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A Primer: Generic Drugs, Patents and the Pharmaceutical Marketplace

Including:

Hatch-Waxman – The Basics
What is the Orange Book?
What is Bioequivalence?
High Anxiety – the BuSpar Case
A Mind-Altering Experience? – Generic Prozac
Medicare, Medicaid and Generic Drugs
State Laws on Generic Substitution
Obstacles to the Wider Use of Generics

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The Hatch-Waxman Act – Key Provisions

This complex law was enacted in 1984. Its formal title is *The Drug Price Competition and Patent Term Restoration Act*. The law amended the Food Drug and Cosmetic Act of 1938 and various federal statutes that govern U.S. patents. Simply put, the law established the framework for the approval of generic drugs and their entry into the marketplace. Here are the law's core provisions:

- Generic manufacturers are permitted to use and reference the safety and effectiveness research conducted by the brand name pharmaceutical companies when they (the generic companies) file with the FDA to market a copy of a brand name drug. They need not do this research and testing themselves. Prior to the Hatch-Waxman law they had to conduct this costly research.
- Generic manufacturers must prove that the copies of brand drugs they seek to market are chemically and biologically equivalent to the original drug; biologically equivalent means it must act in the body in the same way as the original innovator drug.
- Generic manufacturers may begin testing their copycat drugs *before* the patent on the innovator drug expires; brand drug makers must share relevant research data with generic companies so they can perform these tests (such as data on the way the drug acts in the body). This is a unique mandated arrangement. No other industry is required to share some of its core research on a patented product with potential competitors. Generic companies are still not allowed to get trade secret manufacturing information on a drug, however.
- The first generic company to file an application with the FDA for a copy of an innovator drug gets 180 days of “exclusivity” – that is, no other generic copy of the innovator drug can come to market in that period. The 180 days kicks in only when the first generic copy goes on the market. Thus, if the “first filer” company has won the right to the 180 days but does not market the drug for some reason, other companies must simply wait.
- Brand name companies may seek “restoration” of some of the patent life lost during the extensive testing and sometimes lengthy approval process that prescription drugs undergo. The general allowance is for half a day of patent restoration for every day a drug is in clinical trials and a day of restoration for every day a drug is being reviewed by the FDA. But the maximum restored patent life is five years and the maximum total effective patent life (period between approval by FDA and a drug's patent expiration) after any “restored” patent life is 14 years. Virtually all brand companies seek and get restored patent periods for their new drugs once they are approved. As intended, this has lengthened the period of protection from generic competition for most brand drugs. Faster drug approval by the FDA has also in effect lengthened that period.
- Brand name companies may seek periods of “market exclusivity” (freedom from generic entry that are not just add-ons to the patent period) when they seek new uses of a drug

based on research that proves those new uses, or when they slightly alter a drug to make it safer or more effective. In general, the law permits brand name companies three years of added protection from generic competition for an accepted (by the FDA) new use or formulation.

- Brand name drug companies may seek five years of market exclusivity for new drugs whose active ingredients have never been on the market before – a so-called “new chemical entity”. This provision actually prohibits the FDA for five years from accepting from any other drug company an application to market a drug based on that new chemical. That five years does not extend the patent per se; it is an added period of protection that can extend a drug’s effective patent life if the patent term ends before the exclusivity period does.
- Generic companies are required to “certify” with the FDA how their copycat drugs will or will not infringe all existing patents on the innovator drug they seek to copy. *They must certify to each patent listed for a drug, not just the main one.* In cases where the generic company says it intends to challenge a patent or believes a patent (or patents) to be invalid, they must also notify the brand name drug company that makes the drug.
- Brand name drug companies have 45 days to file a patent infringement lawsuit after a generic company has notified them that a patent is being challenged.
- The FDA is required to suspend approval of a generic company’s copycat drug if the brand name company files a patent infringement suit within 45 days of a generic company notifying the brand company that it is challenging a patent or patents on a drug. The suspension lasts either until (a) a *final* judicial ruling on the patent occurs, (b) the patent expires (if the decision is that the patent was infringed), or (c) 30 months from the date the generic company notified the brand company that it was challenging a patent, if no court has yet ruled in the case. Companies may also settle these cases, with the patent challenge and infringement suit withdrawn.

What is the Orange Book?

It's more than just a list of prescription drugs— The debate over listings

Pressed by the states, which persistently complained of confusion over which prescription drugs were approved for what and which generic drugs were maximally equivalent to their brand name counterparts, the FDA sought in the late 1970s to clarify things. On May 31, 1978, the agency announced its intention to prepare a list of all approved prescription (and over-the-counter) drug products. The list was to include indications of “equivalency” for generic drugs.

The first list appeared in October 1980. It has been published every year since in April (for the previous calendar year.) Since 1984, the FDA has also produced a monthly update. The list is formally known as the *Approved Drug Products with Therapeutic Equivalence Evaluations*. But the printed compendium is commonly known as the Orange Book because the actual hard copy has an orange cover. The list is now more commonly accessed on the web (www.fda.gov/cder/ob/default.htm). This version, which is updated monthly with a time lag of six months or so, is called the Electronic Orange Book.

But the Orange Book has become much more than a simple list. The Hatch-Waxman Act in 1984 required that applications to the FDA for approval of a new brand name drug (or any new formulation of an existing patent-protected drug) be accompanied by all relevant patent information on the drug itself and its method of use. (The U.S. Patent and Trademark Office, not the FDA, grants patents.) Drug firms are further required under Hatch-Waxman to list any other patents they obtain on a drug after the FDA approves the drug.

Hatch-Waxman also established detailed procedures for generic firms seeking to market a generic copy of an innovator drug. They are permitted to do so only after they indicate they are not infringing a drug's patents as listed in the Orange Book. Generic firms are also required to indicate if they intend to legally challenge a patent as it is listed in the book. And they must notify both the FDA and the company that owns the patent of the challenge. Importantly, the FDA now records these legal challenges but it plays only a minor role in influencing the outcome litigation (about which more below).

Thus, the Orange Book has become the de facto official repository of critical drug patent information – at least as that information is relevant to the process by which generic firms indicate their intentions and undertake the process of bringing their drugs to market. (The actual technical details of a drug's patents – and most drugs have numerous patents – are not a part of the Orange Book. They are on file at the PTO.)

The importance of Orange Book patent listings has thus grown over time as litigation over drug patents has become more common, intense, and complex. And, most recently, the FDA's role in listing patents in the Orange Book has become the subject of mounting debate.

The central policy and legal issue today is whether brand name companies are abusing the Orange Book listing process by listing *new* patents on drugs soon before the old patent or patents are due to expire. Generic firms can not ignore such late-listed patents. Under Hatch-Waxman rules, supported by court rulings, generic firms must tell the FDA and the companies whether the new patents will be infringed. Litigation may then be triggered if a generic company decides to contest a patent and the brand company decides to defend it. That litigation automatically triggers a delay in the FDA's approval of the generic drug. That delay can last until the courts decide whether the patent is indeed infringed or invalid or, under Hatch-Waxman rules, 30 months after the infringement notification if the courts have not yet acted.

The upshot, either way, is that the generic will not get to market for quite a while, usually at least two and half years and more typically around four years.

