

PART IV

**THE ROLE OF PATENT AND NON-PATENT EXCLUSIVITY
UNDER THE HATCH-WAXMAN ACT**

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PART IV

A. Hatch-Waxman Introduction and Non-patent Exclusivities (5 year, 3 year and generic)

1. Overviews

In 1984, Congress passed amendments to the Food Drug & Cosmetics Act ("FDC Act") that significantly changed the process of approving new drugs and generic products, and created new interactions between the patent and food and drug laws.¹ These amendments, commonly referred to as the Hatch-Waxman Act, represented a political compromise between ethical (or innovative) drug manufacturers and generics. "Congress struck a balance between two competing policy interests: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost generic copies of those drugs to market."² Congress wanted to ensure that lower-cost generic drugs would be available to the public as quickly as possible, while at the same time assuring ethical manufacturers that they would be able to recover their sizeable investments in drug research and clinical activities before generic competitors entered the market. In an attempt to balance these interests, Hatch-Waxman created two routes for generic drug approval that previously did not exist, and created certain marketing exclusivity periods for innovators of new chemical entities³ or new uses of approved

¹ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (Codified at 15 U.S.C. §§ 686-68c, 70b (1994); 21 U.S.C. §§ 301 note, 355, 360 cc (1994); 28 U.S.C. § 2201 (1994); 35 U.S.C. §§ 156, 271, 282 (1994) ("Hatch-Waxman Act").

² *Andrx Pharm. Corp. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002).

³ See 21 U.S.C. § 355(b).

drugs, while according generic manufacturers the right to reference (rather than have to repeat) clinical studies already performed by others for new drug approvals. In order to speed generic drug approvals, Hatch-Waxman also provided a "safe harbor" from patent infringement for certain activities, provided they are related to the FDA (or USDA) approval process. Finally, Hatch-Waxman allows patentees who experienced delays in the regulatory approval to extend the terms of their patents under certain conditions. The safe harbor and patent term extension provisions of Hatch-Waxman apply to drugs, devices, biologics and food and color additives.

2. Drug Approvals

Prior to 1984, the drug approval process was the same for all nonantibiotic drug products.⁴ Each drug product was required to undergo full safety and efficacy testing regardless of whether it was a generic or innovator drug.⁵ Hatch-Waxman changed this framework and set-up a three-pronged drug approval process.

⁴ Antibiotic drugs were regulated under 21 U.S.C. § 357 until 1997 when the FDA Modernization Act (FDAMA; Pub. L. No. 105-115, 111 Stat. 2295 (1997)) established that antibiotics and nonantibiotics should both be regulated under 21 U.S.C. § 355. The implementing regulations for this portion of FDAMA established a list of pre-repeal antibiotics that are not eligible for Hatch-Waxman exclusivity benefits. This list has resulted in some litigation and adversarial proceedings involving the definition of antibiotics and the use of antibiotic drugs for nonantibiotic indications. See e.g., *CollaGenex v. Thompson*, No. 03-1405 (D. D.C. July 22, 2003); Citizens Petition of Allergan, 2003P-0275/CP-1 and PSA-1 available at www.fda.gov (last visited January 5, 2003).

⁵ See Federal Food, Drug & Cosmetic Act, 21 U.S.C. § 355(a) (as amended 1983).

a. Approvals under 21 U.S.C. § 355(b)

Two mechanisms for approving the marketing of drug products are defined under 21 U.S.C. § 355(b). The first mechanism is used for approval and marketing of "pioneer" or new drugs. Before a new drug can be marketed it must obtain FDA approval.⁶ The approval process for a new drug requires the submission of a New Drug Application (NDA) to the FDA that contains, among other things, "full reports of investigations which have been made to show whether or not such a drug is safe for use and whether such a drug is effective in use," and "specimens of the labeling proposed to be used for such a drug".⁷ In addition, the FDA requires an applicant to file the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug.⁸ After an NDA has been approved, the holder must submit the same information for patents that subsequently issue.⁹ Both the pre-NDA patents and the post-NDA patents are listed in what is commonly known as the "Orange Book".¹⁰

The second prong for approval available under §355(b) is what is known as a 505(b)(2) application or "paper

⁶ 21 U.S.C. § 355(a).

⁷ See *Zeneca, Inc. v. Shalala*, 213 F.3d 161, 163 (4th Cir. 2000) (quoting 21 U.S.C. § 355(b)(1)).

⁸ *Id.* § 355(b)(1).

⁹ *Id.* § 355(c)(2).

¹⁰ See Section D *infra*.

NDA".¹¹ Under section 505(b)(2), an applicant submits reports of investigations of safety and effectiveness, but also relies on information required for approval that comes from studies not conducted by or for the applicant and for which the applicant has not received a right of reference. The applicant, for example, can rely on published literature that support findings of safety and/or effectiveness for its drug product.

An applicant can submit two different kinds of applications under § 505(b)(2). The first type of application is for a New Chemical Entity (NCE). This type of application can be used only when some of the information necessary for approval is derived from studies not performed by the applicant and to which the applicant has no right of reference.

The second type of application available under this section is for changes to previously approved drugs. An applicant can rely on the studies for the previously approved drug and add additional studies to support and demonstrate the changes. Examples of changes that can be made with a § 505(b)(2) filing include changes in dosage form, strength, or route of administration, substitution of an active ingredient in a combination product changes in formulation, dosing regimen, active ingredient, indication, Rx/OTC classification, or active ingredient source or to demonstrate bioequivalence.

Section 505(b)(2) applications cannot be filed where: the drug product is a duplicate of a listed drug and is

¹¹ The number 505 comes from the section number associated with the Food, Drug & Cosmetics Act. § 355 of 21 U.S.C. is § 505 of the Food, Drug & Cosmetics Act, thus a 505(b)(2) application is codified at 21 U.S.C. § 355(b)(2). Occasionally, the numbers can get mixed up.

eligible for approval under § 505(j); or the only difference from the reference listed drug is that the extent to which the active ingredient is absorbed or otherwise made available at the site of action is less than the listed drug; or the only difference from the reference listed drug is that the rate at which the applicant's drug product's active ingredient is absorbed or otherwise made available at the site of action is unintentionally less than the listed drug.¹²

Section 505(b)(2) applications have been the source of recent controversy before the FDA and the courts.¹³ In both cases, § 505(b)(2) applications have been filed on different salts of existing drug products and have relied on the safety and efficacy data of the original drug product to gain approval.¹⁴ The FDA denied a series of Citizen's Petitions arguing against the applications, but indicated that there may be public health and policy reasons to revisit the use of the § 505(b)(2) process to approve new salt formulations of existing products.¹⁵

b. Approvals under 21 U.S.C. § 355(j)

The third prong of drug approval is available under 21 U.S.C. § 355(j) in the form of an abbreviated new drug application (ANDA). ANDA's are generally filed when a

¹² Thus, § 505(b)(2) applications cannot be submitted where the drug product is a duplicate of an existing drug product, or where the drug product is less effective than the existing drug product.

¹³ See FDC Reports, 65 "The Pink Sheet" 28, 39, 42 & 43 (July 14, 2003, September 29, 2003, October 20, 2003 and October 27, 2003).

