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Proactive Brand Protection Strategies For Pharma Innovators

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Chinese philosopher, general and military strategist Sun Tzu once said "[k]nowing the enemy enables you to take the offensive, knowing yourself enables you to stand on the defensive." Given the enormous resources it takes for the brand name pharmaceutical manufacturer to successfully bring a drug to market, coupled with the incentives for generic manufacturers to methodically and strategically plot entry into that same market, Sun Tzu's words ring increasingly true for innovator drug companies.

Brand name drug manufacturers are painfully aware that at some point after U.S. Food and Drug Administration approval of most products they will likely face generic challengers by virtue of the Hatch-Waxman Act[1]. For each product challenged, the brand product manufacturer may have to fend off generic entry via complex patent litigation, often against multiple defendants in multiple jurisdictions, coupled with simultaneous validity challenges in inter partes review proceedings before the U.S. Patent and Trademark Office. Expenses associated with these cases quickly add up and are further escalated by regulatory and FDA procedural issues that may arise. But the loss of revenue from a blockbuster drug due to unanticipated early generic entry can be a devastating and irreversible blow to the innovator company that planned to recoup the investment associated with bringing a brand pharmaceutical product to market for the first time. Consequently, many companies aggressively litigate to defend their products despite the high costs of doing so.

Both the financial expenditures and risks of losing market share may be significantly mitigated with early risk assessment and strategic planning by the brand sponsor/patentee. Specifically, by engaging in pre-ANDA strategic legal counseling well before any Paragraph IV certification, ANDA litigation or IPR begins, brand pharmaceutical companies are better able to defend their intellectual property as well as create additional barriers to generic entry. Moreover, while trial attorneys typically must litigate the facts they are "given," pre-litigation analysis of this type provides a rare opportunity for the brand manufacturer to identify weaknesses or strengths in their case early enough to address or enhance them, respectively. Such counseling has the potential to afford the branded manufacturer foresight and with that the chance to potentially shape in advance the record at a trial.

Background

In light of the reduced regulatory barriers to entry associated with approval under the Hatch-Waxman Act and the potential revenue and market share to be gained by early market entry, generic manufacturers are highly incentivized to compete in the market for pharmaceuticals by aggressively challenging brand name patent owners — sometimes immediately upon approval of the brand drug.

A recent report by the Tufts Center for the Study of Drug Development estimates that the cost of developing a prescription drug that gains market approval is $2.6 billion, representing a 145 percent increase since 2003.[2] The Hatch-Waxman Act and subsequent amendments have simplified the FDA generic approval process such that the brand product manufacturer's patents are often the last barrier to entry for the ANDA applicant's launch of a generic product. Not surprisingly, ANDA litigation continues to be robust. From 2009 to mid-2017 there were on average 311 cases filed per year.[3] In addition to challenging the patents on brand drugs in district court via the Hatch-Waxman Act, ANDA filers now often contest the validity of those patents via IPRs before the USPTO. Since 2012, the USPTO has instituted trial on approximately 61 percent of the bio/pharma patents challenged in IPRs, which translates to additional risk to the brand manufacturer and patentee.[4]

Examples of heavily litigated drugs include, for example, Abilify, Vascepa and Effexor XR, all of which are or were highly successful in the market.[5] Abilify, prescribed for mental illnesses, had sales of $2.1 billion in the U.S. in 2012 that declined to $600 million in 2015 due to the approval of generic rivals.[6] Vascepa is prescribed to reduce levels of triglycerides and had an annual revenue of $130.1 million in 2016.[7] Effexor XR, an anti-depressant, was the subject of at least 17 cases spanning five years in varying jurisdictions.

The Generic Manufacturer's Perspective

The Hatch-Waxman Act was intended to promote healthy competition in the marketplace by encouraging pharmaceutical research while facilitating entry of lower-priced generic products by approving generic versions of drugs based on bioequivalence rather than the long, expensive human clinical trials required for initial approval of a branded drug. The key window for sales for the brand manufacturer is obviously the period between the brand product launch and the approval of the first generic competitor. Generic manufacturers are keenly focused on closing that window even before the brand drug is awarded FDA approval.

Given the potential revenue streams and the advantages of the 180-day period of market exclusivity awarded to the first-to-file applicant who submits an ANDA to the FDA and who prevails in a Paragraph IV challenge, generic manufacturers have become sophisticated, strategic and aggressive in their approach to be the first to bring a lower cost alternative to the market. When generic manufacturers begin to target potential products for development, they retain experts, consultants and counsel to map out a strategy to obtain regulatory approval as quickly as possible, including assessing all options for challenging or designing around an innovator's patents, as well as for addressing or avoiding other potential barriers to generic entry. Generic companies may even attempt to prevent other generic companies from entering the market by obtaining their own patents or FDA exclusivities. They may also advocate for favorable changes to the law. The value of their sophisticated long-range planning is not to be underestimated.

