invoke a 30-month stay is akin to a statute of limitations, and therefore Endo's initial complaint should be treated as if it never existed and "should not be allowed to anchor a thirty-month stay." In response, the court first noted that the 45-day time period for filing suit under the Hatch-Waxman Act is not properly characterized as a statute of limitations because failure to file suit within the 45-day window does not bar an infringement action. The court further stated, "While Endo's complaint suffered from certain pleading defects, there is no dispute that it was brought within the forty-five day timeframe, and, despite its pleading defect, the court believes it represents 'an action . . . brought for infringement of the patent that is the subject of the certification' within the meaning of the statutory language."

Losing this argument, however, does not appear to be a great loss for Mylan, since the thirty-month stay runs from January 28, 2011, and so will expire just four and a half months.

Case Study XII: FDA Grants Baxter's Petition for Second 30-Month Stay Relating to Suprane

"The MMA generally precludes multiple 30-month stays for those applications to which it applies." That is a statement from the FDA in a draft guidance document entitled "Listed Drugs, 30-Month Stays, and Approval of ANDAs and 505(b)(2) Applications Under Hatch-Waxman, as Amended by the Medicare Prescription Drug, Improvement and Modernization Act of 2003," published in October 2004. But in the same document, FDA also stated, "Multiple 30-month stays, however, still may be possible in certain cases." This is one such case.

In 2008, Minrad, Inc. (now Piramal Critical Care, Inc.) filed an ANDA for a generic version of Suprane (desfluorane, USP) and submitted a paragraph IV certification to Baxter Healthcare's U.S. Patent No. 5,617,906. Minrad sent a paragraph IV notice letter to Baxter, which Baxter received on December 12, 2008. Within 45 days, Baxter filed suit against Minrad for infringement of the '906 patent, triggering a 30-month stay that expired on June 12, 2011.

On June 7, 2011, just days before the 30-month stay expired, FDA granted Baxter's citizen petition requesting that FDA confirm that Baxter is entitled to a second 30-month stay. The FDA's petition response explains:

On June 23, 2009, Minrad changed the container closure system for its drug product and submitted an amendment to ANDA 90-363 to include the new closure system. Once Minrad submitted the second paragraph IV certification to the '906 patent in connection with the revised product and sent notice to Baxter, and Baxter subsequently sued Minrad within 45 days of receiving that notice, the statutory requirements for a 30-month stay with respect to this paragraph IV certification were met.

The FDA's response continues:

The statute is unambiguous. When a paragraph IV certification has been made to a patent for which information was submitted to FDA before the ANDA was submitted, and an action is brought for infringement of the patent that is the subject of the certification, a 30-month stay dating from receipt of the notice applies (section 505(j)(5)(B)(iii) of the Act). Even if the statute were ambiguous, we would interpret it, consistent with its intent to provide an opportunity to litigate questions concerning patent infringement, to begin a 30-month stay when as here, an ANDA is amended to include a new certification reflecting a change in the product covered by the ANDA.

As a result, FDA granted Baxter second 30-month stay, which will not expire until January 7, 2012.

The lesson for generic drug companies: if possible, do not change your drug product during the approval process. If you do change your product, try to avoid having to send another paragraph IV notice letter. On the flip side, the lesson for brand-name drug companies: if you receive another paragraph IV notice letter from a company you've already sued, file another complaint against that company. You may earn an additional 30-month stay.

Case Study XIII: Federal Circuit Upholds Patent Term Extensions in LEVAQUIN and METVIXIA Cases *Ortho-McNeil and Daiichi Sankyo v. Lupin*, & *Photocure v. Kappos*

In separate cases decided, the Federal Circuit upheld two patent term extensions under 35 U.S.C. § 156--one relating to LEVAQUIN (levofloxacin) and the other relating to METVIXIA (methyl aminolevulinate). The cases were argued on the same day to the same three-judge panel, and Judge Newman authored both of opinions.

In the LEVAQUIN case, the Federal Circuit affirmed a district court decision sustaining the term extension of U.S. Patent No. 5,053,407, assigned to Daiichiand exclusively licensed to Ortho-McNeil, and enjoining Lupin from infringement during the extended term of the patent. The '407 patent claims levofloxacin, which isthe levorotatory enantiomer of racemate ofloxacin. Levofloxacin and ofloxaxin are both antibiotics.

