Review Article

Authorized Generics Practice

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ABSTRACT

Due to lower price and same quality, a number of prescriptions have been increased for generic equivalents of branded products. After the expiration of patent life, profits for an innovator company decline due to market entry of the generic version of same active pharmaceutical ingredient. To regain this loss, some branded companies have started strategies to launch their NDA - approved product under different labels through their subsidiary company or partnering with a generic firm. An authorized generic entry could affect the timing of the generic entry, brand - name and generic prices, and generic penetration. This strategy will provide benefits to customers, generic firms, and innovator firms as well.

Background on pharmaceutical regulation

Food Drug and Cosmetics Act (FDCA) of 1938 governs the manufacturing and marketing of pharmaceuticals in the U. S. A. Food and Drug administration (FDA) is the primary regulatory agency for pharmaceutical marketing approval.[1] The marketing of a new drug requires filing a "New Drug Application" (NDA) with the FDA, along with clinical tests showing that the drug is both safe and effective for the intended use.[2] Approved drugs, and certain underlying patents, are listed in the "Orange Book." An innovator drug applicant must include in its NDA information about any patents that claim the drug product that is the subject of the NDA, or the use of such drug product. The FDA publishes this patent information upon approval of the NDA or a supplemental NDA in Approved Drug Products with Therapeutic Equivalence Evaluations, which is generally known as the Orange Book.[3]

Drug price competition and the Patent Term Restoration Act of 1984 (Hatch Waxman Act)

In 1984, Congress enacted the Hatch Waxman Act with the intent to open up the market for products that were previously patent protected. The goal behind this act was that to expedite the arrival of generic drugs to market and to induce brand name pharmaceutical companies to invest in R&D and develop new drug products. This act benifited both generic and innovator firms. This act has created framework for patent term extensions and nonpatent exclusivity periods for brand name drug products.[4] It has provided for pre -patent expiration testing(BOLAR PROVISION), abbreviated NDA (ANDA) and generic drug exclusivity. The first generic manufacturer to file an ANDA with a successful paragraph IV certification (a patent challenge or claim of noninfringement) is awarded a 180-day marketing "exclusivity" period during which no other ANDA filers can market their version of the drug dose.[5] This act has increased market shares of generic products. In 1984, just 14% of all prescriptions dispensed were for generic drugs. In contrast in 2001, approximately 48% of all prescriptions dispensed were for generic drugs. The frequency of paragraph IV certifications has also increased. Between 1984 and 1989, only 2% of ANDA submissions contained paragraph IV certifications. This share increased to 12% between 1990 and 1997 and then to 20% between 1998 and 2000. Granting of 180 day exclusivity by the FDA also increased, from none between 1992 and 1998 to 31 drugs between 1998 and 2002. An ANDA applicant must include in its ANDA a patent certification as described in section 51 505(j)(2)(A)(vii) of the Act. The certification must make one of the following statements: (1) such patent information has not been filed; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted.

Section 505 of the Federal Food, Drug, and Cosmetic Act describes three basic types of new drug applications:[6]

1. Section 505(b)(1): An application that contains full investigations of safety and effectiveness (NDA),
2. Section 505(b)(2): An application that contains full investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not

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conducted by or for the applicant and for which the applicant has not obtained a right of reference

3. Section 505(j): An application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (ANDA).

Factors encouraging generic market entry

Generics are produced and marketed under ANDA. According to the FDA, "A generic drug is a copy that is the same as the brand-name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use."[7] A generic medicine is a faithful copy of a mature drug, no longer under patent marketed with the chemical name of the active ingredient. It is a pharmaceutical product intended to be interchangeable with the originator, manufactured without a license from the innovating company and marketed after expiry of a patent or other exclusivity rights. Reasons for increased marketing of generics are such as generics generally do not require safety/efficacy data, lower registration fee, 180 day market exclusivity for the first filer challenging the invalid patent or developing non infringing process.[8-9] Patients agreed that generics are less expensive and a better value than brand name drugs and are just as safe.[10] India is the biggest supplier of cheaper versions of essential drugs. India is the main source of cheap and quality medicines to the developing countries. Fifty generic manufacturers are there in USA. Among them, major are Mylan Labs, Sandoz (Novartis), Teva, and Watson [Figure 1].

