A Drug Life: The Chemistry of Patent and Regulatory Exclusivity for Pharmaceuticals

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It seems that the pharmaceutical industry has become one of the industries to bash. In a recent survey of six hundred international, national, and regional patient groups, the pharmaceutical industry was ranked seventh out of eight amongst healthcare industries evaluated in terms of reputation. "[A] lack of fair pricing policies leading to unseemly profits" was the most common factor cited in support of the negative reputation.

Such a reputation would appear to be unwarranted and unfair. Without "big, bad pharma," we would not have the quality of life and quantity of life that we now come to expect. And let us not forget that as individuals we share some responsibility for maintaining our own health and well-being; some of the ailments that big pharma is able to combat are ailments that we brought upon ourselves through unhealthy

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3 Id.

4 Id. See generally PHRMA INNOVATION HUB, http://innovation.org/ (last visited Oct. 14, 2014) (explaining the benefits that pharmaceutical companies have on society).

5 See generally PHRMA INNOVATION HUB, http://innovation.org/ (last visited Oct. 14, 2014) (explaining the benefits that pharmaceutical companies have on society).
lifestyle choices and habits. Drug companies provide life-saving and life-benefiting drugs to patients; however, these drugs do not magically appear. The identification of new drugs and new therapeutic uses of known drugs are the result of painstaking, meticulous research and discovery efforts that often span over a decade or longer.

Only about one in fifty small-molecule drugs tested ever gets to human clinical trials, and of those, the Food and Drug Administration ("FDA") only approves about one in ten. Do the math and that means that a drug has less than a 0.02% to 0.01% chance of making it to market. Reports suggest that it can take twelve to fifteen years from discovery to regulatory approval, and the average cost to bring a new drug to market is now considered to be about $1.3 billion. Recently, it has been suggested that if one were to adjust for all of the failures in drug discovery and development, each drug approved costs from about $1.2 up to $5 billion! Yes, $5 billion. While experts disagree about

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6 See, e.g., Patricia Eifert, 3 Habits That Increase Risk of Fatal Heart Disease, CHEMIST DIRECT (July 30, 2014), http://blog.chemistdirect.co.uk/3-habits-increase-risk-fatal-heart-disease/.
10 Michael Hay et al., Clinical Development Success Rates for Investigational Drugs, 32 NATURE BIOTECH. 40, 41 (2014).
11 See id.; Pharm. Research and Mfrs. of Am., supra note 9.
12 See Nat’l Ctr. for Advancing Translational Scis., supra note 8; PHARM. RESEARCH AND MFRS. OF AM., supra note 7, at 1.
the average cost, they do seem to agree that the costs do appear to be rising.\textsuperscript{15} Even with the unadjusted $1.3 billion average ticket price, only approximately one out of five drugs ever recoups this average research and development cost.\textsuperscript{16} Yet, the pharma business still survives because those “blockbuster” drugs carry it forward and fuel its future innovation.\textsuperscript{17}

Future innovation is key.\textsuperscript{18} Without innovation, we would be left with the existing arsenal of drugs to combat the ever-changing and ever-growing world of disease.\textsuperscript{19} Bacteria and viruses often become resistant to previously efficacious drugs, many diseases still have no suitable treatment, and we live in a world where the status quo is not acceptable.\textsuperscript{20} We are constantly striving to improve the safety, efficacy,
and patient compliance profile of existing drugs by altering the formulation or altering the active therapeutic moiety; we seek out new classes of drugs to provide an effective treatment for previously untreated conditions or to offer an alternative to the existing drug weaponry.\textsuperscript{21} However, this innovation does not come without a cost.\textsuperscript{22} It requires time, money, knowledge, effort, and dedication.\textsuperscript{23} It requires big pharma, specialty pharma, start-ups, researchers, and the like.\textsuperscript{24}

From any perspective, big pharma is vital.\textsuperscript{25} Pharma is vital to our physical health, as well as our financial health, our prominence on


\textsuperscript{23} See id.


\textsuperscript{25} See John LaMattina, \textit{Even Pharma’s Good Deeds Are Criticized}, FORBES (May 6, 2013, 8:40 AM), http://www.forbes.com/sites/johnlamattina/2013/05/06/even-pharmas-good-deeds-are-criticized/.
the world stage, and is part of our moral and social obligation to society.\textsuperscript{26} Whether it is big pharma leaning on the economies of scale and experience, specialty pharma thinking outside of the box and pushing the envelope, or generics relying on those that walked before them, pharma has a positive role in our society and should be fostered.\textsuperscript{27}

The following provides a summary of the approval process in the United States for branded and generic drugs, and the marketing exclusivities available for drugs, including how pharmaceutical patents and the Orange Book interplay to provide a limited extension of protection against generic entry.\textsuperscript{28} Finally, a brief case study on Ampyra (dalfampridine) is presented to illustrate the chemistry of the patent and regulatory exclusivities for small molecule drugs.\textsuperscript{29}

I. FDA APPROVAL PROCESS

A. Drugs

The Federal Food, Drug, and Cosmetic Act ("FDCA") governs the approval of drugs in the United States.\textsuperscript{30} The FDCA prohibits the marketing of any new drug unless it has been found to meet certain safety and efficacy standards promulgated by the FDA.\textsuperscript{31} A "drug" is defined as the following:

\begin{quote}
(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or
\end{quote}


\textsuperscript{27} See supra note 24 (giving examples of the benefits of both big and specialty pharma); infra Part I.C (discussing generic drugs).

\textsuperscript{28} See infra Parts I-IV.

\textsuperscript{29} See infra Part V.


\textsuperscript{31} Id. § 355(a); Is It Really FDA Approved?, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm047470.htm (last visited Sept. 15, 2014).
any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).  

A “new drug” is defined as the following:

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a “new drug” if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.  

32 21 U.S.C. § 321(g)(1). This Article does not address the exclusivity available for biological products, which are considered “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, . . . or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.” 42 U.S.C. § 262(i)(1). The exclusivity available for biological products is found in § 262. See id. § 262.