In the METVIXIA case, the Federal Circuit affirmed a district court decision reversing the USPTO's denial of a term extension of U.S. Patent No. 6,034,267, owned by Photocure. The '267 patent claims methyl aminolevulinate ("MAL"), the methyl ester of the known drug aminolevulinic acid ("ALA"). MAL and ALA are both indicated for the treatment of actinic keratoses--precancerous cell growths on the skin.

Under § 156, the term of a patent that claims a drug product, a method of using a drug product, or a method of manufacturing a drug product may be extended by up to five years if the drug product was subject to FDA regulatory review prior to its commercial marketing or use. The Federal Circuit explained the policy behind § 156:

The Patent Term Extension statute was enacted in recognition of the lengthy procedures associated with regulatory review of a new drug product, for the patent term continues to run although the product cannot be sold or used until authorized by the Food and Drug Administration (FDA). The statute was designed to restore a portion of the patent life lost during the period of regulatory review, in order to preserve the economic incentive for development of new therapeutic products.

A key feature of § 156 is that only one patent term extension is allowed per "drug product". This is reflected in the statutory language: "the permission for the commercial marketing or use of the [drug] product after such regulatory review period [must be] the first permitted commercial marketing or use of the [drug] product." In turn, the statute defines a "drug product" as the "active ingredient" of a new drug, antibiotic drug or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act).

The issue in both of the cases decided was whether the FDA approval sought for each drug was for the "first permitted commercial marketing or use" of the drug. In the levofloxacin case, Lupin argued that the enantiomer levofloxacin is an "active ingredient" of the previously-marketed racemate ofloxacin; levofloxacin is therefore the same "drug product" as ofloxacin; and therefore levofloxacin is not eligible for a patent term extension. Similarly, in the MAL case, the PTO argued that "active ingredient" means "active moiety"; MAL, as the methyl ester of ALA, is the same product as ALA because the "underlying molecule" ("active moiety") of MAL is ALA; and therefore MAL is not eligible for a patent term extension. But the Federal Circuit rejected these arguments.

In the levofloxacin case, the court agreed with Ortho that "an enantiomer has consistently been recognized, by the FDA and the PTO, as a different 'drug product' from its racemate." The court further observed that, in this case, "levofloxacin was viewed by the FDA as a new product requiring full regulatory approval, and that levofloxacin was viewed by the PTO as separately patentable."

The Federal Circuit applied similar reasoning in the *Photocure* case:

As the '267 patent illustrates, the pharmacological properties of MAL differ from those of ALA, supporting the separate patentability of the MAL product. MAL hydrochloride is a different chemical compound from ALA hydrochloride, and it is not disputed that they differ in their biological properties, warranting separate patenting and separate regulatory approval, although their chemical structure is similar.

Notwithstanding this reasoning, the PTO argued that pursuant to *Pfizer v. Dr. Reddy's*, 359 F.3d 1361 (Fed. Cir. 2004), the statutory term "active ingredient" does not mean the compound that is present in the approved drug, but instead it means the "active moiety" of the compound; that is, the part responsible for the pharmacological properties. The Federal Circuit, however, rejected the PTO's construction. Further, the Federal Circuit distinguished the *Pfizer* case, stating: "*Pfizer* did not hold that [an] extension is not available when an existing product is substantively changed in a way that produces a new and separately patentable product having improved properties and requiring full FDA approval."

Thus, after *Photocure*, we will likely see the PTO grant patent term extensions in cases where it would not have granted an extension before.

Case Study XIV: Federal Circuit Affirms Denial of Somerset Pharma's Interim Patent Term Extension on Depression Patch *Somerset Pharmaceuticals v. Dudas*

The Federal Circuit decided an unusual case yesterday respecting Somerset Pharmaceuticals' application for an interim patent term extension for U.S. Reissue Patent No. RE 34,579. The '579 patent covers a method of treating depression using Emsam, a transdermal patch that includes selegiline as the active ingredient.

35 USC 156(e)(1) provides for a patent term extension to compensate for delays in FDA regulatory review of a new drug application. 35 USC 156(e)(2) provides for an interim patent term extension if the patent "would expire before a certificate of extension is issued or denied under paragraph (1)."

Somerset's '579 patent is set to expire on August 18, 2007. In April 2006, Somerset filed a request for patent term extension under Section 156(e)(1) on the '579 patent. In February, the Patent and Trademark Office had still not ruled on Somerset's request, and therefore Somerset filed a request for an interim patent term extension under Section 156(e)(2).

