

GENERIC DRUGS

Introduction and Overview

For many years, generic drugs have been a key tool for helping consumers, health insurers, and public payers to reduce their prescription drug costs. Generic drugs, which accounted for 18.6 percent of U.S. retail prescriptions dispensed in 1984,¹ accounted for nearly half of U.S. retail prescriptions in 2001.² Generic drugs also accounted for nine of the 20 most widely dispensed drugs in the U.S. in 2001 (see Figure 1). However, growth in the role of generic drugs has moderated in recent years: the share of total prescriptions dispensed in generic form has been relatively stable since 1996. In addition, due in part to the slower rate of growth in the average generic drug price compared to the growth in the average brand-name drug price, generic drugs' share of total retail prescription drug sales has fallen steadily, from 20.5 percent in 1996 to 17.8 percent in 2000.

The availability of generic drugs is particularly important in view of renewed rapid health care cost increases, a substantial share of which is attributed to prescription drugs.³ At the same time, the cost savings should not be considered separately from quality of care issues. This *Issue Brief* provides basic information about generic drugs, focusing on their contribution to reducing prescription drug costs; the generic drug approval process; evidence on generic drug safety and effectiveness; state laws regarding generic substitution; and provider and consumer attitudes toward generic drugs.

The main findings of the *Issue Brief* can be summarized as follows:

1. ***Generic drugs' contribution to reducing drug prices and prescription drug expenditures***
 - The first generic substitute typically enters the market at 70 to 80 percent of the brand-name price, and generic drug prices fall to 40 percent or less of the brand-name price as more generic manufacturers enter the market.
 - According to the Congressional Budget Office (CBO), using generic drugs instead of brand-name substitutes saved consumers an estimated \$8 billion to \$10 billion in 1994 (the most recent year for which estimates are available).
2. ***FDA's definition and approval process for generic drugs***
 - According to the Food and Drug Administration (FDA), a generic drug is a "chemical clone" that has the same active ingredients as its FDA-approved brand-name counterpart. The FDA asserts that virtually all generic drugs can be expected to have the same therapeutic effect as their brand-name counterparts.
 - The 1984 Hatch-Waxman Act simplified the process by which the FDA approves generic drugs.
 - To obtain FDA approval, a generic manufacturer must show that the generic drug is *bioequivalent* to the comparable brand-name drug. This means that it (1) has the same active ingredients, strength, dosage form, and method of

Figure 1: Top 20 Prescription Drugs in the U.S., Based on Number of Prescriptions Dispensed, 2001

Drug Rank	Drug Name (shading denotes generic drugs)	Description	Brand Name Equivalent
1	Hydrocodone w/APAP	Narcotic Analgesics	Assorted
2	Lipitor	Cholesterol reduction	-
3	Premarin	Estrogen replacement	-
4	Atenolol	Antihypertensive	Assorted
5	Synthroid	Synthetic thyroid agent	-
6	Zithromax	Antibiotic	-
7	Furosemide	Diuretic	Lasix
8	Amoxicillin	Antibiotic	Assorted
9	Norvasc	Antihypertensive	-
10	Alprazolam	Anti-anxiety agent	Xanax
11	Albuterol Aerosol	Bronchodilator	Assorted
12	Claritin	Non-sedating antihistamine	-
13	Hydrochlorothiazide	High blood pressure	Assorted
14	Prilosec	Anti-ulcer agent	-
15	Zoloft	Antidepressant	-
16	Paxil	Antidepressant	-
17	Triamterene/HCTZ	Diuretic	Dyrenium
18	Prevacid	Anti-ulcer agent	-
19	Ibuprofen	Pain relief	Assorted
20	Celebrex	Arthritis pain relief	-

Sources: Rxlist: The Internet Drug Index, *The Top 200 Prescriptions for 2001 by Number of US Prescriptions Dispensed*, www.rxlist.com/top200.htm; MEDLINE plus, <http://www.nlm.nih.gov/medlineplus/druginformation.html>

administration as the brand-name product (i.e., is *pharmaceutically equivalent*), and (2) can be expected to work the same way in the body as the pharmaceutically equivalent brand-name product (i.e., has comparable *bioavailability*).

- Nearly all FDA-approved generic drugs are “A”-rated. This means that they have been judged to be *therapeutically equivalent* to the brand-name product. A “B”-rated generic drug is one for which

actual or potential bioequivalence problems have not been resolved by adequate evidence.

3. Evidence on the safety and effectiveness of generic drugs

- The FDA asserts that all “A”-rated generic drugs can be expected to have the same clinical effect as their brand-name counterparts.

- There has been some controversy about whether generic versions of so-called Narrow Therapeutic Index (NTI) or Narrow Therapeutic Range (NTR) drugs should be substituted for their brand-name counterparts. (NTI and NTR are informal designations for drugs with less than a twofold difference in the median lethal dose and the median effective dose values or, alternatively, less than a two-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood.) However, the FDA has not been able to validate any assertions of adverse health outcomes arising from alleged differences in bioequivalence between generic and brand-name NTI/NTR drugs.
- The FDA recognizes that there may be circumstances that are unique to a particular patient where generic substitution is not appropriate. For example, some patients might be confused by differences in the shape or color of generic substitutes, while others may be allergic to the coating of the generic drug but not to that of the brand-name product (the converse may also be true). These minor risks are increased when pharmacies dispense different manufacturers' versions of generic drugs.
- From a strictly technical perspective, a small number of multi-source drugs (drugs that have more than one manufacturer) are not considered by the FDA to be generic substitutes because the originator drug was introduced before the FDA had the authority to evaluate drug safety and effectiveness. Examples include digoxin (sold under the brand name Lanoxin®) and levothyroxine sodium (sold under the

brand names Synthroid® and Levothroid®). In addition, other pharmaceutically equivalent drugs, designated by the FDA as “B”-rated, are not considered to be therapeutically equivalent because actual or potential bioequivalence problems have not been resolved.