The Federal Trade Commission. (FTC) is investigating whether brand name companies have abused this process. Specifically, the FTC is probing whether some brand name drug companies have listed frivolous or ineligible last minute patents in the Orange Book simply to cause a delay in generic availability and lengthen the time their patent-protected drug is on the market.

A major complexity in this kind of litigation is that for a single drug, several lawsuits may be pending at once involving different patents. In addition, a brand name drug company may have to fight several generic companies at once, all of which are seeking to copy its drug and have challenged an existing patent. These challenges often involve different modes of administration or versions of a drug, which may have their own patents.

The FDA's role

The FDA has steadfastly maintained for years that it has no expertise in patent law. The agency thus seeks to distance itself as much as possible from involvement in patent disputes and litigation. It wants to let the courts decide, and has suggested that the best venue for challenging an actual listing (rather than the patent itself) is in the context of patent litigation.

But FDA non-involvement has proved impossible given existing law. The FDA has found that it must upon occasion make decisions about some Orange Book filings. This has triggered suits from the brand name drug companies in cases where the agency has declined to list a patent in the Orange Book on technical grounds. The brand name drug companies have won some and lost some of these cases.

At the same time, generic companies have sought to "delist" some patents instead of just challenging them as invalid. These cases have also yielded mixed legal outcomes. In one 1998 decision (*Ben Venue Labs v. Novartis*), the court said generic competitors could raise the issue of Orange Book listings outside the context of the Hatch-Waxman Act and patent litigation. But in an important 2001 decision (in *Mylan Labs v Thompson*), a federal court held that there was no "private cause of action" for delisting an Orange Book patent – no matter when it was listed. Translation: a generic company has no

specific right under Hatch-Waxman to ask the FDA to delist a patent.

A January 2002 court decision further confused things. A federal court (in *Andrx Pharmaceuticals v. Biovail*) said that generic firms could try to delist patents under the Administrative Procedures Act, suing the FDA directly. But the court added that it was not making a substantive judgement about the FDA's role.

All this has debate growing over the depth and breadth of FDA's purview over Orange Book listings. The generic industry would like to see the FDA become more vigorous in screening "late-listed" and other, potentially frivolous patents. Most recently, in February 2002, the industry's trade organization (The Generic Pharmaceutical Association) argued in a white paper that the FDA should require brand name companies to submit more detailed patent declarations when they seek to list a new patent in the Orange Book. These declarations should include, the generic group argued, a complete description of the scientific and legal basis for the new patent. The FDA should then review this declaration before listing the patent, the group argued.

Some attorneys interpret the law as giving the FDA that power to undertake such reviews. But the brand name drug industry opposes such a move. Its lawyers argue that the FDA has only a "ministerial" role in Orange Book patent listings. FDA officials have said they would prefer not to get in the middle of this high stakes legal debate, but have signaled their concern about late patent filings.

Significantly, the two key sponsors of the Hatch-Waxman Act, Sen. Orrin Hatch (R-Utah) and Rep. Henry Waxman (D-Calif), along with Sen. Edward M. Kennedy (D-Mass), recently took tentative positions in this debate. In a letter to the Department of Health and Human Services and the FDA in September 2001, the three lawmakers urged the FDA to exercise "more discretion" in listing patents in the Orange Book. "Nothing in the agency's governing statute, nor in its regulations, precludes it from carefully reviewing an application for an Orange Book listing," the letter said.

In January 2002, the FTC also weighed in. In an *amicus* brief filed in a case involving the anxiety drug BuSpar, the agency said that Orange Book listings do not have the legal status of a "petition" to the government for action and thus are not exempt from antitrust action. This signaled that the agency could pursue antitrust charges against brand companies solely on the basis of potentially frivolous Orange Book patent listings.

In February 2002, a federal judge in New York issued an opinion in that BuSpar litigation. He said Bristol Myers Squibb had improperly listed a patent for the drug and that Orange Book listings are not exempt from antitrust scrutiny.

Bristol Myer Squibb's position in the case was that an Orange Book listing is essentially a petition to the government and a critical component of patent protection and, based on other legal precedents, is protected from antitrust action. Bristol Myers has not appealed the February 2002 decision and generic versions of BuSpar are now on the market. But

ongoing BuSpar litigation is certain to set further precedent in this area.

Sources:

1. FDA “Electronic Orange Book” web site. Preface and Frequently Asked Questions sections, www.fda.gov/cder/ob/default.htm. Accessed Feb 12, 2002.
2. Don Hare and Thomas Foster, “The Orange Book: The Food and Drug Administration’s Advice on Therapeutic Equivalence,” *American Pharmacy Journal*, Vol. NS30, No 7 (July 1990), pages 403-405.
3. James Knoblen et al, “An Overview of the FDA Publication: Approved Drug Products with Therapeutic Equivalence Evaluations,” *American Journal of Hospital Pharmacy*, Vol. 47 (December 1990), pages 2696-2700.
4. Wendy Schacht and John R. Thomas, *Patent Law and its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984*, a Congressional Research Service report (December 2000), (Order Code RL30756)
5. Arthur Y. Tsien, *Orange Book Patent Listing Litigation*, a presentation to the National Association of Pharmaceutical Manufacturers, January 29, 2001.
6. Testimony of Janet Woodcock, M.D., Director of the FDA’s Center for Drug Evaluation and Research, before the Subcommittee on Health of the House Committee on Energy and Commerce, June 13, 2001. Hearing title: *Recent Developments Which May Impact Consumer Access To, and Demand for Pharmaceuticals*.
7. FDC Reports (The Pink Sheet), “Taxol Ruling Re-Emphasizes ‘Ministerial’ Role for FDA on Patents,” (November 12, 2001), page 5.
8. FDC Reports (The Pink Sheet), “Orange Book Listings Are Not Immune From Antitrust Scrutiny, FTC Says,” (January 14, 2002), page 6.
9. FDC Reports (The Pink Sheet), “Orange Book Patent Listing Declarations Need More Detail – GPhA,” (February 11, 2002), page 12
10. Wendy Schacht and John R. Thomas, *The Hatch Waxman Act: Selected Patent-Related Issues*, A Congressional Research Service Report to Congress (April 1, 2002). Order code number RL31379.

Are Generic Drugs as Good as Brand Drugs? ***What is “Bioequivalence?”***

This technical term – bioequivalence – is at the heart of one long-running debate over generic drugs. Are they equal to or as good as the brand name drugs? Are they essentially the same drugs? Or are they different? And if they are different, how different are they?

Today, virtually all generic drugs are essentially the same as the innovator drugs they copy. They must meet stringent FDA requirements to get approved. Essentially, a generic company must show unequivocally (via a series of mandated studies and tests) that the generic drug (a) contains the identical active ingredient or ingredients as the innovator drug in the same amount and (b) behaves in the body in the same way.

For all practical purposes, they are the same drug. And it is thus assumed that the generic will have the same therapeutic effect.

But generic drugs are also different. They typically use different inert ingredients, binding chemicals and colorings, for example. These too must meet FDA specifications.

The FDA goes out of its way to state, on its web site and in official documents, that the generic drug approval process is as scientifically rigorous as the process by which brand drugs are approved. In that context, the agency states that research and clinical experience indicates that generic drugs are not only bioequivalent but also clinically equal to and as safe and effective as the brand name drugs they are copies of.