Shortly thereafter, Somerset filed suit against Mr. Dudas, the director of the PTO, seeking to compel the PTO to rule on its request for an interim patent term extension. Somerset also filed a motion for preliminary injunction at the same time. The district court denied Somerset's motion in June, and Somerset promptly appealed to the Federal Circuit. Meanwhile, on July 12, the PTO denied both Somerset's application for a patent term extension under Section 156(e)(1) and its application an interim extension under Section 156(e)(2).

The Federal Circuit dismissed as moot Somerset's request to compel the PTO to act on its request for an interim patent term extension. Moreover, the Federal Circuit affirmed the district court's denial of Somerset's motion for a preliminary injunction to compel the PTO to grant Somerset's request for an interim patent term extension, finding that because the PTO denied Somerset's application for a patent term extension under Section 156(e)(1), the PTO has no statutory authority to issue an interim extension.

Case Study XV: Merck Prevails in Patent Term Extension Case at Federal Circuit *Merck & Co. v. Hi-Tech Pharmacal*

The U.S. Court of Appeals for the Federal Circuit that a patent term extension under 35 USC 156 may be applied to a patent that is subject to a terminal disclaimer under 35 USC 253, handing a victory to Merck in its battle with Hi-Tech Pharmacal over generic Trusopt (dorzolamide HCl opthalmic solution). Hi-Tech had argued that Merck's patent on Trusopt expired in 2004 because a patent term extension on the patent was invalid.

A loss for Merck in this case would have had drastic effects on pharmaceutical companies and patent owners, since the Patent Office has routinely granted patent term extensions on patents that are subject to a terminal disclaimer. Brand-name drug companies would have lost years of patent protection on some of their best-selling drugs if the Federal Circuit had decided that a terminal disclaimer precludes a patent term extension.

Section 156 was enacted as part of the Hatch-Waxman Act in 1984 to allow restoration of part of a pharmaceutical patent's term "lost" due to lengthy FDA review of a new drug application. Section 253, on the other hand, applies to all kinds of patent applications--not only those relating to pharmaceuticals--and allows the filing of a terminal disclaimer to overcome "obviousness-type double patenting" rejections made by the Patent Office.

In reaching its decision today, the Federal Circuit properly recognized that "the language of Section 156 is unambiguous and fulfills a purpose unrelated to and not in conflict with that of Section 253." The court observed: (1) according to Section 156, a patent term "shall be extended" if five enumerated conditions, none of which concern terminal disclaimers, are met; (2) the legislative history is consistent with the mandatory language of the statute; and (3) Section 154 excludes patents in which a terminal disclaimer has been filed from the benefit of a term adjustment for PTO delays, but Section 156 contains no such exclusion for patents eligible for term extensions for FDA delays, which further supports the court's interpretation of Section 156.

Additionally, the court explained why Section 156 and Section 253 are compatible:

The purpose of the terminal disclaimer--to prevent extension of patent term for subject matter that would have been obvious over an earlier filed patent--remains fulfilled by virtue of the fact that the date from which any Hatch-Waxman extension is computed is the terminally disclaimed date. At the same time, the purpose of the patent term extension--to restore some of the patent term lost due to regulatory review--is also satisfied.

Case Study XVI: **Federal Circuit Upholds Fentora Patents, But Affirms Non- Infringement**

In Cephalon, Inc. v. Watson Pharmaceuticals, Inc., the Federal Circuit reversed the district court's finding that two Orange Book-listed patents for Cephalon's FENTORA® product were invalid, but affirmed the district court's finding that Watson's ANDA product would not infringe the patents. The Federal Circuit decision reviews the "undue experimentation" standard for lack of enablement, and underscores the importance of aligning evidence of infringement with the governing claim construction.

The Patents At Issue

The two Orange Book-listed patents at issue were U.S. Patent 6,200,604 and U.S. Patent 6,974,590. The patents are directed to methods of administering a drug across the oral mucosa. The methods use formulations comprising effervescent agents that promote penetration across the buccal, sublingual, and gingival mucosae.

The ANDA Litigation

FENTORA® is a fentanyl buccal tablet approved for the treatment of breakthrough cancer pain. As set forth in the Federal Circuit decision, FENTORA® contains fentanyl citrate, mannitol, sodium starch glycolate, magnesium stearate, citric acid, sodium bicarbonate, and sodium carbonate, with the sodium bicarbonate and citric acid forming an effervescent couple that reacts to evolve carbon dioxide.