- Some questions have also been raised about whether generic substitution is appropriate in elderly patients. However, the FDA has not been able to validate any assertions of adverse outcomes arising from use of generic drugs by this population.

4. *State laws governing generic substitution*

- Every state allows generic substitution unless the prescribing physician has noted on the prescription, in writing, that such a substitute should not be made (for example, by writing or checking a box that says “Do Not Substitute” or “Dispense as Written”).
- Every state prohibits *therapeutic substitution* by pharmacists—that is, states do not allow pharmacists to dispense, without the physician’s permission, a drug that is therapeutically similar to, but not pharmaceutically equivalent to, the prescribed drug.

5. *Provider and consumer attitudes toward generic drugs*

- Provider groups generally do not oppose generic substitution by pharmacists (that is, substitution of a generic drug for a brand-name prescribed drug without receiving explicit permission from the prescribing physician), as long as the prescribing physician maintains the right

to limit substitution when he or she believes it is medically inappropriate. An exception to this stance is that some provider groups oppose generic substitution of NTI drugs by pharmacists without explicit prior physician approval; however, this position is not universal among providers.

- Consumers generally accept generic drugs as substitutes for brand-name products. However, some organizations that represent patients with specific diseases or medical conditions support efforts to require the express permission of the prescribing physician before a pharmacist can substitute a generic drug.
- For the most part, consumers can be confident that they are getting the appropriate medication when their pharmacist dispenses a generic substitute. However, consumers should always contact their physician if they have a concern about the effectiveness of the drug that has been dispensed, or if they feel their reaction to a drug is different from what they have experienced with a previously dispensed product.

Generic Drugs' Impact on Prescription Drug Prices and Expenditures

It is widely accepted that the growth of generic drug availability since passage of the Hatch-Waxman Act has helped to reduce the costs of prescription drugs. To a large extent, this is attributable to price differences between brand-name and generic drugs and to incentives of many private and public health plans to use generic drugs when available. As a result, generic drugs have had a significant role in reducing total prescription drug expenditures.

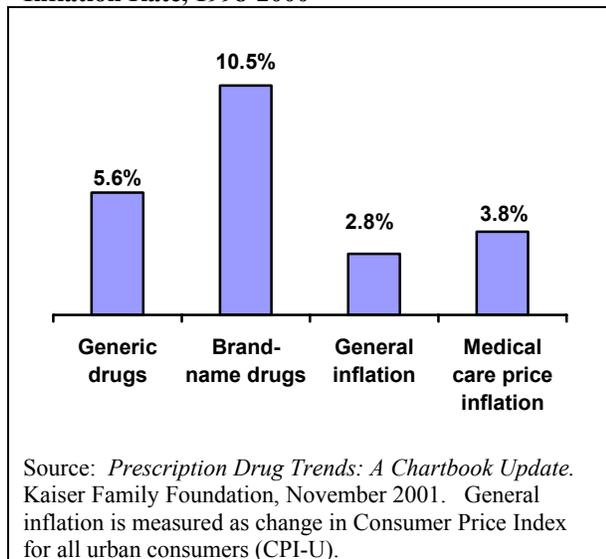
Generic drug prices. Generic drug prices tend to be substantially lower than the prices of their brand-name counterparts. Furthermore, generic drug prices for a single product tend to fall as more generic distributors enter the market, because their products are therapeutically interchangeable and, therefore, subject to price competition. The first generic entrant typically charges 70 to 80 percent of the brand-name price.⁴ This ratio falls to 40 percent or less of the brand-name price as more generic entrants come onto the market.⁵

Generic drug entry does not prevent price increases on corresponding brand-name products, although whether entry affects the rate of price increase is in dispute. CBO found that brand-name drugs that faced their first generic competition in 1991 had the same average annual price inflation from 1991 to 1994 as in the prior three years. However, CBO was only able to measure the retail price and did not capture any discounts or rebates that might have been provided to insurers and health plans. CBO also cites some studies that found no change in the rate of brand-name drug price increases after the entry of generic competitors, while others conclude that the rate of increase actually slowed after generic entry.⁶

Overall, average generic drug price levels have risen faster than both the Consumer Price Index and overall medical care prices but slower than brand-name drug prices. The average price of a retail generic drug prescription increased by 5.6 percent per year between 1998 and 2000, to \$19.33. During the same period, the average retail price of a brand-name prescription rose 10.5 percent, to \$65.29. This compares to a 2.8 percent general rate of inflation and a 3.8 percent rate of overall medical care price inflation (see Figure 2).⁷ (Note that the

average increase in brand-name drug prices represents both price increases on existing products and prices of newly introduced products that, in some cases, replace older, less costly drugs.)

Figure 3: Average Annual Percent Change in Prescription Drug Prices Relative to General Inflation Rate, 1998-2000



Generic drugs' impact on prescription drug expenditures. The simple substitution of a generic drug for its brand-name counterpart cuts the drug's price in half, on average.⁸ Consumers who pay for drugs out of pocket can reap such savings directly. Consumers who have drug benefits under their health insurance would not get this entire savings directly because they don't pay the entire cost of the drug. However, they may face lower health insurance premiums because generic drug use can reduce the plan's overall costs, and consumers typically pay a lower cost-sharing amount for generic drugs. They may also be required to use a generic drug when one is available.

