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The Hatch-Waxman (Im)Balancing Act

Introduction

The Food and Drug Administration (FDA) has been described as "the most important regulatory agency in the world."[1] It has proven remarkably capable at protecting the American public from unsafe drug products, but when it came to promoting competition in the pharmaceutical industry, encouraging the widespread dissemination of affordable versions of safe and effective drug products, it was constrained by external laws and internal procedures, and its resources were limited. The Drug Price Competition and Patent Term Restoration Act,[2] also known as the Hatch-Waxman Act, was passed by Congress in 1984 to accomplish this laudable goal, establishing a delicate balance between the competing interests of brand name drug companies and generic drug companies,[3] with the public as the ultimate beneficiary, reaping the reward of an affordable and diverse drug supply. To promote innovation by pharmaceutical companies, the Act was supposed to partially extend the brand name drug manufacturers' patent monopoly through the period lost to the FDA approval process. To promote early and efficient access to generic drugs, the Act was supposed to allow generic drug companies to partially circumvent patent restrictions and accelerate FDA approval so that they would be able to bring their products to market as soon as the brand name drug companies' patents expired or were found invalid or not infringed. Somewhere along the line, however, these purposes were derailed. Certain loopholes within the Act, unfortunately, create perverse incentives for brand

[1] Philip J. Hilts, Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation xiv (Random House 2003).

[2] Pub. L. No. 98-417.

[3] For the purposes of this paper, brand name drug companies refers to companies that have FDA approval to market drugs that have not received approval previously, and hold patents on these drugs, usually pioneering drug companies with significant research and development or corporate acquisition programs. Generic drug companies refers to companies that have or are seeking FDA approval to market generic versions of drugs that have received approval previously, and typically do not hold patents on these drugs.

name and generic drug companies to enter into collusive agreements, with possible antitrust implications, to the detriment of the public. Recent legislative reform efforts have focused on closing these loopholes, but have not given significant consideration to the broader implications of the Act. The equilibrium point established in 1984 has shifted significantly, with the recent introduction into the field of a new player in the drug development process, the research tools industry. Research tool, brand name drug and generic drug developers each occupy a particular niche in the system, but due to the interpretation of certain Hatch-Waxman provisions, their roles in the statutory framework that governs the system have been conflated in a manner that was probably not anticipated by the drafters of the Act, artificially pitting them against one another in the legal arena, while they operate synergistically in the industrial arena.

In Chapter I, this paper will navigate through the maze of the Hatch-Waxman Act's statutory amendments, describing the Abbreviated New Drug Application (ANDA) and the Patent Term Extension procedures created by the Act, the functions that Congress probably intended these features of the Act to serve, and how successful the Act has been at meeting these goals.

In Chapter II, this paper will focus on those provisions of the Act that have had the unintended consequence of prolonging brand name drug companies' market exclusivity, and incentivizing collusion between brand name and generic drug companies, to the detriment of the public. Special emphasis will be placed on Congress' attempts at legislative reforms that involve either closing these loopholes or increasing the Federal Trade Commission's (FTC) and Justice Department's enforcement power, in response to recent criticisms by the FTC.

In Chapter III, this paper will follow the gradual expansion in scope of the *Bolar* amendment,[4] one of the

[4] 35 U.S.C. § 271(e)(1), so named because it effectively overruled *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984), in which the Federal Circuit held that the manufacture, use, or sale of a patented invention during the term of the patent constituted an act of infringement, even if it was for the sole purpose of conducting tests and developing information necessary to apply for regulatory approval.

provisions of the Act, through progressive iterations in judicial precedent, as it evolved from its originally intended role, as a balancing factor between the interests of brand name and generic drug companies, to its current role, as a potential threat to the legitimacy of the research tools industry. Other threats that certain patent law doctrines pose to this fledgling industry will also be discussed, and possible solutions, reform efforts to preserve the integrity of this industry, will also be suggested.

Chapter I: Navigating the Hatch-Waxman Act

As it stood prior to 1984, the term of a patent for a drug, or a process for manufacturing a drug, or a therapeutic use for a drug, was subject to two distortions.[5] The first distortion took place at the beginning of the patent term, a result of the FDA approval process. With most patented inventions, one could bring a product to market immediately after the patent issued, or even earlier. However, for new drug products, one had to obtain permission from the FDA before going to market, which necessitated conducting the requisite clinical trials, submitting the requisite data, and waiting for the requisite regulatory review period. This implied a long period of time when the patented product was awaiting entry into the market, when the patentees, or assignees thereof, were unable to profit from their invention's market exclusivity, a period of time that ate into the patent term, limiting the economic advantage the patentees could derive from their temporary monopoly.

The other distortion occurred at the end of the patent term. Normally when a patent on an invention expires, the monopoly ends, allowing competitors to immediately enter the market, to offer consumers alternative products, to dramatically bring down the price. This did not occur in the drug industry. Before generic drug companies could offer competing drug products to consumers, they had to subject these products to intense FDA scrutiny. Because they could not manufacture and conduct studies on competing products during the term of the patent without infringing,[6] they had to wait until the patent expired before they could initiate the FDA regulatory review procedure. This meant that even after the drug patents had expired, there was a period of time when competing products, trapped in FDA review, could not enter the market, artificially extending the period of exclusivity conferred by the patent.

[5]Eli Lilly v. Medtronic, 496 U.S. 661, 669 (1990).
[6]Roche Products, Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858 (Fed. Cir. 1984).

One might wonder what the problem was. The two distortions of patent term seemed to cancel each other out, with the brand name drug companies recovering the period of exclusivity they lost in the FDA review process in the form of a period of exclusivity gained while their generic competitors were subject to review. It was a delicately balanced, but stable, equilibrium, at least for the brand name drug companies. The problems in the system affected the development of generics. Generics provided competing products, they kept drug prices low, made them affordable and accessible. Although drug patents were useful in fostering innovation, in allowing brand name drug companies to leverage their market exclusivity to recover their investment in research and development, as a matter of public policy it was to society's benefit to introduce generic versions of as many drugs as possible as quickly as possible, to maximize consumer savings. Unfortunately, in the pre-1984 system, there was little incentive for the generics to do so. If they attempted to prematurely research a competing product, challenging the validity of a patent, they would be subject to an infringement suit, an expense they could ill afford when the potential return on their investment was so far in the future. And once they finally brought a product to market, price competition would have dramatically lowered their profit margins relative to those enjoyed by brand name drug companies, despite the generics' having undergone a significant outlay of expenditures on expensive human clinical trials, almost comparable to the brand name drug companies' clinical studies and research and development expenses, before being able to bring their product to market. Only the most truly altruistic or delusional would have been able to remain in the industry, which is why, prior to 1984, only 36% of top-selling brand name drugs had a competing generic product on the market,[7] and generic drugs accounted for only 19% of prescription drug volume.[8]

[7] Congressional Budget Office, How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry xii (1998) [hereinafter CBO Study].

[8] *Id.* at 27.

The Hatch-Waxman Act

In response to these perceived problems, Congress passed the Hatch-Waxman Act, in 1984. The Act contained two titles. Title I, Abbreviated New Drug Applications, amended the Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. § 355, and part of Title II, Patent Extension, amended the U.S. Patent Code, 35 U.S.C. § 271(e), to address the distortion of patent term caused by the extension of market exclusivity due to the delayed market entry of competing generics as a result of FDA review.[9] The remainder of Title II, Patent Extension, amended the U.S. Patent Code, 35 U.S.C. § 156, to address the distortion of patent term caused by the loss of assertable market exclusivity time to FDA review procedure.[10]

Amendments to accelerate approval of generic drugs

Title I introduced a procedure for filing an ANDA, an abbreviated new drug application, which would accelerate the review process for generic versions of drugs that had previously been approved. It also gave the FDA instructions on how to respond to filings of either ANDAs or NDAs (new drug applications, which have additional data submission requirements relative to ANDAs) for new versions of drugs that it had previously approved.

Under Section 101 of the Act, an ANDA can be filed for a new drug[11] if the applicant can show that the new drug has the same active ingredients,[12] route of administration, dosage form and strength[13] as a previously

[9] H.R. Rep. No. 98-857(I), at 16-17 (1984).
[10] *Id.* at 17-18.
[11] 21 U.S.C. § 355(j)(1).
[12] *Id.* at § 355(j)(2)(A)(ii)(I-II).
[13] *Id.* at § 355(j)(2)(A)(iii).

approved[14] drug, requiring only a demonstration of bioequivalence,[15] thus allowing the applicant to circumvent the more tedious aspects of the FDA application process by "piggybacking" on its predecessor's clinical research. This is a very efficient outcome, as obviates the need for wasteful[16] and ethically questionable research.[17] The ANDA is subject to automatic approval[18] within 180 days of submission[19] unless it fails to meet one of these criteria.[20] In the event of a disapproval, the applicant will have thirty days to request an expedited rehearing, which will commence within ninety days of the end of this thirty day period, before the Secretary of Health and Human Services, who will have ninety days after the termination of the hearing to render a decision.[21] All in all, the FDA review procedure had been significantly streamlined.

Anyone filing an ANDA,[22] or a NDA for a previously approved drug,[23] has to make a certification,[24] that the patent which claims the previously approved drug either: (1) has not been listed with the FDA (a paragraph I certification); (2) has expired (a paragraph II certification); (3) will expire (a paragraph III certification); or (4) is invalid or will not be infringed by the generic drug's manufacture, use or sale (a paragraph IV certification). This certification will determine the date by which approval will be made effective. For a

[14] *Id.* at § 355(j)(2)(A)(i).

[15] *Id.* at § 355(j)(2)(A)(iv). A bioequivalent drug, as defined in 21 U.S.C. § 355(j)(8) is one for which:

"(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."

[16] Insofar as it is duplicative and expensive.

[17] If a drug has already been established as the standard of care for a condition, reproducing a clinical trial that might necessitate treating a patient subgroup with a placebo (i.e. below the standard of care) has troubling ethical implications.

[18] 21 U.S.C. § 355(j)(4).

[19] *Id.* at § 355(j)(5)(A).

[20] *Id.* at § 355(j)(4)(A-K).

[21] *Id.* at § 355(j)(5)(C).

[22] Pursuant to section 101 of the Act.

[23] Pursuant to section 103 of the Act.