¹⁴ The two cases that have been of interest involve a dispute between Dr. Reddy's and Pfizer over a generic version of *Norvasc*®, and a dispute between Synthon and Apotex over a generic version of *Paxil*®.

¹⁵ See FDA Response to Citizen Petition, October 14, 2003. The FDA seems to be concerned about § 505(b)(2) applications that do not result in the approval of new drug products that are innovative, or that offer a new therapeutic benefit or alternative.

generic manufacturer wishes to duplicate an NDA holder's drug product. The ANDA applicant is required to show that the drug product is the same in active ingredient, route of administration, dosage form and strength as the product in the original NDA.¹⁶ In addition, the ANDA applicant must show that the drug product is bioequivalent to the NDA product.¹⁷ After demonstrating these to the satisfaction of the FDA, marketing approval will be granted.

If the applicant wishes to change the route of administration, dosage form, strength or active ingredient, it may file a petition to do so.¹⁸ The FDA must approve such an application unless it finds that investigations demonstrating the safety and effectiveness of the drug are needed, or that the information to be submitted in an abbreviated application would not be sufficient to evaluate a different active ingredient for safety and effectiveness.¹⁹

3. Marketing Exclusivity - 21 U.S.C. § 355

Under Hatch-Waxman, marketing exclusivity is available only for approved drug products. Biotechnology products that are regulated as drugs or as combination drug/biologic products are eligible for market exclusivity under 21 U.S.C. § 355(b). "Pipeline" drugs, i.e., those which were

¹⁶ 21 U.S.C. § 355(j) (2) (A) (ii) (I-III).

¹⁷ *Id.* § 355(j) (2) (A) (iv).

¹⁸ *Id.* § 355(j) (2) (C). Such a filing is called a suitability petition. Note that there is some overlap between the provision for suitability petition and the subject matter of § 505(b) (2) applications. This can be the case because under an ANDA no new clinical investigations are needed, while under a § 505(b) (2) application additional investigations are submitted. Thus, an application that starts as a suitability petition can be denied and forced to follow the § 505(b) (2) route.

¹⁹ *Id.* § 355(j) (2) (C) (I-ii).

pending approval at the time the legislation was passed, were given different exclusivity periods.

a. Five-Year Exclusivity

For new "active ingredients," the statute provides a five-year marketing exclusivity period during which no other new drug applications (NDAs) for the same active ingredient may be submitted to the FDA. 21 U.S.C. § 355(c)(3)(D)(ii). Because FDA review often involves a lengthy process during which the application is evaluated for deficiencies before approval is given, the five-year prohibition on application submissions tends to result in exclusivity for longer than five years.

FDA regulations clarify that the term "active ingredient" means "active moiety," defined as:

The molecule or ion excluding those appended ions that cause the drug to be an ester, salt (including a salt with hydrogen or coordinating bonds or other non-covalent derivative, such as a complex chelate or clathrate of the molecule) responsible for the physiological or pharmacological action of the drug substance.

The effect of this definition is to narrow significantly the scope of drug products that are eligible for five-year exclusivity. The only exception to the rule against accepting competitors' applications is the situation where there is a patent listed for the innovator drug, in which case a competitor's application can be submitted after four years, provided the applicant also certifies as to non-infringement or invalidity.²⁰

²⁰ See *Immunex Corp. v. FDA*, No. 97-1689 (D.D.C. Oct. 31, 1997). **Patent certification is discussed in Section D *infra*.**

b. Three-Year Exclusivity

For drug products that do not feature a new active ingredient but that require new clinical studies to support new therapeutic claims, Hatch-Waxman provides a three-year marketing exclusivity period during which no other applications for the same indications can be approved. 21 U.S.C. § 355(c)(3)(D)(iii). In contrast to the rules regarding five-year exclusivity for new active moieties, generic applications for the same therapeutic claims may be submitted to the FDA during the three-year exclusivity period for approval or as soon as the exclusivity period expires. Three-year exclusivity is given, for example, for a change in dosage form, for a new indication, and for switching from prescription to over-the-counter (OTC) status.

c. 180-Day Generic Exclusivity

When a generic drug product enters the market, the ethical manufacturer typically loses 50% of its market share in the first year and up to 90% by the third year. While these numbers would seem to be sufficient incentive to spur generic competition, Hatch-Waxman also provides a 180-day marketing exclusivity period for the first-to-file generic applicant who submits a paragraph IV certification. However, poorly drafted statutory language led to years of litigation.²¹ New rules proposed by the FDA are intended to clarify abbreviated new drug application (ANDA) exclusivity rights by providing the following guidelines:

²¹ *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998); *Granutec, Inc. v. Shalala*, 46 USPQ2d 1398 (4th Cir. 1998).

(i) only the applicant submitting the first substantially complete ANDA (and paragraph IV certification) will be eligible for the 180-day exclusivity;

(ii) the agency will consider the first applicant to be eligible for exclusivity even if it is not sued by the patent owner or NDA holder (and thus not penalize an ANDA applicant which designs around a patent in order to avoid an infringement suit);

(iii) if a number of applicants file their ANDAs on the same day, all will be eligible for 180-day exclusivity for the strength of the drug which is the subject of their ANDA;

(iv) each strength of a drug will separately be eligible for exclusivity;

(v) the first ANDA applicant will not be eligible for 180-day exclusivity if it is sued and loses; and

(vi) to make sure that the first ANDA applicant brings its product to market promptly, the FDA proposes to adopt a triggering period, as suggested by the court in *Mova*. This would be a 180-day period during which either there must be a court decision regarding the patent that is favorable to the ANDA applicant, or the applicant must begin commercial marketing. If neither of these events occurs during the triggering period, the first ANDA applicant loses its exclusivity and the

next-in-line ANDAs will be eligible for immediate approval.

In addition, Congress passed the Medicare Prescription Drug Improvement and Modernization Act of 2003, which provides five different routes whereby 180-day exclusivity can be forfeited. These include: failure to market within a specific period by the first applicant, withdrawal of the application by the first applicant, amendment or withdrawal of the certification by the first applicant, failure to obtain tentative approval within a certain time period, entering into an agreement that violates antitrust laws, and expiration of all of the listed patents that have been certified.²²

²² S. 1225 , 108th Cong. (2003) .

B. Orphan Drug and Pediatric Exclusivity²³

1. Orphan Drug

Non-patent marketing exclusivities are available for developers of drugs for specific patient populations. The Orphan Drug Act²⁴ was intended to provide incentives for drug companies to develop treatments for rare, or "orphan", diseases. Under the act, the sponsor of an orphan drug can obtain seven years of marketing exclusivity following FDA approval of the drug. Orphan exclusivity is available for drugs ("active moiety") and biologics ("macromolecules") for treatment of diseases or conditions that have a U.S. patient population of less than 200,000. The law also provides protection for drugs for a disease or condition "which affects more than 200,000 people in the U.S., but for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug."

During the seven-year period of orphan exclusivity, no FDA approval will be given to a subsequent sponsor's marketing application for the same product for the same indication unless the subsequent product is shown to be *clinically superior* as defined in 21 CFR § 316.3(b). A second application for a different use for the drug may be approved, however. A single drug may obtain orphan status for multiple indications.

²³ Although orphan drug and pediatric exclusivities are closely related to the Hatch-Waxman Act, they arise from separate legislation.

