Medicare and the New Generic Drug Legislation
Marvin M. Goldenberg, PhD, RPh, MS

The high cost of prescription drugs in the U.S. today is of major concern to many segments of the population, especially the large number of older adults. Because expenditures on medications have risen sharply during the past two decades, Congress has been under great pressure from the elderly and other consumer groups to control drug prices. However, price controls would reduce the number of new drugs introduced into the market; prices are high partly because research and development (R&D) is very expensive.

The recent passage of the Medicare Modernization Act (MMA), formerly known as the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (DIMA) by Congress addresses this concern through the proposed elimination of the loopholes in the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch–Waxman Act). There are now new regulations to help speed the introduction of generic drugs to market, thereby giving patients some lower-cost alternatives.

This article reviews the obstacles that were encountered when generic drugs were first introduced in the U.S. and the federal legislation that ultimately led to the provisions about generics in the recently passed Medicare law.

BACKGROUND

In 1984, the Drug Price Competition and Patent Term Restoration Act, more commonly known as “Hatch–Waxman” patent reform legislation (Public Law 98-417), sought to strike a balance between (1) name-brand (or “pioneer”) drug companies seeking increased patent life because of the long time it took for the U.S. Food and Drug Administration (FDA) to approve a new drug and (2) generic companies that wanted to increase competition by bringing their alternatives to market. The Hatch–Waxman Act was a “compromise” piece of legislation that balanced the needs of the pioneer drug industry to recover part of a drug’s patent term that was lost during the approval process at the FDA and the need to bring generic drugs to market upon the immediate expiration of the drug’s patent term.

The Hatch–Waxman Act initially resulted in a win–win situation for consumers, by providing incentives for generic drug manufacturers to bring their products to market—and they did. Since the passage of the Act, the generic share of the drug market has increased from 19% to 42%. The Act also included patent extensions as incentives for name-brand companies to develop new products. After Hatch–Waxman was passed, name-brand companies spent more money on R&D than they did before passage.

THE HATCH–WAXMAN ACT

A Critical View

Title I of the Act (Table 1), which addressed drug price competition, specifically authorized Abbreviated New Drug Applications (ANDAs) and prohibited the FDA from asking for more than bioavailability studies for approval. In that regard, this piece of legislation was unique because it tied the hands of a regulatory agency in the area of public health by specifying that the FDA could require bioavailability studies only for ANDAs. In contrast, five-year data exclusivity for new molecular entities (NMEs) provided for a period of exclusivity such that once an NME was approved, a generic version could not be approved for five years (Table 2). The Act also called for a three-year data exclusivity period for supplements requiring clinical trials.

According to the Act, one of four certifications (now referred to as paragraphs I, II, III, and IV) had to be made upon the filing of ANDAs (see drug and patent listing requirements in Table 3). Manufacturers had to certify:

1. that the drug had not already been patented, or
2. that the patent had already expired, or
3. that the generic drug would not go on the market until the expiration date of the name-brand drug’s patent had passed, or
4. that the patent was not infringed or invalid.

The need for patent certifications arose from the legislative intent:

1. to permit the marketing of generic copies of pioneer products immediately upon the expiration of any relevant patents,
2. to encourage generic companies to challenge innovator patents,
3. to provide a timely, effective mechanism for patent holders to protect their rights in cases of patents alleged to be invalid or not infringed by the generic product,
4. to prohibit FDA’s approval of any ANDA application whose marketing would infringe a valid patent covering the pioneer product until the parties have had a meaningful opportunity to attempt to resolve the problem.

While the Hatch–Waxman legislation was pending, a major hurdle involved paragraph IV certification. If a generic company said that the patent was invalid or not violated, how long would the FDA need to wait before approving the generic drug for marketing? For much of the debate, that period was 18 months; however, through the work of the research industry, that time period was changed to 30 months. Thus, a 30-month litigation (cooling-off) period exists, so that after a generic company determines that the patent is invalid or not breached, it must notify the patent owner. The patent owner has 45 days in which to file an infringement action and then another 30 months of exclusivity before an ANDA can be approved.

The part of the Hatch–Waxman Act that addresses patent term restoration generally appears in Title 35 of the U.S. Code.
Title II of the Act (Table 4) outlines the preconditions and restrictions for patent extensions. Unfortunately, these are very long, complicated provisions. For the patent term restoration period, a pioneer company receives an extension term equal to one-half the time of the investigational new drug (IND) period (running from the time in which a pioneer company can begin human clinical trials) plus the NDA period (the period during the NDA review). The maximum extension is five years, and the total market exclusivity time cannot exceed 14 years.

