

**PRESENTATION:**

**THE EXPERIMENTAL USE EXCEPTION  
AND THE PHARMACEUTICAL INDUSTRY**

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I will discuss the U.S. perspective on experimental use, specifically under 271(e)(1),<sup>1</sup> interspersed with some background on Dr. Goddar's discussion of clinical trial cases, as well as a little bit of the Japanese perspective. My view is from the perspective of the generic drug industry *vis-a-vis* "big pharma," or brand name pharmaceuticals.

What is at stake? According to data from the 1996-97 Wall Street Journal, the development cost of your average pharmaceutical is about \$400-\$500 million; it takes ten to twelve years from the date it is discovered on the bench to the date it is put on the market. Approximately 1% of all pharmaceutical patents actually make it to clinical trials, and of those that make it to clinical trials only 4% actually make it to market. Therefore, only about 1 in every 2500 patents will have something to do with patent term extension or protection under 271(e)(1).

According to 1996 data from Prozac and Prilosec, their approximate U.S. sales per day were \$4.75 million. The advantage of getting days, weeks or months of extension for such blockbuster drugs is more than worth the cost, even if it means initiating litigation. For example, as you will see later in this discussion, if an ANDA is filed and the brand name company asserts a position that their patent is valid and is infringed, this can delay the approval of the ANDA for thirty months or until the results of a court decision. Therefore, it would be in the best interest of the brand name pharmaceutical company to invest several million dollars in litigation to allow their drug to be sold for several more days. If we have any brand name manufacturers here, I would be happy to be involved on this litigation team because I cannot spend \$4 million per day, so it would be more than worth your money.

The Patent Act provides a twenty-year term from filing in the U.S. for most cases. There are still some pre-GATT cases that have the seventeen-year term from the date of issuance.

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<sup>1</sup> 35 U.S.C. 271(e)(1).

The Hatch-Waxman Act<sup>2</sup> allows for two components: the extension of patent term for brand name companies who have lost term during FDA approval, and protection for generic manufacturers. The Act allows patent holders to seek extension of period lost during FDA approval. It allows for ANDA applications, and it allows for ANDA suitability positions where you can have variations from the drug components.

Incentives for the brand name companies include patent term extension and non-patent market exclusivity. For a new chemical, irrespective of patents, you can have up to five years of market exclusivity because the FDA will not approve a drug of that same chemical entity. Applications for new variations of other drugs that require new clinical investigations can get a three-year extension. There is also a 180-day exclusivity for the first generic to successfully challenge a listed drug's patent.

Essentially, the Hatch-Waxman Act was a repeal of the *Roche v. Bolar*<sup>3</sup> decision, which basically said that any testing prior to the expiration of the patent was an infringement of the patent. In order to obtain patent term extension under Hatch-Waxman Act, the following criteria must be met: (1) the patent must not have expired; (2) the term must never have been extended; (3) the application must be submitted by the record owner, not a licensee; (4) the product must have been subject to a regulatory review period before market approval; and (5) it must be the first permitted commercial marketing or use of the product. The application must be made within sixty days of market approval.

There are also interim extensions that you can get during review, for which you must identify the product, the patent and all other related patents, as well as state the duration and extent of activities for which you are requesting the extension. The scope of extended rights is limited to uses approved for the product, which are strictly correlated to what the clinical trials were and what the marketing is for. New drugs, methods of production, medical devices, food additives and color additives are all eligible for protection. Five years is the maximum extension period, and it is available if you have less than fourteen years left following marketing approval.

Under the Uruguay Round Agreements, there were still some patents that had the greater of seventeen years from issuance or twenty years from filing. Brand name companies were able to take advantage of this to have their patents extended by more than a couple of years.

There are also special laws that can be passed by Congress to protect any number of drugs, but you have to have the right political support. There are only a few drugs that have ever had their patents extended by an act of Congress because it is very difficult to get done; however, it is another option. There have been some international negotiations to remove the amendment in the U.S. which many foreign constituencies call the "*Bolar* Amendment," and to expand market exclusivity protection for new chemical entities from five to ten years, instead of having such allowance by patent term extension.