²⁴ P.L. 97-414. The Orphan Drug Act amended the Federal Food, Drug and Cosmetic Act (FFDCA) as of January 4, 1983. Additional orphan drug amendments were passed in 1984, 1985, and 1988.

"Sameness" for macromolecules has presented certain problems for the FDA.²⁵ While the application of the test is fairly straightforward for protein drugs,²⁶ monoclonal antibodies, because of the unique process involved in their creation, require special FDA guidance.²⁷

a. Obtaining Orphan Drug Designation

A sponsor seeking orphan marketing exclusivity of a drug must first obtain orphan designation for the drug from the FDA. Orphan designation may be sought for a previously unapproved drug, or for a new orphan indication for a drug that is already marketed, regardless of whether the previous indication was an orphan indication. More than one sponsor may receive orphan drug designation (but not exclusivity) of the same drug for the same disease or condition, but each sponsor must file a complete request for designation.²⁸ A sponsor may request orphan designation at any time in the development process prior to submission of a marketing application of the drug for the orphan indication.

In seeking orphan designation, a sponsor must identify and describe the drug, the disease, the proposed indications for use of the drug, and the reasons why the drug is needed for the indication. The sponsor also must provide documentation to prove that the indicated disease affects fewer than 200,000 people in the U.S., or, where the disease affects more than 200,000 people, that there is no reasonable expectation that costs incurred in developing the

²⁵ 21 CFR § 316.3(b)(13)(ii) defines sameness as "a drug that contains the same principal molecular structure feature (but not necessarily all of the same standard features) and is intended for the same use as a previously approved drug".

²⁶ *Id.* § 316.3(b)(13)(ii)(A).

²⁷ Guidance for Industry, Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations, FDA, July 1999.

²⁸ *Id.* § 316.20(a).

drug will be recovered. The FDA may refuse to grant orphan designation if there is insufficient evidence as to the prevalence or nature of the disease, or the intended use or efficacy of the drug.

b. Obtaining Orphan Drug Approval

Once a marketing application for a designated orphan drug is approved, the FDA will not approve another sponsor's application for seven years from the date of the approval. The exclusivity holder may consent to approval of another application. Failure to assure a sufficient quantity of the drug may also permit approval of another application.

c. Other provisions of the Orphan Drug Act

In addition to marketing exclusivity, the Orphan Drug Act provides tax credits, research grants, and fee waivers for regulatory approval. For example, a developer of an orphan drug may obtain a tax credit for up to fifty percent of certain clinical testing expenses for research undertaken to generate required data for marketing approval.²⁹ Information about research grants can be obtained from the FDA Office of Orphan Products Development.³⁰

2. Pediatric Exclusivity

The Food and Drug Administration Modernization Act of 1997 (FDAMA) created section 505A of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(a)), which permits certain new drug applications to obtain an additional six months of exclusivity if the drug manufacturer submits certain FDA - requested information (i.e., a "Written

²⁹ P.L. 104-188, P.L. 105-34.

³⁰ See <http://www.fda.gov/orphan/grants/info.htm>.

Request") relating to the use of the active moiety in a pediatric population. An FDA Guidance for Industry which explains the pediatric exclusivity program is available online.³¹ The original program expired at the end of 2001; however, in January 2002 Congress passed the Best Pharmaceuticals for Children Act (BPCA)³² which made pediatric exclusivity a permanent fixture in the food and drug laws and expanded the opportunities for testing drugs already on the market in pediatric population.

a. Scope of Exclusivity.

Pediatric exclusivity attaches to any existing exclusivities (including orphan exclusivity) and to all patent protections listed in the Orange Book for any drug product containing the same active moiety as the drug studied. For studies conducted on an unapproved drug, pediatric exclusivity will attach to any exclusivity or patent protection that will be listed in the Orange Book upon approval of that unapproved drug.

Pediatric exclusivity adds 6 months to the exclusivities and patent protections³³ listed of each drug product for which the party submitting the studies holds the approved new drug application. For example, if the drug product has 5-year, new chemical entity (NCE) exclusivity, the addition of pediatric exclusivity will give the applicant 5 1/2 years of NCE exclusivity. Pediatric exclusivity does not attach to the end of a

³¹ <http://www.fda.gov/cder/guidance/index/htm>.

³² P.L. 107-109.

³³ Six months of exclusivity automatically attaches where generic drug applicants file patent certifications under Paragraphs II and III. For Paragraph IV certifications, pediatric exclusivity does not attach unless an infringement suit is failed and the 30 month stay provision are triggered under Section 505.

patent term extension under 35 U.S.C. § 156; rather, it extends the period during which the approval of a competitor's ANDA or 505(b)(2) application may not be made effective by FDA.

If a sponsor obtains pediatric exclusivity for studies on a single active moiety that is also included in a combination product, pediatric exclusivity will apply only to the monotherapy and to patents covering the monotherapy. Protections covering the combination therapy alone or just the other ingredient of the combination therapy would not be extended. However, if any of the protections covering the monotherapy also apply to a combination product, pediatric exclusivity would also apply to the same protections listed for the combination therapy. For example, if one active ingredient of a combination product has 5 year NCE exclusivity and the sponsor earns pediatric exclusivity for a study on the active moiety protected by NCE exclusivity, the pediatric exclusivity will extend the 5-year NCE protection for the monotherapy and for the combination therapy. If the same patent is listed for the monotherapy and for the combination therapy, pediatric exclusivity will attach to the patent as it applies to both therapies.

Additionally, if a sponsor conducts studies on a combination product that contains more than one active moiety, pediatric exclusivity would attach to all that sponsor's eligible patent and exclusivity protections for each active moiety contained in the combination product.

b. A Second 6-Month Period of Pediatric Exclusivity

Pediatric studies submitted in a supplemental application for a drug that has already received one period

of pediatric exclusivity may qualify the drug to receive a different 6-month period of pediatric exclusivity, however the second 6-month period will attach only to the 3 year exclusivity period (under sections 505(c)(3)(D)(iv)) and 505(j)(5)(D)(iv)) granted to the supplemental application for which the studies were completed. This means:

- o A second Written Request can result in a 6-month period of exclusivity if and only if the response to the Written Request is a supplement for a new use.
- o A new use is a use that is not included in the approved labeling of an approved drug (21 CFR 99.3(g)) (expansion of a label to include a new pediatric population constitutes a new use).
- o The supplement for a new use submitted in response to the second Written Request must qualify for 3-year Waxman-Hatch exclusivity or no 6-month period of pediatric exclusivity will attach.
- o The 6-month period of pediatric exclusivity attaches *only* to the 3-year exclusivity applied to the supplement for a new use containing the studies submitted in response to the second Written Request and not to any other exclusivity or patent protections applicable to the active moiety.

c. Later filed Applications Containing the Same Active Moiety

Previously earned pediatric exclusivity will not apply to new patents or exclusivities covering later-filed applications (or supplemental applications) covering the same active moiety (e.g., for which a sponsor previously earned pediatric exclusivity), unless the data that earned

the prior pediatric exclusivity are essential to approval of the new application or supplement.