The length of the exclusivity periods was determined by strictly arbitrary legislative numbers. Pipeline drugs (drugs for which applications were pending when the Act was passed) received two years or less of exclusivity; it was assumed that if they were in a pipeline already, they would be approved in a year or two, so there was no need to give them more time.

Last, the pioneer company must exercise due diligence in order to achieve patent term restoration, or a period of lack of diligence will be subtracted from the equation; that provision has never been used. Thus, the day after the patent is ineffective or the pioneer Act: 

Suppositions of Hatch–Waxman
Several assumptions were made regarding the Hatch–Waxman Act:

### Table 1: Title I: Amendments to the Federal Food, Drug, and Cosmetics Act

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
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<tr>
<td><strong>1. Generic drug “ANDA” applicants must:</strong></td>
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<td>• show the FDA the therapeutic equivalence or bioequivalence to the pioneer product.</td>
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<td>• show the FDA that manufacturing, processing, and packing facilities and controls meet FDCA requirements.</td>
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<td>• inform the FDA about the patent status of the pioneer product (from data filed earlier by the pioneer), or certify invalidity, non-infringement, or inapplicability of the pioneer patent with regard to the ANDA product.</td>
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<td>• notify the pioneer NDA holder and patent holder of the ANDA applicant’s grounds for challenging the validity of the pioneer’s patent or the patent’s applicability to the pioneer product upon which the ANDA is based.</td>
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<td><strong>2. Generic drug ANDA applicants no longer need to:</strong></td>
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<td>• conduct well-controlled clinical safety and efficacy studies to support application for approval of a drug that is identical to the pioneer product.</td>
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<td>• show that the generic product is safe if it is identical to the pioneer product (although FDA has authority to deny or withdraw approval of the generic on safety grounds not related to the pioneer product).</td>
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<td>• demonstrate that the generic drug is identical to the pioneer product, but only if the FDA approves a petition allowing this difference.</td>
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**Table 2: Marketing Exclusivity Periods for Innovators of New Drugs (per the Hatch–Waxman Act)**

**The Hatch–Waxman Act:**
1. provides exclusive marketing rights outlined below for “new drugs” (or “new chemical entities”); however, it does not provide such rights for “new biologicals”
2. prohibits the FDA from approving generic copies of new chemical entities before expiration of the following periods:
   - five years + the ANDA review period for post-1984 “new chemical entities” [NCEs]
   - up to 2.5 years may be added to the five-year exclusivity period for post-1984 NCEs to pursue litigation if the patentee promptly files an infringement action
   - three years for new indications for post-1984 non-NCEs if supported by new clinical investigations (other than bioavailability studies) essential to approval
   - special transitional 10-year exclusivity for NCEs approved during 1982–1984
   - special transitional two-year exclusivity for non-NCEs and new indications for NCEs approved during 1982–1984 and for “changes” in pre-1982 drugs

Up to 2.5 years may be added to any other specified period for all other drugs and indications to pursue litigation after the generic company gives notice of ANDA filing (whether or not the exclusivity period has expired) if the patentee promptly files an infringement action.

**Anda=Abbreviated New Drug Application; FDA = Food and Drug Administration.**

**Adapted from the statement of the Biotechnology Industry Organization (BIO), July 1, 1999.**

**Accessed January 20, 2004.**

1. Duplicates of generic drugs will be the same as the innovator’s drug in terms of chemical composition. The FDA still uses the plus-or-minus 20% test to determine blood serum bioavailability (i.e., the amount of active ingredient in the blood over a period of time must come within plus-or-minus 20% of that which is observed when the innovator’s drug is ingested). Twenty percent is a fairly good margin, and many medical professionals believe that for drugs with a wide index of tolerance, 20% is not important at all; in such instances, twice as much or half as much of the active ingredient in a generic product would still work.

For example, a drug might have a very narrow therapeutic band for a patient who takes antiseizure medication. In this case, plus-or-minus 20% might not be appropriate, especially if a drug is at that higher end of bioavailability and the patient’s dose is titrated on the higher end (plus 20%) and if a second generic drug is dispensed with the active ingredient at the lower end (minus 20%). Mathematically, this is a 50% swing, which might not be safe or effective.

It is curious that the FDA did not alter its regulatory approach to this situation. With the advances in modern pharmaceutics, those standards could be tightened. Although such tightening might not be to the advantage of the name-brand companies, it might be to the advantage of patients.