Accordingly, the FDA must approve any drug before the drug is able to be lawfully sold and marketed in the United States.34

The process for FDA approval is either through (1) a new drug application ("NDA"); (2) an abbreviated new drug application ("ANDA" or "section 505(b)(2)" application); or (3) compliance with the appropriate preapproved monograph.35 This Article will briefly describe the NDA and the ANDA processes.36 In the last category, the FDA has preapproved regulations specifying conditions where certain drugs are generally recognized as safe and effective if they are labeled in accordance with their applicable drug monograph as set forth in the regulations.37

Certain drugs are considered safe and effective only if used under the supervision of a licensed medical practitioner; such drugs are referred to as "prescription drugs."38 Other drugs are considered safe and effective for use without a prescription by a licensed medical practitioner; such drugs are referred to as "over-the-counter" drugs.39 Other categories of drugs exist, including "behind-the-counter" drugs; however, prescription and over-the-counter drugs are the most common.40 The category of drug (e.g., prescription or over-the-counter) does not determine the process of approval.41 For example, if a developer wanted to market a drug for over-the-counter use, but there

36 See infra Part I.B.2-C.2.
38 21 U.S.C § 353(1).
was not a preapproved monograph for the particular drug, dose, or indication desired, the developer would need to use the new drug application process. Notwithstanding, many over-the-counter drugs utilize the preapproved monograph as the basis of their approval.

An approved drug may be referred to as the “brand,” “branded,” “innovator,” or “reference-listed” drug if it is the approved drug product to which new generic versions have or will be compared in order to show that they are identical in the eyes of the FDA. It is also a designation that usually signifies that the drug company sought approval of the drug through the standard NDA process and generally markets the drug under a proprietary, trademark-protected name. On the other hand, generic drugs or “generics” are drugs that have been approved through an abbreviated pathway, which relies on the FDA’s previous finding of safety and efficacy of the reference-listed drug. Generic drugs usually are not separately marketed and are typically identified only by the generic name and manufacturer.

The Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the “Hatch-Waxman Act,” amended the FDCA for the purpose of encouraging entry of generics to foster price competition, along with encouraging new drug development and innovation. Of its more significant roles, the Hatch-Waxman Act does the following:

44 See Drugs @ FDA Glossary of Terms, supra note 39.
45 See id.; see also infra Part I.B.2.
• governs the process of how a generic may obtain marketing approval for the same drug as the innovator by relying on the safety and efficacy data of the innovator;

• provides marketing exclusivity for a generic in certain situations;

• provides a statutory exemption from patent infringement for acts reasonably related to seeking FDA approval;

• provides provisions for challenging the enforceability, validity, or infringement of drug patents covering innovator drugs;

• provides a statutorily-created patent infringement for the filing of an abbreviated new drug application;

• provides marketing exclusivity for innovators; and

• provides patent term extension for patents covering approved drugs.  

B. Innovator Drugs

1. Preclinical and clinical development.

In order to demonstrate that a new drug meets the FDA’s safety and efficacy standards, the applicant is required to conduct both preclinical and clinical investigations with the drug. Preclinical investigations usually involve in vitro testing, ex vivo testing, and in vivo animal testing (such as mice, rats, or primates) to determine whether the drug has any effect on the target disease. If the drug appears to have sufficient effect, the developer will file an

49 See Wooster, supra note 48.
investigational NDA with the FDA to obtain approval to test the drug in humans.  

While there are exceptions, human clinical testing usually comprises three phases that are conducted in sequential order. Phase I clinical trials investigate the drug’s safety in a small group of healthy human subjects. Phase II clinical trials investigate the safety and efficacy of the drug in a set of patients with the target disease. Short-term side effects and risks of the drug are often identified. Finally, phase III clinical trials again investigate the safety and efficacy of the drug, but in a much larger number of patients with the target disease. A phase III clinical trial often identifies additional information on side effects and drug interactions. For many drugs, the FDA will require the successful completion of two phase III clinical trials. Once the clinical testing for a drug is complete, the drug developer (or sponsor) will then prepare and file the appropriate application for approval by the FDA.

2. New drug application.

Upon successful completion of the clinical trials, the innovator will prepare and submit a NDA to the FDA for review and approval, providing the authorization to market and sell the drug in the United States. A NDA is a very complex and lengthy application containing

53 See 21 C.F.R. § 312.21.
54 See id. § 312.21(a).
55 See id. § 312.21(b).
56 See id.; see also PHARM. RESEARCH AND MFRS. OF AM., supra note 7, at 7.
57 See 21 C.F.R. § 312.21(c).
60 The FDA’s Drug Review Process: Ensuring Drugs are Safe and Effective, supra note 50.
information on chemistry, manufacturing, controls, preclinical data, clinical data, toxicology, human pharmacokinetics, and bioavailability and safety information. The applicant is also required to list any patents that claim the drug or claim the approved method of using the drug.

A team of FDA reviewers reviews the application, and the FDA is required to approve or deny the application within 180 days of submission; however, it is common for the FDA and the applicant to agree to extensions.

3. The Orange Book and patent listing.

While it may not be the official name, the “Orange Book” is certainly descriptive of the FDA’s Approved Drug Products and Therapeutic Equivalence Evaluations annual publication, which lists all of the FDA-approved drugs, dates of approval, the approved indication, and the dates and types of regulatory exclusivities that apply to the particular drug, if any. A therapeutic equivalence code is also provided for each drug, which indicates the FDA’s determination of whether a particular generic drug may be substituted for a brand drug without the prescribing physician’s approval when dispensed to a patient. “A”-rated drugs (e.g., AB, AT) are drugs that the FDA has determined are bioequivalent to a branded drug, and therefore may be freely substitutable for the branded drug. The Orange Book also

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62 See 21 C.F.R. § 314.50(c).
63 Id. § 314.50(h)-(i); see also infra text and accompanying notes 69-73.
64 See 21 U.S.C. §355(c) (mandating a response within 180 days, unless the FDA and the applicant agree to a different period); see also 21 C.F.R. § 314.110(c) (establishing a one-year deadline to take action after an FDA response letter is issued); Sandoz, Inc. v. Leavitt, 427 F. Supp. 2d 29, 40-41 (D.D.C. 2006) (holding that the 180-day period is enforceable against the FDA).
67 See ORANGE BOOK, supra note 65.
includes a list of all patents that cover the approved drug product that is submitted by either the patent owner or the drug application owner.68

Any applicant submitting a NDA (or supplement thereto) to the FDA "shall submit . . . each patent that claims the drug or a method of using the drug that is the subject of the new drug application or amendment or supplement . . . and with respect to which a claim of patent infringement could reasonably be asserted," against an unauthorized third party that manufactures, uses, or sells the drug product.69 Despite the broad scope of the mandate, the regulations go on to state that only patents that claim the approved drug substance (active ingredient), the approved drug product (formulation and composition), and the approved method-of-use of the drug may be listed.70 Patents claiming a polymorph of the approved drug product fall within the approved drug substance category of patents, and therefore may be eligible for listing; but such polymorph patent may only be listed if the patent claims the polymorph that is the same as the active ingredient described in the approved application.71 The regulations specifically prohibit the list of patents that claim a method of manufacture, packaging, metabolites, or intermediates of the drug product.72

An applicant is required to submit the requisite patent information within the later of thirty days after the approval of its drug application (or supplement) or issuance of the patent through FDA Form 3542.73