That said, the agency continues to grade generic drugs for bioequivalence, and it publishes that information in an annual compendium called *Approved Drug Products with Therapeutic Equivalence Evaluations* (which is also updated monthly). This publication is more often referred to as the Orange Book.

The purpose of grading generic drugs for bioequivalence is to assure scientific rigor in their evaluation and because, for a small proportion of drugs, bioequivalence issues do arise. They arise largely because the testing available today is very sophisticated and can detect even small differences in, say, the rate at which a drug is absorbed or the quantity of its breakdown products in the body. Some of the differences these tests pick up may be meaningful and some are not. The FDA renders judgment on that in its ratings.

As of March 2002, there were 10,357 prescription drugs listed in the Orange Book. Of that number, 7,602 were so-called multi-source drugs – that is, drugs which have generic copies (usually many) on the market. Of that 7,602, the FDA rates 7,309 (96%) as bioequivalent and therapeutically equivalent and 293 (4%) as non-therapeutically equivalent. Such drugs are clearly indicated in the Orange Book. Of that 4%, the majority are older drugs on which modern tests have not been conducted. A handful are drugs whose level in the body is very sensitive, and therefore the FDA puts it in the non-equivalent category.

Over the last 20 years, as FDA rules have become stricter and testing methods better, the proportion of generic drugs that are non-equivalent has declined. It was 10% in 1990, for example.

Even so, equivalence issues continue to be controversial for some generic drugs. In 2001, the FDA recommended that Zenith-Goldline conduct a fresh round of bioequivalent studies on generic clozapine, used primarily to treat schizophrenia. Novartis, which makes the now off-patent brand version of the drug, Clozaril, made FDA aware of studies showing that the generic may not be equivalent. Clozapine is known to be a drug whose safety and effectiveness can vary sharply if the proper dose is not administered. Users' names must be registered.

In addition, the brand name drug industry continues to claim, from time to time, that its products are subjected to more rigorous testing and standards than generics. Most recently, in February, 2002, the Pharmaceutical Research and Manufacturers of America (PhRMA) alleged in a white paper that the FDA "deviates from the term of the [Hatch-Waxman law]...to approve generic products that, although plainly not identical to the reference product as required, are viewed by the FDA as close enough." The paper also alleges that the FDA has "adopted additional definitions of bioequivalence beyond what appears in the statute and recently waived "bioequivalence testing in certain circumstances even though no waiver authority can be found in the statute."

Sources:

1. Food and Drug Administration, Orange Book web site, preface, introduction and ratings explanation, www.fda.gov/cder/ob/default.htm. Accessed Feb.14, 2002.
2. Lynda Welage et al, "Understanding the Scientific Issues Embedded in the Generic Drug Approval Process," *Journal of the American Pharmaceutical Association*, Vol. 41. No 6 (November/December 2001), pages 856-867.
3. Don Hare and Thomas Foster, "The Orange Book: The Food and Drug Administration's Advice on Therapeutic Equivalence," *American Pharmacy Journal*, Vol. NS30, No 7 (July 1990), pages 403-405.
4. James Knoblen et al, "An Overview of the FDA Publication: Approved Drug Products with Therapeutic Equivalence Evaluations," *American Journal of Hospital Pharmacy*, Vol. 47 (December 1990), pages 2696-2700.
5. FDC Reports (The Pink Sheet), "Zenith-Goldline Clozapine Bioequivalence Study Suggested by FDA," (February 5, 2001), page 29.

Hatch-Waxman Reform

Basic Provisions of the Proposed McCain-Schumer Legislation

Senators John McCain (R-Arizona) and Charles Schumer (D-New York) have proposed legislation that would substantially alter portions of the Hatch-Waxman law. This legislation, formally titled the Greater Access to Affordable Pharmaceuticals Act (GAAP, S.812) and also introduced in the House of Representatives (Brown-Emerson – H.R. 1862), has become the focal point for debate over Hatch-Waxman and drug patent law reform.

GAAP's core provisions:

- Eliminate the automatic 30-month period that takes effect, preventing generics from coming to market, when a generic firm challenges a brand drug's patent (or patents) and the brand manufacturer brings a lawsuit alleging patent infringement. Brand name companies instead would have to apply to the courts for a preliminary injunction and show how the generic may infringe a patent or patents. If a company showed that their allegation of patent infringement was plausible, the court could impose an injunction of whatever length it wants.
- Require brand drug companies to list (with the FDA) all patents on a drug which a generic company would have to consider when seeking to make a copy and which could spark patent infringement litigation. The brand company would have to certify that the list is complete. This measure aims to reduce the filing of multiple patents and late or potentially "frivolous" patents which can trigger delays in generic availability.
- Permit generic drug companies to seek a court order to nullify a patent listing in the FDA's Orange Book. Current law does not permit generic firms to take issue with a patent listing. Such listings delay generic drug availability if and when litigation over a patent ensues.
- Eliminate (in some cases) the current Hatch-Waxman provision which forces both generic and brand firms to wait 45 days to file a lawsuit after a patent has been listed at the FDA. This change would apply only in cases in which a patent (or patents) are listed a year or more after the submission by a generic company of an application to market a copy of the drug. This provision aims to speed resolution in cases where new patents have been listed for a well-established product.
- Alter the rules for the award of 180 days of market exclusivity (freedom from competition) granted to the first generic company that successfully wins approval to market a copy of a brand drug whose patent has expired. Under current rules, only the "first filer" obtains the 180 days of market exclusivity. Under GAAP if the first generic filer (a) failed to market its drug within 90 days of approval, (b) delayed marketing its drug because it reached an accord with a brand name company not to, (c) failed to challenge a new patent on the drug within 60 days, or (d) withdraws its application to market the drug

for any reason, the company would lose the 180 days of exclusivity and that 180 day period would transfer to the next generic company in line with an application to make the generic. In addition, the clock on the 180 days starts ticking under current law when the generic company goes to market or litigation is resolved in a district court. Under GAPP, the 180-day period would begin when the generic goes to market or when an appellate court reaches a decision in a patent dispute. This aims to prevent generic firms from having to choose between losing part or all of the 180-day exclusivity period while a patent case is on appeal and risking a judgment of treble damages if they go to market and the final court decision goes against them. The damages result if the brand firm wins the infringement case.

- Alter the rules for citizen petitions to the FDA questioning a drug's approval. Current rules allow pretty much anyone to raise questions about a proposed new drug under review at the FDA. These petitions usually focus on a drug's safety and effectiveness or on the studies companies have submitted to support a drug's approval. Brand companies are permitted to question generic drug applications, and do so on a fairly regular basis. This can delay the FDA's review of a drug. New rules under GAAP would (a) increase the amount of evidence citizen petition filers would have to submit to support their concerns before the FDA could formally undertake a review and (b) open filers of citizen's petitions to scrutiny from the Federal Trade Commission if any evidence suggests the petition's main goal was to delay approval of a generic drug.

High Anxiety: The BuSpar Story

Many drugs could serve as examples of the complex issues that emerge in patent litigation cases. But the tortuous case of BuSpar (buspirone), an anti-anxiety drug, is among the most compelling – and telling. And its evolving resolution is already having broad implications for patent law and patent reform efforts as they relate to prescription drugs.