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<sup>2</sup> Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 1984 Stat. 1538 (codified as amended in scattered sections of 21 & 35 U.S.C.).

<sup>3</sup> *Roche Prod. Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 856 (1984).

I would like to focus on 271(e)(1) barriers to market entry and what brand name companies are doing to point out that this is where the conflict arises. Brand name company strategies to extend their position in the marketplace, which some refer to as “ever-greening,” include product reformulation, changes in formulation, and changes in dosage. For example, a brand name company at the end of their patent term, when the generic company is ready to enter the market, introduces an extended release formulation to a drug that previously required four doses. Although not patented, doctors think it is great because now patients only have to take the drug once a day instead of four times a day. Realizing that patients are not very good at taking their medication four times a day, most doctors may prescribe the one-time-a-day drug. This allows the brand name company to keep the market share they may not have so tied up. This strategy works better if they can patent the reformulation. Note that to do an ANDA, the generic company’s drug must be of the same strength, as well as contain the same active ingredient and formulation in order to rely on the brand name company’s data. The FDA does permit suitability petitions to change the strength of formulation but not the active ingredient.

The Hatch-Waxman Act provides market exclusivity irrespective of patents. If you design a new chemical entity, you get protection irrespective of patents, plain and simple. You also have exclusivity under what is called “orphan drug protection,” where you can get up to seven years if your drug is for treating under 200,000 patients per year that have a particular affliction. There are four exclusivity clauses in the qualifying criteria, which I won’t go through in detail. There is a five-year exclusivity term for new chemical entities and a three-year exclusivity term for a new use of an old chemical. There is a six-month pediatric exclusivity provision as well.

Remember, with a blockbuster drug, a six-month exclusivity provision could be quite lucrative. The exclusivity provisions do not allow for infringement or suits for infringement; instead, they just prohibit the FDA from approving the drug. This is similar to supplementary protection certificates in Europe, which protect marketing but not necessarily the other bundle of rights that come with a patent.

With all laws there are exceptions and exceptions to the exception. The exception under the market exclusivity provision is that a person may not even submit an ANDA until the exclusivity expires. The exception to the exception is that if an ANDA is to challenge a patent for a drug that has a five-year exclusivity provision, then the ANDA may be submitted only after the fourth year.

Another strategy to prohibit generics from entering the market, even though they may be testing under 271(e)(1), involves bio-equivalents. You can file a citizen petition with the FDA stating that the generic company’s drug is not good enough. For example, the purity is not good enough or their bio-equivalency data is not good enough. Whether this strategy is effective or not, it could potentially work as a delaying tactic – which could be well worth its weight in gold if you have a drug like Prilosec and you are making \$4.5 million per day.

In addition to the citizen petition, in several states, proceedings may be instituted before regulatory authorities to restrict the use of a generic drug. Texas, Virginia, and North Carolina are examples of where this has been done. For example, there could be state regulations that prohibit pharmacists from substituting a generic, unless the physician actually

writes on the prescription, “O.K. to substitute generic.” That is all regulated by local agencies.

Another interesting area that is often overlooked is trademark and trade dress. For example, if the pill is crosshatched and has a particular color – Prozac looks a particular way – there may be protection available for the look of the pill itself. Therefore, the generic company could not practice the crosshatch shape and colorization.

Copyright and labeling protection may be available as well. In 1999, there was a *SmithKline*<sup>4</sup> case that was appealed and it may or may not have been resolved yet. When you are filing an ANDA you have to copy the instructions or the insert of the original drug, to be used with the generic drug. SmithKline objected to this on grounds that it violated their copyrighted labels and inserts. Once again, even if this argument does not end up winning, it may provide a little more extension to market share.