[24] Under either 21 U.S.C. § 355(j)(2)(A)(vii) for an ANDA, or 21 U.S.C. § 355(b)(2)(A) for a NDA on a previously approved product.

paragraph I or II certified application, approval will be made effective immediately.[25] For a paragraph III certified application, approval will be made effective upon expiration[26] of the patent.[27] A paragraph IV certification complicates things.

A paragraph IV applicant must give notice[28] to each owner of the patent[29] and each holder of the approved application[30] that an ANDA or NDA has been filed, and include in this notice "a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed."[31] The patent holder then has forty-five days from receipt of this notice, during which time the possibility of a declaratory judgment action[32] with respect to the patent is suspended, to bring an action for infringement.[33] If an action is not brought, approval will be made effective immediately.[34] However, if an infringement action is brought, approval will be made effective at the end of the thirty month period beginning with receipt of this notice (which can be varied at the court's discretion to reflect the cooperativeness of the parties)[35] unless, before this period expires, the court finds the patents invalid or not infringed (in which case approval is made effective at the time of this determination),[36] or valid and infringed (in which case approval is made effective at the expiration of the patent),[37] or the court grants a preliminary injunction to prevent the applicant's commercial manufacture or sale of the drug (in which case approval is made effective at the time of this decision).[38] If the thirty month period expires prior to resolution of the infringement action, the

[25] *Id.* at § 355(j)(5)(B)(i) for an ANDA; *Id.* at § 355(c)(3)(A) for a NDA.
[26] *Id.* at § 271(e)(4)(A).
[27] *Id.* at § 355(j)(5)(B)(ii) for an ANDA; *Id.* at § 355(c)(3)(B) for a NDA.
[28] *Id.* at § 355(j)(2)(B)(i) for an ANDA; *Id.* at § 355(b)(3)(A) for a NDA.
[29] *Id.* at § 355(j)(2)(B)(i)(I) for an ANDA; *Id.* at § 355(b)(3)(A)(i) for a NDA.
[30] *Id.* at § 355(j)(2)(B)(i)(II) for an ANDA; *Id.* at § 355(b)(3)(A)(ii) for a NDA.
[31] *Id.* at § 355(j)(2)(B)(ii) for an ANDA; *Id.* at § 355(b)(3)(B) for a NDA.
[32] Which, if brought, must be brought in the defendant's (i.e. the patentee's) jurisdiction. *Id.* at § 355(j)(5)(B)(iii) for an ANDA; *Id.* at § 355(c)(3)(C) for a NDA.
[33] *Id.* at § 355(j)(5)(B)(iii) for an ANDA; *Id.* at § 355(c)(3)(C) for a NDA.
[34] *Id.* at § 355(j)(5)(B)(iii) for an ANDA; *Id.* at § 355(c)(3)(C) for a NDA.
[35] *Id.* at § 355(j)(5)(B)(iii) for an ANDA; *Id.* at § 355(c)(3)(C) for a NDA.
[36] *Id.* at § 355(j)(5)(B)(iii)(I) for an ANDA; *Id.* at § 355(c)(3)(C)(i) for a NDA.
[37] *Id.* at § 355(j)(5)(B)(iii)(II) for an ANDA; *Id.* at § 355(c)(3)(C)(ii) for a NDA.
[38] *Id.* at § 355(j)(5)(B)(iii)(III) for an ANDA; *Id.* at § 355(c)(3)(C)(iii) for a NDA.

generic is left with a difficult choice to make, since it has been granted the ability to enter the market, but would probably have to disgorge its profits, or, even worse, compensate for the loss of the brand name drug company's profits, should the patent ultimately be found valid and infringed.

The incentive for an ANDA filer to challenge potentially weak or invalid drug patents, to brave the murky waters of a paragraph IV certification and an infringement action, is a 180 day period of exclusivity,[39] triggered by either the first commercial marketing of the drug[40] or by a court decision holding the relevant patent invalid or not infringed,[41] awarded to the first company to file an ANDA with a paragraph IV certification, during which no other ANDA approvals on the product can be made effective. This strategic provision was designed to motivate generic drug companies to challenge patents early and often, although its potential use as a bargaining chip to leverage favorable terms in collusive agreements will be discussed further in Chapter II.

There are, however, limits on just how early a brand name drug's exclusivity can be challenged. An ANDA, or a NDA for a previously approved drug, cannot be filed within five years of the approval date of the first application for the drug, unless the new drug ANDA or NDA contains a paragraph IV certification, in which case it can be filed within four years of the approval of its predecessor, but if the thirty month suspension of approval is triggered by the initiation of an infringement action in the fourth year, the suspension of approval must be extended (by up to twelve months) such that it terminates seven and a half years after the initial approval.[42]

In order for the ANDA and NDA filers to know which patents to challenge, the Act introduced the Orange

[39] *Id.* at § 355(j)(5)(B)(iv).
[40] *Id.* at § 355(j)(5)(B)(iv)(I).
[41] *Id.* at § 355(j)(5)(B)(iv)(II).
[42] *Id.* at § 355(j)(5)(D)(ii) for an ANDA; *Id.* at § 355(c)(3)(D)(ii) for a NDA.

Book provisions.[43] NDA applicants have to disclose in their application, for eventual listing in the FDA's Orange Book, the patent number and expiration date of any patents that claim the drug, or its method of use, that could be asserted against potential infringers who engage in the manufacture, use or sale of the drug.[44] If a relevant patent has not issued by the time the application is approved, the Orange Book listing must be updated within thirty days of the issuance of said patent.[45] Failure to list a relevant patent is considered grounds for a refusal of an application,[46] or withdrawal of approval.[47]

Of course, the careful timing of the ANDA procedures would be irrelevant if the brand name drug companies could assert their patent rights against generics for conducting even the most preliminary research. For the legal framework of the Act to operate, the act of infringement has to occur at a specific point in time. To this end, Title 2 of the Act, section 202, introduced the *Bolar* amendment to the Patent Code as a complement to the ANDA procedure. It insulates research activities performed in anticipation of an FDA filing from an assertion of infringement,[48] an exception that cannot be curtailed by injunctive relief.[49] However, the actual filing of the ANDA, or NDA for a previously approved drug, is a constructive act of infringement,[50] in Justice Scalia's words, "a new (and somewhat artificial) act of infringement for a very limited and technical purpose that relates only to certain drug applications,"[51] to give the brand name drug companies a legal basis for their infringement action, although it is unclear what the scope of this infringing act is in litigation. Does it encompass those infringing activities that were conducted during the research process, or does it anticipate those infringing acts that will occur should the product enter the market? The limitation of damages and

[43] Title I, section 102.
[44] 21 U.S.C. § 355(b)(1).
[45] *Id.* at § 355(c)(2).
[46] *Id.* at § 355(d)(6).
[47] *Id.* at § 355(e)(4).
[48] 35 U.S.C. § 271(e)(1).
[49] *Id.* at § 271(e)(3).
[50] *Id.* at § 271(e)(2).
[51] Eli Lilly v. Medtronic, 496 U.S. 661, 676 (1990).

other monetary relief to instances where there has been commercial manufacture, use and sale of the drug[52] suggests the latter. The *Bolar* amendment seems innocuous, but it disguises a potential for abuse that will be discussed in further detail in Chapter III.

Amendments to recoup patent term lost to FDA review

Title II introduced a procedure for extending the term of patents on products, or methods of use or manufacture thereof, that are subject to a regulatory review period before the first[53] commercial marketing or use.[54] An application for an extension of patent term can only be submitted within sixty days of receiving regulatory approval,[55] before the term of the patent has expired,[56] by the owner of record.[57] Such an application can only be submitted once per patent,[58] and a particular regulatory review period delay can only be applied to one patent,[59] creating a one to one patent to regulatory review period correlation that limits to a considerable extent the potential for abuse of this provision, forcing brand name drug companies to carefully select a patent to apply the term extension to, although the limitations of the Act are demonstrated in situations where the FDA approves a combination therapy containing multiple independently patented products, or when a single patent covers multiple products that require independent review periods.[60]

[52] 35 U.S.C. § 271(e)(4)(c).
[53] *Id.* at § 156(a)(5)(A).
[54] *Id.* at § 156(a)(4).
[55] *Id.* at § 156(d)(1).
[56] *Id.* at § 156(a)(1).
[57] *Id.* at § 156(a)(3).
[58] *Id.* at § 156(a)(2).
[59] *Id.* at § 156(c)(4).
[60] See proposed amendment by Senators DeConcini and Hatch. 134 Cong. Rec. S1164 (daily ed. Aug. 11, 1988) (statement of Sen. DeConcini). The specificity of this correlation could be threatened by recently proposed legislation to reward small biotech firms for the development of bioterrorism countermeasures with the extension of term of any patent in their portfolio. *Biological and Chemical Weapons Act*, 2001 S. 1764 (2001).

The extension of patent term is not necessarily applied across the entire breadth of the claims of the patent, but is limited in scope to the subset of claimed subject matter that encompasses the uses or products that have actually been approved through the regulatory review procedure applicable under the relevant provisions of law.[61]

The term of the patent extension[62] is equal to the sum of the period of time running from when the application was submitted for approval to the time of approval,[63] and half[64] of the clinical trial period, the period of time running from when the drug product or medical device was cleared for investigational use, or when clinical investigation was initiated should such clearance not be required,[65] to the time of submission. However, if the applicant was found[66] not to have acted with due diligence[67] for any period of time during the regulatory review process, they would be not be entitled to count that period towards the patent term extension. In no circumstances, however, is the patent term extension to exceed five years,[68] or the sum of the original term remaining on the patent after regulatory approval and the patent term extension to exceed fourteen years,[69] and the patent term extension should be reduced accordingly to comply.[70] Some critics[71] claim that these changes in patent term are inconsistent with U.S. obligations under the agreement on Trade-

[61] 35 U.S.C. § 156(b).
[62] *Id.* at § 156(c).
[63] *Id.* at § 156(g)(1-5)(B)(ii).
[64] *Id.* at § 156(c)(2).
[65] *Id.* at § 156(g)(1-5)(B)(i).
[66] Under 35 U.S.C. § 156(d)(2)(b), if a petition is submitted to the Secretary of Health and Human Services within 180 days of the Secretary's determination of the scope and duration of the patent term extension, the Secretary shall determine if the applicant acted with due diligence over the course of the regulatory review period within ninety days of receipt of the petition, and will publish that determination, and the factual and legal basis for it, in the Federal Register.
[67] 35 U.S.C. § 156(c)(1). Due diligence is defined in 35 U.S.C. § 156(d)(3) as "that degree of attention, continuous directed effort, and timeliness as may reasonably be expected from, and are ordinarily exercised by, a person during a regulatory review period."
[68] *Id.* at § 156(g)(6)(A)
[69] Unless, of course, the original patent term remaining after approval exceeded fourteen years, but in that case the patent would be ineligible for extension. This situation has become more common due to the recent amendment to the patent code that changed the expiration date of a patent from seventeen years after issuance to twenty years after filing, combined with increasing efficiency in the USPTO and FDA, which minimizes loss of term to regulatory review.
[70] 35 U.S.C. § 156(c)(3).
[71] *See generally* Heidi Grygiel, *Now They GATT Worry: The Impact of the GATT on the American Generic Pharmaceutical Industry*, 6 U. Balt. Intell. Prop. J. 47, (1997); Ned Milenkovich, *Deleting the Bolar Amendment to the Hatch-Waxman Act: Harmonizing Pharmaceutical Patent Protection in a Global Village*, 32 J. Marshall L. Rev. 751 (1999).