Bristol Myers Squibb patented the active ingredient (buspirone) in BuSpar in 1980. Notably, at the time, the company said it was not sure exactly how the drug worked. The FDA approved BuSpar in September 1986. The drug has been a commercial success. It's one of the most widely prescribed medicines to treat anxiety. In 2000, it was Bristol Myer Squibb's fifth best seller, with U.S. sales of \$709 million.

BuSpar's first brief bout of patent litigation occurred in 1993. Schein Pharmaceuticals, a generic company, challenged the drug's main patent. Bristol Myers Squibb filed a patent infringement suit. The two companies reached an out-of-court settlement in 1994 that kept the generic off the market. Bristol Myers Squibb paid Schein \$72.4 million in a settlement some analysts have argued was anti-competitive.

More recently, BuSpar's key patent was due to expire on November 22, 2000. Mylan Laboratories had in early 2000 won the right to make the first generic copy. It launched production in the summer of 2000 and on November 21, 2000 began loading trucks at its plant in Morgantown, W.Va. to deliver its first batches of the generic drug.

But those trucks never left the loading ramps. On November 21 – one day before the patent was due to expire—the Patent and Trademark Office (PTO) issued a new patent on BuSpar. Bristol Myers Squibb hand delivered the paper work on the new patent (within an hour) to the FDA. The company requested that the patent be immediately listed in the Orange Book. The FDA complied. The listing triggered a delay in the generic drug's market entry since the generic firm would now have to decide whether the new patent was an obstacle to its product or not.

Bristol Myers' journey to that day had begun several years earlier. In the late 1990s, the company began a search, using research tools that did not exist in the 1970s and 1980s, for a byproduct (or metabolite) of buspirone in the body that would: (1) help explain how the drug worked and (2) possibly be used as the basis for a new, even better anti-anxiety drug. The company says the research was linked to plans for an extended release and/or patch version of BuSpar.

The search proved fruitful. One metabolite (6-hydroxy-buspirone) appeared to be the most active in easing the symptoms of anxiety. On August 5, 1999, Bristol Myers Squibb filed a patent application for the metabolite. Importantly, it asked the PTO to issue the patent before November 22, 2000. The story enters a technical phase at this point since the PTO initially rejected the new patent application as duplicative of the original 1980

patent on buspirone. But Bristol Myers circumvented that obstacle with a refilling on June 6, 2000. The most significant aspect of the new request was that it specifically applied only to swallowing the metabolite, not BuSpar.

Fast forward again to November 2000. Mylan immediately objected to the last minute granting of the new patent and filed suit on November 30 to block it. (Another generic company, Watson also filed suit. That company was poised to make a generic version of a different dose of BuSpar.) Meanwhile, the FDA sought a clarification from Bristol Myers Squibb. It asked the company whether the new patent actually affected BuSpar at all given that the patent covered the metabolite molecule and not buspirone itself.

On December 6, 2000, Bristol Myers answered that query. In a letter, the company stated that it interpreted the patent to cover BuSpar/buspirone as well as the metabolite since anyone taking BuSpar would be producing the metabolite in their bodies. It presented that same argument to a U.S. district court judge (hearing Mylan's suit) in Washington, D.C. on January 24, 2001. The essential claim was that the new metabolite patent effectively overrode the original BuSpar (buspirone) patent.

But the judge disagreed. On March 13, 2001 Judge Ricardo Urbina ruled that Bristol Myers Squibb misrepresented the scope and nature of the new patent to the FDA. He ordered that the patent be "delisted" (from the FDA's Orange Book) and that Mylan be allowed to immediately start selling the generic. In his ruling, the judge said: "By creating new ways to extend its monopoly, [Bristol] not only limits the public's access to low cost drugs but impedes the very innovation that Hatch-Waxman is designed to promote."

Mylan and Watson began shipping generic buspirone in early April, 2001. By late June 2001 the generics had captured two-thirds of buspirone sales.

But the story wasn't – and still isn't – over. Bristol Myers appealed Judge Urbina's ruling to a federal appeals court. The case was heard on July 12, 2001. The company brought a new and unique argument to court. It alleged that Mylan circumvented Hatch-Waxman procedures by filing suit against Bristol Myers Squibb before it had filed a formal notice with the FDA that it was challenging the patent. (This procedure is called a Paragraph IV certification.) Mylan countered that it had not needed to file such a notice with FDA because the patent was improperly listed in the first place and thus did not warrant challenging under Hatch-Waxman rules.

On October 12, 2001, a federal appeals court overturned Judge Urbina's ruling. The appeals court essentially agreed with Bristol-Myers Squibb's argument. It said that Mylan's effort to "delist" Bristol Myer's latest patent amounted essentially to an effort to challenge an Orange Book listing and that under existing law (Hatch Waxman) the generic company has no right to do so.

Put in layman's terms, the ruling, if it stands, means that generic companies would be precluded from challenging a patent *listing* outright in court, even a last minute or

potentially frivolous one. (This is different from challenging a patent itself). Instead, they would have to go through the existing channels of putting the FDA and the brand manufacturer on notice that they intend to challenge a patent. This triggers a countersuit and an automatic delay in the generic's market entry. In short, bypassing the automatic delay (of 30 months) would not be an option.

Mylan appealed the federal appeals court decision on December 21, 2001, specifically seeking an injunction to stop the FDA from relisting the late patent. Watson also sued the FDA to stop the listing. On January 29, 2002, Bristol Myers sent a letter to Judge Urbina saying the company would not seek a relisting of the patent while its validity and FDA's oversight role were being considered by the courts. That meant, in short, that generic buspirone would stay on the market.

While all this was going on, several other parties joined the fray, filing suit in New York against Bristol Myers Squibb over the late-listed BuSpar patent. The Prescription Drug Access Project, a coalition of consumer groups, in April 2001 alleged that Bristol Myers violated antitrust laws by filing the patent. And in December 2001, attorneys general from 29 states and Puerto Rico filed a similar lawsuit.

These suits have been consolidated in the United States District Court in New York City. Bristol Myers Squibb in January 2002 sought to have them all dismissed, arguing on legal grounds that the circumstances were exempt from antitrust law. But on February 14, 2002, in a decision that reverberated throughout the pharmaceutical industry, Judge John G. Koeltl rejected that argument and ruled that the consolidated antitrust case can go forward. In addition, his decision stated that in his opinion Bristol Myers acted improperly when it filed the late patent with the FDA and that that patent "does not cover uses of buspirone." The case is pending.

As a footnote, even as it was involved in this multi-front litigation, Bristol Myers Squibb successfully delayed approval of other generic versions of buspirone until February 2002. It did so by asking the FDA in September 2001 to review whether a recent (July 2001) change in the drug's labeling (related to the drug's use in children) permits BuSpar an additional three years of patent protection. The FDA ruled against such a patent extension and in February, 2002 approved the other generic forms of the drug.

Sources: Available on request.

A Mind-Altering Experience? The Case of Prozac

The potential for cost savings from the more rapid uptake of generic drugs is illustrated by the recent launch of generic fluoxetine (Prozac). Fluoxetine/Prozac also highlights some other key issues in generic substitution.