If previously earned pediatric exclusivity has been applied to a patent or exclusivity that also protects the new application or new supplement, it will continue to apply. For example, if a sponsor earns a 6-month extension on 5-year NCE exclusivity, the extension will apply to all applications protected by the NCE exclusivity, regardless of when the new application or supplement is filed.

Consider the following examples:

Example 1

FDA grants pediatric exclusivity on Active Moiety 1 (AM1). After FDA grants the pediatric exclusivity on AM1, the sponsor files a different application for a drug containing AM1 or a supplement to an existing application for a drug containing AM1. FDA does not need any of the data the sponsor submitted for pediatric exclusivity to approve the new application or new supplement. FDA will not apply the previously granted pediatric exclusivity to any exclusivities or patents that apply solely to the new application or supplement to the application.

Example 2

FDA grants pediatric exclusivity on AM1. After FDA grants the pediatric exclusivity on AM1, the sponsor files a different application for a drug containing AM1 or a supplement to an existing application for a drug containing AM1. Data the sponsor previously submitted for pediatric exclusivity is essential to approval of the new application or new supplement. FDA will apply the previously granted

pediatric exclusivity to any exclusivities or patents that apply to the new application or the new supplement.

d. FDA's Written Request for Pediatric Studies

A Written Request is a specific document from FDA which requests submission of certain studies to determine if the use of a drug could have meaningful health benefits in the pediatric population. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors are required to obtain a Written Request before submitting pediatric studies to an NDA. However, studies submitted to an Investigational New Drug Application ("IND") before FDA issues a Written Request but not submitted as part of an NDA, an amendment to an NDA, or a supplement, may be used as part of a proposed pediatric study request. FDA may issue a Written Request for those studies at the request of an interested party or on its own initiative. Issuance of a Written Request to a sponsor does not require the sponsor to conduct pediatric studies described in the Written Request. FDA publishes a list of approved active moieties for which it has issued Written Requests, which is available on the internet at <http://www.fda.gov/cder/pediatric>.

e. Labeling Exclusivity and Generic Approvals

The BPCA instructs FDA on how to balance the competing goals of protecting intellectual property rights and speeding generic approvals when essential pediatric safety information is covered by exclusivity. Section 11 of 21 U.S.C § 355a(1) of the BPCA is designed specifically to ensure that protection for pediatric labeling for a

reference listed drug (RLD) will not block generics from entering the market.³⁴

This section provides that, where appropriate, pediatric labeling protected by patent or exclusivity can be carved out and replaced with a disclaimer (21 U.S.C. § 355(a)(1)(2)(A)). In cases where FDA finds that pediatric labeling is essential to the safe use of the product and cannot be carved out without jeopardizing that safety of the product, FDA may require that the labeling of a generic version of a drug "include a statement of any appropriate pediatric contraindications, warnings, or precautions that [the Agency] considers necessary" (21 U.S.C. § 355(a)(1)(2)(B)).

3. Generic Biologics - Is There a Future?

The Hatch-Waxman Act contemplated that only drug products (i.e., small molecules) would be eligible for generic (i.e., ANDA and 505(b)(2)) approvals. In 1984, it was difficult to characterize biologics adequately, and each lot had to be tested for purity and potency. This made abbreviated, or generic, approvals impractical. Although much has changed since that time, the FDA has still not determined how equivalence with an innovator's product can be demonstrated under the current legal framework. FDAMA unified much of the Public Health Service Act (PHS Act) (under which most biologics are approved) and the FD&C Act,

³⁴ Section 11 provides, "a drug for which an application has been submitted or approved under 505(j) shall not be considered ineligible for approval under that section or misbranded under section 502 on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling related to pediatric use when the omitted indication or other aspect of labeling is protected by patent or exclusivity" (21 U.S.C. § 355(a)(1)).

but made no provisions for an abbreviated, or generic, biologic approval process.

Biologic products with drug-like properties include drug proteins, both those isolated from blood, such as Factor VIII, and those made by biotech processes. Several companies that are preparing to produce generic recombinant medicines as the patents on these products expire may force the FDA to look into new regulations. It is not clear, however, whether the FDA would, or could, model such regulations on the Hatch-Waxman Act by providing innovators with five- and three-year marketing exclusivity *vis a vis* generics, nor whether it will accept applications establishing sameness without safety and effectiveness testing.

C. Patent Term Extension

The patent term extension provisions of Hatch-Waxman were coupled with the "safe harbor" amendments (see IV below) specifically to eliminate the "dual distortions" to the patent term of products required to undergo FDA review.³⁵ The first distortion, which tends to shorten the patent term, arises from the lengthy FDA approval process experienced by a patentee while the term is running. The patent term extension provisions partially alleviate this distortion in certain cases. The second distortion, which tends to lengthen the patent term, arises from the marketing delay experienced by generic manufacturers who could not use the product even to conduct the studies needed to apply for FDA approval until after the product came off patent. The "safe harbor" provisions are intended to remove this distortion by permitting generics to test and experiment with patented products.

1. Patents Eligible for Term Extension

Patents eligible for term extensions are those which claim a product, a method of using a product or a method of manufacturing a product. For these purposes, a "product" is the active ingredient of a new drug,³⁶ antibiotic drug or human biological product (as these terms are defined in the FD&C Act or PHS Act), including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.³⁷ "Product" also includes medical

³⁵ *Eli Lilly v. Medtronic, Inc.*, 496 U.S. 661 (1990).

³⁶ "Drug" means the drug substance (i.e., active ingredient), drug product (i.e., formulation, composition or combinations) and any components used in the manufacture of the drug product. See *U.S. v. Cenex*, 460 U.S. 453 (1983).

³⁷ "Product" also includes a new animal drug or veterinary biological product (as those terms are used in the FD&C Act and the Virus-Serum-

devices, color additives, and food additives subject to regulation under the FD&C Act.

2. Conditions for Term Extension

In order for a patent to be eligible for extension, several statutory conditions must be met:

- o the patent term must not have expired before the term extension application is filed with the USPTO (§ 156(a)(1));
- o the patent must never have been previously extended, not including temporary extensions (§ 156(a)(2)) or extensions brought about by the GATT reforms³⁸;
- o FDA authorization of the drug product must be the first permitted commercial marketing or use of the drug product's active ingredient (§ 156(a)(5)(A)).³⁹ In the case of a patent that claims a method of manufacturing a product which primarily uses recombinant DNA technology in the manufacture of the product, the first commercial marketing is considered to be the first marketing or use of a product manufactured under the process claimed in the patent (§ 156(a)(5)(B)). For animal drugs and certain veterinary biologics, first commercial marketing is based on first

Toxin Act) which is not primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology or other processes involving site specific genetic manipulation techniques, including any salt or ester of the active ingredient as a single entity or in combination with another active ingredient.

³⁸ *Merck v. Kessler*, 903 F. Supp. 964, 36 USPQ2d 1727 (E.D. Va. 1995).