Substitution of generic drugs for their brand-name counterparts saved consumers an estimated \$8 billion to \$10 billion in 1994 (the most recent year for which national estimates are available), according to the

CBO.⁹ A more recent study shows the extent of generic substitution among well-insured individuals age 65 and older. This study analyzed prescription drug claims over a 12-month period for 300,000 individuals age 65 and older who were enrolled in one of 428 health plans. For these individuals, 91 percent of prescriptions for multi-source drugs—drugs for which a generic substitute was available—were dispensed with generic substitutes.¹⁰

FDA's Definition of and Approval Process for Generic Drugs

According to the FDA, a generic drug is a "chemical clone" that has the same active ingredients as its FDA-approved brand-name counterpart.¹¹ The FDA asserts that virtually all generic drugs can be expected to have the same therapeutic effect as their brand-name counterparts.¹² Generic drugs need not be exactly identical to brand-name drugs because FDA allows them to differ in shape, scoring configuration (i.e., presence or absence of indentations in the pills), release mechanisms, packaging, inactive ingredients (such as colors, flavors, preservatives), expiration date/time, minor aspects of labeling (e.g., the presence of specific pharmacokinetic information), and storage conditions.¹³

FDA approval process for generic drugs.

The increasing role of generic drugs was facilitated by passage of the Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Act after its legislative sponsors). This legislation greatly expanded availability of generic drugs by clarifying and simplifying the process by which generics could be approved by the FDA.¹⁴ Under the provisions of the Hatch-Waxman Act, generic versions of brand-name drugs can seek FDA approval through an

Abbreviated New Drug Application (ANDA).¹⁵ This law removed the requirement that generic drug manufacturers perform clinical trials to demonstrate safety and efficacy¹⁶ or submit a paper New Drug Application, i.e., a New Drug Application (NDA) that cites published data rather than new clinical studies. According to the FDA, such trials are not necessary because safety and efficacy have already been established in the brand-name product. Instead, the ANDA requires the generic manufacturer to demonstrate bioequivalency to the brand-name product.¹⁷

Specifically, to obtain FDA approval, the manufacturer of the generic product must show:

- *Pharmaceutical equivalence.* The generic manufacturer must show that there is an FDA-approved brand-name drug that has the same active ingredient or ingredients, strength, dosage form, and method of administration as the generic product (see Figure 3).

Figure 3: FDA Definition of Pharmaceutical Equivalence

Pharmaceutically equivalent drugs are products that:

- contain the same amount of active ingredient in the same dosage form,
- use the same route of administration, and
- are identical in strength or concentration.

They may differ from one another in shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and—within certain limits—labeling.

Source: FDA, *The Orange Book*.
<http://www.fda.gov/cder/orange/default.htm>

- *Comparable bioavailability.* The generic manufacturer must show that the generic drug can be expected to work the same way in the body as the comparable brand-name drug. *Bioavailability* refers to the rate and extent to which a drug is

absorbed or is otherwise available to the treatment site in the body. The generic drug manufacturer must show that the bioavailability of the brand-name and generic drugs do not differ significantly when the two products are given in the same dosage and under the same conditions.¹⁸

The FDA judges a drug to be *bioequivalent* to a reference drug if the two drugs are pharmaceutically equivalent and there is no statistically significant difference in bioavailability of the active ingredients in the generic and brand-name drugs when studied under similar experimental conditions (see Figure 4).

Figure 4: FDA Definition of Bioequivalence

Bioequivalent drugs are products that:

- are *pharmaceutically equivalent*, and
- display comparable *bioavailability* in the body—that is, show no statistically significant difference in the rate and extent of absorption of the active ingredients—when studied under similar experimental conditions.

Source: FDA, *The Orange Book*.
<http://www.fda.gov/cder/orange/default.htm>

A typical test for establishing bioequivalency is for the manufacturer to compare the bioavailability of the generic and brand-name products in 24 to 36 healthy adult volunteers.¹⁹ The FDA considers the products to be bioequivalent if certain measures of the bioavailability of the drugs are within 20 percent of one another (there are other related requirements). This standard is much broader than what is often observed in practice. In two reviews of bioequivalence studies—the first examining 224 generic drugs approved during 1985 and 1986, and the second examining 127 generic drugs approved in 1997—the FDA found average observed differences in

bioavailability between brand and generic products of 3.5 percent.²⁰

Other FDA standards for approving a generic drug are essentially the same as those applied when the formulation of a brand-name drug is changed from what was approved initially.^{21,22} For example, the generic manufacturer must show that the generic drug's labeling contains essentially the same information as the approved brand-name drug; that the raw materials and finished product meet predetermined specifications; that the drug is stable under extremes of heat and humidity; and that the drug's container and closure system do not interact with the drug. The generic drug manufacturer must also fully document to the FDA the drug's chemistry, steps for manufacturing, and quality control measures. It must provide a full description of the facilities that it uses to manufacture, process, test, package, label, and control the drug; certify that these facilities comply with federal regulations on good manufacturing practices; and allow these facilities to undergo FDA inspection to assure compliance.²³

FDA ratings of therapeutic equivalence.

The FDA considers pharmaceutically equivalent drugs to be *therapeutically equivalent*—appropriate for substitution—if they have been shown to be safe and effective, are bioequivalent, are adequately labeled, and are manufactured in compliance with the FDA's Current Good Manufacturing Practice regulations. According to the FDA, therapeutically equivalent drugs can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling (see Figure 5).

The FDA lists approved generic drugs in a publication entitled *Approved Drug*

Products with Therapeutic Equivalence Evaluation, more commonly known as the *Orange Book*. The *Orange Book* lists all prescription and nonprescription drug products approved by the FDA on the basis of safety and effectiveness and provides information about the therapeutic equivalence of these products.