Prozac (Eli Lilly) – a poster child of the drug revolution of the 1980s – lost patent protection in July 2001 after a five-year legal battle. Generic fluoxetine (in various dosage forms from four generic companies) went on the market in early August. Prozac was the nation's best selling antidepressant and fourth best selling drug overall in 2000, with U.S. sales of \$2.6 billion. It had a 25% share of the crowded antidepressant market. At the end of July 2001, just before its patent expired, Prozac still held 21% of the new prescriptions being written for antidepressants. But by mid-September, 2001, six weeks after generic fluoxetine went on the market, brand name Prozac's share of new prescriptions had plummeted to 5.3% of new antidepressant prescriptions. And by the end of 2001, brand name Prozac's share of the antidepressant market overall had fallen to 16%.

Doctors, pharmacy benefit managers (PBMs) and patients had turned to the generic in what has been hailed as one of the quickest uptake of a generic drug *ever*. What drove this, analysts agree, was:

- The high profile of the drug and the generic launch (much covered in the mass media)
- Prozac's high price (\$110 on average for a prescription in 2000), and
- Mounting pressure on PBMs and managed care plans to show they could save their customers (employers and government) money by a quick switch to a new generic.

[All the various dosage forms of fluoxetine had 180 days of market exclusivity and were priced at a discount of 25% to 40% off Prozac's price. With that 180 days of exclusivity now up, the price has been dropping. In early June 2002, Drugstore.com had a list price of \$85.98 for 30 capsules of brand name Prozac (20mg) and \$45.99 for 30 capsules of generic fluoxetine (20mg).]

Merck-Medco claims to have achieved an 80% generic substitution for Prozac within one week of the generic's launch. Express Scripts similarly claims a 90% conversion of Prozac prescriptions to generic fluoxetine in its mail order business within a few weeks of the generic's launch. By comparison, most brand name drugs that go off patent experience a 40% to 75% erosion in their market share over nine months to a year.

The rapid uptake of generic fluoxetine is widely expected to serve as both an example and an impetus for other drugs whose patents are soon to expire.

But it is also serving as a case study of the economic and clinical vagaries of modern day drug pricing and generic substitution.

Some state Medicaid programs, for example, were paying more for generic fluoxetine than Prozac even months after the generic's launch. This occurred because states must abide by complex federal rules governing drug prices and volume-based rebates, and may have their own rules on top of that. In Maine, for example, the generic cost 19% more – an average of \$2.83 a pill versus \$2.37 for Prozac – a few months after generic fluoxetine came on the market. And Minnesota officials estimated in February 2002 that the state's Medicaid program would spend about \$170,000 *more* buying generic fluoxetine than brand name Prozac during the 180-day generic exclusivity period. To be sure, most states understand that the additional cost is temporary. But it rankles state Medicaid and budget officials nonetheless.

On the clinical side, generic fluoxetine got a big boost with the release of a study in December 2001. The study, in the *Journal of the American Medical Association*, (JAMA) found that the three most widely prescribed antidepressants – Prozac (fluoxetine), Paxil (paroxetine) and Zoloft (sertraline) – had equal effectiveness. (All are in a class of antidepressants known as the selective serotonin reuptake inhibitors, or SSRIs.)

The study, consistent with previous research, is powerfully relevant to an issue at the heart of generic versus brand competition and substitution. The brand drug industry often argues that a single new generic in a therapeutic category often means little (except to the brand drug it copies) because other patent-protected drugs may be of superior clinical effectiveness and value for some, perhaps even most, patients.

Marketing campaigns aimed at doctors play on this routinely once a generic is available in a category. Brand name drug companies try to dissuade doctors from switching to the generic just to save money, and are often successful.

But the JAMA study of antidepressants gave ammunition to those who argue that substitution to save money ought to be more routine. Indeed, the study's results are already being used by managed care plans and PBMs to justify switches to generic fluoxetine from patent-protected (and more expensive) Paxil and Zoloft.

But not so fast. In an editorial accompanying the JAMA study, Dr. Gregory Simon of Group Health Cooperative in Seattle, a large HMO, concurs with pharmaceutical industry orthodoxy that equal effectiveness on average in a population does not mean equal effectiveness for individual patients. "Among patients who do not respond to one SSRI antidepressant, half or more will experience significant benefit from another drug in the same class," Simon wrote. He says genetics likely explains a good deal of this variable response.

Indeed, the study found that 20% of depression patients switched SSRI drugs and two-thirds of all participants had a successful outcome over the nine months of the study.

Simon goes on to say, however, that, "given the available evidence, it is difficult to criticize formulary policies recommending or requiring one SSRI drug for first line treatment....An

initial choice based on prescription costs is prudent, ethical and clinically reasonable.”

Over the next several years, fluoxetine will likely be a test case. Will doctors switch patients now taking other SSRIs to generic fluoxetine? Will health plans press doctors and patients to make this switch? Will generic fluoxetine become the preferred cost-effective first line treatment for one of society’s most costly conditions?

Postscript: Just three weeks after the publication of the study discussed above, researchers reported in JAMA that between 1987 and 1997 the proportion of the population with depression who were getting treatment increased more than three-fold, from 0.73 per 100 persons to 2.33 per 100 persons. The rise in the use of antidepressants accounted for the bulk of the change. And in May 2002, the U.S Preventive Services Task Force, a government-sponsored expert group, issued guidelines calling for primary care doctors to screen all their adult patients for depression.

A large volume of research indicates a persistent under-diagnosis and under-treatment of depression in the U.S. The advent of generic fluoxetine may help rectify that situation. Zoloft is scheduled to go off patent in 2005 and Paxil in 2006.

Sources:

1. Joseph Brown, “Quick Uptake: Generic Competitors have Devoured Prozac Sales Faster than Eli Lilly Marketers Had Anticipated,” *Med Ad News*, (December 2001), page 26.
2. Andrew Caffrey, “Why Generics Can Cost States More Money,” *The Wall Street Journal*, (February 14, 2002), page B1.
3. FDC Reports (The Pink Sheet), “SSRI Study Finds Equivalence for Depression; Broader Uses Key to Formulary?” (December 24, 2002), page 11.
4. Kurt Kroenke et al, “Similar Effectiveness of Paroxetine, Fluoxetine, and Sertraline in Primary Care,” *Journal of the American Medical Association*, Vol. 286, No.23 (December 19, 2001), pages 2947-2955.
5. Gregory Simon, “Choosing a First Line Antidepressant,” *Journal of the American Medical Association*, Vol. 286, No 23 (December 19, 2001), pages 3003-3004
6. Mark Olfson et al, “National Trends in the Outpatient Treatment of Depression,” *Journal of the American Medical Association*, Vol 287, No 2 (January 9, 2002), pages 203-209.
7. Shankar Vedantam, “Routine Screening for Depression Urged,” *The Washington Post* (May 21, 2002), page A1

Medicare, Medicaid & Generic Drugs

The federal government pays just under half the nation's total health bill and about 22% of the tab for prescription drugs. Most of that spending occurs in the Medicaid and Medicare programs, but active and retired members of the military, veterans, and nine million federal workers and their dependents have part of their drug costs covered by the federal government, too.