Related Aspects of Intellectual Property Rights (TRIPS)[72] provisions under the World Trade Organization administered General Agreement on Tariffs and Trade (GATT), which mandate a twenty-year patent term, and led to the 1995 amendment of 35 U.S.C. § 154 to increase the term of protection of a patent from seventeen years after issuance to the period between issuance and twenty years after filing, although many would suggest that this amendment alone resolved the problem,[73] which effectively added on to the patent term of all inventions subject to less than three years of USPTO scrutiny.

The extension procedure begins within sixty days of obtaining regulatory approval, with the submission of an application containing the identity of the product,[74] the patent,[75] and other requisite information,[76] to the Director of the United States Patent and Trademark Office (USPTO),[77] who will, within sixty days of receipt, send a copy of the application to the Secretary of Health and Human Services,[78] who will, within thirty days of receipt, use the information in the application to determine the appropriate scope and term of the patent extension, notify the Director of the determination, and publish it in the Federal Register, at which point the Director shall issue a certificate of extension to append to the original patent.[79]

The passage of the patent extension provisions ultimately forced the brand name drug industry to make a strategic trade-off. Under the old system, once their patents expired, they had to rely only on the probability that potential generic competitors would be held up in FDA review for an indeterminate period of time, through a process over which they had no influence. After the passage of the Act, once the patents' initial terms expired, they still retained a period of exclusivity with terms that they could calculate, and take into

[72] TRIPS, Art. 33.

[73] Although significant Congressional debate arose concerning the failure to take into account the interests of generics relying on the earlier seventeen year term. *See generally Partial-Birth Abortion Ban Act*, 141 CONG. REC. S18183 (daily ed. Dec. 7, 1995); *GATT and Prescription Drugs*, 141 CONG. REC. S15421 (daily ed. Oct. 23, 1995).

[74] 35 U.S.C. § 156(d)(1)(A).

[75] *Id.* at § 156(d)(1)(B).

[76] *Id.* at § 156(d)(1)(C-E).

[77] *Id.* at § 156(d)(1).

[78] *Id.* at § 156(d)(2)(A)(ii).

[79] *Id.* at § 156(e).

account in market projections. If a generic competitor attempted to enter the market, they had the ability to block it directly, asserting specific patent rights. What they lost in terms of potentially longer market exclusivity, they gained in predictability and a more express delineation of their rights.

The results

The intended results of the amendments in the Hatch-Waxman Act can be seen in the following hypothetical timelines, comparing the generic response to a brand name drug that, after its patent issued, underwent four years of clinical trials and two years of FDA review. As can be seen in figure 1, prior to the passage of the Act, the brand name drug would enjoy eleven years of exclusivity under its patent, and six years of pseudo-exclusivity as its potential competitors were subjected to FDA review, allowing the public to benefit from drug price competition twenty-three years after the drug patent issued. In figure 2, after the passage of the Act, the brand name drug would be entitled to a three year patent term extension. However, a generic competitor submitting an ANDA would not lose any time to clinical trials, and would be able to enter the market as soon as the term extension expires, allowing the public to benefit from drug price competition twenty years after the drug patent issued. This three year acceleration of generic market entry could save the public billions of dollars. The effect is even more dramatic if the generic drug manufacturer files a paragraph IV certification. Even assuming the duration of the infringement litigation is maximally prolonged, the generic competitor could obtain FDA approval, and the six month period of exclusivity that motivated it to challenge the patent, as soon as thirteen and a half years after the original patent issued, granting the public almost an entire additional decade in which to enjoy lowered drug prices.

The Hatch-Waxman Act has been successful in accomplishing its stated goals. In 2002 generics accounted for 47% of prescription drug volume,[80] more than doubling the 1983 level of 19%.[81] And while only 36% of the top-selling brand name drugs had generic competitors in 1983, by 1998 the competition level was almost 100%.[82]

[80] Federal Trade Commission, Generic Drug Entry Prior to Patent Expiration: An FTC Study i (July 2002) [hereinafter FTC Report].
[81] CBO Study, *supra* note 7, at xii.
[82] *Id.* at 27.

Chapter II: Paragraph IV certifications: A temptation to collude

Certain provisions in the Hatch-Waxman Act, particularly those that control exactly when the FDA's approval of an application with a paragraph IV certification is to take effect, were written to strike a balance between the competing interests of brand name and generic drug manufacturers, to prevent either side from losing significant ground in the compromise. Unfortunately, brand name drug companies have discovered that they can be exploited in ways that allow them to maintain their market exclusivity indefinitely. Particularly problematic provisions include the automatic thirty month stay of approval following filing of an infringement action,[83] which was originally intended to reflect the period of time expected to be lost to concurrent litigation and FDA review,[84] but which can be abused by being repeatedly renewed through listing of new patents to the Orange Book after the filing of the ANDA, each of which would require a new paragraph IV certification and provide the opportunity to obtain a new thirty month stay,[85] and the 180 day period of exclusivity for the first successful filer of a paragraph IV certification, which, due to the fact that the period of exclusivity can be "parked,"[86] i.e. not triggered, indefinitely, opens the door for situations in which it is more profitable to the generic to accept payments from the brand name company to stay off the market than it is for the generic to enter the market, laying the groundwork for collusive agreements that restrain competition and keep drug prices high. A recent FTC study on generic drugs challenging the patents of brand name drug manufacturers showed some distressing recent developments.

[83] 21 U.S.C. § 355(j)(5)(B)(iii) for an ANDA; 21 U.S.C. § 355(c)(3)(C) for a NDA.
[84] FTC Report, *supra* note 80, at 39.
[85] *Id.* at 40
[86] *Id.* at 58

Exploiting the thirty month stay of approval

Normally, when an ANDA with a paragraph IV certification is filed, the brand name drug manufacturer will, upon notice, initiate an infringement action based on an Orange Book listed patent, triggering a stay of ANDA approval until the earlier of a judicial determination of non-infringement of the patent, or a thirty month period, elapses. The thirty month stay of approval was consistent with the expected duration of such litigation. Should another patent issue after the filing of the ANDA, the ANDA applicant will have to recertify it, and the new paragraph IV certification can trigger a new thirty month stay. Prior to 1998, most[87] litigations between generic and brand name drug companies triggered only a single thirty month stay, and the litigations themselves concerned infringement of only one or two patents.[88] Many of the litigations were resolved before the expiration of the thirty month period. However, two trends have arisen since 1998.

There has been a trend, in recent years, for the complexity of the patent infringement actions between brand name and generic drug companies to increase, with significantly more patents being asserted in an average case.[89] The major effect of this shift is an increase in the average[90] duration of litigation,[91] normally beyond a thirty month period, which means that, in determining the timing of ANDA approval, the thirty month stay is becoming a more significant determinant, being invoked more often, relative to an actual court decision.

The other recent trend[92] is the tendency of brand name drug companies to list additional issued patents in

[87] All but two. *Id.* at 39.

[88] For 8 out of 9 pre-1998 "blockbuster" drug litigations, only 1 or 2 patents were asserted. *Id.* at 47.

[89] For 3 out of 8 post-1998 "blockbuster" drug litigations, only 1 or 2 patents were asserted. 3 or more patents were asserted in the remaining 5 actions, with some brand name drug companies asserting infringement of as many as 12 patents. *Id.* at 47-48.

[90] 25 months, 13 days to a district court decision, 37 months, 20 days to a Federal Circuit decision. *Id.* at 47, Table 4-1.

[91] Of the 7 cases that have been pending for 30 months without a district court determination, 6 have involved 3 or more patents. *Id.* at 48.

[92] Of the 8 such filings, 6 have occurred after 1998. *Id.* at 48, Table 4-2.

the Orange Book after the generic's ANDA filing, forcing the ANDA applicants to recertify their application with regard to the newly listed patent, potentially triggering a new thirty month stay. The most vigorous users of this method have, to date, been GlaxoSmithKline, the makers of the antidepressant Paxil™,[93] who listed five sequential patents on the drug substance, formulation and method of use, extending the stay on approval of several competing generics' ANDAs out to 65 months,[94] and Abbott Laboratories, the makers of the antihypertensive Hytrin™,[95] who listed three separate patents on their drug substance, creating a total of 70 months[96] of suspension of Geneva Pharmaceutical's ANDAs.[97] In this manner, through limited strategic control of patent issuance, a brand name drug company could prolong its monopoly indefinitely, asserting a sequence of patents, bringing out a new one just before the previous one is found invalid or not infringed.[98] Of the eight products for which patents were listed to the Orange Book after filing of a competing ANDA, four (Hytrin, Paxil, BuSpar and Tiazac)[99] involved patents that the drug companies had filed more than a year after obtaining FDA approval for their products, making them facially invalid as being in violation of the on-sale bar of 35 U.S.C. § 102. None of the cases involving patents listed after the filing of a generic ANDA, for which court determinations have been made, found the patents in question valid and infringed,[100] suggesting that the subsequent patent listings are frivolous to some degree, performed for the express purpose of extending the suspension of ANDA approval, making the underlying litigation a sham that "may have little to do with the underlying value of the patent(s) at issue, and amounts, in some cases, to a stipulated preliminary injunction without judicial review."[101] A patent must be listed in the FDA's

[93] *Id.* at. A-33.
[94] *Id.* at 49, Table 4-3.
[95] *Id.* at A-29
[96] *Id.* at 49, Table 4-3.
[97] *Id.* at A-29-30.
[98] This is often referred to as the "evergreening" of the Orange Book. 148 Cong. Rec. S6906 (daily ed. July 17, 2002) (statements of Sen. Corzine).
[99] *Id.* at 50.
[100] *Id.* at iii-iv.
[101] Julia Rosenthal, *Hatch-Waxman Use or Abuse? Collusive Settlements Between Brand-Name and Generic Drug Manufacturers*, 17 Berkeley Tech. L.J. 317, 327 (2002).