Figure 5: FDA Definition of Therapeutic Equivalence

Therapeutically equivalent drugs are pharmaceutically equivalent drugs that have been judged by the FDA to be:

- safe and effective,
- *bioequivalent*,
- adequately labeled, and
- manufactured in compliance with the FDA's Current Good Manufacturing Practice regulations.

FDA's definition of *therapeutic equivalence* does not include drugs with different active ingredients that are used to treat the same condition.

Source: FDA, *The Orange Book*.
<http://www.fda.gov/cder/orange/default.htm>

The FDA's *Orange Book* contains a coding system for therapeutic equivalence evaluations that allows users to determine quickly whether the agency has ascertained that a particular approved product is therapeutically equivalent to other pharmaceutically equivalent products. The FDA uses two basic categories for classifying approved multi-source drugs (i.e., drugs with generic substitutes). The codes apply to both the generic and brand-name versions:

- Generic and multi-source brand-name drugs with an "A" code are those the FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products. "A" drugs are those for which either there is no known or suspected bioequivalence problem, or

the actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence.²⁴ According to the FDA, virtually all generic drugs listed in the *Orange Book* are “A” products.²⁵

- Generic and multi-source brand-name drugs with a “B” code are those that the FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products, i.e., drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence.²⁶ According to the FDA, drugs rarely receive a “B” code.

Safety and Effectiveness of Generic Drugs

In general, FDA’s standards for generic drug approval are viewed as sufficient for guaranteeing that an “A”-rated generic will be as safe and effective as a pharmaceutically equivalent brand-name product. While some concern has been raised about the appropriateness of generic substitution for certain drugs or certain patients, the preponderance of scientific evidence suggests that there is no adverse relationship between generic drug use and health outcomes. However, the prescribing physician should maintain the authority to require that a brand-name drug be dispensed in those individual cases where there is a special need or a generic drug may not be appropriate.

FDA position on appropriateness of generic substitution. The FDA asserts that all “A”-rated generic drugs can be expected to have the same clinical effect as their brand-name counterparts.²⁷ The FDA is not aware of any documented example of a generic drug that has been designated as therapeutically

equivalent to a brand-name product and could not be substituted with its corresponding brand-name drug.²⁸ It has not successfully validated any of the concerns about the use of generic drugs. In some cases, the FDA concluded that adverse health impacts cited by others were not attributable to generic substitution.

The FDA’s assertion of the safety of generic substitution extends to products unofficially known as Narrow Therapeutic Index (NTI) or Narrow Therapeutic Ratio (NTR) drugs—drugs with less than a twofold difference in the median lethal dose and the median effective dose values or, alternatively, less than a twofold difference in the minimum toxic concentrations and minimum effective concentrations in the blood.²⁹ (Currently, the NTI designation is not a formal designation used by the FDA.)

A prominent example of an NTI drug is Coumadin® (generic name warfarin), which is used to help prevent harmful clots from forming in the blood vessels. A number of published reports have focused on the issue of whether the FDA’s standards of therapeutic equivalence are sufficient to prevent harm when a patient is switched from generic warfarin to Coumadin® or vice versa. While the medical literature includes cases where individual patients were reported to have experienced adverse medical outcomes or differences in therapeutic value after using warfarin,³⁰ numerous other studies have supported the therapeutic equivalence of warfarin and Coumadin®.³¹

Furthermore, the FDA’s review of reports of decreased efficacy or greater toxicity associated with use of generic NTI drugs revealed no problems that could be attributed to substitution of an approved generic drug for the brand-name version, or

vice versa.³² The FDA has also stated that safe and effective use of NTI drugs requires careful titration (determination of appropriate dose) and patient monitoring, regardless of whether the brand or generic is used.³³

When generic substitution may not be appropriate. The FDA recognizes that there may be circumstances where a generic substitution may not be appropriate, even though it considers the generic and brand-name drug to be therapeutically equivalent. The *Orange Book* states that “in those circumstances where the characteristics of a specific product, other than its active ingredient, are important in the therapy of a particular patient, the physician’s specification of that product is appropriate.” For example, some patients might be confused by differences in color or shape of tablets, while others might reduce their compliance if they dislike the flavor of the substituted medication. A patient who is supposed to take a partial dose may face difficulties splitting the pill if the generic version is scored differently. Some patients might be allergic to the coating of a generic substitute but not to the coating of the brand-name version. Some individuals may store their medications under adverse conditions that would affect the stability of the generic more than its brand-name version.³⁴

From a strictly technical perspective, a small number of multi-source drugs are not considered by the FDA to be generic substitutes because the originator drug was introduced before the FDA had the authority to evaluate drug safety and effectiveness. As a result, FDA has never assessed their bioequivalence to a reference drug and, therefore, does not consider them to be therapeutically equivalent products. In practice, however, these drugs often are used as generic substitutes.

Two prominent examples of such drugs are digoxin (brand name Lanoxin®) and levothyroxine sodium (also sold under the brand names Synthroid® and Levothroid®). There are no available studies showing bioequivalence between digoxin and Lanoxin®; there is published literature that claims bioequivalency between levothyroxine sodium and Synthroid®. However, the FDA has not evaluated the bioequivalence of these drugs (in fact, in 2000, the FDA issued a notice that levothyroxine products are now considered to be new drugs, and that manufacturers selling these products must submit an NDA to the FDA by 2004).³⁵ Substitution of drugs such as these may require careful physician monitoring because the FDA has not evaluated them for therapeutic equivalence.

There is some controversy about the appropriateness of generic substitution for certain “A”-rated multi-source drugs, particularly NTI/NTR drugs. The two contrasting views in this debate are: (1) the FDA’s view, noted in the previous section, that these drugs should be expected to have the same therapeutic effect when used according to instructions, and (2) concern among some providers and patients about potential adverse effects, given how the drug is actually used in practice.