Watson filed an Abbreviated New Drug Application ("ANDA") seeking approval to market a generic version of FENTORA®, and including a Paragraph IV certification against the patents. As set forth in the Federal Circuit decision, Watson's ANDA products contain the active ingredient fentanyl citrate and the inactive ingredients mannitol, sodiumstarch glycolate, potassium bicarbonate, and magnesium stearate.

In response to Watson's Paragraph IV certification, Cephalon, Inc. and CIMA Labs, Inc. (collectively, "Cephalon") brought suit in the U.S. District Court for the District of Delaware. The district court found that the patents were invalid for lack of enablement and would not be infringed by Watson's product. On appeal, the Federal Circuit reversed on enablement and affirmed on non-infringement.

Enablement

As noted above, the district court construed "effervescent agent" as requiring the presence of a single compound that "evolves gas by means of an effervescent reaction." The enablement issue therefore turned on whether the patents enabled methods where the soluble acid source of the effervescent reaction is administered in a separate dosage form from the effervescent agent.

Non-Infringement

The infringement issue turned on whether the potassium bicarbonate and mannitol in the Watson products would undergo an effervescent reaction in saliva. Because Cephalon only had provided evidence on the acid properties of mannitol in water, the Federal Circuit upheld the district court's finding of non-infringement.

Thus, Cephalon was able to restore the validity of these patents. And, even though Cephalon lost on the infringement claims, according to Watson's press release, a third patent will keep Watson's ANDA products off the market until October of 2019.

CONCLUSION

The statutory thirty-month stay of approval triggered by paragraph IV certification and subsequent patent infringement suit by the NDA holder is not efficient when evaluated under any of the prevalent norms justifying intellectual property regimes. The thirty-month stay provision allows NDA applicants to prevent generic drugs from entering the marketplace on the basis of expired patents, unsustainably broad readings of core patents on the NDA product, and "trip wire" or "evergreening" patents which do not reflect substantial change or improvement over an original patent but are prosecuted for the sole purpose of triggering the stay provision.

The problems created by Hatch-Waxman Act's creation of the thirty-month stay provision should be addressed at many levels. First and most obviously, Congress should repeal the certification requirement for ANDA applicants. NDA holders would still be able to protect their innovations through standard patent law enforcement just like any other inventors. NDA holders would simply no longer benefit from special

treatment. Even if Congress does not act, other entities can minimize the problems created by the thirty-month stay provision.

The FDA should interpret Hatch-Waxman Act within statutory constraints in order to minimize the stay provision's effect. The FDA could reasonably interpret the Hatch-Waxman Act to only allow core patents directly covering the NDA product to be listed in the Orange Book, and rigorously review all patents submitted for inclusion in the Orange Book for suitability. Additionally, the FDA could evaluate the expiration of dates submitted to the Orange Book rather than simply taking applicants at their word. These two steps would eliminate the problem the stay provision being triggered by “trip wire" patents and by expired patents.

Third, courts should more freely exercise their discretion under the Hatch-Waxman Act to modify the length of the stay based on the plaintiff or defendant's failure “to cooperate reasonably in expediting the action."Courts could potentially, under this provision, reduce the length of the thirty-month stay to zero where the plaintiff's action has such an extremely small chance on the merits that the NDA's filing of the suit or the NDA holder's failure to settle the action for a nominal amount constitutes failure to expedite the action. By utilizing available discretion in this manner, the courts can reduce the problems caused by thirty-month stay provision while discouraging frivolous and nearly frivolous actions in their court. A court utilizing this discretion brings might analyze the thirty-month stay provision using standards similar to those historically accepted for preliminary injunctions.

Fourth, the FTC and parties excluded from the generic drug market because of the thirty-month stay provision may seek remedies through antitrust laws in some cases. Although the burden of proving that a claim is objectively baseless may not be easy to overcome and the process of litigating an antitrust trial may take well over thirty months, the possibility of treble damages calculated on the basis of the generic drug manufacturer's lost profits during the thirty months could bring enough pressure on NDA holders that at least the most frivolous patent cases would be settled.