C. Generic Drugs

A "generic drug" is defined as a drug product that is comparable to a reference-listed drug product in terms of active ingredient, dosage form, strength, route of administration, quality and performance characteristics, and intended use.74 For example, if the reference-listed

68 See id. at AD1-ADA215.
69 21 C.F.R. § 314.53(b).
70 Id.
71 Id.
72 Id.
73 See 21 C.F.R. § 314.53(c)(2)(ii).
drug is Crestor marketed by AstraZeneca, Crestor contains the active ingredient rosuvastatin calcium and has been approved in tablet forms containing 5, 10, 20, or 40 milligrams of rosuvastatin calcium. It is approved as adjunctive therapy to diet to reduce elevated cholesterol, low-density lipoprotein and triglyceride levels, and to increase high-density lipoprotein levels in patients with primary hyperlipidemia or mixed dyslipidemia when taken orally at 5 to 40 milligrams once daily. Any generic of Crestor would need to contain rosuvastatin (not necessarily rosuvastatin calcium), in 5, 10, 20, or 40 milligrams, in tablet form, for oral administration and be labeled for the same use—as adjunctive therapy to diet to reduce elevated cholesterol, low-density lipoprotein and triglyceride levels, and to increase high-density lipoprotein levels in patients with primary hyperlipidemia or mixed dyslipidemia.


An ANDA is just as it sounds—an *abbreviated* version of a NDA. With an ANDA, the manufacturer is not required to generate its own preclinical or clinical data to support its application; rather, the manufacturer must demonstrate that its drug product is bioequivalent to a previously approved reference-listed drug (“RLD”). If the drug product is shown to be bioequivalent, then the applicant can rely on the FDA’s earlier finding of safety and efficacy for the RLD to support approval of its application.

As noted above, the generic product is identical to the RLD in terms of active ingredient, dosage, form, strength, route of administration, quality and performance characteristics, and intended
use. There are, of course, exceptions.

The ANDA also includes chemistry, manufacturing, and control information about the generic product. Finally, and most important, the generic applicant must demonstrate that its product is bioequivalent to the RLD. A generic drug is bioequivalent if,

(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

In a nutshell, the generic must show that its drug product delivers the same amount of the active ingredient in the patient’s bloodstream in the same amount of time as the RLD. If the generic product delivers the same amount of the active ingredient into the patient’s bloodstream in the same amount of time as the RLD, then logic tells us that the appropriate amount of the active ingredient is present in the body in order to treat the disease—as already proven by the RLD through its human clinical trials.

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81 See supra text accompanying note 74.
83 Id. § 355(j)(2)(A)(iv).
84 Id. § 355(j)(8)(B).
85 See id.
86 See id.
2. Section 505(b)(2) or "Paper NDA."

A section 505(b)(2) application is when the applicant is using one or more studies that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."87 It too is considered an "abbreviated" pathway for application because while the 505(b)(2) application itself contains all of the same information as a NDA (such as preclinical and clinical), some of this data was not generated by the applicant itself.88 In many instances, this data may be scientific literature or may be from other approved drug applications (hence the unofficial "Paper NDA" designation).89


When either an ANDA or section 505(b)(2) application is filed, the applicant is required to state its position with respect to every patent listed in the Orange Book for the reference-listed drug.90 These so-called "patent certificate statements" fall within four categories:

I. the patent information on the drug has not been filed (i.e., that no patent information appears in the Orange Book);

II. the patent has already expired;

III. "the date on which [the] patent will expire"; or

IV. the patent "is invalid or will not be infringed by the manufacture, use, or sale" of the drug for which the ANDA or section 505(b)(2) application is submitted.91

87 Id. § 355(b)(2).
88 Id. § 355(b).
91 Id. § 355(b)(2)(A) (with respect to § 505(b)(2) applications); Id. § 355(j)(2)(A)(vii) (with respect to ANDAs).
The patent certification statement determines when FDA approval of the abbreviated application can be made. For example, an abbreviated application containing a paragraph I or II certification can be approved at any time after the FDA determines that its requirements have been satisfied, and an abbreviated application containing a paragraph III certification can be approved once the applicable Orange Book-listed patent(s) expires. Approval of an abbreviated application containing a paragraph IV certification, however, is more complex.

In some instances, an applicant can file a section viii statement, rather than one of the four patent certification statements with its abbreviated application. While not common, the section viii statement is gaining popularity and is utilized when the generic applicant is seeking approval of a method of use that is not covered by an Orange Book-listed patent. With section viii statements, the abbreviated application may be approved immediately because the thirty-month stay is not applicable, however, the generic is not entitled to the 180-day exclusivity period of first-entry generics.

4. Paragraph IV certification and the thirty-month stay.

If an applicant files a paragraph IV certification, the applicant is required to notify both the patent owner and the NDA owner of the certification, including “a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.” If the patentee takes no action, the FDA can immediately approve the abbreviated application once it determines that the application meets all of the FDA’s requirements. In many

92 See id. § 355(j)(5)(B).
93 See id.
95 See 21 U.S.C. § 355(b)(2)(B) (with respect to § 505(b)(2) applications); id. § 355(j)(2)(A)(viii) (with respect to ANDAs); see, e.g., PurePac Pharm. Co. v. Thompson, 238 F. Supp. 2d 191, 192 (D.C. Cir. 2002).
97 See Purepac Pharm. Co., 354 F.3d at 880; see also infra Part II.E.
98 21 U.S.C. § 355(b)(3)(C)-(D) (with respect to § 505(b)(2) applications); id. § 355(j) (2)(B)(iii)-(iv) (with respect to ANDAs).
99 See id. § 355(c)(3)(C) (with respect to § 505(b)(2) applications); id. § 355(j)(5)(B)(iii) (with respect to ANDAs).
instances, however, the patentee does act by filing a patent infringement suit against the generic applicant. As part of the Hatch-Waxman Act, 35 U.S.C. § 271(e)(2) was codified, which states that it shall be an act of infringement to file an ANDA or section 505(b)(2) application with a paragraph IV certification. If the patentee files this suit within forty-five days of receiving notice from the generic applicant of the paragraph IV certification, the FDA is prohibited from approving the generic application for thirty months from the date the patentee received notice. Notably, if the RLD enjoys NCE exclusivity, an applicant can file an ANDA or section 505(b)(2) application with a paragraph IV certification as early as four years from approval of the RLD; however, in such instance, the thirty-month stay is to be extended "by such an amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval" of the RLD's NDA. This is to ensure that the RLD receives full enjoyment of the five-year NCE exclusivity plus a full thirty-month stay, while also encouraging abbreviated applicants to enter the market and appropriately challenge the validity or scope of the Orange Book-listed patents.