2. Bioequivalence data are effective surrogates for safety and efficacy, and products approved pursuant to ANDAs will meet the
same regulatory requirements as name-brand drugs. This was a good assumption, but the research-based industry always sensed that, in FDA's view, name-brand companies were the "bad" guys and generic companies were the "good" guys; thus, review and approval were slightly relaxed for generic drugs. However, ANDA applicants need not meet additional requirements other than bioavailability, the only test required by the FDA.3

3. Drugs in the pipeline will be approved shortly after passage of the Act, and two-year extensions are adequate. In one instance, it took eight years for a drug to be approved.4 Two key assumptions were that five years of extension and 14 years of market exclusivity, numbers that had been arbitrarily chosen, were sufficient to stimulate research and development again. The reasoning used in determining the patent term restoration part of the Act was along the lines of "If a widget gets 17 years of protection, why not a new life-saving drug?" If a widget gets 17 years or 20 years of protection from the time of filing, why would a pioneer research-based drug be limited only to 14 years?

Table 3  Drug and Patent Listing Requirements

The drug and patent listing provisions in the Hatch–Waxman Act:
1. require all NDA holders and NDA applicants to file with FDA:
   • the patent number and expiration date of any effective patents that "claim the drug or a method of using such drug" (but not patents claiming a method of manufacturing)
   • notification of claimed periods of market exclusivity for drug products under Title I of the Act
2. require all ANDA applicants to file with the FDA:
   • an acceptable bioavailability or bioequivalence study or protocol (where in vivo studies are required)
   • a certification for all relevant patents on the approved drug upon which the ANDA filed one of the following:
     o no patent information has been filed by the NDA holder;
     o the patent has expired
     o the date on which the patent will expire, or
     o the patent filed is invalid or will not be infringed by the manufacture, use or sale of the new drug for which the application is submitted
3. require the FDA to:
   • publish and update monthly a list of all marketed drugs approved for safety and effectiveness along with their approval dates. (This publication, The Approved Prescription Drug Product List, is also referred to as the Orange Book.)
   • specify in the "List" whether in vitro and/or in vivo bioequivalence studies are required for approval of the ANDA of each listed drug
   • publish patent information and information about periods of market exclusivity for submission or approval of ANDAs for specific products that are required to be supplied by pioneer companies under the Act
   • publicly release the safety and efficacy data of approved NDA products after the first ANDA approval

ANDA = Abbreviated New Drug Application; FDA = Food and Drug Administration; NDA = New Drug Application.

Table 4  Title II: Amendments to the Patent and Trademark Act

Patent Term Restoration
1. Drugs, biologicals, food and color additives, and medical devices are eligible for patent term restoration.
2. Key conditions for patent extensions:
   • The patent must not have expired before the application for an extension is filed.
   • The patent has never been previously extended.
   • No other patent has been extended for the same regulatory review period for the product (the applicant can select which patent is to be extended—"product," "method of use," or "method of manufacture").
   • The regulatory approval of the product covered by the patent is the first permitted commercial marketing of that product (except for patents claiming a method of manufacturing with recombinant DNA technology where the regulatory approval must be the first permitted commercial marketing of the product made by that process).
3. Restrictions on the period of patent extensions:
   • The calculated period of patent extension for drugs, biologicals, and medical devices shall equal half of the period that the IND or IDE became effective and the NDA, BLA, or PMA/510(k) is filed plus all of the period that elapses between the filing of the NDA, BLA, or PMA/510(k) and the FDA approval or licensure of the NDA, BLA, or PMA/510(k).
   • Similar rules for other products are based on half of the length of major health/environmental safety testing period plus the total agency review period.
   • A five-year maximum is required for patents issued after September 24, 1984, and for patents issued after that date if the regulatory review period began after that date.
   • A two-year maximum is required if the patent was issued and the regulatory review period began before September 24, 1984.
   • All of the foregoing rules are subject to a 14-year cap on the total period between the date of regulatory approval of any product and the date that the product’s extended patent expires.

BLA = Biologics License Application; DNA = deoxyribonucleic acid; FDA = Food and Drug Administration; IDE = Investigational Device Exemption; IND = Investigational New Drug; NDA = New Drug Application; PMA = Pharmaceutical Manufacturers’ Association.

4. Developing generic products before the patent expires will have minimal effects on name-brand products. In practice, many generic drugs have rapidly affected name-brand sales.

Problems with the Act
The Hatch–Waxman Act was predicated on the desire to enhance the growth of the generic drug industry and to make prescription drugs more affordable while extending and revising patent protection for research-based name-brand drugs. Although the law has established a larger market for generic drugs, many in the name-brand drug industry who have used...
patent law loopholes to delay and impede the introduction of less expensive generic alternatives into the market have subverted the law. The loopholes have led to numerous lawsuits that often extended the life of the name-brand drug company patents. During that time, generic drug companies could not bring their drugs to market. Examples of some tactics that the name-brand companies used in such lawsuits include changing the scoring (the grooves on a tablet) and the patenting (the color of the bottle), which protect the drug from losing its potency.