Orange Book if an action for its infringement is to trigger the thirty month stay.[102] Patents listed to the Orange Book must meet certain requirements, insofar as they have to claim the drug, or a method of using the drug, in such a way that a claim of patent infringement could reasonably be asserted against a generic competitor.[103] However, there is currently no way to privately challenge an improper listing.[104] The FDA has declared that it does not have the resources to police listing, and can only manage the Orange Book in a ministerial fashion.[105]

The FTC report's recommendation, to challenge these abuses of the Hatch-Waxman litigation procedure, was to amend the Act to permit only one thirty month stay to be triggered by any ANDA.[106] This limitation would not affect the brand name drug company patentees' potential for remedies in other infringement actions, merely curb potential misuse of the offending provision.

Exploiting the 180 day period of exclusivity

To give generic drug manufacturers a reason to file ANDAs with paragraph IV certifications to challenge weak listed patents,[107] and risk the expense of the inevitable infringement action, the drafters of the Hatch-Waxman Act included a provision granting a 180 day period of exclusivity to the first generic to successfully file an ANDA, during which no other ANDA for the product can be approved.[108] Unfortunately, the triggering mechanism for this provision leaves it open to abuse. The 180 day period starts running upon

[102] FTC Report, *supra* note 80, at 53.
[103] 21 U.S.C. § 355(b)(1).
[104] *See* Mylan Pharmaceuticals, Inc. v. Thompson, 268 F.3d 1323 (Fed. Cir. 2001).
[105] This position has been upheld by the court in *Watson Pharm., Inc. v. Henney*, Civil Action No. 00-3516 (D.Md. 2001).
[106] FTC Report, *supra* note 80, at iii-iv.
[107] Mova v. Shalala, 140 F.3d 1060 (D.C. Cir. 1998).
[108] 21 U.S.C. § 355(j)(5)(B)(iv).

either the first commercial marketing of the drug,[109] or a court decision holding the patents invalid or not infringed.[110] What happens when an ANDA is approved, for instance when the thirty month suspension of ANDA approval, in response to a paragraph IV infringement action, has expired, but there is no court decision, because the generic and brand name drug companies settled, and there is no commercial marketing, because the generic has chosen not to produce or sell the drug product? Technically, in this situation, the commencement of the 180 day exclusivity period is suspended, but no competing generic product can enter the market until it expires.

Why would a generic drug company want to delay triggering the exclusivity period, when it had worked so hard to challenge the brand name drug company's monopoly? The answer, of course, is profit. Without competition, a brand name pharmaceutical can have a very high profit margin. Should a generic competitor enter the market, drug prices go down, as do profit margins. If the potential loss of profit margin to the brand name drug company exceeds the potential profit margin of the generic drug, it is to the economic benefit of both parties for the brand name drug manufacturer to pay the generic to delay entry into the market.[111] Unfortunately, a collusive agreement of this nature, despite its economic attractiveness to the parties involved, artificially inflates drug prices, at incredible cost to the public, and is illegal as a horizontal market allocation under antitrust law.[112]

Collusive agreements to limit the entry of generics to market are a relatively recent development. This is not due to a recent resurgence of unscrupulousness in the pharmaceutical industry, but because such collusive arrangements are based on an enforceable 180 exclusivity period, which was largely unavailable to generics

[109] *Id.* at § 355(j)(5)(B)(iv)(I).
[110] *Id.* at § 355(j)(5)(B)(iv)(II).
[111] This disparity in profit margins would also explain why generics normally wait until after a court determination of invalidity or non-infringement before entering the market: "[the] potential liability for lost profits on the brand-name drug usually will vastly exceed [the generic's] own potential profits." FTC Report, *supra* note 80, at viii.
[112] In re Cardizem CD Antitrust Litig., 105 F. Supp. 2d 682, 695 (E.D. Mich. 2000).

between 1992 and 1998, due to the FDA's unusual interpretation of the exclusivity provision, 21 U.S.C. § 355(j)(5)(B)(iv), which required generics to meet a "successful defense" standard, mandating significant investment in litigation on the generic's part, rather than simply the "first to submit" requirement of the statute. The FDA had imposed this standard specifically to address the fear of collusive agreements delaying drug entry. However, this standard was overruled by the court as inconsistent with the plain meaning of the statute in *Mova v. Shalala*, 140 F.3d 1060, 1069 (D.C. Cir. 1998), in which a generic drug manufacturer who had been challenged by the brand name patentee, thus initiating the thirty month stay, sued the FDA because it was about to grant the ANDA of a competing generic, who the patentee had not sued, while the litigation was still progressing. The court required the FDA to interpret the provision literally, and delay the approval of the second generic until the first generic could invoke its exclusivity. From 1998 on, several generic manufacturers have taken advantage of the 180 day exclusivity provision, and in many respects, it seems to operate as its drafters intended. Since 1998, the exclusivity period has been triggered 31 times, 19 times in response to commercial marketing of a generic, and 12 times in response to a court determination of non-infringement or invalidity,[113] which, to some extent, allays fears that the period of exclusivity exists for the express purpose of not being triggered. However, problems arise when patent infringement litigation between generics and brand name drug companies is resolved by settlement. In an FTC analysis, 70% of these settlements, at the time of execution, contained provisions that could defer the triggering of the period of exclusivity, potentially delaying the entry of subsequent generics to the market.[114]

The FTC's recommendation to address this issue is to propose legislation that mandates that copies of certain agreements between generic and brand name drug manufacturers are filed with the FTC, facilitating their monitoring activities. How would the FTC determine whether a particular agreement contained

[113] FTC Report, *supra* note 80, at 60, Table 5-1.
[114] *Id.* at 58.

anticompetitive collusive provisions? Antitrust law may be inapplicable, because the settlement agreements involve the assertion of patent rights, which authorize otherwise impermissible monopolies. Former FTC Commissioner Mary Azcuenaga suggested a simple two-part test, under which, if a patent was properly obtained, and its scope was not improperly expanded, an antitrust analysis would be inapposite.[115] FTC Commissioner Thomas Leary proffered a simpler test, one that looks for reverse payments, consideration granted by the patentee to the accused infringer, which, since they run counter to an expected negotiated license, render the agreement presumptively anticompetitive.[116]

The FTC also called for minor reforms to clarify the exact triggering terms of the 180 day exclusivity period, specifying that "commercial marketing"[117] should include any marketing by the generic of the product specified in the ANDA, even of the brand name version,[118] and that "court decision"[119] should include any decision[120] by any court.[121]

Responding to the FTC's recommendations, various legislative responses have been proposed.

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[115] Julia Rosenthal, *Hatch-Waxman Use or Abuse? Collusive Settlements Between Brand-Name and Generic Drug Manufacturers*, 17 BERKELEY TECH. L.J. 317, 332 (2002).

[116] Thomas Leary, Antitrust Issues in the Settlement of Pharmaceutical Patent Disputes, Part II, Speech Before the American Bar Association's Antitrust Healthcare Program (May 17, 2001), available at http://www.ftc.gov/speeches/leary/learypharmaceuticalsettlement.htm.

[117] 21 U.S.C. § 355(j)(5)(B)(iv)(I)

[118] FTC REPORT, *supra* note 80, at ix. This is a response to concerns raised by a generic applicant's marketing of Procardia™ under a supply agreement with the brand name company.

[119] 21 U.S.C. § 355(j)(5)(B)(iv)(II)

[120] FTC REPORT, *supra* note 80, at x. This is in support of a recent decision by the court in *Teva Pharmaceuticals, USA, Inc. v. FDA*, 182 F.3d 1003 (D.C. Cir. 1999), which held that even a dismissal of a declaratory judgment action for failure to state a case or controversy should be sufficient the trigger the exclusivity.

[121] *Id.* at ix. *Teva Pharmaceuticals, USA, Inc. v. FDA*, 182 F.3d 1003 (D.C. Cir. 1999), and *Granutec, Inc. v. Shalala*, 139 F.3d 889 (4^{th} Cir. 1998) held that the provision could be triggered by the determination of any district court, overruling an FDA regulation that required a decision from a court for which no appeal, short of a writ of certiorari to the Supreme Court, could be taken.

Proposed reforms: Drug Competition Act of 2002

Senator Leahy's proposed Drug Competition Act of 2002[122] is a direct response to the FTC's request to be notified of certain agreements. It would mandate filing with the FTC and the Assistant Attorney General any agreement regarding the manufacture, marketing or sale of either the brand name or the generic drug that is the subject of the generic applicant's ANDA, or regarding the 180 day period referred to in 21 U.S.C. § 355(j)(5)(B)(iv) within ten days of the execution of said agreement. A civil penalty for non-compliance, of not more than $11,000/day,[123] could be imposed in an action brought by the Department of Justice or the FTC, but no private right of action would be available.

The Drug Competition Act does a good job of addressing some of the FTC's concerns regarding the 180 day period of exclusivity, but it may be underpunitive, especially considering that the artificially inflated drug prices sustained by these potentially collusive agreements could produce a profit margin differential of hundreds of thousands to millions of dollars a day. A benefit of this proposal is its relatively limited scope. Beyond imposing a reporting requirement, it doesn't extensively modify the provisions of the Hatch-Waxman Act, which means that the risk that the Drug Competition Act will imbalance the delicate equilibrium of concessions established by the Hatch-Waxman Act is minimal at worst, and non-existent at best. It would serve as an ideal complement to legislative amendments of the Act itself.