U.S. generic drug sales reached an estimated $70 billion in 2015, representing a quarter of the global market.[8] While generics make up only 22 percent of total prescription sales, their share of filled

prescriptions has risen from 19 percent in 1984 to 88 percent in 2015,[9] reflecting an extremely competitive sector. Furthermore, over time even blockbuster drugs typically lose their profitability. When a brand-name drug loses its patent protection due to a single generic competitor, prices initially decline slowly. The first generic manufacturer need only price its product at just below the branded drug's price. A price point of even 90 percent of the brand name is typically competitive. But over time, as more generics enter the market, the price falls precipitously — frequently settling at 15-20 percent of the original price of the innovator drug.[10] For example, Lipitor — once a blockbuster product priced at hundreds of dollars per month — now costs as little as $10 for a monthly prescription.[11] As a result of this downward pricing pressure the brand company eventually ceases marketing the product or markets its own competing generic product.

Considerations and Strategies for Innovator Pharmaceutical Companies to Protect their Investments

To meet the competitive challenges posed by generic manufacturers, an innovator pharmaceutical company's pre-ANDA litigation due diligence and counseling should be undertaken well before the threat of litigation arises. Indeed, for high value drugs such as Harvoni (sales of $10 billion in 2016 or $27 million per day), Lantus Solostar (sales of $5.7 billion in 2016 or $15.6 million per day) or Januvia (sales of $4.8 billion in 2016 or $13.15 million per day), which are among the top 10 branded medicines by sales in 2016[12], the investment in pre-ANDA strategizing is minimal when compared to the risk of permanent loss of intellectual property protection and market share.

A multipronged drug development and pre-ANDA litigation strategy should include:

- Early and coordinated effort during drug development and patent prosecution to prepare for the likely possibility of a generic entrant. Patent counsel with regulatory experience and Hatch-Waxman counsel should work closely with the research, business and legal departments to identify potential weaknesses in patents as well as enforce barriers to generic entry, including by building a strong Orange Book with as many patents and exclusivities as possible. Early identification of key issues and weaknesses affords the time necessary for a fulsome investigation and avoids surprises during litigation. Further, brand manufacturers are often forced to defend their patents and products against multiple ANDA filers in different venues with different local patent rules. This early preparation may help avoid chaos and missed opportunities for victory or a favorable settlement, as well as unnecessary shortening of the brand product's lifespan on the market.

- Evaluation of potential bases for filing a citizen petition[13] with the FDA to maintain safety and efficacy standards. One potential practical effect of, for example, challenging the less stringent bioequivalence standard or identifying possible safety or efficacy issues associated with a different generic dosage form via citizen petition is to compel generic companies to take additional time to ensure that their products are in fact safe and effective. This sometimes requires the generic company to use a patented dosage form or process. In those cases, either a patent challenge, license or both is typically required of the generic manufacturer to obtain marketing approval. However, timing is key when using this process because the FDA has instituted strict time limits within which to assess such petitions and pre-ANDA citizen petitions filed by the brand company may even influence evaluation of ANDA or 505(b)(2) applications.[14]

- Consider the impact of a "risk evaluation and mitigation strategies" or REMS program. If a REMS program or system is approved and required for a branded drug in order to ensure a patient's health and safety, then a potential generic entrant would likewise be required to address the REMS requirement and undertake efforts to meet such safety standards for FDA marketing approval. REMS programs may also soon be required to be shared between innovators and generic companies, but some companies have obtained patents on REMS safety programs, adding roadblocks and increasing the expense to generic challengers seeking FDA approval.[15]

- Early retention of experts. Pharmaceutical litigation is often distilled into a "battle of the experts." Early retention of expert consultants and witnesses gives the innovator a better chance of retaining the best expert, particularly in fields with a discreet number of qualified candidates. It also provides the opportunity to thoroughly test strategies on infringement, invalidity and unenforceability early enough to potentially mitigate weaknesses through USPTO procedures or to facilitate making moderate improvements (without affecting safety or efficacy) to the brand product, i.e., patented reformulations that may be listed in the Orange Book, thereby potentially compelling the generic company to likewise improve its product.