Authorized generic practice overview

As we all know, an innovator loses 40 - 50% of the market within 2 - 3 weeks after the loss of the patent term. This realization has caused many innovator companies to rethink their business strategies when a blockbuster drug loses patent protection.[11] Many pharmaceutical companies are experimenting with a relatively new kind of product called an authorized generic (AG) to hold on to a larger share of a revenue stream from the drug once it loses patent protection and it falls prey to generic manufacturers. The first challenger to break the patent on a billion dollar blockbuster can expect to reap $400 - $500 million in sales during those initial 180 days. That 80% failure

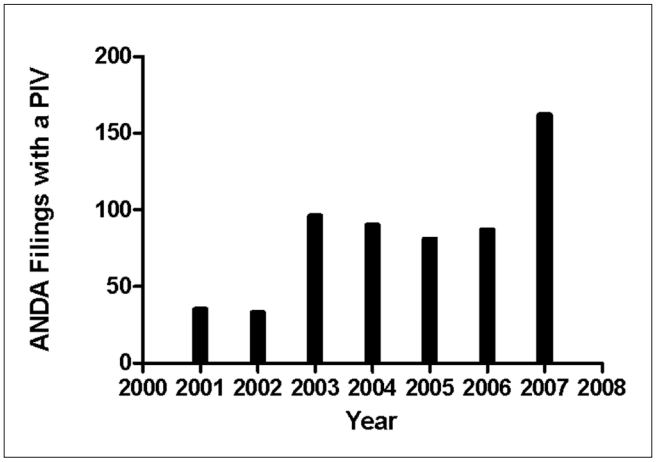

Figure 1: ANDA fillings with a para IV[28]

record encouraged brand-name makers to search for other ways to defend their products and revenues. According to the Generic Pharmaceutical Association (GPHA), nearly every successful patent challenge since 2003 has been met with an AG counterattack. If the brand maker issues an authorized generic, generic sales fall to $150 - $200 million.

According to US FDA, AGs may be defined as any marketing by an NDA holder or authorized by an NDA holder, including through a third party distributor, of the drug product approved under the NDA in a manner equivalent to the marketing practices of ANDA applicants. An AG is a pharmaceutical product that was originally marketed and sold by a brand company, but is relabeled and marketed under a generic product name. An innovator's drug product is sold as a generic with no trademark or branding containing a different new drug code (NDC) number as a generic substitute for the brand. AGs are considered brand products by the FDA, so the AG does not have to go through the rigorous, abbreviated approval process required by a true generic. AGs compete on pricing, quality, and availability with generic products approved by the FDA as substitutable for specific brand products. AGs are also called as Branded, Pseudo, Flanking, Authorized Copy, or Brand in bottle. The FDA treats the new drug as a brand product and that allows the new manufacturer to market it during another generic firms 180-day market exclusivity period. An AG may be marketed by the brand company itself or through a subsidiary, or the brand company may license the product to another company for marketing in return for royalties. The brand companies may choose to launch an AG for a variety of reasons, including to settle patent litigation with a generic company by partnering with it, to participate in the generic market once the generic competition starts, or to maintain manufacturing capacity for the drug substance or the drug product.

Actually, the intent of authorized generic drugs is not to provide benefits to consumers but competition and to capture the market share by keeping the drug price low by the innovator companies while launch it.[12] Others' thinking is that innovator companies launch authorized generic drugs to discourage the generic companies from challenging patented drugs but they have not proved it. As a defensive move to offset generic competition, brand manufacturers are striking distribution and manufacturing agreements with generic companies. Under these deals, brand companies manufacture products at their plants and generic companies distribute the " authorized generics " in exchange for royalty payments. Partnerships between innovator pharmaceutical and generic companies may seem unlikely with so many court battles over patents, but AGs offer substantial benefits to both sides, according to industry observers. Certainly, both sides also reduce the legal costs of fighting each other in court. More recently, 19 AGs were launched from 1992 to 2002 and since 2003, 121 AGs have been launched. Among them, 64% were launched by generic drug companies and only 36% were launched by brand subsidiaries. Brand products with over $138 billion in sales could face generic competition between now and 2015. AGs practice can be traced back to the 1990s where Bradley Pharmaceuticals had launched its authorized generics Pamine® (methscopolamine bromide) through its subsidiary company A. Aarons [Figure 2].[13]

Marketing of AGs

Some firms market AGs through their subsidiary such as Sandoz (Pfizer), Greenstone (Pfizer), or Patriot (Johnson & Johnson). Other