That gives the government a large stake in the debate over rising prescription drug costs. Indeed, expenditures for prescription drugs have been rising so fast in the joint federal/state Medicaid program that the nation's governors asked Congress in February 2002 to address the issue.

Medicaid spending for outpatient prescribed drugs increased an average 18% a year from 1997 to 2000, almost three times the rate of increase of all medical services combined. In 2000, states and the federal government spent \$20 billion on outpatient prescription drugs for Medicaid beneficiaries, up from \$12.1 billion in 1997.

Government attention to rising drug costs is also prompted by the continuing debate over a Medicare drug benefit. Outpatient prescription drug costs for the nation's 39 million Medicare beneficiaries represents 43% of total national prescription drug costs (\$62.3 billion of \$145 billion in 2000). In 2000, Medicare beneficiaries paid 47% (\$29.3 billion) of that bill out of their own pockets.

Optimal use of generic drugs is highly likely to be a part of the cost containment strategy in both Medicare and Medicaid. But lawmakers are also sensitive to issues surrounding innovation in the pharmaceutical industry and to equity issues. Thus, heavy restrictions on access to the latest brand name drugs in either the Medicaid or Medicare programs would likely be politically unpalatable.

That said, studies indicate substantial savings in both programs from the optimal use of generics.

Stephen Schondelmeyer of the PRIME Institute at the University of Minnesota found that prescriptions for generic drugs declined as a proportion of all prescriptions in the Medicaid program between 1995 and 1998. In 1995 generics represented 54% of prescriptions in the Medicaid program; by 1998, that had declined to 51%. The NIHCM Foundation estimates that a return to a 55% generic share could save Medicaid between \$1 billion and \$1.5 billion a year over the next several years.

Medicare

A study released in January 2002 found that optimal use of generic drugs could yield similar significant savings for the Medicare program if a drug benefit were added to the program.

The study based longer-term projections on current experience in a sample of Medicare managed care plans. About five million Medicare beneficiaries are currently enrolled in managed care plans and about 70% of them have some prescription drug coverage.

The study found that overall expenditures for prescription drugs used by Medicare beneficiaries in managed care plans would be reduced 16.3% if all such health plans matched the generic use patterns of plans that achieve the highest generic prescription rate.

Conducted by researchers at Brandeis University with funding from the Generic Pharmaceutical Association, the study found that generic drugs currently represent an average 38% of prescription for seniors in managed care plans. But some plans achieve a 51% generic prescription rate. If all plans were to achieve that rate, spending would be reduced 16.3%.

That savings rate would translate to a projected \$14 billion in savings (\$350 per Medicare beneficiary) in drug expenditures in 2003 were a drug benefit in place for all Medicare beneficiaries and were generics to represent 50% of total prescriptions. Over 10 years, the projected savings would total approximately \$250 billion.

These projections assume a drug benefit for all beneficiaries similar to that found in most managed care plans now. That may not be far off the mark of what is doable, at least to start, given current federal budget constraints. Most health plans cap the annual prescription drug benefit at \$2,000 or less and most require beneficiaries to pay a higher share of the costs for brand name drugs. Some plans specifically cap coverage of the costs of brand drugs while having no cap for generics.

Clearly, under such a benefit design beneficiaries will continue to pay a large share of their prescription drug costs out of pocket, as they do now. So any savings produced by greater use of generics will accrue to them directly as well as to the government.

The Congressional Budget Office in March 2002 projected that prescription drug expenditures for all Medicare beneficiaries will total \$87 billion in 2002, rising to \$100 billion in 2003, \$113 billion in 2004 and \$278 billion by 2012. The estimated total over the period 2003-2012: \$1.8 trillion.

Thus, the projected 10-year \$250 billion potential savings from greater use of generics would represent 13.9% of total costs.

Caution: (1) The Brandeis study's projections were based on earlier Medicare expenditure assumptions and (2) 10-year projections of costs and savings rates are highly speculative and should serve only as indicators of magnitude.

In March 2002, key Republicans in Congress who are drafting legislation to add a drug benefit to Medicare said they would seek to encourage the use of generic drugs through high co-pays for brand name drugs. The lawmakers said they were also considering a

proposal to require enrollees in a future drug benefit plan to pay the difference between the cost of a generic and brand name drug under some circumstances.

Sources:

1. Stephen Scholdelmeyer, *Patents, Intellectual Property, Innovation and Prescription Drugs: Do the Rules Benefit Consumer*, Presentation made at a congressional briefing, (September 25, 2000).
2. Grant Ritter, Cindy Thomas, and Stan Wallach, *Greater Use of Generics: A Prescription for Cost Savings*, a report by the Schneider Institute for Health Policy, Brandeis University and funded by the Generic Pharmaceutical Association (January 2002). Available at www.gphaonline.org.
3. *Medicare and Prescription Drugs: Fast Facts*, a fact sheet prepared by the National Institute for Health Care Management Foundation (July 2001)
4. Lori Achman and Marsha Gold, *Medicare + Choice, 1999-2001: An Analysis of Managed Care Plan Withdrawals and Trends in Benefits and Premiums*, a Mathematica Policy Research Inc report funded by the Commonwealth Fund. (February 2002). Available at www.cmf.org.
5. Lori Achman and Marsha Gold, *Out-of-Pocket Health Care Expenses for Medicare HMO Beneficiaries: Estimates by Health Status, 1999-2001*, a Mathematica Policy Research, Inc report funded by the Commonwealth Fund. (February 2002). Available at www.cmf.org.
6. Dan Crippen, "Projections of Medicare and Prescription Drug Spending," Testimony before Senate Finance Committee (March 7, 2002). Crippen is Director of the Congressional Budget Office. www.cbo.gov.
7. Robert Pear, "Medicare Proposal Promotes Generic Drugs," *The New York Times* (March 6, 2002), page A17.

Obstacles to the increased use of generic drugs in the U.S. – a quick digest

Patent protection and intellectual property laws.

Current federal laws, cumulatively, gives brand name prescription drugs additional patent life and protection from generic competition to a degree that may not have been intended by Congress. The laws do this primarily by (a) permitting brand companies to file additional patents on their drugs even as old patents are just about to expire, and (b) by mandating delays in generic competition when there is a legal dispute over a drug's patent. Such delays can stall the market entry of generic drugs for several years. Congress has also granted additional periods of patent protection or "market exclusivity" to brand drugs that meet certain requirements, such as those tested in children and those for which new uses are found or new formulations developed. Most brand name prescription drugs have gained from one to six years of added freedom from generic competition because of these provisions in current law.

Deals between brand and generic companies

Some brand and generic companies have sought to reduce their legal costs by reaching settlements which can delay the market entry of generics drugs. Such settlements occur in the context of patent litigation and usually take place when both sides perceive a financial advantage over continued litigation. The Federal Trade Commission (FTC) is currently probing whether and when such settlements violate antitrust law. Several drug companies have already been required to abide by FTC consent decrees that bar them from making such arrangements. That has led some drug company analysts to speculate that the practice will decline.