This so-called "thirty-month stay" can be extended or shortened as follows:


100 See 35 U.S.C. § 271(c)(2).

102 21 U.S.C. § 355(c)(3)(C) (with respect to § 505(b)(2) applications); id. § 355(j)(5)(B)(iii) (with respect to ANDAs).

103 Id. § 355(c)(3)(E)(ii) (with respect to § 505(b)(2) applications); id. § 355(j)(5)(F)(ii) (with respect to ANDAs).


b. If the district court determines that the patent is invalid, not infringed, or is unenforceable before the thirty-month stay expires;  

c. If the district court grants a preliminary injunction prohibiting the manufacture or sale until the court renders its decision on the validity and infringement of the patent; or  

d. If the court determines the patent is valid, infringed, and enforceable, the stay can be extended (and shall be extended until the patent naturally expires).

Importantly, once the thirty-month stay has expired, then the FDA is free to approve the abbreviated application once it determines that the application meets all of the FDA’s requirements. Upon approval, the generic can begin to market its drug; however, if final resolution of the patent infringement litigation is not decided (by the district court or any applicable court if appealed) the generic would be launching “at risk.”

Notably, a patent owner is only entitled to one thirty-month stay against a particular abbreviated application. Prior to legislation in 2003, many innovators would obtain multiple thirty-month stays by submitting additional patents to the Orange Book after filing the application, often forcing the abbreviated applicant to submit another paragraph IV certification with respect to the “late-listed” patent.

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106 *Id.* § 355(c)(3)(C)(i) (with respect to § 505(b)(2) applications); *id.* § 355(j)(5)(B)(ii)(I) (with respect to ANDAs).

107 *Id.* § 355(c)(3)(C)(iii) (with respect to § 505(b)(2) applications); *id.* § 355(j)(B)(B)(iii)(IV) (with respect to ANDAs).

108 *Id.* § 355(c)(3)(C)(ii) (with respect to § 505(b)(2) applications); *id.* § 355(j)(5)(B)(iii)(II) (with respect to ANDAs); *see* 35 U.S.C. § 271(e)(4)(A) (stating that the infringing drug may not be approved before the expiration of the infringed patent).


111 *See* Apotex, Inc. v. Thompson, 347 F.3d 1335, 1341 (Fed. Cir. 2003); Robert A. Matthews, Jr., Additional Stays Based on Later-Listed Patents Not Permitted, 2 *ANNOTATED PATENT DIGEST,* § 10:154 (2014).

112 *See* Apotex, Inc., 347 F.3d at 1341; Robert A. Matthews, Jr., *supra* note 111.
However, it has not been statutorily clarified that the thirty-month stay is only available for those patents that were listed in the Orange Book before the filing of the abbreviated application. Interestingly, the FDA has identified one situation where it believes that multiple thirty-month stays are still authorized.

Of note is the fact that the thirty-month stay does not appear to have been arbitrarily selected. It was meant to reflect the average amount of time to finally resolve the applicable patent litigation, and to encompass the period of time it would take for the FDA to otherwise review and approve the abbreviated application. In doing so, an RLD is entitled to an automatic stay of the approval of a generic entry only for the period of time that it should take to decide the patent litigation. If the RLD prevails in the litigation, likely the approval will be further stayed until the patent naturally expires; however, if the generic prevails in the litigation, the generic can be immediately approved and will not have to wait an additional period of time for the FDA to actually review and approve its abbreviated application.

II. REGULATORY EXCLUSIVITY

A. New Chemical Entity Exclusivity

New chemical entity ("NCE") exclusivity is generally considered the most robust FDA exclusivity available in the United States. If a drug is afforded NCE exclusivity, the FDA would be prohibited from reviewing or approving any section 505(b)(2) or

116 Id.
119 See 21 U.S.C. § 355(c)(3)(E)(ii), (j)(5)(F)(ii) (providing five-year exclusivity); cf. infra Part II.B (three years for clinical investigation exclusivity); infra Part II.C (seven years for orphan drug exclusivity); infra Part II.D (five-year exclusivity extension for qualified infectious disease product ("QIDP") exclusivity).
ANDA for the same active moiety (including any ester of salt thereof) for a period of five years from the date of marketing approval by the FDA. The FDCA essentially defines an NCE as an approved drug consisting of active ingredients, including the ester or salt of an active ingredient, none of which has been approved in any other application.\footnote{21 U.S.C. § 355(c)(3)(E)(ii), (j)(5)(F)(ii); 21 C.F.R. § 314.108(2) (2014); Actavis Elizabeth LLC v. U.S. Food & Drug Admin., 689 F. Supp. 2d 174, 175-76 (D.D.C. 2010).}

It is important to note that the five-year NCE exclusivity does not prohibit the FDA from accepting and approving another NDA, if the sponsor of the second NDA has done all the human clinical trial work itself.\footnote{21 U.S.C. § 355(c)(3)(E)(ii); 21 U.S.C. § 355(j)(5)(F)(ii); 21 C.F.R. § 314.108; see, e.g., Actavis Elizabeth LLC, 689 F. Supp. 2d at 178.} However, filing an NDA is, in itself, a regulatory hurdle and a time-consuming barrier to market entry.\footnote{JOHN R. THOMAS, CONG. RESEARCH SERV., THE ROLE OF PATENTS & REGULATORY EXCLUSIVITIES IN PHARMACEUTICAL INNOVATION 1, 5 (2013), available at http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/R42890_01072013.pdf; Timothy A. Cook, Pharmaceutical Patent Litigation Settlements: Balancing Patent & Antitrust Policy Through Institutional Choice, 17(2) MICH. TELECOMM. & TECH. L. REV. 417, 425-26 (2011).} Accordingly, it is not common for multiple NDAs to be filed for the same active moiety; rather, a second applicant will often utilize one of the abbreviated pathways for approval, such as an ANDA or section 505(b)(2) application.\footnote{See generally 21 U.S.C. § 355(b)(1) (providing the procedure for and the content for an NDA); U.S. DEP’T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., THE CDER HANDBOOK 4 (1998), http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM198415.pdf (outlining the new drug development process, of which the NDA is the final step).}