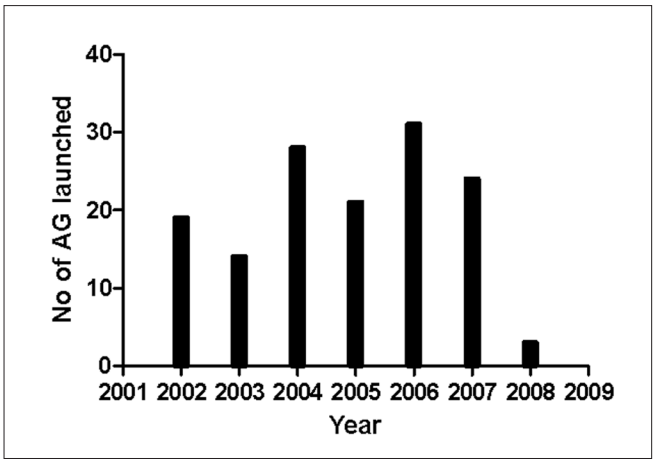

Figure 2: No. of AGs launched from 2001[28]

firms license AGs to generic companies such as Teva, Mylan, and Barr in order to settle or forestall patent challenges.Some companies use third-party generic firms such as Prasco to distribute AGs. And some firms use all three strategies, depending on the drug and the potential competition. In the case of "unilateral" AGs practice, innovator companies by own or through their subsidiary company launch their branded generics., e.g., Pfizer has its subsidiary Greenstone. And in the case of Via License Agreements, innovator companies are giving license to generic companies to launch their branded generics. Like innovator companies are Pfizer, GSK, Proctor and Gamble, while generic companies are Mylan, Par, and Watson [Table 1].[14]

Typical timing of AGs market entry

The authorized generic drugs are generally launched during a drug's 180-day exclusivity period of ANDA filer with paragraph IV certificates or simultaneously on the first day when the first ANDA filer launches its generic version. An AG may enter in the market during NDA holder's exclusivity period.

Benefits of launching an authorized generic

The authorized products usually look just like their brand name counterparts, so dispensing is easier, and pharmacists say that they like a brand manufacturer's products. Because AGs are the already approved brand product under a different label, they do not require marketing approval from the FDA. Health plans often require or encourage generics over the brands due to cost advantage.[15,16] This strategy also provides bargaining chip in patent litigation to avoid loss during patent litigation with a generic counterpart. The settlement of patent litigation saves resources of courts/parties, and permitting generic entry prior to patent expiration. Launching an AG will increase competition in the market and hence will reduce prices. AG marketing recoups some losses of the brand firm which occur after generic entry. One hypothesis is that it reduces challenges to NDA's but it had been proved wrong. AGs provide consumers the highest brand quality at generic prices. A generic company may get the benefit of launching branded generics by partnering with an innovator company and share the profits or pay royalties to the innovator firm. For example, a generic company may be first on a 5 & 10 mg product, but not on the 15 mg. An AG deal on the 15 mg will allow the company to offer a full complement to its customers.

Criticism of AGs

Some generic companies had criticized about launching AGs during the 180days exclusivity period given by the Hatch Waxman Act. They had told that it violates the FDCA, 1938. It violates the first ANDA's statutorily granted 180 day exclusivity. Packaging and labeling the branded drug as a generic is "misbranding" under the FDCA and misleading to consumers. But Watson and par pharmaceuticals had preferred the strategy of launching branded generics by innovator company through partnering with generic firms.[17]

Do AGs further the goals of Hatch Waxman?

Answer is both yes and no. Yes in the sense that AGs increase the competition in the market during generic companies 180 day exclusivity and thus reduce the price of a product or before patent expiration patients can get the branded product in a generic version at lower cost. There is no evidence that AGs slows the filing of ANDA's or paragraph IV challenges. ANDA filings have increased every year since 2002. In fact, filings in 2007 were nearly five times the filings in 2002. Paragraph IV filings have remained steady from 2003 to 2006, and almost doubled in 2007. The number of companies filing Paragraph IV challenges has increased from 42 to 78 between 2003 and 2007. No answer is in the sense that AG launching during 180 day exclusivity violates Hatch Waxman benefits to the first filer with paragraph IV certification or an AG may deter entry, which may lead to higher prices. AG launching

Table 1: Examples of authorized generic products[27]

Generic company	Patent holder	Product	Date of approval
Par pharmaceutical	GlaxoSmithKline	Paroxetine	April 2003
Andrx	Pfizer/ALZA	Glipizide ER Tablet	September 2003
Watson	GlaxoSmithKline	Bupropion	Jan 2004
Watson	Procter & Gamble	Nitrofurantoin	March 2004
Prasco laboratories	Sanofi-aventis	Leflunomide	July 2005
Par pharmaceuticals	Bradley pharmaceuticals	Doxycycline monohydrate Tablet	Dec 2005
Par pharmaceuticals	GlaxoSmithKline	Fluticasone propionate	April 2006
Dr Reddy's	Merck & Co	Finasteride	June 2006
Dr Reddy's	Merck & Co	Simvastatin	June 2006
Par pharmaceuticals	Astra Zeneca	Metoprolol succinate	November 2006
Actavis	Pfizer	Glipizide ER Tablet	November 2006
watson	Savient pharmaceuticals	Oxandrolone	December 2006
Par pharmaceuticals	GlaxoSmithKline	Ranitidine hydrochloride syrup	April 2007
Prasco laboratories	Sanofi-aventis	Zolpidem tartarate Tablet	May 2007