"Evergreening"

This is the increasingly prevalent practice on the part of the brand companies of altering, reformulating, and repackaging their existing patent-protected drugs to retain market share as the drugs near the end of their patent lives. For example, one popular method is to produce an "extended release" form of a drug whose patent is just about to expire. These new formulations may have to be taken once every few days or even once a week instead of every day. Such new formulations win three years of patent protection (for the new formulation but not the "mother" drug). When the patent on the mother drug expires and generics of it become available, the brand company wages a marketing campaign to switch users to the extended release form of the drug. Importantly, such reformulated drugs may provide distinct advantages to some patients. And as a business strategy, the practice of building on existing successful brands is hardly new. But the practice in pharmaceuticals may have wider public health implications not applicable to other products. Some patients, for example, can be inappropriately switched to extended release or other reformulations. The practice also has cost implications.

The marketing prowess of brand name drug companies

The brand name industry spent approximately \$23 billion in 2001 promoting and marketing prescription drugs to doctors and consumers. The generic industry spent less than \$1 billion. A large brand company will employ a full time sales force of as many as 7,000 people. The brand name industry's total sales force in 2000 was 87,000. A large generic company typically employs a sales force of less than 500. Brand company sales representatives in 2001 provided millions of free samples to doctors to give out to their patients; such samples had a retail value of \$10 billion in 2001, according to IMS Health. The generic industry provides few free samples of its products. Brand name companies also use lists of patients they obtain from pharmacies to promote their drugs through direct mail campaigns. This practice is rare in the generic industry. Increased advertising to consumers is also believed to be driving increased sales of brand name drugs. Sales of the top 50 most heavily advertised brand name drugs rose 32% from 1999 to 2000 while sales of all other drugs (around 70% of which are generic) rose 13.6%, according to a previous NIHCM Foundation study.

Drug payment arrangements

Prescription drugs are paid for in a complex manner. Buyers (such as federal government agencies, states, employers and pharmacy benefit management companies) that purchase drugs in large volumes negotiate discounts and /or rebates. Most consumers who have private health insurance fill prescriptions for which a discount has been negotiated. These arrangements exist for both brand and generic drugs and make drugs less expensive overall. However, the discounts and rebates for brand name drugs are usually deeper and may be linked to volume incentives. That is, the more of a brand drug that a bulk purchaser buys, the deeper the discount or greater the rebate. This arrangement, many critics argue, provides a disincentive to the increased use of generics. Purchaser may perceive greater savings over time with the use of some brand name drugs, most of which are better known by physicians and may be "preferred" by them anyway. Pharmacy benefit managers (PBMs), which manage the drug benefit for most people with private health insurance, also have disincentives to promote the use of generic drugs if they make more money from the rebates from brand name drug manufacturers. In this way, critics allege, PBMs can have a conflict of interest with respect to promoting generics. They'll make more money off rebates for brand name drugs but their customers would save more with an increased use of generics.

The growth of mail order drug sales

Mail order sales of prescription drugs have grown sharply in recent years. They doubled between 1998 and 2001, from \$10.4 billion to \$20.7 billion. Mail order sales now represent 12% of U.S. prescription drug sales, up from 9.8% in 1998. This growth is occurring because pharmacy benefit managers are urging enrollees who take drugs regularly to order their prescriptions by mail. The drugs are then supplied through distributors at prices that are both reduced for the customer and the PBM's client (such as an employer). The potential problem is that, as stated above, the PBMs sometimes have incentives to sell brand name drugs over generics because the brand drugs net larger rebates, a major source of PBM revenue. In addition, many consumers inclined to order

drugs by mail have chronic conditions requiring drug treatment over a long period. Such customers are more likely to fill the same prescription again and again since they will not have access to a pharmacist who might recommend a lower cost generic alternative. In contrast to the incentives in some PBM arrangements, “brick and mortar” pharmacies have financial incentives to switch patients to generics. That’s because the retail mark up for generics is higher and pharmacies pay less to stock an inventory of drugs that is weighted towards generics. In addition, a fixed dispensing fee is the same whether the drug is a generic or brand. As a result of these dynamics, according to data from IMS Health and the National Association of Chain Drug Stores, chain stores fill 50% to 55% of prescriptions with generics while the mail order generic rate is 28%. Overall, 41% of all prescriptions in the U.S. are for generic drugs.

“OBRA 90”

OBRA 90 refers to the Omnibus Budget Reconciliation Act of 1990. This law contained a provision establishing a new formula under which the federal government and states would pay for drugs prescribed for Medicaid beneficiaries. Medicaid accounts for 14% of annual prescription drug expenditures in the U.S. Prior to 1990, states were permitted to have so-called closed formularies (a list of covered and preferred drugs). In addition, in 1987, in the wake of the Hatch-Waxman Act, the federal government made it easier for states to promote the use of generics in the Medicaid program. OBRA 90 replaced the old formulary program with a rebate program. To receive the federal payment share (Medicaid is a joint federal-state program), drug manufacturers are required to rebate a portion of a drug’s price back to states and to the federal government. In return, the government pledged to cover *all* of a company’s drug products. The rebate now averages 15% for brand drugs and 11% for generics. Virtually all pharmaceutical companies have rebate agreements with the government. The law essentially creates open formularies. States are still permitted to bar certain drugs from coverage (such as amphetamines, anabolic steroids, growth hormones and acne medicines). And the law permits states to require beneficiaries to get approval to fill prescriptions for some high-priced drugs; 35 states and the District of Columbia do so, according to recent studies by the Kaiser Family Foundation (*Medicaid: Purchasing Prescription Drugs*, January 2002 and *Outpatient Prescription Drug Benefits: Findings from a National Survey*, October 2001). But the law does not permit a state to remove a drug from a formulary if the drug’s maker offers a rebate. Critics allege that this structure prohibits states from evaluating drugs more aggressively and undermines the wider use of less expensive generics. The structure may also foster abuse. Several states are now suing brand name drug makers alleging that they manipulated the prices paid under Medicaid. The issue has emerged full force recently because prescription drugs costs under Medicaid are soaring. While drug costs in the Medicaid program rose slightly less steeply after OBRA 90 took effect (13.4% annually from 1992 to 1995 compared to 17% from 1990 to 1992), costs have accelerated sharply recently. They rose an average 18.1% annually between 1997 and 2000. (Kaiser Family Foundation, *States Strive to Limit Medicaid Expenditures for Prescribed Drugs*, February 2002 and *Medicaid: Purchasing Prescription Drugs*, January 2002). Overall Medicaid spending on prescription drugs rose from \$4.8 billion in 1990 (6.6% of total Medicaid costs) to \$21 billion in 2000 (10% of total Medicaid costs).

Quality and “bioequivalence” questions

Brand name drug makers have a long history of questioning the quality of generic drugs. They question them on the technical grounds of bioequivalence. But they also question them on the grounds of faulty production. Fifteen years ago such complaints had more basis. Quality standards for generic drugs were not optimal and some generic companies were small and paid less than close attention to quality. But today better company practices, stricter scientific standards, improved FDA oversight, and better testing methods for bioequivalence mean that generic drugs are equal in quality to brand name drugs. The FDA monitors production standards in both industries and takes the official position that the generic industry produces pills of equal quality to the brand name industry. Even so, many physicians may still be vulnerable to the raising of such issues because they recall past quality problems and scandals. In the period 1989 to 1992, for example, a congressional investigation found that several generic companies submitted false data to the FDA; some 30 generic drugs were removed from the market as a result.