³⁹ See *Pfizer v. Dr. Reddy's* 359 F.3d 1361 in which the court ruled that active ingredient, in effect, means "active 359 F.3d 1361 moiety." But see, *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392, 13 USPQ2d 1628 (Fed. Cir. 1990); *Fisons, plc v. Quigg*, 8 USPQ2d 1491 (D.D.C. 1988), *aff'd* 876 F.2d 99, 10 USPQ2d 1869 (Fed. Cir. 1989).

administration to a food-producing animal (§ 156(b)(5)(C));

- o the extension cannot exceed five years (§ 156(g)(6)) and the remaining patent term plus extension cannot exceed 14 years (§ 156(c)(3));
- o any extension is limited to the product that is covered by FDA's authorization, meaning that patentees are required to justify their term extensions on a claim by claim basis (§ 156(b));
- o only one patent may be extended per regulatory review period (§ 156(c)(4))

3. Computing the Regulatory Review Period

The regulatory review period used to calculate a patent term extension is computed, beginning after the patent has issued, by adding (i) one-half of the time during which the product was in clinical trials (which for drugs and biologics begins with FDA "acceptance" of an IND), to (ii) the entire time during which the product was undergoing FDA review, (which begins with an "initial submission" of the application for product approval), and subtracting (iii) any time during which the applicant failed to act with due diligence (§ 156(c)(1)). As noted, this total cannot exceed five years, and the total time period remaining (following FDA approval) on the patent, plus extension, cannot exceed 14 years.

4. USPTO Procedures

To obtain a term extension, the patentee must file a Petition for Patent Term Extension with the USPTO within 60 days of FDA approval of the NDA or Biologics License Application (BLA). The petition must set forth the patentee's computation of the regulatory review period,

together with a detailed showing of how each claim to be extended covers the approved product or a method of making or using the approved product. § 156(d)(1). Within 60 days of receipt, the petition is sent by the USPTO to the FDA (or USDA if the drug is subject to the Virus-Serum-Toxin Act) for comment and input. Following receipt of the petition, the FDA is required to calculate, within 30 days, the applicable regulatory review period, and publish this calculation in the Federal Register. A 180 day public comment period follows to assess whether or not the applicant acted with due diligence. Subsequently, the FDA affirms or revises its determination of the applicable regulatory review period. The USPTO then determines whether the patent is eligible for extension and whether the petition meets the filing requirements, and issues its order granting or denying the Applicant's request for term extension.

5. Patent Prosecution Strategies

It is often difficult for patent prosecutors to foresee patent term extension issues at time of claim drafting. Only a fraction of potential drug or biologic products ever makes it to clinical trials, and only a small number of these ever receive FDA approval. Moreover, on average, it takes eight to ten years for a new drug or biologic to work its way through the FDA review process. All this may seem to make the idea of implementing a patent term extension strategy early in the patent drafting process hardly worth the effort. Still, for blockbuster drugs, each day of exclusivity can represent millions of dollars in revenue -- rendering any term extension, regardless how small, worth the effort.

a. Eligibility for Extension and Related Discoveries

Consider the situation where two (or more) related chemical entities are discovered simultaneously, which can occur, for instance, with a family of components sharing a core structural formula, or with homologs or isoforms of the same protein. For patent purposes, each different molecule may be considered a new active ingredient for which a separate patent term extension is potentially available. However, if all of the related molecules are claimed in the same patent, the patentee's term extension opportunity is limited to the first active ingredient approved by FDA. Recall that a patent can be extended only once, and that it must be in connection with the first commercial marketing of the active ingredient. A patent prosecution strategy that is designed to maximize the Hatch-Waxman Act benefits can take these factors into account by ensuring that different active ingredients are claimed in separate patents in order to preserve the possibility of extending the patent life for each ingredient.

Several cases illustrate that a patentee should take care in claiming "products" for which patent extension will be sought, particularly where related molecules may be an issue. In *Merck v. Teva*,⁴⁰ a generic drug manufacturer argued that Merck was not entitled to patent term extension for Fosamax® (4-amino-1-hydroxybutane-1,1-biphosphonic acid monosodium salt trihydrate) because Merck's patent claimed the acid, but did not claim the salt that the FDA had approved. The court interpreted the statutory definition of

⁴⁰ 228 F.Supp.2d 480 (D. Del. 2002), *aff'd* 347 F.3d 1367, 68 USPQ2d 1857 (Fed. Cir. 2003).

"product" as including "any salt or ester of the active ingredient" (§ 156(f)) to mean that the claim directed to the acid (the active ingredient) was eligible for the extension. In *Pfizer Inc. v. Dr. Reddy's Laboratories, Ltd., et al.*, eligibility of multiple products incorporating same active moiety and claimed in a single patent was examined.⁴¹ There, a generic manufacturer argued that Pfizer's patent term extension applied only to the approved product, amlodipine besylate, and not to a second product claimed in Pfizer's patent, amlodipine maleate, for which the generic manufacturer had filed a 505(b)(2) application. The Federal Circuit, however, agreed with Pfizer that the term "product" in the statute is not limited to the "approved product", but includes all products containing the "active moiety" of the approved product and, therefore, encompasses both derivatives claimed in the patent. Citing Congress' intentions in enacting the Hatch-Waxman Act and the language of the statute, the court held that the term "product" containing the amlodipine ion was eligible for extension⁴² even if it had not undergone regulatory review⁴³. In an earlier ruling in *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman*,⁴⁴ a patent holder was denied term extension on the grounds that claims to 1-hydroxy-tacrine and a method of treating a patient with 1-hydroxy-tacrine (a metabolite

⁴¹ 359 F.3d 1361 (Fed.Cir.2004).

⁴² Although the Federal Circuit did not expressly overrule *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392, 13 USPQ2d 1628 (Fed. Cir. 1990), there is almost no way to reconcile *Glaxo v. Quigg* with the most recent line of cases. See also *Cardiac Pacemakers v. St. Jude Medical*, 2001 WL 483973 (S.D. Ind.) in which court held each Class III PMA was a separate product for purposes of term extension

⁴³ Judge Rader, citing section 156(a)(4), dissented in both *Merck v. Teva* and *Dr. Reddy's* on the grounds that a patent (or claim) could not properly be extended if the drug that it claimed had not undergone regulatory review.

⁴⁴ 109 F.3d 756, 42 USPQ2d 1220 (Fed. Cir. 1997).

of tacrine hydroxchloride) did not cover the approved product, tacrine hydrochloride.

b. Bundling Claims

A slightly different problem involves the use of separate patents to cover different aspects of a single drug product, for example, one patent which claims the composition and another patent which claims its method of use. Because both patents will presumably correspond to a common FDA regulatory review period, a term extension will be available for only one of these patents. To maximize a patentee's term extension benefits, the compound and method of use claims should be combined, if possible, into a single patent so all claims are eligible for extension.⁴⁵ Likewise, one should consider bundling in any manufacturing process and formulation claims, for term extension benefits to be fully realized.

Such combinations can be problematical, however, if the USPTO imposes a restriction requirement forcing a divisional application, such as where combined claims are "independent and distinct,"⁴⁶ fall under different USPTO classifications, or require the scope of the patent examiner's search to be too broad.⁴⁷ In these situations, the patentee may choose to use the "rejoinder" procedure to rejoin method of making

⁴⁵ § 156(b) limits extensions for product patents to the "use approved for the product," and for method of use patents to uses "claimed by the patent and approved for the product."

⁴⁶ 37 CFR §§ 1.141, 1.142.