[122] 148 Cong. Rec. S11339 (daily ed. Nov. 13, 2002).

[123] This seems like an arbitrary amount, probably the result of some unspecified compromise, especially since earlier versions of this Act had a $20,000/day penalty.

Proposed reforms: Greater Access to Affordable Pharmaceuticals Act of 2003

A more ambitious and expansive legislative proposal, and one which, through significant amendment of provisions of the Hatch-Waxman Act, runs a much higher risk of upsetting the balance established in 1984, is embodied in the Greater Access to Affordable Pharmaceuticals Act of 2003 bill.[124]

The Greater Access Act addresses systemic abuses of the thirty month stay by imposing more stringent Orange Book listing requirements, including a certification on a claim by claim basis that each listed patent's claims meet the 21 U.S.C. § 355(b)(1) requirements,[125] and requiring all relevant patents to be listed. As a penalty for non-compliance, in addition to the existing risk of disapproval of a pending application[126] or withdrawal of approval for a product,[127] the Greater Access Act would add forfeiture of all claims of infringement against ANDA or NDA filers for unlisted patents. This would, unfortunately, create an incentive for potentially frivolous listings, as brand name drug manufacturers would feel compelled to list all patents they may eventually want to enforce. To counteract this eventuality, the Greater Access Act also creates a private right of action, reserved to ANDA, or NDA for a previously approved drug, applicants, to challenge an improper Orange Book listing, with correction of the listed patent information or delisting as the exclusive remedies. In response to the more stringent Orange Book listing requirements, paragraph IV certifications would also be subject to a heightened notice requirement.

The Greater Access Act would also limit invocation of the thirty month stay to patents that were listed prior to the approval of the brand name drug's application. Subsequently listed patents would be unable

[124] 2003 S. 54 (2003).
[125] I.e. that they claim a drug, or method of using a drug, and that they could reasonably be asserted in an infringement action against a generic who manufactures, uses or sells the drug.
[126] 21 U.S.C. § 355(d)(6)
[127] *Id.* at § 355(e)(4)

to take advantage of the provision.[128] This seems unduly harsh, potentially penalizing brand name drug companies for delays caused by the USPTO. A reasonable concession would be some period of opportunity after approval to make subsequently issued patents eligible for the stay, such as additionally granting the opportunity to invoke the stay to all patents filed within the first year after FDA approval, or all patents issued in the automatic exclusivity periods defined in 21 U.S.C. § 355(c)(3)(D) and (j)(5)(D).

Hatch-Waxman Act litigation would also be made the exclusive litigation procedure. Failure to assert infringement within the forty-five days following notification of the filing of a paragraph IV ANDA would preclude the subsequent filing of such an action.

To address abuses of the 180 day exclusivity provision, the Greater Access Act would more clearly define the triggering events, limiting the term "court decision" to a court from which no appeal short of a Supreme Court writ of certiorari could be taken,[129] but allowing a Federal-judge-signed settlement order or consent decree that includes a finding of non-infringement or invalidity to trigger the period. The reforms do not address settlements that do not include such a finding,[130] nor do they address the FTC's recommendation to expand the definition of "commercial marketing" to include resale, by the generic, of brand name products.

The Greater Access Act would also create conditions under which the 180 day period could be forfeited, allowing the benefit of the exclusivity, and risk of forfeiture, to pass to the first subsequent ANDA applicant. Most notably, one of these forfeiture events is a failure to market the drug by a certain, but as yet unspecified, deadline.[131] The 180 day period may be less valuable to subsequent ANDA applicants, however, as the

[128] But they would still be listed, to avoid forfeiture of infringement claims.

[129] Overruling the holdings of *Teva Pharmaceuticals, USA, Inc. v. FDA*, 182 F.3d 1003 (D.C. Cir. 1999), and *Granutec, Inc. v. Shalala*, 139 F.3d 889 (4^{th} Cir. 1998), contrary to the FTC's recommendations. FTC Report, *supra* note 80, at ix-x.

[130] It may be possible to correct this deficiency by expanding the provision to allow any settlement order or consent decree that does not include a finding of infringement to trigger the 180 day period.

[131] The deadline, if or when Congress decides on one, should give the generic drug company some lead time in which to build up its supplies, or else legislatively overrule *Biogen v. Schering AG*, 954 F. Supp. 391 (D.Mass. 1996), which held that stockpiling in anticipation of ANDA approval does not fall within the 35 U.S.C. § 271(e)(1) exemption.

previous forfeiting generics will still, presumably, be able to market their products during the subsequent applicant's period. Pairing forfeiture of the exclusivity period with a temporary withdrawal of approval could correct this discrepancy in the proposed Act.[132] In the current bill, the period of exclusivity would only be available to those ANDA applicants against whom an infringement action has been brought,[133] limiting it to its originally intended use as a reward for challenging patents.[134]

Possible rationale for brand name drug companies' actions

Any attempts at reform must take into consideration the possibility that brand name drug companies may have legitimate concerns, beyond the maximization of profit and maintenance of their market exclusivity, that can, at present, be addressed only by resorting to these illegitimate anticompetitive techniques. What both methods have in common are that they allow brand name drug companies to circumvent an actual judicial determination of the validity of their patents. Fear of such a determination might not necessarily arise from any inherent weakness in, or distrust in the integrity of, their patents, but from a recent line of cases in the Federal Circuit that dramatically altered the background against which a determination of validity of a pharmaceutical or biotechnological patent was to be made, threatening the validity of older patents, and justifying a resurgence in the issuance and listing of new patents which take this change into account.

[132] Although one of the benefits of the bill as it stands is that even if the brand name manufacturer is willing to orchestrate collusive agreements, it will have to enter multiple such agreements, until it will eventually become more profitable to just open the market.

[133] Which could, ironically, give brand name drug companies holding weak patents some leverage, by threatening not to sue.

[134] Although this provision would effectively overrule part of the holding of *Mova v. Shalala*.

This line of cases developed gradually,[135] but reached their peak in 1997[136] with *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997), in which a heightened written description requirement[137] was imposed on a patent for recombinant plasmids, and microorganisms that have incorporated the recombinant plasmids, that produce human insulin. This was the first time that a separate, specific written description requirement had been found (up until that point, the written description requirement analysis had been conflated with the enablement requirement analysis) and used to invalidate a patent.[138] The introduction of a new standard of adequacy for a patent specification, although the *Eli Lilly* court claimed that that standard had always been in effect, could easily have threatened the validity of any patent filed before the formal acknowledgment of an independent written description requirement. This may be one reason why 75% of patent litigations between brand name and generic drug manufacturers that are resolved by court decisions come out in favor of the generic.[139]

[135]The expansion in doctrine was suggested in *Amgen v. Chugai*, 927 F.2d 1200 (Fed.Cir. 1991) and *Fiers v. Revel*, 984 F.2d 1164 (Fed.Cir. 1993).

[136]Which, coincidentally, correlates with the recent resurgence of post-ANDA Orange Book listings of new patents and recent increases in the complexity of infringement actions, as described in FTC Report, *supra* note 80, at iii.

[137]35 U.S.C. § 112 ¶1: "The specification shall contain a written description of the invention, and of the manner of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. . . "

[138]The Federal Circuit chose to curtail itself, limiting further expansion of the written description doctrine in 2002 with *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002).

[139]FTC Report, *supra* note 80, at viii.

Chapter III: The *Bolar* amendment: The death of research tools?

Generic drug companies have been able to circumvent the intended purposes of the Hatch-Waxman Act by leveraging their exclusive rights under the Act in collusive arrangements with brand name drug companies, to the detriment of the public, but they, have also been able to circumvent those intended purposes to the detriment of the brand name drug companies, exploiting a provision of the Act, the 35 U.S.C. § 271(e)(1) "research safe harbor," also known as the *Bolar* amendment, in a manner that threatens not only the temporary market exclusivity of the brand name drug companies, but the structure of the pharmaceutical research field, and the viability of the currently emerging research tools industry, which could have serious repercussions on the development of the next generation of drugs.

The Bolar amendment

The Hatch-Waxman Act amended § 271 of the Patent Code, adding section (e)(1), which provided that it was not "an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs or veterinary biological products." The terms in the statutory language differ in certain respects from those in other provisions of the Act, and the nuances inherent in those terms underscore the importance of responsible

judicial interpretation in applying the provision in accordance with its underlying legislative intent. Several words and phrases in the *Bolar* amendment raised several important questions that were left to the courts to determine. This chapter will examine the efforts of several courts to respond to these questions, whether their responses can reasonably be aligned with the legislative intent underlying the Act, and the potential consequences, both intentional and unintentional, of their determinations.

Questions of interpretation

The *Bolar* amendment doesn't mention a particular party that is to benefit from the infringement immunity, although an analysis of the legislative intent behind the Act, and the partial symmetry between the *Bolar* amendment and 35 U.S.C. § 271(e)(2),[140] suggests that this provision was designed to protect generic drug companies, i.e. entities that file or intend to file ANDAs, from premature actions for infringement. Should the research exception defense be provided to defendants that are not in the process of preparing to file, nor ever intend to file, an ANDA?

The amendment permitted research activities for submission of information under Federal laws that regulate "drugs." Is the word "drugs" to be narrowly construed to apply to pharmaceuticals, or can it also be applied to biologics, or medical devices? If the word "drugs" is applied broadly, such as in the context of medical devices, does it apply equally to products that are subject to abbreviated review periods or less stringent standards?

[140] "The result is to bar a patent holder from suing for infringing use during the development and testing stage, but allow the patentee to sue under an expedited process once the infringer files for approval of the drug. Thus, what Congress taketh away in Section 271(e)(1), it gives in Section 271(e)(2)." Allergan v. Alcon Labs, 200 F. Supp. 2d 1219 (C.D.Cal. 2002).

The *Bolar* amendment refers to acts "solely for uses" of FDA submissions, but what clause does the word "solely" modify? Does the exclusive purpose of the potentially infringing acts have to be generation of information required or potentially required by the FDA, or can the research be employed to other ends, in addition to responding to FDA information requests?