Now let us look at experimental use in the United States. Under 271(e)(1) it is not an act of infringement to make, use, offer to sell, or sell, as long as it is for uses solely reasonably related to development and submission of information for the FDA. The first few cases interpreting the words “solely reasonably related” were very restrictive, saying in effect, “if it is not particularly for FDA approval we will not allow it.” Later, in *Intermedics*<sup>5</sup> the court said no, it is “solely uses” and anything reasonably related was okay. That opened the flood gates. It allowed for ANDAs, the Hatch-Waxman Act, and what is called a Paragraph IV Certification in ANDA. If there is a patent on the compound, you can either say that you do not want your approval to come into effect until the patent expires, or you can assert that the patent is invalid. Now, if you assert that the patent is invalid, the patent holder has forty-five days to respond and initiate a suit against you – which, as I mentioned earlier, can delay approval for thirty months or upon resolution by a court.

Historically in Europe, the testing of a generic copy of a patented drug constituted infringement. In some countries, there is no infringement if a drug is used to prove claims of a patent. That is kind of the old standard in the U.S. If you are just testing to prove that it works as it says it does and you have no commercial goal, then potentially there is no infringement. But, as Dr. Goddar stated, recent German decisions have liberalized this approach, such that all experimental uses directed towards gaining knowledge are exempt and the permissibility of experimentation is not contingent on the purpose they seek to achieve. That was the *Clinical Trial I* case that Dr. Goddar spoke of. One question remaining in that case is that the facts were based on a new use. So is the case limited? The *Clinical Trials II* case indicated that in fact it is not limited.

Uncertainty remains in many other jurisdictions. There has been a mini-*Bolar* provision instituted by France to protect a minimum amount of experimental use, which is supposed to be followed by a more expansive provision. Here again, the question is whether there is saving grace in the Supplementary Protection Certificate in Europe. That would be the extension that allows for market exclusivity only for your patent. I ask

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<sup>4</sup> *SmithKline Beecham Consumer Healthcare, L.P. v. Watson Pharm. Inc.*, 211 F.3d 21 (2<sup>nd</sup> Cir. 2000).

<sup>5</sup> *Intermedics, Inc. v. Ventritex, Inc.*, 152 F.R.D. 188 (N.D. Cal. 1991), *aff'd.*, 991 F.2d 808 (Fed. Cir. 1993) (non-precedential decision).

because blockbuster drug companies will likely seek Supplementary Protection Certificates. If you are solely under the Supplementary Protection Certificate, then you could do the testing.

In March 1996 in Japan, the Nagoya District Court ruled that clinical testing of generic copies constituted infringement. In April 1999, the Japanese Supreme Court ruled that performing tests does not constitute infringement under Section 69(1) of the Patent Law. In that particular case, Ono Pharmaceuticals requested an injunction, which the Osaka High Court denied. Ono Pharmaceuticals appealed and the Second Petty Bench of the Supreme Court affirmed the High Court. Basically, Kyoto Pharmaceuticals asserted that it was not an infringement because the acts complained of were working a patent for experimental research, under Section 69(1). The Court ruled that it was not infringement to carry out experiments necessary to obtain data for market approval. It reasoned that one should be free to exploit the invention as soon as the patent expires.

Similar reasoning has been used in Germany and in the United States. Infringement, however, could still be asserted if, during the patent term, manufacturing were going beyond what is necessary for testing. The summary being that all testing necessary for regulatory approval is non-infringing.

In conclusion, most testing for generic versions of drugs is allowed in several European countries, the U.S., and Japan. In Europe, your safest bet, as Dr. Goddar said, is Germany. Such testing in the U.S. is covered by 271(e)(1), and in Japan under Section 69(1). Negotiations are currently underway in the Congress to revisit Hatch-Waxman, but it is going to be a long battle because there are a lot of competing interests. There are recent court decisions in the U.S. that affirmatively expand 271(e)(1) coverage to cover nearly all medical devices. There was some question early on that they only covered class III medical devices due to the extensive testing required, but that has since been expanded.

Thank you.