- Pursuing a portfolio of non-Orange Book patents. Identifying potential design-around strategies and possibly filing for patents on processes that cannot be listed in the Orange Book, but which could be asserted separately, should be explored.

- Testing theories by conducting mock hearings or mini-trials in advance of submission of an ANDA or 505(b)(2) ("paper NDA"). Retaining outside counsel to conduct mock arguments, mini-trials on discrete issues or inter partes review, for instance, will help in understanding the generic challenger's perspective as well as in sharpening the brand drug manufacturer's position. A more realistic mock adversarial contest provides the opportunity to confidentially test the strengths and weaknesses of potential infringement and invalidity theories without the chaos of active litigation. It also allows for an unbiased and more realistic review of the innovator's own strategies by understanding how judges may view their case. In addition, if affords the opportunity to evaluate lay and expert witnesses. Based on the insights gained, the innovator can modify its approach to litigation, for example, by correcting patentability issues, resolving regulatory errors or fortifying defenses to inequitable conduct claims. Given the inevitability of ANDA litigation, especially over high value products, a simulated adversarial contest is a cost-effective tool for helping to stave off generic entry for as long as possible.

In short, Sun Tzu's words are applicable not only to warfare, but to competition in the marketplace as well — the key to effectively prepare for battle over a product that may be worth billions of dollars and avoid irreversible loss of market share to a generic opponent whose attack was silently launched and executed years in advance is to strategize as early as possible.

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[1] Drug Price Competition and Patent Term Restoration Act (Public Law 98-417)(1984), codified at 21 U.S.C. § 355(j).

[2] Rick Mullin, Cost to Develop New Pharmaceutical Drug Now Exceeds $2.5B, Scientific American, November 24, 2014, available at https://www.scientificamerican.com/article/cost-to-develop-new-pharmaceutical-drug-now-exceeds-2-5b/

[3] See Lex Machina Press Release, Pharmaceutical Patent Litigation Filings Have Declined for the First Time in Three Years According to Lex Machina's Hatch-Waxman/ANDA Litigation Report, April 27, 2017, available at https://lexmachina.com/media/press/pharmaceutical-patent-litigation-filings-declined-first-time-in-three-years/

[4] USPTO Trial Statistics, October 2017, available at https://www.uspto.gov/sites/default/files/documents/trial_statistics_october_2017.pdf

[5] Id.

[6] Bristol-Myers Squibb Reports Fourth Quarter and Full Year 2016 Financial Results, available at https://news.bms.com/press-release/financial-news/bristol-myers-squibb-reports-fourth-quarter-and-full-year-2016-financia

[7] Amarin Corporation plc Press Release, AMARIN REPORTS RECORD FOURTH QUARTER AND FULL YEAR 2016 FINANCIAL RESULTS AND PROVIDES UPDATE ON OPERATIONS, Feb. 28, 2017, available at http://investor.amarincorp.com/releasedetail.cfm?releaseid=1014797

[8] 2016 Top markets Report Pharmaceuticals, U.S. Department of Commerce, International Trade Administration, available at https://www.trade.gov/topmarkets/pdf/Pharmaceuticals_Executive_Summary.pdf

[9] 2016 Top markets Report Pharmaceuticals, U.S. Department of Commerce, International Trade Administration, available at https://www.trade.gov/topmarkets/pdf/Pharmaceuticals_Executive_Summary.pdf

[10] FDA.gov, Generic Drug Facts, available at https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM575213.pdf

[11] Charles Ornstein and Katie Thomas, Generic Drug Prices Are Falling, but Are Consumers Benefiting?, The New York Times, August 8, 2017; Aaron Smith, War Against Cholesterol Gets Cheaper, CNN Money, available at http://money.cnn.com/2011/11/30/news/companies/pfizer_lipitor/index.htm

[12] See Marcia Frellick, Top-Selling, Top-Prescribed Drugs for 2016, Medscape.com, Oct. 2, 2017, available at https://www.medscape.com/viewarticle/886404

[13] A citizen petition is a communication to the FDA and may be submitted to request the Commissioner of Food and Drugs to issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action. See 21 C.F.R. 10.30

[14] 81 Fed. Reg. 78500, 78501 (Nov. 8, 2016) in which the FDA noted, "[w]hen submitted early, such as when we are making decisions about the bioequivalence requirements for a generic drug product or before we have received the first ANDA, 505(b)(2) application, or 351(k) application for a drug or biological product, a [citizen] petition may contain information that can contribute towards our evaluation of an application."

[15] FDA.gov, Use of a Drug Master File for Shared System REMS Submissions Guidance for Industry, November 2017, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm584202.pdf