is a means of protecting weak patents. The study, "The Impact of Authorized Generic Pharmaceuticals on the Introduction of other Generic Pharmaceuticals", noted that generics that launched without a competition from AGs produced 4.6% higher margins than generics launched with a competition from authorized generics. The report concluded, however, that the prospect of AGs does not discourage generic drug makers from mounting patent challenges or introducing their own generic products.

AGs - The antitrust risks

The practice of AGs can be challenged under Section 1 or 2 of the Sherman Act or State Unfair Competition Acts.A predatory pricing claim under Section 2 of the Sherman Act alleges that the brand company priced its AG in an unfair manner with an object to eliminate or retard generic competition and thereby gains and exercises control over the price.[18]

Battle over generic exclusivity in U. S. courts

Some innovator companies had launched their patented product as an AG by own or third party license during the 180 day exclusivity period of generics products. Therefore some generic companies had filed a petition against brand company in US FDA,. e.g., Mylan Pharmaceuticals reportedly lost an estimated $30 million in revenues when Proctor & Gamble licensed Watson to sell the authorized generic version of nitrofurantoin for urinary tract infection treatment just as Mylan was about to bring its own generic version to the market. A citizen petition had been filed by Teva and Mylan Pharmaceuticals in US FDA that the AG violated the policy and intent of the Hatch-Waxman Act.[19,20] AGs undermine the balance created by Hatch-Waxman, of encouraging generic entry while maintaining sufficient incentives for innovation. Teva petitioned the FDA to prohibit Pfizer Inc. from marketing a generic version of Accupril® until after Teva's 180-day exclusivity.[21] Mylan petitioned the FDA to prohibit the marketing and distribution of AGs until the expiration of the 180-exclusivity period. But US FDA has denied both petitions. FDA had denied both petitions by giving reasons that marketing an AG during the exclusivity period does not violate the FDCA and FDA lacks authority to require FDA approval and the filing of a supplemental NDA prior to marketing an AG.

Opponent views

For a generic drug company filing an ANDA for generic drug approval on an existing drug and a paragraph IV challenge to the patent are major and risky investment. After approval, if the successful generic drug company needs to compete against the innovator company's AG during the 180-day market exclusivity period, then there is no reward for risk. And core purpose of Hatch Waxman is to expedite and maximize the introduction of cost-saving generic drugs, while protecting all legitimate patent rights of drug product innovators but without unintended windfalls to crafty companies.[22] Congress did not intend for brand-name companies to benefit from the 180 day exclusivity provision. Only qualified ANDA applicants are entitled to market and sell generic versions of a branded product prior to the expiration of a 180-day exclusivity period. GPHA believes that the use of AGs undermines the Hatch-Waxman Act by devaluing the 180-day exclusivity period incentive. Ultimately, consumers pay the price as brand companies keep drug prices high and access to affordable medicine is delayed.[23]

Proponent views

A central goal of Hatch Waxman is to promote price competition in prescription drugs upon expiration or resolution of an NDA holder's patent rights. Congress intended that first ANDA filers would receive a limited competitive advantage over subsequent ANDA filers but would be forced to compete with the approved NDA product. AGs do not discourage patent challenges. AG practice promotes competition and consumer welfare. AG arrangements promote the early introduction of multiple competitively priced products and provide consumers with faster access to lower priced drugs. AG practice permits brand-name firms to recoup the costs of drug development and may fuel innovation.[24] Watson and Par supported the availability of AGs, claiming that partnering with brand manufacturers benefited consumers.[25]

Conclusion

The strategy of a launching branded product under approved NDA with a different label is beneficial for the innovator company to regain some losses which occur after patent life expiration The prospect of competition to generics from AGs during the 180-day exclusivity period, on balance, benefits consumers. No empirical evidence was found that the prospect of competition from AGs has reduced either patent challenges by other generic manufacturers or the development of new generic products. Even without competition from an AGs, a generic manufacturer that successfully challenges a patent may face competition during the 180-day period from other generic manufacturers offering the same molecule in different dosages.[26] The ability of drug developers to market or license authorized generic versions of their products also increases their R&D investments, leading to more new drugs. The competition from AGs does not reduce R&D by generic manufacturers, and therefore should not reduce or delay the introduction of future generic products.

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