The Hatch–Waxman Act serves as a disincentive for the development of new targets for therapeutics to treat and to prevent degenerative diseases, the types of therapies that tend to require extended review and clinical trials. Companies and their investors need to know that if these products were developed, a full patent term would be available to enable them to recoup the cost of their development expenses.

The Hatch–Waxman Act should provide the same incentive for the development of all therapeutic agents, not just those that do not—because of the nature of the disease and treatment—require extended reviews and prolonged clinical trials. Patients with these diseases should not be disadvantaged by the discriminatory effect of the terms of the law. This is unsound policy that raises serious ethical dilemmas.

The costs of developing drugs and biological products have skyrocketed. Emerging biotechnology companies and biotechnology-based product divisions of larger pharmaceutical and chemical companies face the same kinds of higher start-up costs and long lead times, and they incur substantial costs before they can commercialize a product and recoup their investments. The emerging biotechnology companies face the added risks and challenges to attract timely sufficient investment capital for extended periods of time in order to sustain their operations until (and if) their products can be commercialized. These factors have rendered the “caps” on patent restoration under the Hatch–Waxman Act obsolete and more obviously arbitrary.

These stalling tactics by the pioneer companies have caused drug prices to soar and have forced the gap between the cost of name-brand drugs and their generic alternatives to grow in the last decade. In 1990, the average cost of each prescription for a name-brand medication was $27.16; the average cost of a generic drug was $10.29. By 2000, the average cost of each prescription had reached $65.29 but the generic price increased to $19.33. Changes in the provisions of the Hatch–Waxman Act were needed, and legislation (the Schumen–McCain bill and the Gregg–Schumer amendment) was passed in an effort to rein in high prescription costs.

**THE SCHUMER–MCCAIN BILL OF 2002 (S. 812)**

The Greater Access to Affordable Pharmaceuticals Act (GAAP), which significantly overhauled the Hatch–Waxman Act, allows generic drug companies to compete with name-brand manufacturers by eliminating the major obstacles that delay the approval of generic drugs. GAAP was designed to restore competition to the prescription drug market by preventing many of the anticompetitive tactics employed by name-brand drug companies (and some generic drug companies) that were used to keep lower-priced generics from coming to market. The bill stops citizens from filing frivolous petitions with the FDA to delay the approval of generic drugs.

The legislation gives name-brand drug manufacturers only one 30-month patent extension per product. The bill also prevents name-brand companies from paying generic companies to keep competing products off the market and allows generic companies to sue name-brand companies over frivolous patents designed to extend the market exclusivity of their products. The bill prevents name-brand companies from attempting to delay the approval of generic drugs by challenging the “sameness” or “bioequivalence” of generic products. Only patents listed up to 30 days after the time of approval of the name-brand drug would be eligible for the automatic 30-month stay; late-listed patents would not be eligible for this stay.

For example, Bristol-Myers Squibb kept drugs that compete with its antianxiety agent BuSpar® off the market for almost half a year by obtaining a patent on one of the breakdown products (metabolites) created naturally in the body. The company obtained the patent on November 21, 2000, the day before its existing patent on the drug was scheduled to expire and generic competition was set to begin. One of the generic competitors, Mylan Laboratories, was ready to ship its version of BuSpar® that day. As a result of this late-listed patent, Mylan had to cease and desist. This would not have happened had the GAAP been in place.

Name-brand companies would still be able to defend their late-listed patents, but instead of being given an automatic 30-month stay delaying generic competition, as under the Hatch–Waxman Act, the name-brand company would have to convince a judge to prevent the generic drug from coming to market by issuing a preliminary injunction.

**THE GREGG–SCHUMER AMENDMENT OF 2003 (S. 1225)**

The latest generic drug legislation, the Gregg–Schumer amendment (also known as GAAP) would achieve savings comparable to those of the original Schumen–McCain legislation of 2002 but would use a different approach to modify the patent laws. The key elements of the Gregg–Schumer proposal are described next.

**A Single 30-Month Stay**

In contrast to the law under Hatch–Waxman, the name-brand company under GAAP would get a single 30-month stay. The stay would be initiated if a name-brand company sued a generic company for any application that it claimed to be infringing on a patent on a blockbuster drug that was filed before a generic application was submitted to the FDA.