In addition to the Coumadin®/warfarin example already discussed, a prominent recent example is substitution between the brand-name drug Dilantin® and its generic equivalent, phenytoin, both of which are used to control seizures in persons with epilepsy. A recent study estimated that differences in bioavailability between Dilantin® and generic phenytoin, when taken with a high-fat meal, could result in 46 percent of epilepsy patients who take the

generic product not having enough of the drug in their bodies to control seizures.³⁶

FDA officials have disputed this conclusion, criticizing the study's methodology and noting the low level of adverse effects reported from using the generic drug (63 lack-of-effect cases were reported to the FDA out of more than three million prescriptions dispensed from the time when the generic product was launched through May 2001, and 23 of these were definitively attributed to factors other than bioavailability).³⁷ In response to FDA officials' criticisms, the study's authors noted that their estimates apply only to persons who take their medication on a full stomach and do not apply when the products are taken on an empty stomach. They also suggested that there may be underreporting of lack-of-effect cases other than in cases of death because persons with epilepsy may not report adverse reactions (i.e., an increase in seizures) for fear of losing their driver's license, employment, or health insurance, or for other personal reasons.³⁸

Special issues for older patients. In its guidelines for bioavailability and bioequivalence studies for orally administered drug products, the FDA notes that if the drug product is to be used predominantly by elderly persons, the sponsor should attempt to include as many subjects age 60 years or older as possible. However, there is little literature on the effects of specific generic drugs versus their brand-name counterparts among older patients.

Exceptions are three studies that tested the bioequivalency of particular products in elderly populations—two studies of the antihypertensive drug verapamil, and another of the antiseizure drug carbamazepine. One study compared the

bioavailability of generic verapamil in both younger and older subjects and concluded that a generic verapamil product that is bioequivalent in young subjects may not be bioequivalent in elderly patients.³⁹ A second study also found differences in bioequivalency between brand-name and generic verapamil in older patients but concluded that the observed differences were not clinically significant.⁴⁰ The carbamazepine study found differences in absorption rates between branded and generic products, but none that would yield significant differences in clinical effects.⁴¹ Each of these studies involved a small patient sample—16 in the first verapamil study (eight older and eight younger subjects); eight in the second verapamil study; and 18 in the carbamazepine study.

Despite the scant literature on this topic, there are different views about whether the bioavailability of generic drugs in older patients differs from that in younger patients. At least one review contends that there is no evidence that older patients are more or less likely than their younger counterparts to have different clinical outcomes from substituting brand-name for generic drugs. This article attributes individual variations in bioavailability to unique aspects of the patient, not to a systematic variation associated with the patient's age.⁴² According to this view, the prescribing physician should consider any basis for potential adverse impacts of generic substitution on the individual patient, including characteristics of both the drug and the patient. However, some providers have expressed concern about generic substitution in the elderly, particularly for NTI drugs, citing differences in the physiology of older people that could affect both the rate at which the drug is absorbed and the rate at which it leaves the body.⁴³

A separate issue from bioequivalence of generic drugs in older adults is whether older adults might be affected by differences between generic and brand-name drugs that are not related to the active ingredients. As previously noted, the FDA acknowledges that generic substitution might not be appropriate if patient compliance could be affected because of confusion over differences in the appearance of two bioequivalent drugs or if the patient suffers an adverse reaction from an inactive ingredient contained in a substituted bioequivalent drug. This risk, while seemingly minor when due to a single switch, is increased if a pharmacy changes its generic drug supplier regularly, resulting in frequent changes in the color and shape of the medication dispensed. Older adults might be more at risk from such factors merely because of the greater number of prescriptions used. Individuals who suffer from any degree of cognitive or physical impairment—particularly in the case of pill splitting by the individual—might also be affected by these factors. The actual risk associated with such factors—as well as the extent to which they are of greater concern to an older population—has not been determined.

State Laws Affecting Dispensing of Generic Drugs

States—through their regulation of general pharmacy practice—are responsible for establishing rules regarding the practice of *generic substitution*. Every state allows generic substitution unless the prescribing physician has noted on the prescription, in writing, that such a substitution should not be made (for example, by writing or checking a box that says “Do Not Substitute” or “Dispense as Written”). More than half of states require that the consumer

be told when a substitution is made. In contrast to their policies on *generic substitution*, every state prohibits *therapeutic substitution* by pharmacists—that is, they do not allow pharmacists to dispense, without the physician’s permission, a drug that is therapeutically similar, but not pharmaceutically equivalent, to the drug that was prescribed.⁴⁴

State regulation of general pharmacy practice also determines what is considered to be a therapeutically equivalent generic substitute in each state. Many states will only allow pharmacists to perform generic substitution with products deemed therapeutically equivalent in the *Orange Book*. Other states have developed their own lists, known as formularies.⁴⁵ For example, North Carolina does not allow pharmacists to substitute generic NTI drugs without discussing the change with the prescribing provider and the patient.⁴⁶

States may also encourage generic use in publicly funded programs that provide prescription drug benefits. For example, a number of state Medicaid programs require pharmacists to dispense generic drugs when they are available. State employee benefit plans, like plans administered by private payers, may also require generic substitution or may promote greater use of generic drugs through a cost-sharing system that imposes lower cost sharing for generic drugs and higher cost sharing for brand-name drugs.