Physician habits and inertia

Surveys show that most doctors believe generic drugs to be equivalent to brand name drugs in quality, safety and effectiveness. But a recent review of the literature shows a disparity between that favorable attitude and doctors' actual prescribing patterns. In one survey, 52% of doctors said they allowed substitution of generics (by a pharmacist) rather than write a prescription for the generic. Some specialists allowed substitution much less; cardiologists, for example, reported allowing substitution only 29% of the time. This passive approach can undermine the use of generics since pharmacists must proactively seek patient approval to substitute the generic. In addition, consumers' familiarity and perhaps trust of the brand name drug is fostered when they see its name on the prescription. The literature review cited below also found that physicians more easily recognized the names of brand drugs and were not as familiar with generic (chemical) names. (Source: Kirking et al, "Physicians' Individual and Organizational Views on Generic Medications," *Journal of the American Pharmaceutical Association* (September/October 2001), page 718)

Consumer misconceptions and inertia

As with physicians, most consumers have a positive view of generic drugs. But that does not always lead to increased use of generics. A recent review of consumer surveys done since the 1970s showed growing faith over time that generics are as safe as brand drugs and work just as well. But most people say they usually do not ask for a generic from a doctor or pharmacist and some population subgroups (minority and lower income) did not understand as well what generics were and thus held more negative views of generic substitution. The findings of a 1999 survey of 1,000 people (aged 18 and over) are typical. Twenty percent did not understand at all what a generic drug was and how it differed from a brand drug. Fifty-three percent said a doctor or pharmacist had never talked with them about switching from a brand to a generic; of those for whom a switch had been recommended, 91% said they took the generic. Most did so to save money. A 1995 survey of 355 adults found consumers more concerned about the risk of taking a generic if the drug was for a serious medical condition. For example, 54% said it might

be risky to take a generic for a heart problem versus 14% who thought it might be risky to take a generic drug for strep throat. The authors of this recent review (see below) recommend that “mass educational efforts should be directed...towards consumers to make them more knowledgeable about generic medications and to encourage them to take an active role in managing their medical conditions.” (source: Giather et al, “Consumers’ Views on Generic Medications,” *Journal of the American Pharmaceutical Association* (September/October 2001), page 729)

Therapeutic Interchange

Pharmacists in most states can substitute a generic version of a brand name drug (with the patient’s consent and unless a physician has specifically indicated not to.) But pharmacists are not permitted to substitute *another brand drug or generic* unless they get permission from the prescribing physician. This practice is called therapeutic interchange. Not surprisingly, it’s been a battleground between pharmacists and doctors. Physician groups (such as the AMA) vigorously opposed the practice in the 1980s, seeking to retain control of drug prescribing. More recently, however, the two sides have agreed that pharmacist-based therapeutic interchange in some circumstances has merit and value. The practice has become fairly common in hospitals, for example, and has generated savings in that setting. Many analysts believe that giving pharmacists the power to interchange drugs is vital to the increased use of generic drugs and less expensive brand drugs in the outpatient prescription marketplace. The reasoning is simple enough: There are many more drugs on the market now to treat most conditions. Many of these drugs are interchangeable – that is, they produce essentially the same clinical benefits in populations of patients. But individual patients may respond better to one or another equivalent drug. Doctors no longer have a monopoly on the knowledge of which drugs work best. Therefore, it behooves doctors and pharmacists to work together to choose the best drug for individual patients. That choice should be driven primarily by the clinical needs of the patient but should factor in the cost and clinical value of equivalent drugs. If it does, payers and consumers will save money because more generics will be used. Cost pressures could force some states to revisit their generic substitution laws. But the issue is likely to remain contentious. (Source: Ascione et al, “Historic Overview of Generic Medication Policy,” *Journal of the American Pharmaceutical Association*, (July/August 2001), page 567)

Biologic Drugs

Some see this as primarily an issue for the future. But that future could come faster than they think. The issue is this: there is no established process by which a drug made from human proteins and/or through generic engineering can be copied and sold as a generic once its core patent has expired. This is because the process by which such drugs are made differs substantially from the process by which drugs based on synthesized chemicals are made. The Biotechnology Industry Organization (BIO), representing the interests of major biotechnology firms, takes the stand that “approval of follow on biotechnology products must be based on the same rigorous standards applied by the FDA for the approval of pioneer biotechnology products.” Generic drug firms are pressing the FDA to establish a generic biologics “pathway.” But until they do the biologic drugs now on the market will likely be unchallenged by generics when their patents expire.

State Laws on Generic Drugs

All states have laws that regulate generic drug substitution — that is, filling a prescription with a generic drug even if the doctor has written a prescription for a brand name drug. The laws vary widely in scope and detail but conform to some general trends. This table presents the number of states (includes all 50 states, District of Columbia, Puerto Rico and Guam) with the following key laws and regulations. The laws are not mutually exclusive. All states have at least two and most have several of the regulations listed below.

Law/Regulation	Number of states
<i>Overall</i>	
Permit pharmacists to substitute generic at their discretion unless otherwise directed by the doctor or patient	40
Mandates pharmacists to substitute generic unless specifically overridden by doctor's orders	12
Actively bars pharmacists from substituting generic without authority of prescriber (usually doctor) or patient	1 ^a
<i>Rules to prevent generic substitution</i>	
Pharmacist can substitute generic unless prescriber's signature is on appropriate line of a standard two-line prescription form that indicates not to substitute	13
Mandated two line prescription form	14 ^b
Pharmacist can (or must) substitute generic unless prescriber indicates in writing "no substitution" or that the brand is "medically necessary," either in a designated area of the form or somewhere on the prescription	41
<i>Consumer/patient consent and notification</i>	
Requirement that consumer/patient give consent or be informed of generic substitution	41
No requirement that consumer/patient give consent or be notified of generic substitution	12
Patient may override prescriber and request brand drug but can not override prescriber and request generic if brand has been prescribed with indication of "no substitution."	2 ^c
<i>Cost savings</i>	
Drug dispensed (usually generic) must be less or no more expensive than the drug prescribed	28
Full savings must be passed on to consumer (Pharmacy can not mark up price of generic when making substitution)	12
Pharmacist must pass on 50% of difference between cost of brand and generic drug	1 ^d
Pharmacist must pass on 60% of difference between brand and generic drug	1 ^e
Pharmacists must dispense lowest priced drug which is therapeutically equivalent to the prescribed drug	1 ^f
Pharmacist may charge no more than is "usual or customary" for any drug	2 ^g
No cost savings provisions	7
<i>Formulary</i>	
Formulary lists brand drugs that can not be substituted with generics	5
Formulary lists brand drugs that can be substituted with generics	15
No state wide formulary that specifies which drugs can or can not be substituted	31
Pharmacist must use Food and Drug Administration (FDA) "therapeutic equivalency list" when making judgments about generic substitutions	15
Each pharmacy must develop its own drug selection list	1 ^h

NOTES: ^a Oklahoma, through a 1961 law; ^b Texas, required until 6/1/02; ^c Washington and Guam; ^d Iowa; ^e Washington; ^f Georgia; ^g Vermont, Maine; ^h Florida

SOURCE: National Association of Boards of Pharmacy, November 2001