\subsection*{B. Clinical Investigation Exclusivity}

Even if a small molecule drug has been previously approved by the FDA (and therefore, is not entitled to NCE exclusivity), it may still

\begin{footnotes}
\item[\footnote{Cf. ELLERY & HANSEN, supra note 48, at 8 (discussing high development costs for new molecular entities); id. at 17-18 (discussing early genericization in view of Hatch-Waxman incentives for generic entry); id. at 62-63 (discussing impact of the Hatch-Waxman Act on market entry of generic drugs).}]
\end{footnotes}
be entitled to receive some marketing exclusivity.\textsuperscript{125} If additional clinical testing to support changes to an approved drug is essential for FDA approval, the product may be eligible for clinical investigation ("CI") exclusivity.\textsuperscript{126} CI exclusivity prevents the FDA from approving an ANDA or section 505(b)(2) application for the modification for which the innovator conducted the new clinical investigation for a period of three years after the approval of the RLD.\textsuperscript{127} Specifically, an ANDA or section 505(b)(2) application may be filed at any time, but the FDA may not approve such an application until expiration of the three-year period.\textsuperscript{128} CI exclusivity is available if the application contains "reports of new clinical investigations (other than bioavailability studies) \cite{DickinsonNote126} that were conducted or sponsored by the applicant that were essential to approval of the application . . . ." \textsuperscript{129} Such new clinical investigations are often required if the drug product is a new formulation or requires a new dosing regimen in comparison to the drug product containing the same active moiety that is already marketed.\textsuperscript{130} Because this three-year exclusivity is limited to the indication approved in the supplemental approval, a generic applicant can obtain approval through an ANDA if the ANDA carves out the specific indication covered by the three-year CI exclusivity.\textsuperscript{131}

\section*{C. \textit{Orphan Drug Exclusivity}}

Under the current regulatory scheme, the FDA may afford drugs an orphan drug designation if (1) the indication affects less than 200,000 people in the United States, or (2) the drug is essentially not profitable.\textsuperscript{132} Orphan drug designation entitles the application to a fifty-

\begin{footnotesize}
\begin{enumerate}
\item See AstraZeneca Pharms. LP, 713 F.3d at 1136; Elizabeth Dickinson, \textit{FDA’s Role in Making Exclusivity Determinations}, 54(2) FOOD & DRUG L. J. 195, 201 (1999).
\item See Dickinson, \textit{supra} note 126.
\item See id.
\item See Dickinson, \textit{supra} note 126.
\item See id.
\item See id.
\end{enumerate}
\end{footnotesize}
percent tax credit and possible accelerated approval.\textsuperscript{133} If a drug is afforded orphan drug designation, the drug may be eligible for the corresponding orphan drug exclusivity if the innovator is the first to receive market approval for the active moiety for an orphan disease.\textsuperscript{134} Such a designation prohibits the FDA from approving any NDA, ANDA, or section 505(b)(2) application that contains the same active moiety for the same indication for a period of seven years from the date of marketing approval by the FDA.\textsuperscript{135} Accordingly, the FDA can approve any NDA, ANDA, or section 505(b)(2) application that contains the same active moiety for a different indication.\textsuperscript{136} Orphan drug exclusivity is not mutually exclusive, but rather can be awarded alone or along with NCE or CI exclusivity (which are mutually exclusive).\textsuperscript{137}

The FDA is able to accept and tentatively approve third-party applications for the same drug during the seven-year exclusivity period if the drug is not also entitled to NCE exclusivity; however, the approval becomes effective only upon expiration of the orphan drug designation period.\textsuperscript{138} If the drug is also entitled to NCE exclusivity, then the FDA is not able to accept and tentatively approve third-party applications until after the first five years of the seven-year exclusivity


\textsuperscript{134} See 21 U.S.C. § 360cc(a).

\textsuperscript{135} See id.; Dickinson, supra note 126, at 202.

\textsuperscript{136} See 21 U.S.C. § 360cc(a); Dickinson, supra note 126, at 202.


\textsuperscript{138} See 21 U.S.C. § 360cc(b).
period.  

Importantly, a third party may circumvent orphan drug designation and obtain approval for the same active agent for the same indication if the third party can demonstrate "clinical superiority"—that is, the third-party product is safer, more effective, or significantly more convenient. Of course, the FDA can approve the same active agent for another indication, which would likely be used "off-label" for the same orphan drug indication, despite any orphan drug designation period. It is important to note that a drug product may be eligible for both NCE exclusivity and one or more orphan drug exclusivities. If a drug product is considered an NCE, then a third party cannot avail itself of the clinical superiority provision for the first five years of its orphan drug designation where the NCE exclusivity is still effective.

D. Qualified Infectious Disease Product

A qualified infectious disease product ("QIDP") is "an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by—(1) an antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens; or (2) qualifying pathogens listed by the Secretary under subsection (f)." Exemplary qualifying pathogens include resistant gram-positive pathogens, such as methicillin resistant *Staphylococcus aureus*. The FDA is required to establish and maintain a list of qualifying pathogens, which it is still in the process of preparing. Once a drug is designated as QIDP the designation cannot be revoked, even if there is a change to the status of the qualifying

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139 See 21 C.F.R. § 316.20(a).
140 See id. § 316.3(b)(3), .20(a).
142 See, e.g., Karst, supra note 137.
In order to incentivize their development, QIDPs are given a five-year extension on any marketing exclusivity awarded to the drug upon its approval. If a QIDP is a NCE, the NCE exclusivity is extended from five years to ten years. If a QIDP is entitled to CI exclusivity the three years is extended to eight years. Similarly, orphan drug exclusivity would be extended to twelve years. QIDPs are also subject to priority review and approval by the FDA.

E. Generic Exclusivity

As an incentive, the first ANDA drug applicant to file a paragraph IV certification is awarded 180 days of exclusivity. That is, once a first ANDA is filed with a paragraph IV certification, the FDA may not approve any other abbreviated application for the same drug product for 180 days from the earlier of (i) the date of the first commercial marketing of the generic drug, or (ii) the date of a court decision holding the certified patent invalid or not infringed. Notably, the first ANDA drug applicant actually means all ANDA applicants that filed a substantially complete ANDA with a paragraph IV certification on the first day that such an application was filed. Accordingly, if multiple applicants file substantially complete ANDAs with paragraph IV certifications on the same day, each of those applicants will enjoy the 180-day generic exclusivity—resulting in a “shared exclusivity.”

An ANDA applicant can also forfeit its 180-day generic exclusivity through the following “forfeiture events”:

148 See id. § 355f(a).
149 See id.
150 See id.
151 See id.
152 Id. § 360n-1.
153 Id. § 355(j)(5)(B)(iv).
154 See id.
156 See Dr. Reddy’s Labs., Inc. v. Thompson, 302 F. Supp. 2d 340, 359 (D.N.J. 2003) (explaining that the FDA has not articulated the rule in regulations yet, but rather applies it on a case-by-case basis).
Failure to market.— The first applicant fails to market the drug by the later of—

(aa) the earlier of the date that is—

(AA) 75 days after the date on which the approval of the application of the first applicant is made effective under subparagraph (B)(iii); or

(BB) 30 months after the date of submission of the application of the first applicant; or

(bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification qualifying the first applicant for the 180-day exclusivity period under subparagraph (B)(iv), at least 1 of the following has occurred:

(AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.

(BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed.

(CC) The patent information submitted under subsection (b) or (c) of this section is withdrawn by the holder of the application approved under subsection (b) of this section.

Withdrawal of application.— The first applicant
withdraws the application or the Secretary considers the application to have been withdrawn as a result of a determination by the Secretary that the application does not meet the requirements for approval under paragraph (4).

(III) Amendment of certification.— The first applicant amends or withdraws the certification for all of the patents with respect to which that applicant submitted a certification qualifying the applicant for the 180-day exclusivity period.

(IV) Failure to obtain tentative approval.— The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

(V) Agreement with another applicant, the listed drug application holder, or a patent owner.— The first applicant enters into an agreement with another applicant under this subsection for the drug, the holder of the application for the listed drug, or an owner of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV), the Federal Trade Commission or the Attorney General files a complaint, and there is a final decision of the Federal Trade Commission or the court with regard to the complaint from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the agreement has violated the antitrust laws (as defined in section 12 of title 15, except that the term includes section 45 of title 15 to the extent that that section applies to unfair methods of competition).

(VI) Expiration of all patents.— All of the patents as to
which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired.\footnote{21 U.S.C. 355(j)(5)(D)(i).}

\section*{III. \textsc{Patent Exclusivity}}

\subsection*{A. \textit{Patents}}

Any new, useful, and nonobvious process, machine, manufacture, or composition of matter is eligible for patent protection in the United States.\footnote{See 35 U.S.C. §§ 101-03.} Once granted, a patent gives the patent owner the right to exclude others from making, using, selling, offering to sell, or importing into the United States the claimed invention.\footnote{See id. § 271(a).}

For small molecule drugs, there are a number of common types of claims that an innovator will try to obtain in order to protect its drug.\footnote{See infra notes 161-64 and accompanying text.} Common types of claims include: composition of matter claims that are directed to the active moiety itself, such as rosuvastatin (the active moiety of Crestor);\footnote{See, e.g., \textit{In re Rosuvastatin Calcium Patent Litigation}, 703 F.3d 511 (Fed. Cir. 2012) (discussing the challenges to patents claiming the active ingredient of Crestor, rosuvastatin).} methods of using the drug, such as for lowering cholesterol;\footnote{See, e.g., U.S. Patent No. 5,166,142 (filed June 10, 1991).} methods of manufacturing the drug and formulations; and claiming the active ingredient,\footnote{See, e.g., U.S. Patent No. 8,114,455 B2 (filed May 25, 2011).} as well as the inactive ingredients, in a particular dosage form (e.g., a tablet).\footnote{See, e.g., U.S. Patent No. 7,955,632 B2 (filed Nov. 14, 2007).} For many drugs, composition of matter claims directed to the active moiety are not available because the active moiety is a known compound; however, strong and valuable patent protection can still be obtained by protecting new uses of the known compound or new formulations of the known compound.\footnote{See Paul G. Alloway, \textit{Inherently Difficult Analysis for Inherent and Accidental Biotechnology Inventions}, 38 \textsc{Suffolk U.L. Rev.} 73, 80 (2004). See generally Dawson Chem. Co. v. Rohm & Haas Co., 448 U.S. 176 (1980) (explaining that even when a composition of matter patent is unavailable, it may be possible to obtain a valuable patent on a method of using that compound); Hodosh v. Block Drug Co., 833} Other claims may be directed to intermediates,
polymorphs, metabolites, and prodrugs. These noncomposition of matter patents are often referred to as “secondary patents.” Such secondary patents can provide valuable patent protection for the product, but importantly, certain types of these claims may not be eligible for listing in the Orange Book, even though they may otherwise cover an aspect related to or part of the drug, its manufacture, or its use.

B. Patent Term Extension

Another key provision of the Hatch-Waxman Act is “patent term restoration,” which provides that the term of one patent that covers the approved drug product may also be extended. In particular, the term of a single patent that claims an approved product, approved method of using a product, or a method of manufacturing the approved product can be extended. The extension is generally equal to half of the time spent from the date the IND was effective, to the date of the drug application submission, plus the time spent from drug application submission to drug application approval, less any period of time that the applicant did not act with diligence, only to the extent such time period occurred after issuance of the relevant patent; provided, however, that this extension period may not exceed five years and the extension period when added to the period remaining on the life of the patent may not exceed fourteen years.

Importantly, the rule of ones applies to patent term extension. That is to say that only one patent may be extended per product, only

F.2d 1575 (Fed. Cir. 1987) (demonstrating that a compound that is itself ineligible for composition of matter protection may be used in a novel manner, and thereby receive patent protection).

See Natalie M. Derzko, The Impact of Recent Reforms of the Hatch-Waxman Scheme on Orange Book Strategic Behavior and Pharmaceutical Innovation, 45 IDEA 165 (2005); 21 C.F.R. § 314.53(b) (2014).

Derzko, supra note 166.


Id. § 156(a).

Id. § 156(c), (g).

Id. § 156(g)(6)(A).

Id. § 156(c)(3).

See Boehringer Ingelheim Int’l GMBH v. Barr Labs. Inc., 592 F.3d 1340, 1346 (Fed. Cir. 2010).
one patent extension may be awarded per product, and only one patent extension may be awarded to a patent. Notably, the entire scope of the patent rights is not extended, but rather the rights extended are limited only to the approved product and any use approved for the product prior to expiration (as it may be extended) of the patent. That is to say that if a patent claims a genus of small molecule compounds, including molecules X, Y, and Z, and the approved product contains compound Z and was approved for treating high cholesterol, the extended term of the patent will only be enforceable against an unauthorized third party who is making, using, or selling compound Z for treating high cholesterol. The patentee would not be able to enforce the extended patent against a third party who is making compound Z for treating low blood pressure or for compound X for any use.

IV. THE CHEMISTRY: ORANGE BOOK-LISTED PATENTS AND THE THIRTY-MONTH STAY

In addition to standard market exclusivity available pursuant to its patent coverage, a drug product may be entitled to additional exclusivity vis-à-vis the listing of applicable patents in the Orange Book. Under the current FDCA regulations, patents claiming the drug substance (active ingredient), the drug product (formulation and composition), and methods of using the drug shall be listed in the Orange Book. For patents that claim a method of use, the patent must claim indications or conditions of use that are described in the pending or approved NDA, and the NDA holder must identify the individual patent claims.