For the *Bolar* amendment to apply, the potentially infringing act must be "for uses reasonably related" to submission of information to the FDA. Who is more capable of determining whether an action is "reasonably related," the courts or the FDA, and who should the final determination be left to? What qualifies as a "reasonably related" use, and how attenuated can the relationship between a potentially infringing act and a submission of information to the FDA be before a use is deemed unreasonable?

One of the primary divergences from the statutory language of the rest of the Act is found in the *Bolar* amendment's reference to a "patented invention," rather than to "a drug claimed in a patent or the use of which is claimed in a patent," as in 35 U.S.C. § 271(e)(2), which raises important concerns about the breadth of the exemption, and the range of patents over which a researcher can be immunized from infringement. Did Congress really intend this provision to allow a defense against infringement, and a concomitant curtailment of the exclusivity rights, of a much larger group of patents than those that could be benefited by the accompanying term extension? The resolution of this issue is of particular importance to the burgeoning research tools industry.

Expansion of scope in the courts

The signposts for statutory interpretation of the *Bolar* amendment were set by the Supreme Court in 1990 in the case of *Eli Lilly v. Medtronic*, 496 U.S. 661 (1990). In this case, Eli Lilly's predecessor-in-interest held two patents with claims that encompassed an implantable cardiac defibrillator. Medtronic tested and marketed its model of an implantable cardiac defibrillator in anticipation of a submission of information under the FDCA as a Class III medical device, a category of products with a regulatory review procedure similar to that mandated for new drugs. Eli Lilly sued Medtronic for infringement, and the district court ruled in Lilly's favor, permanently enjoining Medtronic from further infringement, despite Medtronic's asserted defense that its activities were non-infringing under the *Bolar* amendment.[141] The court of the Eastern District of Pennsylvania held that the statutory language "regulates the manufacture, use or sale of drugs" limited the applicability of the exception to drug products.

The district court's holding was reversed by the Federal Circuit,[142] who gave a broader interpretation to this clause, allowing it to encompass medical devices as well. It turned to the legislative intent as justification, asserting that Congress had created 35 U.S.C. § 271(e)(1) to overrule the Federal Circuit's earlier decision in *Bolar*, and that, although the patented invention in that case had been a drug product, the holding in that case had not been expressly limited to drug products, and, as a consequence, the statutory provision that overruled that holding should not be limited to drug products. The Federal Circuit remanded the case back to the district court, who were to operate on the assumption that 35 U.S.C. § 271(e)(1) did apply to medical devices, for a determination of whether Medtronic's activities were, in fact, "solely for uses reasonably related" to the FDA application procedure, an issue raised primarily by Medtronic's marketing

[141] Eli Lilly & Co. v. Medtronic, Inc., 696 F. Supp. 1033 (E.D.Pa. 1988).
[142] Eli Lilly & Co. v. Medtronic, Inc., 872 F.2d 402 (Fed. Cir. 1989).

activities.[143]

The Supreme Court affirmed this judgment, with Justice Scalia's opinion providing two possible justifications for its holding, one narrow and one broad, and ultimately settling on the broader one. Eli Lilly had claimed that the *Bolar* amendment should be limited to drug products to effect a statutory symmetry with 35 U.S.C. § 271(e)(2) and (4), which produce the "highly artificial act of infringement,"[144] the statutory infringement of a paragraph IV certification ANDA, and which are limited to patents for drugs or drug methods of use. The Supreme Court proffered a narrow justification for its holding, countering Eli Lilly's assertion with the suggestion that § 271(e)(1) had not been effected simply to limit the timing of an infringement action in response to a paragraph IV certification ANDA, but to correct the distortion in patent term, due to the brand name drug companies' loss of patent term to regulatory review and their gain of patent term through obstruction of generic drug companies' regulatory review, that the Hatch-Waxman Act had been designed to remedy, leading to the implication that the proper source for establishing statutory symmetry was the 35 U.S.C. § 156 patent term extension provision, which did encompass medical devices and other products subject to a regulatory review period. However, the Court settled on the broader justification that the contested clause modified the term "Federal law" in the provision, which made it a reference to "an entire statutory scheme of regulation," to the Food, Drug and Cosmetic Act (which did, in part, regulate drugs) in its entirety, such that the *Bolar* amendment's exception to infringement was not limited to those products mentioned in the patent term extension provision, but was applicable to any patented invention, any product, mentioned anywhere in the entirety of the Act. It is this interpretation that Justices Kennedy and White criticized in their dissent, decrying it as an unprecedented divergence from the norms of statutory

[143]The District Court granted Eli Lilly an injunction to prevent Medtronic from all non-§ 271(e)(1)-exempted infringement, which Eli Lilly used to curtail Medtronic's marketing activities. On appeal from this order, the Federal Circuit found for Medtronic, holding that their marketing activities were merely a threat of sale, which did not rise to the level of infringement. Eli Lilly v. Medtronic, 915 F.2d 670 (1990).

[144]496 U.S. at 678.

construction. Reliance on this broader justification laid the groundwork for subsequent broad interpretation of the *Bolar* provision by other courts. Has the breadth of interpretation gone too far? Have courts abdicated their duty to reasonably construe this statute?

In the case of *AbTox v. Exitron*, 122 F.3d 1019 (Fed.Cir.1997), the Federal Circuit carried the Supreme Court's reasoning to the next logical level.[145] AbTox and MDT, an affiliate of Exitron, both held patents on plasma sterilization devices for medical instruments. AbTox was marketing a plasma sterilizer, and MDT was experimenting with one to gather data necessary for filing an application with the FDA for approval of as a Class II medical device. MDT sued AbTox for infringement of its patent, which AbTox claimed was not infringed because the claims did not read on to its product, and AbTox sued MDT for infringement of its patent, which MDT claimed was not infringed because its activities were exempt under the *Bolar* amendment. The court of the District of Massachusetts found non-infringement on both counts, and certified the case to the Federal Circuit.[146] The Federal Circuit affirmed on both counts. In upholding MDT's defense, it held that the *Bolar* amendment applied to Class II medical devices, despite the fact that Class II medical devices are subject to an abbreviated review, can actually be marketed without advance approval provided they comply with federal performance regulations, and are ineligible for patent term extension. To support this expanded defense, the Federal Circuit discussed the Supreme Court's decision in *Eli Lilly*, both the narrow holding derived from symmetry between 35 U.S.C. § 271(e) and § 156, which would not extend *Bolar* amendment protection to Class II medical devices, and the broad holding derived from interpretation of "a Federal law," which would. The Federal Circuit ultimately had to follow the reasoning behind the broader holding, even if, in this case, the result was in conflict with the Court's narrower reasoning, claiming that the

[145] As it had threatened to do in *Chartex International v. M.D. Personal Products Corp.*, 1993 U.S. App. LEXIS 20560 (Fed. Cir. 1993), which applied the *Bolar* exception to a Class II medical device, a female condom, but only because the patentee had not raised the argument of its applicability.

[146] Abtox v. Exitron, 888 F. Supp. 6 (1995).

Court "command[ed] that statutory symmetry [was] preferable but not required."[147] The Supreme Court's mandate that 35 U.S.C. § 271(e)(1) be interpreted broadly had begun to bear fruit, results that conflicted with its preferred interpretation, and threatened to frustrate the legislative intent behind the provision.

AbTox also objected to the rather attenuated link between MDT's testing activities, which it outsourced to Exitron in the hope that Exitron would purchase its patent, and FDA pre-market approval, which was not even entirely necessary for Class II devices provided they complied with FDCA "special controls," an objection the Federal Circuit addressed through reference to *Telectronics Pacing Sys., Inc. v. Ventritex Inc.*, 982 F.2d 1520 (Fed.Cir.1992). Ventritex had been conducting clinical trials of its implantable defibrillator, during which it had been selling the product, at cost, to investigators. It had also publicized its product to investors and journalists, and displayed its product to physicians and non-physicians at medical conferences. Telectronics sued for infringement of its defibrillator patents, alleging that displaying the product to non-physicians, and using data for commercial purposes unrelated to FDA approval, fell outside the scope of the *Bolar* amendment exemption. Losing at trial, they appealed. The Federal Circuit affirmed, holding that Congress did not intend to "prevent[] competitors from using . . . the derived test data for fund raising and other business purposes,"[148] laying out the groundwork for the contention in subsequent cases that the clause "solely for uses reasonably related" requires only that the uses be reasonably related to FDA approval, but need not have FDA approval as their exclusive purpose. In *AbTox*, MDT's "intent or alternative uses are irrelevant to its qualification to invoke the section 271(e)(1) shield."[149]

[147] 122 F.3d at 1029.

[148] 982 F.2d at 1524-25. Supporting its later, unpublished, non-precedential decision in *Intermedics v. Ventritex*, 991 F.2d 808, 1993, another implantable defibrillator case, in which it asserted that "[t]here is no suggestion that a producer may only rely on the exemption if it does not intend to commercialize the product before expiration of the patents," affirming the court of the Northern District of California's contention that the relevant inquiry was to determine if it "would [] 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." Intermedics v. Ventritex, 775 F. Supp. 1269, 1280 (N.D.Cal. 1991).

[149] 122 F.3d at 1030.