⁴⁷ U.S. Dep't Of Commerce, Patent & Trademark Office, Manual of Patent Examining Procedure § 803 (8th ed. 2003).

and/or method of using claims into the same application as the elected composition claims.⁴⁸

Some companies have a policy of canceling and not pursuing method of use claims in favor of composition claims when a restriction is imposed. While the company can save extra filing, prosecution, and maintenance fees by not pursuing the method claims in a divisional application, it is being "pound foolish" should the composition claims ever be invalidated.

While a patent may be extended only once, approval and marketing of a claimed product may not bar extension of the patent for a second product. Class III medical devices subject to premarket approval, for example, are considered different products for patent term extension.⁴⁹

c. Multiple Patents and Joint Ventures

When two or more patents cover the same approved product, the patentee must decide which one to extend. Companies that find themselves in this situation may wish they had adopted a different prosecution strategy at the outset. A composition patent typically is the preferred choice for obtaining an extension, but this may not be the best strategy, particularly when a second (e.g., formulation) patent with a longer remaining term is the key to a product's success.⁵⁰

⁴⁸ U.S. Dep't Of Commerce, Patent & Trademark Office, Manual Of Patent Examining Procedure § 821.04 (8th ed. 2003).

⁴⁹ See *Cardiac Pacemakers v. St. Jude Medical*, 2001 WL 483973 (S.D. Ind.). In *Cardiac*, extensions of medical device patents were upheld where the "approved products" were not the first claimed product to be approved and marketed.

⁵⁰ An example of this situation is where a patented compound is found to be much more effective for its intended use when formulated with a controlled release substance. Here, a patent covering the controlled release substance is the patent blocking generic competition.

Another difficulty arises where the patentee and the drug applicant are different entities with corporate interests that do not necessarily coincide. Such a situation could occur when two participants in a joint venture, each of which licensed its own patents to the venture, disagree over which one to extend. With no prior agreement on the issue and a considerable financial benefit at stake, the companies could be forced to renegotiate their joint venture to avert litigation.

In *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman*,⁵¹ a patentee with no involvement in the regulatory review process for the licensed product sought to extend the term of its patent. The USPTO refused to grant an extension because the patentee did not take an active role in the prosecution of the NDA regulatory approval process, as required by USPTO rules.⁵² The patentee sued the USPTO and although the case was decided on other grounds, in its aftermath many drug patentees began to re-examine and redraft their license agreements to ensure that they included a provision giving them "direct or indirect participation" in any NDA prosecution in order to secure their term extension rights on the underlying patents. Where multiple patentees seek an extension, USPTO rules expressly require the existence of an agency relationship with the NDA holder prior to FDA approval in order to extend the patent.⁵³

⁵¹ 109 F.3d 756, 42 USPQ2d 1220 (Fed. Cir. 1997).

⁵² 60 Fed. Reg. 25,619 (May 12, 1995).

⁵³ See 37 CFR 1.785(c).

d. Special Problems for Orphan Indications

In the case of orphan drug indications, the patent term extension analysis can be particularly challenging because of the social pressures on drug companies to bring such products to market. Although products with orphan drug approvals are given seven years of market protection, patent extension rights will be lost for all non-orphan indications due to the first permitted commercial marketing bar that is triggered by the orphan approval. In some cases, the term extension opportunities may be more valuable than the economic and social advantages the Orphan Drug Act seeks to achieve. The same is true for "fast track" drugs, which, because they treat life threatening conditions for which no market alternatives are available, are given expedited handling by FDA staff. Uses claimed in patents for more common, albeit non-life threatening, indications will not be eligible for term extension once fast-track approval of the active ingredient has been obtained (although a term extension of a claim drawn to the drug composition itself applies to any approved uses regardless when approved).

e. Bootstrapping Claims

In the case of combination products such as drug or biologic delivery devices (e.g., metered dose inhalers, transdermal patches, etc.), dependent device claims can sometimes be "bootstrapped" to drug or biologic claims with favorable results. Under the Hatch-Waxman Act, only Class III medical devices are eligible for patent term extension, yet most delivery mechanisms are Class I or II medical devices, which by themselves are ineligible for patent term extension. When these latter devices are

combined with a new active ingredient, however, they become an integral part of the "approved product," and claims covering them should be fully extendible under the Hatch-Waxman Act.

While claims directed to combinations of known drugs may be patentable, these may not be eligible for term extension. In *Arnold Partnership v. Dudas*,⁵⁴ a patent holder was denied extension of a patent claiming a combination of two previously marketed drugs, ibuprofen and hydrocodone bitartrate. While the "approved product" itself was new, each active ingredient had been previously approved in separate NDAs. The Federal Circuit held that at least one of the active ingredients must be new in order to be eligible under § 156(a)(5)(A).

D. Orange Book Practice, 271(e)(2) Litigation and 271(e)(1) Safe Harbor

1. Orange Book Listing Practice

Approved drug products (though not biologics) are required to be listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the "Orange Book."⁵⁵ When an NDA is filed, the applicant is

⁵⁴ 362 F.3d 1338 (Fed.Cir.(VA))

⁵⁵ The Orange Book contains a list of all patents submitted by NDA holders to the FDA under the requirements of 21 U.S.C. § 355(b)(1)(F). On August 18, 2003, the FDA promulgated new rules regarding Orange Book listings. The new rules provide guidance on what types of patents should be submitted for listing, and change nature of the declarations that must be made when submitting patents. The final rule identifies the types of patents to be submitted for listing in the Orange Book by NDA holders to be patents on: the drug substance (active ingredient) including polymorphs (e.g., different crystalline structures or waters of hydration); the drug product (formulation and composition); and methods of use. Specifically prohibited from being listed are process patents and patents claiming packaging, metabolites, or intermediates. For patents that contain product by process claims, the patent will be

required to submit to FDA a list of all patents that claim the drug or method of using the drug with respect to which a claim of infringement could reasonably be asserted against one who is not licensed, but who is engaged in the manufacture, sale, or use of the drug.⁵⁶ FDA publishes these patent listings, along with the patents' expiration dates, in the Orange Book to give notice to future generic drug applicants that such patents may block the introduction of generic products.

When a generic drug application is submitted to the FDA, the generic drug applicant is required to certify to the FDA, for each patent (if any) listed in the Orange Book, one or more of the following;⁵⁷

- (1) that such patent information has not been filed;
- (2) that such patent has expired;
- (3) the date on which the patent will expire; or
- (4) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug for which the application is submitted.

listed and should be submitted only if the patent claims the drug product that is the subject of the NDA, and if the product claimed in the patent is novel.

⁵⁶ 21 U.S.C. § 355(b)(1)(F); 21 CFR §314.53. Note that this is not limited to patents held by the NDA holder. Thus, if an NDA holder is aware of patents held by others that meet the statutory standard, these patents should also be listed by the NDA holder. This situation has always been the case, but because of the phrasing of the old declaration, NDA holders did not submit patents they did not own because they were required at the time to make an admission that the submitted patents covered their product. The new declaration does not require this admission, but does include language that would make an NDA holder subject to penalty of perjury if it does not list patents of which it is aware and that could meet the statutory standard. For this reason, where there is a patent that is questionable with regard to the statutory standard, an opinion of counsel should be sought. Note that there is no other current penalty for failing to properly list patents. See discussion about the ministerial nature of the FDA's listing requirements *infra*.