175 Id. § 156(b). See generally Pfizer, Inc. v. Dr. Reddy’s Labs., Ltd., 359 F.3d 1361, 1366 (Fed. Cir. 2004) (explaining that § 156(b) limits the extension of patent protection to the pharmaceutical uses approved for that drug product).
177 See Arnold P’ship, 362 F.3d at 1341; MOY, supra note 176.
179 See 21 C.F.R. § 314.53(a)-(c) (2014).
180 Id. § 314.53(b)(2)(O).
By listing patents in the Orange Book, any third-party applicant who is seeking to market a drug prior to expiration of the Orange Book-listed patents must certify that either the unexpired patent(s) is (i) invalid, (ii) unenforceable, or (iii) infringed (a "paragraph IV certification") when it files a section 505(b)(2) or ANDA application.\textsuperscript{181} If the patent owner brings a suit against the third party within forty-five days of receiving notice of the paragraph IV certification, the FDA’s final approval to market cannot be effective until the earliest of (i) patent expiration, (ii) a final judicial determination favorable to the third-party applicant, or (iii) thirty months after the filing of the third-party applicant’s ANDA or section 505(b)(2) application.\textsuperscript{182} One caveat to listing a patent in the Orange Book is that it allows the third-party applicant to file the paragraph IV certification with its application at the end of the fourth year of the NCE exclusivity time period, rather than at the end of the fifth year.\textsuperscript{183}

V. \textbf{CASE STUDY: AMPYRA}

\textbf{A. The Facts}

The FDA approved Ampyra on January 22, 2010 through a NDA.\textsuperscript{184} Ampyra is an extended-release tablet for oral administration containing ten milligrams of dalfampridine and is indicated to improve walking in patients with multiple sclerosis when taken twice daily.\textsuperscript{185}

\textbf{B. The Patent and Regulatory Exclusivity}

Upon its approval, Ampyra was awarded NCE exclusivity, since dalfampridine had never been approved by the FDA before and was also given orphan drug exclusivity.\textsuperscript{186}

\textsuperscript{181} Troy, supra note 178.
\textsuperscript{182} See supra notes 102, 109 and accompanying text.
\textsuperscript{184} ORANGE BOOK, supra note 65, at 3-96.
\textsuperscript{186} See ORANGE BOOK, supra note 65; see also supra notes 122, 133 and accompanying text (discussing the requirements for NCE and orphan drug exclusivities); Memorandum from Chad J. Reissig, Pharmacologist, Ctr. for Drug
At the time of its approval, one patent was listed in the Orange Book for Ampyra: U.S. Patent No. 5,540,938. This patent was awarded five years of patent term extension under 35 U.S.C. § 156, which extended the expiry of the '938 Patent from July 30, 2013 to July 30, 2018. The FDA determined that the regulatory review period for Ampyra was 9,845 days, of which 9,569 days were spent in the clinical testing phase and 276 days were spent in the NDA approval phase; based upon these calculations, the U.S. Patent and Trademark Office found that 4,920 days of this time period was prior to the patent issuing. This provided 2,601 days (7.1 years) of extension, which was statutorily limited to the five-year maximum extension. Claim 1 of the '938 Patent is as follows:

A method for the treatment of a neurological disease where the disease is characterized by a slowing of nerve impulse transmission, which comprises administering to a patient in need thereof a medicament containing a mono- or di-aminopyridine active agent, said medicament being effective to permit sustained release of said mono- or di-aminopyridine active agent at a rate allowing controlled absorption thereof which achieves therapeutically effective blood levels over a 12-24 hour period when administered on a once- or twice-daily basis.


See ORANGE BOOK, supra note 65.


Id.

In its application for patent term extension, the applicant stated that claim 1 reads upon the method of using the approved product, Ampyra.\textsuperscript{193} In particular, the applicant stated:

As shown in the approved labeling (attached as Exhibit 6), AMPYRA is a medicament approved for treatment to improve walking in patients with multiple sclerosis (MS) as demonstrated by an increase in walking speed. MS is a disease characterized by a slowing of nerve impulse transmission. The active ingredient of AMPYRA, dalfampridine, is a mono-aminopyridine. AMPYRA is a controlled release (specifically, an extended release) tablet that is recommended for twice daily administration and that allows the controlled absorption of dalfampridine and achieves therapeutically effective blood levels over a 12-24 hour period. As noted, AMPYRA is recommended for twice-daily administration.\textsuperscript{194}

Subsequently, four additional patents were listed in the Orange Book for Ampyra upon their respective issuances.\textsuperscript{195} The four additional patents are generally directed to methods of improving walking or lower extremity function in a human multiple sclerosis patient by orally administering a sustained release composition of less than fifteen milligrams (e.g., ten milligrams) of four-aminopyridine (i.e., dalframpidine) twice daily to the patient (although the claims do differ with respect to various limitations recited in the claims).\textsuperscript{196} The patents naturally expire on May 26, 2027; December 22, 2026; April 8, 2023; and June 3, 2023.

\begin{flushleft}
\textsuperscript{194} Request for Extension of Patent Term, supra note 193.
\textsuperscript{196} See U.S. Patent No. 8,007,826 (filed Dec. 13, 2004); U.S. Patent No. 8,354,437 (filed Apr. 8, 2005); U.S. Patent No. 8,440,703 (filed Nov. 18, 2011); U.S. Patent No. 8,663,685 (filed July 20, 2011).
\end{flushleft}
2025; and January 18, 2025. Notably, none of the foregoing patents are directed to dalfampridine, as a composition of matter; rather, each of the patents is directed to the drug product, formulation, or methods of using dalfampridine. The projected exclusivity for Ampyra may resemble the timeline set forth in Exhibit A.

C. The Impact of the Chemistry

At first glance, the foregoing timeline appears simple; but each piece plays an interactive role with the others to create a chemistry, which is “a drug life.” One change could significantly impact the scope or length of exclusivity for Ampyra, allowing for the approval and market entry of a generic product of Ampyra at a much earlier point in time.

For example, if Ampyra had not been eligible for NCE exclusivity, orphan drug exclusivity, or was not covered by an Orange Book-listable patent, a generic product could be approved by the FDA and marketed at any time following Ampyra’s approval in January 2010, essentially immediately subsequent to the approval of the reference-listed drug. This hardly seems desirable for any innovator who spent significant time and resources researching and developing the drug product.