After a generic application is filed, the name-brand company would have 45 days to challenge the generic application in court. If the name-brand company does not challenge the generic company’s application within 45 days, the generic company would be able to seek a declaratory judgment stating that it has not violated the name-brand drug’s patents.

The single 30-month stay would run concurrent with the FDA’s consideration of the generic company’s application. As such, the 30-month stay would probably not cause a significant delay in the generic drug’s introduction to the marketplace. (It usually takes the FDA 18 to 25 months to approve a generic drug.) In contrast, the FDA’s proposed rule would allow the stay to be triggered up until the eve of the generic drug’s coming to market.
Enforcement

The Gregg–Schumer plan does not specify which patents can be listed in the FDA’s Orange Book, which identifies FDA-approved drug products on the basis of safety and effectiveness under the Federal Food, Drug, and Cosmetics Act. To ensure that the name-brand companies do not use frivolous patents to keep generic drugs from the market, the proposal would create a new mechanism of enforcement.

This legislation would allow generic companies to file counterclaims if a name-brand company sued them for violating a patent. For example, if a name-brand company filed a frivolous patent and sued a generic applicant for violating that patent in order to trigger the 30-month stay, the generic company could countersue the name-brand company and argue that the patent should never have been listed in the Orange Book in the first place.

180-Day Exclusivity

Currently, the first generic drug company that is able to come to market with a competitive product wins 180 days (six months) of exclusivity. The Gregg–Schumer proposal sets up forfeiture provisions, similar to those in earlier generic drug legislation, that prevent generic companies from abusing this incentive. Under the law, a generic drug company would forfeit its rights to this exclusivity if it were found to have made an anti-competitive deal with a name-brand company or had otherwise failed to come to market in a timely manner. If one of the forfeiture provisions outlined in the bill occurred, the exclusivity would be forfeited and the marketplace would open itself up to any generic company ready to come to market.

Bioequivalence

Under the current statute, the primary method by which the FDA determines whether a generic drug is equivalent to a name-brand product (bioequivalence) is by measuring the rate and absorption of the drug into the bloodstream. For certain drugs that are not absorbed into the bloodstream (e.g., topical agents and inhalers), the FDA uses different tests to determine bioequivalence, as defined in its regulations.

Name-brand companies have challenged the FDA’s use of these regulations, which has led to delays in the approval of the generic versions of these drugs. The Gregg–Schumer legislation would clarify that the FDA does have the authority to establish separate tests for determining the bioequivalence of drugs that are not absorbed into the bloodstream—as long as those tests are scientifically valid and meet rigorous standards.

UPDATE

On January 6, 2004, The New York Times reported that a federal judge ruled that Purdue Pharma, the maker of the highly profitable painkiller OxyContin®, deliberately misled federal officials in order to win patents protecting its drug and improperly delayed a generic competitor, Endo Pharmaceuticals Holdings, from introducing its generic version.1 In its countersuit, Purdue claimed that the agency should not approve generic versions of OxyContin® until its makers came up with plans to restrict abuse of the drug. Purdue added to its label a reference to its abuse-management program just before the expiration of its patent, eight years after the company first introduced the drug, and about two years after its abuse became widely known. Purdue contends that other generic companies must develop their own plans to restrict abuse.9

SUMMARY

The Hatch–Waxman Act started the ball rolling for the introduction of generic drugs to the market, but because of the many loopholes associated with it, name-brand companies were able to stall legally (and sometimes illegally) the placement of these generic drugs on the market. Because of the awareness among consumers and their sensitivity to drug prices and the differences between name brands and generics, political pressure was exerted and Congress subsequently responded. Although the response was slow, changes to the law finally appeared in 2003. It is hoped that there will be less confusion regarding product placements for name-brand and generic companies.

The Gregg–Schumer legislation clarifies that the FDA has the authority to allow generic drugs to enter the market for the original use, with modified labeling that ensures that products are safe and effective for use but does not include any information that is protected by patent or market exclusivity. For example, if a name-brand company is marketing a drug approved to treat hypertension and conducts studies revealing that the drug can also be used to treat cancer, a generic company is entitled to market the product for hypertension but not for cancer.

This legislation would also allow generic companies to countersue and possibly avoid delay in getting their products to market. It also would block other tactics, including using payoffs to generic companies to keep cheaper products out of the market.

Because generics often grab 80% of a branded drug’s sales within just a few months after introduction, however, consumers, especially senior citizens, will continue to experience problems related to the high R&D costs of prescription drugs.

For more information about the MMA, see the article by Dr. Stefancacci on page 95.

REFERENCES