⁵⁷ 21 CFR § 314.94(a)(12)(i)(A).

In the case of a certification as to the fourth item listed above (i.e., a paragraph IV certification), the applicant also must notify the patentee *and* the holder of the NDA for the approved drug claimed by the patent why the patent is invalid or will not be infringed by the generic product.⁵⁸

The patentee and

NDA holder then have 45 days to review the paragraph IV notice,⁵⁹

during which time FDA will take no action on the generic filing.

If the patentee or NDA holder files an infringement suit within the 45-day period, FDA approval of the generic application is suspended for up to thirty months unless the matter is disposed of sooner by a court.⁶⁰ A failure to bring an action within the 45-day grace period permits FDA to proceed with its review and approval of the generic drug application.

Orange Book listing makes every patent a potential source of delay for generic competition. As both innovative

⁵⁸ 21 U.S.C. § 355(j)(2)(A)(vii); 21 CFR § 314.95(a). The timing of this notification is different when submitting an ANDA versus when submitting an ANDA amendment. The FDA maintains that for an original ANDA filing, the statute says that the applicant will give the notice required, where as when submitting an amendment to an ANDA, the statute says required notice shall be given when the amended application is submitted. See "The Pink Sheet", *Ivax Glucophage XR Generic Exclusivity Rights Questioned by Judge*, F-D-C-Reports, November 17, 2003 at 12.

⁵⁹ 21 U.S.C. § 355(j)(4)(B)(iii); 21 CFR § 314.95(f). In accordance with FDA and USPTO practice, statutory notification can be accomplished by sending to any one of what may be several addresses on file at each agency. If sent to a "listed address," an NDA holder's claim that notice was sent to the wrong address is not likely to prevail once the 45-day period has run. Under the August 18, 2003 final rules promulgated by the FDA, only one 30-month stay is allowed per ANDA regardless of the number of patents included in the Orange Book. This rule changes the original practice of allowing a 30-month stay for each newly listed patent.

⁶⁰ 21 U.S.C. § 355(j); 21 CFR § 314.95(f).

and generic drug manufacturers have learned, the Orange Book can be a strategic weapon, providing an advance warning mechanism to the marketing department for possible tactical response, and giving the patentee/NDA holder the equivalent of automatic injunctive relief for even marginal infringement claims. The FDA's long-standing policy of avoiding patent disputes,⁶¹ evidenced by its willingness to list virtually any patent submitted by NDA applicant (or holder)⁶² and its reluctance to delist any patents that have been challenged encouraged NDA holders to "evergreen" their drug patents.⁶³ The Federal Trade Commission has expressed

⁶¹ See 59 Fed. Reg. 50,338, 50,345 (Oct. 3, 1994). The D.C. Circuit's decision in *Am. Bioscience v. Thompson*, 269 F.3d 1077 (D.C. Cir. 2001) will likely make the FDA even more conservative about disputing patents which the NDA holder claims are required to be listed in the Orange Book.

⁶² The FDA views its listing of patents as purely a ministerial requirement of the statute and thus is unwilling to undertake any kind of review of the submissions by the NDA holders or the challenges by the generic companies. This view has been upheld by some courts and denied review by the Supreme Court. See *Apotex, Inc. v. Thompson*, 347 F.3d 1335 (Fed. Cir. 2003); *aaPharma v. Thompson*, 296 F.3d 227 (4th Cir. 2002) *cert. denied* 123 S. Ct. 1582 (2003). The result is that there is little that can be done to require correction of information in the Orange Book (either delist patents or add patents). New FDA listing requirements and a new declaration requirement imposing a perjury penalty are intended to cast down on Orange Book evergreening. See 21 CFR §314.50

⁶³ Attempts by generic applicants to end run the Paragraph IV notice and 30 month stay requirements and challenge Orange Book listing directly in court have proved unsuccessful. In *Mylan v. Thompson*, 268 F.3d 1330 (Fed. Cir. 2001), the Federal Circuit found no private rights of action for delistings under the patent laws, the Federal Food, Drug and Cosmetic Act or the Hatch-Waxman Amendments. However, such actions may be brought directly against FDA under the Administrative Procedures Act (APA) based upon the grounds that the agency's action is arbitrary or capricious or not in accordance with law. *Andrx Pharmaceuticals v. Biovail* at 17. *Purepac Pharma. Co. v. Thompson*, No. 02-1657 (D.D.C. January 6, 2003). There is also no private right of action for an NDA holder to challenge the information provided in the paragraph IV certification as being inadequate. *LePage's Inc. v. Minnesota Mining and Manufacturing Co.*, 289 F.3d 775 (2002) *rehearing denied, rehearing en banc denied*, 295 F.3d 1274 (2002).

its concerns that overly aggressive use of the Orange Book may adversely affect entry of new generic drug products into the market, and thus unfairly cushion pioneer manufacturers from generic competition.⁶⁴

2. 35 U.S.C. § 271(e) (2) Litigation

Section 271(e) (2) defines as an act of infringement the submission of an ANDA application to obtain approval for the "commercial manufacture, use, or sale of a drug" claimed in a patent before the expiration of that patent.⁶⁵ The Supreme Court has referred to this as a "highly artificial" act of infringement.⁶⁶ When the ANDA applicant also submits a paragraph IV certification that the patent is either invalid or not infringed, the NDA holder is given forty-five days to sue and thereby claim entitlement to a thirty-month stay of ANDA approval.

Litigation in this area is frequent and hotly contested by parties with large amounts of money at stake. Under the FDA's new Hatch-Waxman regulations, effective August 18, 2003, only one thirty-month stay is available per generic drug application.⁶⁷ On December 8, 2003, Congress passed legislation also limiting NDA holders to one thirty-month

⁶⁴ "FTC Probes Drug Patent Listings," Reuters, Jan. 12, 2002. (Discussing pending non-public investigations of GlaxoSmithKline, Bristol-Meyers Squibb and Biovail for inappropriately listing patents in the Orange Book.)

⁶⁵ ANDA submissions under sections 505(j), 505(b) (2), and 512 (for certain drug or veterinary biological products) all qualify under § 271(e) (2).

⁶⁶ *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990).

⁶⁷ Applications for FDA Approval To Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed; Final Rule, 68 Fed. Reg. 36,676 (June 18, 2003); *Apotex, Inc. v. Thompson*, 347 F.3d 1335 (Fed. Cir. 2003) (noting that the regulations are only prospective in effect).

stay, and only for patents submitted prior to an ANDA applicant's submission.⁶⁸ The Medicare Prescription Drug, Improvement and Modernization Act of 2003 also permits approval of an ANDA before expiration of the 30-month stay if a "district" court (rather than a "court" generally, as before, which had been interpreted to include the Federal Circuit) finds the patent invalid or not infringed. In addition, the new legislation amends the provisions in § 355(j)(5)(B)(iii)(III) relating to the availability of a declaratory judgment action upon expiration of the forty-five days after the paragraph IV certification has been filed. In order to bring such an action for noninfringement (but not for invalidity), an ANDA applicant must submit, along with its notice of a paragraph IV certification, a document providing a right of confidential access to the ANDA applicant's application for the purposes of determining whether a lawsuit should be brought.