Provider and Consumer Attitudes toward Generic Substitution

Provider groups. Provider groups generally do not oppose generic substitution by pharmacists, as long as the prescribing physician maintains the right to limit such substitution when he or she believes it is medically inappropriate. For example, the

American Academy of Family Physicians (AAFP), the American College of Cardiologists (ACC), and the National Association of Boards of Pharmacy (NABP) state that they do not oppose generic drug substitution by pharmacists—even of NTI drugs. The AAFP, in particular, has stated, “There appears to be no substantive evidence that bioequivalence does not equal therapeutic equivalence” and that “products approved by the FDA should be expected to be clinically equivalent to brand-name products.”⁴⁷

However, not all provider groups have the same level of confidence in the therapeutic equivalence of generic and brand-name drugs. Some providers have expressed concern about whether generic substitution is always appropriate for an elderly population that may not be well represented in bioequivalency studies. In addition, some providers and patient groups have expressed concern about whether generic substitution—without prior authorization of the prescribing provider—is appropriate for NTI/NTR drugs.

The American Medical Association (AMA), in particular, opposes generic substitution by pharmacists of NTI drugs without prior affirmative physician approval (i.e., physician approval cannot be assumed simply because the physician does not indicate “dispense as written” on the prescription).⁴⁸ In adopting this policy in 2000, the AMA House of Delegates overrode the recommendation of its “Reference Committee,” which opposed this position because of: (1) a lack of universal agreement on what drugs constitute NTI drugs; (2) the lack of published evidence documenting safety concerns with any “A-rated” drugs currently on the market (NTI generic drugs are “A-rated”); and (3) variability in state approaches to the problem. The Committee noted that

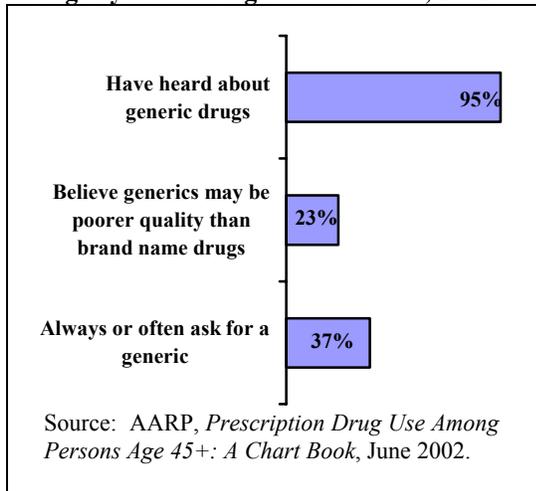
physicians who had concerns about generic substitution of NTI drugs could indicate on their prescriptions that a substitution was not permitted.⁴⁹

Provider organizations do tend to oppose *mandatory* generic substitution—that is, pharmacy dispensing of a generic even if the prescribing provider has designated that a generic substitution is not appropriate. For example, the AAFP states that the family physician is best suited to make the determination of when a generic drug is appropriate and that mandatory substitution distorts the physician-patient relationship.⁵⁰ Provider attitudes toward mandatory generic substitution seem to be rooted less in concern about the bioequivalence of generic drugs than in concern about preserving the role of the physician—not the health plan or other third-party payer—as the key decision-maker of the appropriate treatment.

Consumers. Surveys indicate a general—though not total—acceptance among consumers of generic drugs as acceptable substitutes for brand-name products. For example, a 2001 National Consumer League survey found that more than 80 percent of consumers age 65 and older believe that generic drugs are generally just as effective as their brand-name counterparts, and more than 90 percent would be very likely or somewhat likely to try a generic drug if their doctor or pharmacist recommended it as a safe, effective, and less costly alternative to brand-name drugs.⁵¹ A 2002 AARP survey found slightly less acceptance of generic drugs among persons age 45 and over (see Figure 6). While 95 percent of respondents reported hearing about generic drugs, 22 percent of those respondents felt that generic drugs may be less effective or of poorer quality than brand-name drugs. Only 37 percent of respondents in the AARP survey reported that they always or often ask their

doctor or pharmacist for generic prescription drugs when they are available.⁵²

Figure 6: Awareness and Acceptance of Generic Drugs by Persons Age 45 and Older, 2002



Attitudes toward generic substitution among organizations that represent patients with specific medical conditions or diseases are mixed. For example, the American Heart Association, which has a joint policy with the American College of Cardiologists on generic drugs, does not oppose generic substitution.⁵³ By contrast, the Epilepsy Foundation has stated that generic substitution of Dilantin® without prior physician and patient approval could be harmful for persons with epilepsy.⁵⁴ It believes that the FDA's guidelines allow for too broad a therapeutic range to ensure that each individual receives the same amount of antiepileptic drug when switching from a brand-name to a generic antiepileptic drug or from one generic to another.

Conclusions

As health care costs continue to rise, consumers, providers, and policymakers need to assess the best way to keep health care affordable without adversely affecting access to quality care. With prescription drug costs serving as a major contributor to recent cost increases, generic drugs offer an

important tool for reducing the rate of growth in overall health expenditures.

With a few exceptions in some states for NTI/NTR drugs, every state allows pharmacists to substitute generic drugs for a brand-name prescription without prior authorization from the prescribing physician, unless the physician has designated that generic substitution is not appropriate. While questions have been raised about whether generic substitution is appropriate in select circumstances, there is little—if any—scientific evidence to support these concerns on a broad basis. The FDA has repeatedly asserted that once it determines a generic drug to be therapeutically equivalent to the brand-name product, it can be expected to be as safe and effective as that product. Furthermore, the FDA has not been able to validate any studies that assert adverse health outcomes arising from actual differences in the bioavailability of generic drugs. While there is some evidence that bioequivalence studies of brand and generic drugs may have different results when performed in older persons, there is no evidence that these differences result in different clinical outcomes among elderly persons.