Finally, individual attorneys should refuse to pursue patent prosecution or litigation that has little merit even if the client desires to trigger the thirty-month stay provision. An attorney's interest in maintaining a professional reputation by advancing only positions with potential merit before the Patent and Trademark Office and before the Federal Courts along with the attorney's individual sense of morality and justice should serve, to some extent, to prevent the attorney from engaging in litigation and patent prosecution that is merely tactical. To best serve society, attorneys should aspire to substantively promoting justice and the state of the law through client advocacy rather than invoking meritless suits merely because the suit serves a client's immediate interest such as triggering the thirty-month stay provision.

REFERENCES

1. 21 C.F.R. x 314.94(a)(12)(i)(A).
2. 21 C.F.R. x 314.94(a)(12)(i)(A); see also 21 U.S.C. x 355(j)(2)(A)(I)-(IV).
3. Markman v. West view Instruments, Inc., 116 S.Ct. 1384 (1996) (holding that the judge must determine the scope of patent claims as a matter of law).
4. Claim Interpretation in a Post Markman Environment, 572 PLI/Pat 681, 692 (1999) (discussing various possibilities regarding time and scope of Markman hearings and noting that Markman hearings are most often held immediately before the close of discovery).
5. Amazon.com v. Barnesandnoble.com, Inc., 2001 WL 123818 (Fed. Cir. 2001) (citing Reebok Int'l Ltd. V. J. Baker, Inc., 32 F.3d 1552, 1555 (Fed. Cir. 1994)).
6. Hybritech, Inc. v. Abbott Labs., 849 F.2d 1446, 1451 (Fed. Cir. 1988).
7. Amazon.com v. Barnesandnoble.com, Inc., 2001 WL 123818 (Fed. Cir. 2001).
8. Genetech, Inc. v. Novo Nordsik, A/S, 108 F.3d 1361, 1364 (Fed. Cir. 1997).
9. 140 F.3d 1060, n.14 (D.C. Cir. 1988).
10. FTC Settles Complaint, Charges Two More with Anticompetitive Conduct, 11 Andrews Antitrust Litig. Rep. 6 (May1, 2000).
11. 21. C.F. R. x 314.53.
12. The Federal Circuit has stated, \It cannot be said { thought it often is, incorrectly, by the uninitiated, that a part of a claim is `claimed' subject matter." See General Foods Corp. v. Strudiengesells graph Kohle mbh, 972 F.2d 1272, 1274 (1992). In other words, if patent claim includes a certain active ingredient and a certain crystalline structure or tablet shape for utilizing that active ingredient, it cannot be said that the patent claims the active ingredient. An ANDA