In the preceding cases, it was not contested that the potentially infringing activities were, at least in part, undertaken to prepare information for FDA filing. What is the FDA's role in the determination of whether or not activities are reasonably related to a filing? That question was recently addressed in *Nexell Therapeutics v. AmCell* 199 F.Supp.2d 197 (D.Del. 2002). Nexell held patents on a method for purifying human stem cells for therapeutic use, which it employed in its product, a magnetic cell separator. AmCell introduced a competing product, which it distributed to clinicians below cost in order to compile data for submission to the FDA as a Class III device application. The FDA had expressed concerns regarding deficiencies in the design of AmCell's study that unnecessarily prolonged the investigation. The court initially deferred to the FDA,[150] and the parties submitted questions to the FDA Deputy Chief Counsel concerning the appropriateness of AmCell's actions. The FDA predictably responded that it had made, and would continue to make, determinations regarding the degree of AmCell's compliance with FDA regulations, but that it was not in a position to independently determine (probably because its resources were already stretched to their limits, and such a determination would open the floodgates to requests by parties to other litigations) whether particular activities fell within the *Bolar* amendment exception, noting that "the ultimate construction and application of [patent law] lies with the court and that as such the court could determine to what extent, if any, the actions and statements of the FDA are relevant indicators of which activities are reasonably related to the approval process and which are not,"[151] also noting that the FDA's standards may be wholly unrelated to the criteria the courts use to construe the provision. The court went on to determine that, despite the FDA's disapproval concerning certain of AmCell's methods, AmCell had not received communications from the FDA that clearly indicated that AmCell could not have reasonably believed its activities were related to obtaining FDA approval. Absent a clear statement otherwise by the FDA, the established precedent mandates that courts give considerable deference to defendants asserting a *Bolar* amendment defense, and "if the defendant

[150] *See* Nexell Therapeutics v. AmCell, 143 F.Supp.2d 407 (D.Del. 2001).
[151] 199 F.Supp.2d at 202.

reasonably believes that certain otherwise infringing activities would yield necessary information for FDA approval, but the FDA subsequently disagrees, the FDA's opinion does not convert those activities from exempt under § 271(e)(1) to infringing activities."[152]

In most of the cases where a *Bolar* amendment defense has been asserted, it has been at least partially successful, thanks to the gradual case-by-case expansion of its scope.[153] However, building on this precedent, the exemption is about to grow too far, verging on an interpretation that might destroy the research tools industry, an industry whose existence Congress was probably unaware of in 1984, when the Act was passed, but whose existence Congress could not possibly object to today, as it underlies almost all modern pharmaceutical research. The first threatened step off the brink, into the abyss,[154] is *Bristol-Myers Squibb Co. v. Rhône-Poulenc Rorer, Inc.*, 2001 U.S. Dist. LEXIS 19361 (SDNY 2001). Rhône-Poulenc held patents on preparing the cancer drug taxol, and intermediary compounds, taxane derivatives. Bristol-Meyers included the taxane derivatives as part of a molecular library for use in its research and development program, searching for taxol analogues. Rhône-Poulenc sued for infringement. Despite the fact that Bristol-Myers' research was in the early stages, that they were in the process of running "hundreds of experiments for purposes of possibly identifying a drug candidate,"[155] where it was uncertain that any functional compound would be found, much less one that would warrant submission of an application to the FDA,[156] the patents

[152] *Id.* at 204

[153] Of course, there is a small subset of cases in which attempts to push to push the *Bolar* amendment beyond reasonable limits have been thwarted. *See e.g.* NeoRx Corp. v. Immunomedics, Inc., 877 F. Supp. 202 (D.N.J. 1994) (patent for labeling proteins with radioactive metal isotopes was infringed by tests and shipments of samples where activities had been clearly designated as being required for foreign, but not FDA approval); Biogen v. Schering AG, 954 F. Supp. 391 (D.Mass. 1996) (stockpiling beta-interferon in anticipation of FDA approval does not fall within § 271(e)(1) exception); PharmaStem Therapeutics v. ViaCell, 2003 U.S. Dist. LEXIS 3047 (D.Del. 2003) (for infringement suit regarding methods for collecting, processing, and storing umbilical cord blood stem cells, defendant's summary judgment motion was denied because § 271(e)(1) applicability remained unresolved, as genuine issue of material fact existed concerning whether stem cells were considered drugs under FDCA, and whether exception was applicable to party filing an investigational new drug (IND) application).

[154] A major step toward the edge, however, was *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104 (D.Mass. 1998), in which use of patented erythropoietin as a reference standard against a competing product-in-development was deemed to fall within the exemption, despite the fact that the ultimate product of the eventual FDA submission would not infringe the contested patent, primarily because use of a reference standard was FDA mandated procedure.

[155] 2001 U.S. Dist. LEXIS 19361, at 4.

[156] And much pharmaceutical research operates serendipitously, with R&D programs churning out several failed compounds

that were allegedly infringed were not ones that Bristol-Myers' end product could ultimately infringe, and Bristol-Myers was not a generic drug manufacturer, the court of the Southern District of New York held that the *Bolar* amendment exempted Bristol-Myers' activities. Rhône-Poulenc unsuccessfully argued that the term "patented invention" should be considered in the context of the Act as a whole, attempting to impose a statutory symmetry that limited it to inventions subject to a 35 U.S.C. § 156 patent term extension, but this ran contrary to the *Eli Lilly* and *AbTox* line of cases, and the court construed it to encompass any and all inventions. Rhône-Poulenc had a more legitimate argument with its contention that Bristol-Myers' infringing activities were not "reasonably related to the development and submission of information" to the FDA, that the connection between its present activities and an FDA filing were incredibly attenuated. Bristol-Myers might potentially have developed a new drug product, which might potentially have passed initial screening and testing, which might eventually have led to the decision that an FDA application was warranted. The court described the standard established in *Intermedics*, i.e. "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 process by which the FDA would decide whether to approve the product?"[157] This is already a very loose standard, but the Special Master that the *Bristol-Myers* court assigned to the case opened it even further, stating that there was a "decent prospect" that Bristol-Myers would eventually meet the *Intermedics* standard, and granting Bristol-Myers the exemption. Pursuant to the reasoning in this case, the *Bolar* amendment exemption would apply even before a candidate for submission to the FDA has been identified. Courts would now be able to entirely abrogate their duty to determine what uses are "reasonably related," and could grant a blanket exemption from infringement of any patent for any product used at any time in the drug research and development process.

for each successful drug, although modern research tools are gradually changing the R&D landscape, allowing for more targeted drug development.

[157] 775 F. Supp. at 1280.

A step back from the edge took place in *Infigen, Inc. v. Advanced Cell Tech. Inc.*, 65 F.Supp. 2d. 967 (W.D.Wisc. 1999), in which the defendant was actually denied a *Bolar* amendment defense. Infigen held patents on a process for activating oocytes for use in cloning, a process that Advanced Cell used in attempting to develop transgenic cattle capable of supplying human serum albumin in their milk, a protein which would require FDA approval to commercialize. Infigen sued for infringement, and actually prevailed. The court had dared to apply the Supreme Court's narrower holding in *Eli Lilly*, that of the congressionally intended symmetry between 35 U.S.C. § 271(e)(1) and § 156. Because, ultimately, the patent that was infringed did not cover a drug product or process as broadly defined within the Hatch-Waxman Act, the *Bolar* amendment was held not to apply.

Infigen is in direct conflict with *Bristol-Myers*. The *Infigen* court's reasoning seems to be significantly more in line with the Congressional intent behind the Hatch-Waxman Act than *Bristol-Myers'*, but it is apparently based on a line of Supreme Court reasoning that the Federal Circuit and other district courts have commented on but disclaimed. *Bristol-Myers*, relative to *Infigen*, is more consistent with relevant precedent, although it pursues it to a dangerous conclusion. Should the *Bristol-Myers* holding stand, the research tools industry could collapse. Their products are specifically designed for use in research and development programs. They would no longer be able to collect royalties on their products, because any use of their products by researchers would automatically be insulated from a claim of infringement by the *Bolar* amendment. The current status of the *Bristol-Myers* holding is ambiguous. The Federal Circuit recently affirmed the district court's decision, but on the entirely different ground of inequitable conduct before the patent office, rendering the patents in question unenforceable.[158] However, the original holding was never explicitly overruled.

[158]Bristol-Myers Squibb Co. v. Rhône-Poulenc Rorer, Inc., 2003 U.S. Dist. LEXIS 7103 (Fed.Cir. 2003).

Threats to the research tools industry

This is where the Hatch-Waxman Act runs up against the complex research tools industry. Its growth is a fairly recent phenomenon, and although it was not particularly influential in the Congressional considerations leading up to the Act, it is a major player in the current pharmaceutical industry, and has significantly shifted the equilibrium position away from the delicate balance between brand name drug companies and generics that the Act sought to establish. In the old paradigm, brand name drug companies developed new drugs, and generics made those drugs affordable to those who needed them. The research tools industry has been appended to the other end of the equation. In the modern pharmaceutical field, they provide the techniques that lead to simultaneous development of vast numbers of next generation drug candidates, or techniques that allow the targeted development of new and important subcategories of drugs, while the brand name drug companies create these drug candidates and filter them through their research and development programs to determine which ones are effective and warrant IND filings with the FDA, with the generics eventually bringing them to the people. Although the situational calculus has changed, the development of the research tools industry is not necessarily intrinsically hostile to the growth of the generic industry. It is only the current language of the Act, and its interpretation or misinterpretation by the courts, that has indirectly pitted them against each other, forcing one to gradually concede power to the other in the legal arena, although they rarely interact directly, preferring, instead, to use the brand name drug companies as intermediaries, in the industrial arena. Ironically, the greater the encroachment on the research tools industry of laws designed to protect generics and limit the powers of brand name drug companies, the more powerful the brand name drug companies become. The research tools industry is assailed on all sides by laws and legal doctrines that were probably never intended to apply to it.

The problem of utility

The research tools industry holds patents on products that are characterized by their use in biotechnological and pharmaceutical research, and by the fact that they usually are not ultimately incorporated into the end-marketed drug products they are used to develop. Examples of these research tools include combinatorial chemistry libraries, isolated targets and active sites, and high throughput biotechnological assays.[159] They can be distinguished from patents on expressed sequence tags (ESTs) and drug precursors, which claim a product to be sold, often without significant practical utility, or requiring intensive research to determine their ultimate utility. Unfortunately, grouping research tools with ESTs often raises vehement objections concerning their patentability, driven by a line of cases concerning the utility requirement for patented inventions.