Nonetheless, there are relatively rare circumstances where substituting a generic drug for a brand-name product (or vice versa) may not be appropriate for a particular individual. The medical literature cites examples of individuals for whom generic substitution was inappropriate because of reactions to inactive ingredients or problems with the pill shape, color, or related characteristics.⁵⁵ These findings support the FDA's recommendation that physicians should be aware of circumstances where the characteristics of a specific product other than its active ingredient are important in the therapy of a particular

patient and, therefore, generic substitution is not appropriate. In addition, there are certain drugs—such as digoxin (brand name Lanoxin®) and levothyroxine sodium (also sold under the brand names Synthroid® and Levothroid®)—that are widely used as substitutes but have never been evaluated for bioequivalence by the FDA and, therefore, do not have FDA approval as therapeutically equivalent substitutes. Finally, while the FDA asserts that generic versions of NTI drugs should not react differently in an individual from their brand-name counterparts, some consumers and physicians continue to have concerns about the appropriateness of generic substitution of those drugs. In these cases, the FDA recommends careful titration and patient monitoring, regardless of whether the generic or brand-name product is used.

For the most part, consumers can be assured that they are getting safe and effective medication when their pharmacist dispenses a generic substitute. However, consumers should always contact their physician if they have a concern about the effectiveness of the drug that has been dispensed, or if they feel their reaction to a drug is different from their reaction to a previously dispensed product. Older persons and their caregivers, in particular, should ask their pharmacist to inform them if they are being given a different generic version from what has been dispensed to them in the past. Furthermore, physicians should always have the opportunity to state on a prescription that a generic substitution is not allowed when they believe that such a substitution would not be appropriate for the patient.

Issues for Further Analysis

While this *Issue Brief* does not address the cost savings generic drugs can produce within broader pharmacy benefit

management procedures, the topic warrants further assessment. As background, it is important to note that a significant portion of health spending growth is attributable to spending on relatively new and costly single-source drugs (i.e., brand-name drugs that have no generic substitutes),⁵⁶ some of which may offer little advantage over older, therapeutically similar medications (some of which may be available in generic versions), or offer a therapeutic advantage over such medications only for certain populations.⁵⁷

One pharmacy benefit management tool that requires further assessment is the practice of *therapeutic substitution*, in which a drug that has a similar therapeutic effect for most individuals, but is not pharmaceutically equivalent to the originally prescribed medication, is substituted with the prescribing physician's consent. Health plans have used therapeutic substitution to encourage physicians to prescribe generic drugs as substitutes for costlier brand-name drugs that are not bioequivalent.⁵⁸ (This broader application of therapeutic substitution is not limited to generic-brand substitutions. Plans may also promote less costly brand-name drugs over other brand-name drugs, or may promote a more costly brand-name drug over a generic if the brand-name drug produces better outcomes or has fewer side effects.)

From a consumer and health system perspective, it is important to understand health plan approaches toward using generic drugs as therapeutic substitutes as well as the medical appropriateness of these approaches (i.e., whether the drug being dispensed is the appropriate drug rather than simply the least costly drug) and their impact on health care costs. Consumers and physicians could also gain value from studies that compare the relative cost and effectiveness of high-cost single-source

drugs to therapeutically similar multi-source or single-source drugs. Such studies would better inform consumer and physician choice and enhance the quality of health care while contributing to cost reduction.

This *Issue Brief* does not address barriers to generic drug availability that stem from violation of either current antitrust law or the intent of the Hatch-Waxman Act. In recent years, some drug manufacturers have tried to forestall generic competition on drugs with high sales volumes. One frequently used approach is for a manufacturer to list additional patents on brand-name drugs in the FDA's *Orange Book* shortly before the original patents expire; under the provisions of the Hatch-Waxman Act, such actions trigger an automatic 30-month stay on FDA approval of the generic drug and allow the brand-name manufacturer to continue selling the drug without generic competition. Other techniques used to forestall generic competition include paying generic manufacturers not to sell their product;⁵⁹ receiving FDA approval to market new medical indications for existing drugs;⁶⁰ and engaging in extensive, albeit unsuccessful, lobbying efforts to extend the patents on their products.⁶¹ Some of these practices have led to investigation by the Federal Trade Commission,⁶² while others have led to proposals for federal legislation that would close perceived loopholes in the Hatch-Waxman Act.⁶³ The policy implications of these developments also warrant further examination.

¹ Pharmaceutical Research and Manufacturers of America (PhRMA), *Pharmaceutical Industry Profile, 2001*. <http://www.phrma.org/publications/publications/profile01/chapter5.phtml#competition>. Accessed February 25, 2002.

² IMS Health, *Retail and Provider Perspectives and National Prescriptions Audit TM, 2002*.

³ Katharine Levit et al., "Inflation Spurs Health Spending in 2000." *Health Affairs* 21 (1) (January/February 2002): 172-81.

⁴ Federal Trade Commission (FTC). *Competition in the Pharmaceutical Marketplace: Antitrust Implications of Patent Settlements*. Testimony before the Committee on the Judiciary, United States Senate, May 24, 2001.

⁵ Congressional Budget Office (CBO). *How Increased Competition from Generic Drugs Has Affected Prices and Returns on the Pharmaceutical Industry*. Washington, DC: Congressional Budget Office, July 1998.

⁶ Ibid.

⁷ Kreling et al., 2001.

⁸ CBO, 1998.

⁹ Ibid.

¹⁰ Grant Ritter, Cindy Thomas, and Stanley S. Wallack. *Greater Use of Generics: A Prescription for Drug Cost Savings*. Schneider Institute for Health Policy, Brandeis University, January 2002.

¹¹ U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research. *From Test Tube to Patient: Improving Health through Human Drugs*, September 1999.

¹² Ibid.