The new legislation also addresses issues raised by *Mylan*, which held that the FDCA provides no private right of action for delisting.⁶⁹ If sued by a patent owner, the ANDA applicant may assert a counterclaim seeking an order requiring the NDA holder to correct or delete the patent information. That provision is specifically limited to counterclaims.⁷⁰

⁶⁸ Medicare Prescription Drug, Improvement and Modernization Act of 2003, P.L. 108-173 (enacted December 8, 2003). The FDA has yet to issue regulations to implement the new legislation. The text of the legislation is available at <http://thomas.loc.gov/cgi-bin/bdquery/z?d108:HR00001:|TOM:/bss/d108query.html>. A helpful general discussion of the legislation, as proposed, is available at <http://www.fda.gov/ola/2003/genericdrugs0801.html>.

⁶⁹ *Mylan v. Thompson*, 268 F.3d 1330 (Fed. Cir. 2001).

⁷⁰ In *Mylan*, the original cause of action, rather than a counterclaim, concerned delisting. Thus, while the new legislation does not overrule *Mylan*, it does make clear that district courts can adjudicate

Under the new legislation, the 180-day exclusivity period for the first ANDA applicant is triggered only by commercial marketing, whereas it has previously been triggered by either commercial marketing or a court determination of noninfringement, invalidity, or unenforceability, whichever date was first. New forfeiture provisions apply to ANDA applicants who fail to market the drug by certain deadlines, however.

One frequent area of contention that has seemingly been put to rest is whether a patentee can sue for infringement under § 271(e) (2) for inducing infringement of a patent listed in the Orange Book and claiming only "off-label" uses of the drug. In *Warner-Lambert*, the Federal Circuit held that the patentee could not maintain such a suit.⁷¹ The Court reasoned that because an ANDA applicant may not seek approval for an off-label use of a drug under 21 U.S.C. § 355(j) (2) (A) (i), "it necessarily follows" that 35 U.S.C. §271(e) (2) (A) does not apply to a use patent claiming only such a use. Shortly thereafter, a different panel of the Federal Circuit disagreed with that conclusion, but nevertheless felt bound by precedent to adhere to *Warner-Lambert*⁷². The latter panel did clarify, however, that § 271(e) (2) applies to inducement of infringement, not just direct infringement.

3. Safe Harbor - 35 U.S.C. § 271(e) (1)

A matter of concern, particularly within the biotechnology industry, is whether the "safe harbor"

counterclaims for delisting among private parties without involving the FDA.

⁷¹ *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003).

⁷² *Allergan, Inc. v. Alcon Research, Ltd.*, 324 F.3d 1322 (Fed. Cir. 2003).

provision of 35 U.S.C. § 271(e) (1) may exempt from infringement a variety of activities in addition to those that Congress intended to protect. Section 271(e) (1) states, in pertinent part: "It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention ... solely for uses reasonably related to the development and submission of information [to the FDA]."

Congress enacted § 271(e) (1) to allow generic drug manufacturers to test their products against patented pioneer drugs so that the generic version could be marketed as soon after expiration of the pioneer drug patent as possible. Despite this rather narrow legislative intent, the plain language of § 271(e) (1) is broad, and the majority of cases to date indicate that courts will interpret § 271(e) (1) broadly and literally.

For example, courts have extended the safe harbor to cover activities such as using clinical trial data to solicit investment capital to fund additional clinical trials; displaying products at trade shows; conducting studies of consumer response; selling products to international distributors to sell to foreign clinical investigators; demonstrations at conferences; disseminating data to journalists, analysts, and investors; publishing articles relating to trial data; selling devices to patients for clinical trials; obtaining more data than are actually submitted to the FDA; making arrangements for overseas manufacture and importation of the product; using data to obtain importation approval from foreign governments for purposes of conducting clinical trials to support an application to the FDA;

obtaining foreign patent rights on the product; and manufacturing sufficient quantities to create an inventory.⁷³

The inclusion of these activities within the safe harbor exemption was spurred by a relaxed interpretation by courts of the scope of § 271(e)(1). For example, the standard enunciated by the Northern District of California, and followed by several other courts, seems to encourage an attenuated construction of the scope of § 271(e)(1):

[W]e should ask: would it have been reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the "use" in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the processes by which the FDA would decide whether to approve the product? If the answer is yes, it should not matter that other reasonable persons might have concluded that FDA approval could be secured even without the information in question.⁷⁴

The safe harbor, however, does not extend to any exploratory research that could rationally form a basis for future FDA clinical tests.⁷⁵ Otherwise, many of the "crown jewels" of the biotechnology industry, such as a patented drug screening method to identify new drugs, or a "research tool" used to screen drug candidates, would be denied significant protection from infringing use by

⁷³ A good overview of the "safe harbor" cases can be found in *Can the Safe Harbor of 35 U.S.C. §271(e)(1) Shelter Pioneer Drug Manufacturers*, C. Brinckerhoff, Food and Drug Law Journal, Vol. 53, No. 4 (1998).

⁷⁴ *Intermedics v. Ventritex Inc.*, 20 USPQ2d 1422, 1430 (N.D. Cal. 1991).

⁷⁵ *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003) ("§ 271(e)(1) simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process.").

pharmaceutical companies actively engaged in drug development using such tools.

The few court decisions taking a narrow view of § 271(e) (1) have excluded the following activities from the safe harbor: general biomedical research to identify potential drugs of interest;⁷⁶ performance of an agreement to develop a product on a commercial scale;⁷⁷ substantial stockpiling in preparation to market a drug when FDA approval is imminent;⁷⁸ preparation of a foreign patent application;⁷⁹ contemplated marketing of the product outside the U.S.;⁸⁰ shipment of products abroad to regulatory agencies;⁸¹ and shipments of product to a foreign investigator.⁸² No hard-and-fast rules govern whether any given activity will be within the safe harbor, and the cases tend to be very fact-specific as to whether the asserted activity was actually undertaken for purposes of obtaining regulatory approval.

While the majority of the § 271(e) (1) decisions interpret the safe harbor broadly, recent case law from the Federal Circuit has taken a narrower view, and in fact emphasized that Congress intended the § 271(e) (1) exemption "to have only a de minimis impact on the patentee's right

⁷⁶ *Id.*

⁷⁷ *Scripps Clinic and Research Found. v. Genentech, Inc.*, 666 F. Supp. 1379 (N.D. Cal. 1987).

⁷⁸ *Biogen, Inc. v. Schering AG*, 954 F. Supp. 391 (D. Mass. 1996).

⁷⁹ *Scripps*, 666 F. Supp. 1379.

⁸⁰ *Id.*

⁸¹ *NeoRx Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 207 (D.N.J. 1994).

⁸² *Id.*

to exclude.”⁸³ In narrowing the safe harbor, *Integra v. Merck* held that the safe harbor applies to activities related to acquiring FDA approval of drugs “already on the market,” which raises the question of what preclinical activities fall within § 271(e)(1). Post-*Integra*, a reasonable test for the safe harbor inquires whether the activity focuses on the good faith development of a candidate drug, rather than the discovery of a new drug, and whether the activity is likely to generate information used by the FDA in its “safety and effectiveness” approval processes. The *Integra* current pro-patent pronouncement will undoubtedly influence future district court decisions concerning the scope of the safe harbor.

⁸³ *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003).