applicant would be free to manufacturer anything using the active ingredient as long as its use does not include every element of a claim of the NDA holder's patent.
13. 45Terry G. Mahn, The Hatch-Waxman Act During Patent Prosecution and Beyond, Food and Drug Law J. (1999).
14. 21 C.F.R. x 314.94(a)(12)(i)(A).
15. General Foods Corp. v. Studiengesellschaft Kohle mbh, 972 F.2d 1272, 1274 (1992).
16. 21 C.F.R. x 314.53; 21C.F.R. x 314.3.
17. Abbott Laboratories v. Zenith Laboratories, Inc., 934 F.Supp. 925, 934 (N.D. Ill. 1995) (quoting FDA decision regarding Docket No. 94P-0144/CP1 and PSA1, January 6, 1995 at p. 7).
18. 21 C.F.R. x 3114.94(12)(vii).
19. United States v. Riverside Bay view Homes, Inc., 474 U.S. 121, 131 (1985).
20. Eli Lilly and Company v. Medtronic, Inc., 496 U.S. 661 (1990).
21. Abbott Laboratories v. Zenith Laboratories, Inc., 934 F.Supp. 925, 933 (N.D. Ill. 1995) (holding that “an ANDA need provide certification . . . only for patents listed by an NDA applicant in its application and subsequently, by the FDA in the Orange Book").
22. 21 C.F.R. x 314.53(f).
23. Abbott Laboratories v. Novopharm Limited, 104 F.3d 1305 (Fed. Cir. 1997) (holding that an order requiring patent assignee to remove an expired patent from the Orange Book was proper); Ben Venue Laboratories, Inc. v. Novartis Pharmaceutical Corp., 10 F.Supp. 2d 446, 457 (D.N.J. 1998) (ultimately denying a preliminary injunction to remove a patent listing from the Orange Book because the disputed patent claimed a drug substance that was an ingredient of the approved drug product).
24. 10 F.Supp. 2d 446, 457 (D.N.J. 1998) (noting Pfizer, Inc. v. Food and Drug Administration, 753 F.Supp. 171 (D.Md.1990) (upholding the FDA's refusal to enter Pfizer's composition patent into the Orange Book)).
25. The harm to the NDA holder if the ANDA product was approved yet infringed may be purely economic and therefore not irreparable.
26. Notably, Islamic law does not recognize intellectual property rights.
27. U.S. Const., Art. I, cl. 8.
28. Graham v. John Deere Co., 383 U.S. 1, 9, 86 S.Ct. 684, 689 (1966).
29. Roberts v. Sears, Roebuck & Co., 723 F.2d 1324, 1345 (7th Cir. 1983) (Posner, J., concurring and dissenting).
30. Also, the very basic principle of supply and demand. If the price of the invented product is high, consumers will buy less of the product (assuming some elasticity), and output of the invention is reduced compared to a situation with high competition.
31. Alfred Engelberg, Special patent Provisions for Pharmaceuticals: Have they Outlived Their Usefulness?, 39 IDEA 389, 414 (1999).
32. Cross v. Iizuka, 753 F.2d 1040, 1051 (Fed. Cir. 1985).
33. Bayer AG v. Elan Pharmaceutical Research Corp., 212 F.3d 1241, 1248 (Fed. Cir. 2000).
34. Even if the case is decided on motion for summary judgment, it could easily be thirty months from the time the suit is initiated to the time summary judgment motions are decided. See, e.g., Marrion Merrell Dow Inc. v. Baker Norton Pharmaceuticals, Inc., 948 F.Supp. 1050 (S.D.Fla. 1996).
35. For example, it seems unlikely that any patent attorney would not realize that a patent would expire twenty years from the date of its earliest parent application even in light of the GATT changes. See Abbott Laboratories v. Novopharm Ltd., 38 U.S.P.Q.2d 1309 (N.D.Ill. 1996).
36. FTC Settles Complaint, Charges Two More with Anticompetitive Conduct, 11 Andrews Antitrust Litig. Rep. 6 (May1, 2000).
37. 105 F.Supp. 2d 618 (E.D. Mich 2000).
38. Eastern R.R. Presidents Conference v. Noerr Motor Freight, Inc., 365 U.S. 127, 143-44 (1961).
39. In re Cardizem CD Antitrust Litigation, 105 F.Supp. 2d 618, 637 (E.D. Mich. 2000) (citing McGuire Oil Co. v. Mapco, Inc., 958 F.2d 1552, 1558-60 (11th Cir.1992)(pre- litigation threats of suit); Coastal States Marketing, Inc. v. Hunt, 694 F.2d 1358, 1366-67 (5th Cir.1983) (same); and Barq's, Inc. v. Barq's Beverages, Inc., 677 F.Supp. 449, 453 (E.D.La.1987) (observing that threatened litigation and attending publicity was considered part and parcel of the petitioning immunity of Noerr-Pennington if the litigation itself was in good faith and thus holding that the

plaintiff's pre-litigation demand letters were also protected under the Noerr-Pennington petitioning immunity)).

40. id. at 638 (citing Columbia Pictures Industries, Inc. v. Professional Real *639 Estate Investors, Inc., 944 F.2d 1525, 1528-29 (9th Cir.1991), aff'd sub nom, Prof'l Real Estate Investors, Inc. v. Columbia Pictures Indus., Inc., 508 U.S. 49, 113 S.Ct. 1920, 123 L.Ed.2d 611 (1993); Prime Time 24 Joint Venture v. Nat'l Broadcasting Co., Inc., 21 F.Supp.2d 350, 358-59 (S.D.N.Y.1998); Modesto Irrigation Dist. v. Pacific Gas & Elec. Co., 61 F.Supp.2d 1058 (N.D.Cal.1999).
41. Eastern R.R. Presidents Conference v. Noerr Motor Freight, Inc., 365 U.S. 127, 144 (1961).
42. Prof'l Real Estate Investors, Inc. v. Columbia Pictures Indus., Inc., 508 U.S. 49, 60 (1993).
43. 21 C.F.R. x 314.107(b)(3)(i)(A).
44. http://investor.mylan.com/releasedetail.cfm?ReleaseID=406712
45. http://www.law360.com/articles/62128/astrazeneca-files-ninth-suit-over-crestor-patent
46. http://www.ranbaxy.com/us/ranbaxy-and-pfizer-settle-lipitor-litigation-worldwide/
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