In *Brenner v. Manson*, 383 U.S. 519 (1966), the Supreme Court raised the bar for patentability of inventions, for chemical and biotechnological inventions in particular, in a holding that may have had unintended consequences for the present day research tools industry. A utility requirement for patentability is imposed by 35 U.S.C. § 101, which requires that patented inventions be "useful." In an interference proceeding in the Patent Office, Manson asserted that he had discovered a process for making certain steroids, but the primacy of his patent was denied because he had apparently disclosed no utility for his steroid products, although they were homologous to functional steroids, which made them useful for research purposes. The Court of Customs and Patent Appeals (predecessor to the Federal Circuit) reversed, applying the previous utility standard that a process patent was useful if it created the product it described, and that " 'where a claimed process produces a known product it is not necessary to show utility for the product' as long as it is not detrimental to the

[159]Robert B. Blackburn, Chief Patent Counsel of Chiron Corporation, Remarks before the National Academy's Board on Science, Technology and Economic Policy's Conference on Intellectual Property Rights (February 2, 2000).

public interest."[160] The Supreme Court reversed the CCPA's ruling, holding that mere non-detrimentality, or homology to useful compounds, or the fact that the compound is being screened by scientists for possible uses, is insufficient to establish utility. The precedential value of the decision may be limited, because it arose from an appeal of an action by the Patent Office, which imposes a significant burden of proof on the petitioner to overcome a prima facie rejection, and because, although it offered examples of facts that were insufficient to establish utility, raising the bar of patentability, it gave no clear indication of where the bar was raised to, what facts would be sufficient to satisfy the utility requirement. The Federal Circuit addressed this issue in *In re Brana*, 51 F.3d 1560 (Fed.Cir. 1995), holding that a patent applicant's non-symmetrically substituted anti-tumor compounds did not have to rise to the level of FDA approval to be considered useful, and that "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility."[161] This is still a heightened utility standard relative to inventions in other industries, as reflected in the USPTO's Revised Interim Utility Guidelines Training Materials, which direct examiners of biotechnological inventions to determine if the applicant's invention meets the criteria of several gradations of utility, increasing in specificity from credible utility, to specific utility, to substantial utility, to well-established utility. Research tools, which are not intended to have applications beyond the research stage of product development, may have difficulty meeting any but the broadest and most inclusive utility requirements, but they are distinguishable from ESTs, which the utility guidelines were probably specifically drawn up to address, insofar as they serve their function, which is as tools in drug development. No one asserts that they are end products with multiple potential unspecified functions.

[160] 383 U.S. at 519.
[161] 51 F.3d at 1567.

Reach-through royalties

Research tools are usually designed by university laboratories, or small independent firms. Since research tools derive their profitability from the drug products they are used to discover, in order to maximize both overall economic (i.e. profits) and societal (i.e. new effective drug products/classes) benefits, these firms should maximize the probability that new drugs, generated using their tools, will be brought to market. The underlying nature of the industry, therefore, encourages widespread licensing of tools to many competing companies on the next rung of the drug development ladder, both the major brand name pharmaceutical companies and the smaller biotechnology startups that hope to discover a breakthrough therapy that they can leverage to become an attractive acquisition target for the major brand name pharmaceutical companies.

In order to derive a profit from their inventions, research tool firms often employ a controversial licensing scheme, that of reach-through royalties. The licenses are usually offered for a relatively small initial payment, as well as a small percentage of any profits derived from the sale of drugs that are ultimately developed using the tools.[162] Curiously, the National Institutes of Health[163] object to the reach-through royalties strategy, ostensibly on a policy basis, as they see the minor increase to the royalty stack on the end-marketed drug product as a disincentive for research and development programs seeking to acquire new research techniques, as a barrier to the widespread dissemination of tools, but this policy appears to be based on a false economic model, one in which disallowing reach-through royalties reduces the ultimate cost of the research tools. In reality, however, elimination of this potential revenue source would simply drive the research tool developers to compensate by increasing the initial lump sum payment requirement to obtain a license. This would raise the bar for entry into the research field outside the reach of small firms, eventually concentrating research

[162]Gerald J. Flattmann and Jonathan M. Kaplan, *Licensing Research Tool Patents*, 20 Nature Biotechnology 945 (Sept. 2002).
[163]Thomas J. Kowalski and Christian M. Smolizza, *Reach-through licensing: A U.S. perspective*, J. Commercial Biotech. (July 14, 2000).

tools in hands of major brand name pharmaceutical corporations, who would be the only ones who could afford to purchase the current generation of research tools, and to design the next generation. Because of the failure of patent licensing as a system of extracting profits from these technologies, the brand name pharmaceutical companies would likely keep the next generation research tools as trade secrets, withholding the potential benefits derived from the public disclosure aspect of patenting, and slowing the overall rate of innovation. Of course, this calamitous situation has not yet arisen. A licensing strategy employing reach-through royalties is still potentially feasible for research tools developers. This strategy establishes a form of economic parity, making the tools affordable to major drug companies and small biotech ventures alike, and maximizing the potential profitability of the tool while linking that profitability directly to the tool's actual usefulness in an economically efficient manner. Unfortunately, this licensing scheme also runs up against the doctrine of patent misuse, although there is relatively little precedent that is specifically relevant to the field.

The problem of patent misuse

Patent misuse involves using a patent anticompetitively, to assert exclusivity and obtain concomitant concessions, such as an agreement to pay royalties, in an area that the patent does not cover, either because the activity lies outside the scope of the claims specified in the patent,[164] or outside the group of activities that are generally considered infringing, or the schedule of payments goes beyond the term of protection of the patent.[165] Because a reach-through royalty scheme could be seen as patent licensing conditioned on payment of royalties based on sales of commercial products outside the scope of the patent or not enabled

[164] *See* Zenith Radio Corp. v. Hazeltine Research, Inc., 395 U.S. 100 (1969); Virginia Panel Corp. v. MAC Panel Co., 133 F.3d 860 (Fed.Cir. 1997).
[165] Brulotte v. Thys Co., 379 U.S. 29 (1964).

by the patent's specification, a potential infringer could assert patent misuse as a defense against a breach of contract for failure to pay royalties. This problem was addressed peripherally by the Supreme Court in *Zenith Radio Corp. v. Hazeltine Research, Inc.,* 395 U.S. 100 (1969), when they held that Hazeltine had committed patent misuse by "conditioning the grant of a patent license upon payment of royalties on products which do not use the teaching of the patent"[166] (i.e. demanding a percentage of the total sales of Zenith radios and televisions, even those products in which the Hazeltine invention was not incorporated). This is, arguably, distinguishable from arguments that would arise in the research tools context, insofar as the ultimate drug product, while not directly incorporating the patented invention, would not exist but for the research tool. The Supreme Court did offer a way out of the patent misuse dilemma for reach-through licensors, as their primary objection was not to the payment of royalties on products outside the scope of the patented invention, but to conditioning the grant of a patent license on such royalties. They did "not purport to prevent the parties from serving their mutual convenience by basing royalties on the sale of all [products], irrespective of the use of [patentee]'s inventions," but to preclude "only situations where the patentee directly or indirectly conditions his license upon the payment of royalties on unpatented products – that is, where the patentee refuses to license on any other basis and leaves the licensee with the choice between a license so providing and no license at all."[167] Therefore, a policy of reach-through licensing would probably be feasible, so long as the research tools companies offer licensees the option of a license on different terms, terms not contingent on payment of royalties on products outside the scope of the patent, and so long as the potential licensee agrees to reach-through royalties as a matter of convenience, as an effective way of determining the value of the patent, and not as a matter of coercion. This reasoning has been used successfully in recent cases. In *Sibia Neurosciences v. Cadus Pharmaceutical*, 225 F.3d 1349 (Fed.Cir. 2000), a jury in the Southern District of California awarded a verdict of damages for infringement of a cell based

[166] 395 U.S. at 135.
[167] 395 U.S. at 135.

screening method, using a damages calculation that clearly included royalties from products the infringer discovered using the research tool at issue (the judgment was reversed by the Federal Circuit, but on grounds of patent invalidity). In *Bayer AG v. Housey Pharmaceuticals, Inc.*, 228 F. Supp. 2d. 467 (D.Del. 2002), the court of the District of Delaware finally took the last step and actually upheld a reach-through licensing arrangement for a research tool. Housey held patents on a method of screening for protein inhibitors and activators, which, though covering no drug products directly, did have significant use in determining the potential of screened compounds to be developed as pharmaceuticals. Housey offered two possible licensing arrangements, one involving reach-through royalties (which had been agreed to by two licensees: Eli Lilly and SCIOS, Inc.), and one requiring a lump sum payment determined as a percentage of the licensee's research and development budget, taking into account anticipated use of the research tool (which had been agreed to by one licensee, Takeda Chemical Industries, Ltd.). Considering the influence of Housey's clients in the pharmaceutical industry, it was unlikely that Housey had exerted undue influence over them. The court found no evidence that Housey had impermissibly conditioned the license grant on the reach-through royalty provisions, determining that they were agreed to at the convenience of the bargaining parties, as the most efficient means of valuation of the patent license. Should the *Bayer* decision stand, it will provide a valuable bulwark in the storm of conflicting legal doctrines that surround the fledgling research tools industry.

Possible reforms

The current structure of the research tools industry, which relies on the legitimacy of its patents, of its assertions of infringement, and of its reach-through royalties, is assailed on all sides, by the *Bolar* amendment, by the doctrine of patent misuse, and by the old precedents and USPTO guidelines that create a heightened

35 U.S.C. § 101 utility requirement. Probably the most direct way to reinforce this structure is to include, in the overall scheme of Hatch-Waxman Act reforms, language that would limit the *Bolar* amendment in such a way as to reinforce the narrower holding of the Court in *Eli Lilly*. The other major threat to the research tools industry, the Court's decision in *Brenner*, is difficult to overrule legislatively, although its limited value as precedent, and the fact that it did not actually create an affirmative standard, make it more feasible to circumvent it through internal USPTO regulations that would relax the utility requirement.

Conclusion

In 1984 the Hatch-Waxman Act revolutionized the pharmaceutical industry, striking a balance between the interests of brand name and generic drug companies, fostering innovation while giving the public access to cheaper drugs, sooner. The current prescription drug market share held by the generic drug companies suggests that the Act was, in large part, successful at meeting these goals.

However, the playing field of the pharmaceutical industry has changed dramatically in recent years. Brand name drug companies have learned to exploit loopholes in the Act, prolonging their monopolies. The research tools industry, a significant new player on the field, has entered at a disadvantage, its rights artificially pitted against those of the generic drug industry by laws that never anticipated its arrival.

Current legislative reform efforts, prompted by FTC recommendations, are, to a considerable extent, addressing the former problem, and ignoring the latter. To successfully address these issues, to restabilize a system that is gradually descending into chaos, attempts to mend provisions of the Act have to take into account the fact that the economic and innovative calculus applied to the pharmaceutical industry has shifted, from the zero-sum game between the generic and brand name drug industries of the Hatch-Waxman era, to a new state of shifting equilibria between the synergistically operating research tools, brand name, and generic drug industries that can potentially be successfully harnessed for the benefit of all.