An Orange Book-listable patent, a generic product of Ampyra, could be approved by the FDA and marketed as early as January 22, 2015, upon expiry of the NCE exclusivity, if the generic product demonstrates it is clinically superior to Ampyra or, on January 22, 2017,

197 ORANGE BOOK, supra note 65.
200 See id.
201 See supra Parts V.A-B. This scenario assumes that there are not any non-Orange Book-listed patents that the innovator owns that cover Ampyra, such as a method of manufacture patent, that the generic application might otherwise be infringing with the manufacture or sale of its generic product.
upon expiry of the orphan drug exclusivity.\textsuperscript{202} Notably, under either scenario, the FDA could not have submitted and reviewed the abbreviated application until January 22, 2015, upon expiry of the NCE exclusivity.\textsuperscript{203}

Additionally, the presence of the Orange Book-listable patents provides further protection against generic entry of Ampyra.\textsuperscript{204} With the five Orange Book-listed patents, any abbreviated applicant seeking approval prior to the natural expiry of all of the patents (e.g., May 26, 2027) would need to submit a paragraph IV certification for each listed patent asserting that each patent is either invalid or not infringed.\textsuperscript{205} If the NDA holder brings suit against the generic application within forty-five days of receiving notice of the paragraph IV certifications alleging infringement of one or more of the Orange Book-listed patents, the FDA will be prohibited from approving the abbreviated application for an additional thirty months (as it may be extended or shortened).\textsuperscript{206} Notably, since Ampyra enjoys both NCE exclusivity and orphan drug exclusivity, but does have at least one Orange Book patent, an applicant could actually file an ANDA or section 505(b)(2) application alleging clinical superiority along with a paragraph IV certification as early as January 22, 2014 (one year prior to expiry of the NCE exclusivity); however, the thirty-month stay would preclude the FDA’s approval until July 22, 2018 (seven and one-half years from NDA approval of Ampyra), unless decreased or extended by a court decision.\textsuperscript{207} If the product is not clinically superior then an applicant could not file an ANDA or a section 505(b)(2) application with a paragraph IV certification until January 22, 2017 (upon expiry of the orphan drug exclusivity); however the thirty-month stay would preclude the FDA’s approval for an additional thirty months from the date that the innovator received the paragraph IV notification, unless decreased or extended by

\textsuperscript{202} See 21 C.F.R. § 316.3(b)(3), .20(a) (2014); supra Part V.B.

\textsuperscript{203} See supra notes 120-22, 185 and accompanying text.

\textsuperscript{204} Troy, supra note 178.

\textsuperscript{205} See supra Parts I.C.4, V.B.

\textsuperscript{206} See supra Parts I.C.4, V.B.

a court decision.  

The '938 Patent was the only patent originally listed in the Orange Book for Ampyra upon its approval. The natural expiry date of this patent (with the awarded extension) is July 20, 2018. Importantly, the NDA holder issued subsequent patents covering Ampyra that were eligible for listing in the Orange Book, which have significantly longer patent terms—up to at least 2027. By listing the additional patents with later expiry dates in the Orange Book the innovator has a greater chance of enjoying the full term of the thirty-month stay rather than the thirty-month stay prematurely terminating because the sole Orange Book-listed patent expired. Ultimately, if the innovator would prevail in any patent litigation suit against a generic entrant, it is likely that the innovator would obtain a permanent injunction preventing the approval of the first generic of Ampyra until expiry of all of the Orange Book-listed patents, which is currently May 26, 2027.

Based upon the foregoing, the innovator may enjoy at least five years of marketing exclusivity and possibly up to a little over seventeen years of marketing exclusivity for Ampyra. This period of marketing exclusivity will enable the innovator to recoup its costs of development and marketing and will hopefully fuel its future innovation of new drug products.

VI. CONCLUSION

Patents play a critical role in establishing and maintaining

\[208\] See 21 C.F.R. § 316.3(b)(3), .20(a), .31(a) (2014); supra notes 204, 207-08 and accompanying text.
\[209\] See ORANGE BOOK, supra note 65.
\[210\] Id.
\[211\] Id. (as of Dec. 21, 2014).
\[212\] See supra Parts IV, V.A-B.
\[213\] See supra text accompanying notes 211-13.
\[214\] See supra Part V.B.
exclusivity for a drug. 216 So-called “secondary patents,” which are not directed to the active ingredient per se, but are directed to methods of use and formulations, can provide critical protection against generic entry. 217 In some cases, such secondary patents can provide protection that is as strong as the perceived “holy grail” of all patents—the composition of matter patent. 218 However, patent exclusivity is only as strong as the scope, validity, and enforceability of the patent. 219 In contrast, regulatory exclusivity, once ordained, is generally a certainty; it cannot be revoked or shortened. 220 Yet, regulatory exclusivity is short when compared to the potential length of patent exclusivity. 221

The Hatch-Waxman Act was meant to strike a balance between incentivizing innovation and the availability of lower cost generic alternatives through the award of regulatory exclusivities and abbreviated approval pathways. 222 However, when Congress passed the Hatch-Waxman Act thirty years ago, the costs were significantly less to develop a drug and arguably, the clinical hurdles were not as great. 223 Congress should consider extending either the length of the applicable

216 See supra Parts I.C.3-4, III-IV.
217 See supra notes 162-68 and accompanying text.
218 See, e.g., supra text accompanying notes 193-99 (illustrating the protection additional patents provide even though they are not directed at the active ingredient).
219 See 35 U.S.C. § 271(e)(2)(A) (2012) (specifying that an act of infringement must infringe on the use that it was patented on); see, e.g., Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1354-55 (Fed. Cir. 2003) (“[I]t is not an act of infringement to submit an ANDA for approval to market a drug for a use when neither the drug nor that use is covered by an existing patent, and the patent at issue is for a use not approved under the NDA.”).
220 See, e.g., supra note 148 and accompanying text (explaining that once a drug is classified as a qualified infectious disease product, which benefits from regulatory exclusivity, its designation cannot be revoked).
221 See supra Parts II-III (discussing regulatory and patent exclusivity terms).
222 See Crawford, supra note 216 (stating the dual goals of Congress in enacting the Hatch-Waxman Act); Am. Bioscience, Inc., v. Thompson, 269 F.3d 1077, 1079 (D.C. Cir. 2001) (discussing how the Hatch-Waxman Amendments make it easier to bring generics into the market, while also protecting patent holders whose rights might be infringed upon by the generic drugs); see also Jacob S. Wharton, “Orange Book” Listing of Patents Under the Hatch-Waxman Act, 47 ST. LOUIS U. L.J. 1027, 1031 (2003) (discussing publication of these patents in the Orange Book’s role in “effectuating the dual goals articulated by Congress”).
223 See generally Herper, supra note 14 (discussing the high price tag of modern drug development); Roy, supra note 15 (discussing the rising costs of drug development).
regulatory exclusivities available to innovators or the period by which a patent’s term may be extended to provide greater incentives for innovation. Without the chemistry between the regulatory and patent exclusivity, a drug’s life may be short and bittersweet.224

EXHIBIT A

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224 See, e.g., supra Part V.B (illustrating the chemistry of the patent and regulatory exclusivities for small molecule drugs).