¹³ U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research, *Approved Drug Products with Therapeutic Equivalence Evaluations* (The Orange Book), 22nd Ed., Section 1.2: Therapeutic Equivalence-Related Terms.

[http://www.fda.gov/cder/orange/adppreface.htm#Therapeutic percent20Equivalence-Related percent20Terms](http://www.fda.gov/cder/orange/adppreface.htm#Therapeutic%20Equivalence-Related%20Terms), last updated April 8, 2002.

¹⁴ The Hatch-Waxman Act provided incentives for producing generic drugs and for research-based drug manufacturers to engage in pharmaceutical research and development. For research-based drug manufacturers, the Act offered patent extensions to partially offset the time between which a drug is granted a patent from the Patent and Trademark Office and when it is approved for marketing by the FDA (Congressional Budget Office [CBO]. *How Increased Competition from Generic Drugs Has Affected Prices and Returns on the Pharmaceutical Industry* Washington, DC: Congressional Budget Office, July 1998.)

¹⁵ CBO, 1998.

¹⁶ The term *efficacy* differs from the term *effectiveness* in that *efficacy* refers to the ability of a treatment to achieve the desired results under ideal study conditions, whereas *effectiveness* refers to the ability of a treatment to achieve the desired results

under real life conditions (e.g., patients not always remembering to take their doses, physicians not always prescribing the lowest dose recommended by the FDA, or side effects not always being controlled). Most clinical trials of drugs evaluate efficacy rather than effectiveness. However, effectiveness is the legal standard for gaining FDA approval. See Alliance of Managed Care Pharmacy, *AMCP's Glossary*, http://www.amcp.org/education_ce/student/glossary.asp. Accessed April 23, 2003; FDA, *The Orange Book*.

¹⁷ FDA, *From Test Tube to Patient*.

¹⁸ *Ibid*.

¹⁹ FDA, *Orange Book*, Section 1.3.

²⁰ *Ibid*.

²¹ One study found that 58.9 percent of new molecular entities (new drugs) approved between January 1, 1981, and December 31, 1990, had a different marketing formulation from that used in clinical trials. L. Z. Benet and J. E. Goyan "Bioequivalent and "Narrow Therapeutic Index" Drugs." *Pharmacotherapy* 15 (1995): 433-40, as cited in John E. Murphy, PharmD, FCCP. "Generic Substitution and Optimal Patient Care." *Archives of Internal Medicine* 159 (5) (March 8, 1999).

²² Murphy, 1999.

²³ *Ibid*.

²⁴ Food and Drug Administration, personal communication, March 5, 2002.

²⁵ *Ibid*.

²⁶ *The Orange Book*.

²⁷ See, for example, Jane E. Henney, MD. "Review of Generic Bioequivalent Studies." *Journal of the American Medical Association* 282 (21) (December 1, 1999); FDA. *From Test Tube to Patient*, September 1999; Stuart L. Nightingale, MD. *Therapeutic Equivalence of Generic Drugs: Letter to Health Practitioners*. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, January 28, 1998; Stuart L. Nightingale, MD. "Generic Substitution." *Journal of the American Medical Association* 279 (9) (March 4, 1998).

²⁸ Nightingale, January 1998; March 1998.

²⁹ The FDA has stated that safe and effective use of NTI drugs requires careful titration (determination of appropriate dose) and patient monitoring, regardless of whether a brand or generic is used. 21 CFR 320.33 (c), cited in April 16, 1997, letter from Roger L. Williams, MD, Deputy Center Director for Pharmaceutical Science, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, to Mr. Carmen A. Catizone, Executive Director/Secretary, National Association of Boards of

Pharmacy.

<http://www.fda.gov/cder/news/ntiletter.htm>, posted February 6, 1998.

³⁰ See, for example, Kimberly A. Hope and Dawn E. Havrda. "Subtherapeutic INR Values Associated with a Switch to Generic Warfarin" *The Annals of Pharmacotherapy* 35 (February 2001): 183-7.

³¹ See, for example, Joel M. Neutel, MD, and David H.G. Smith, MD. "A Randomized Crossover Study to Compare the Efficacy and Tolerability of Barr Warfarin Sodium to the Currently Available Coumadin®." *Cardiovascular Reviews Reports* 19 (2) (February 1998); Joel Handler, MD, et al. "A Blinded, Randomized, Crossover Study Comparing the Efficacy and Safety of Generic Warfarin Sodium to Coumadin®." *Preventive Cardiology* (Fall 1998); "Generic Versus Branded Warfarin: Observational Experience Finds Equivalency in the 'Real World,'" *Formulary* (June 1998).

³² Stuart L. Nightingale, MD. "Generic Substitution." *Journal of the American Medical Association* 279 (9) (March 4, 1998).

³³ 21 CFR 320.33 (c), cited in April 16, 1997, letter from Roger L. Williams, MD, Deputy Center Director for Pharmaceutical Science, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, to Mr. Carmen A. Catizone, Executive Director/Secretary, National Association of Boards of Pharmacy.

<http://www.fda.gov/cder/news/ntiletter.htm>, posted February 6, 1998.

³⁴ FDA, *The Orange Book*, Section 1.6, Practitioner/User Responsibilities.

³⁵ James D. Henderson and Richard H. Esham. "Generic Substitution: Issues for Problematic Drugs." *Southern Medical Journal* 94 (1) (2001): 16-21.

³⁶ B. J. Wilder, MD, et. al, "Effect of Food on Absorption of Dilantin Kapseals and Mylan Extended Phenytoin Sodium Capsules." *Neurology* 57 (2001): 582-9; The Epilepsy Foundation of America, *Substitution of Generic Drugs May Cause Problems for Epilepsy Patients*.

<http://www.efa.org/epusa/generic.html>, accessed March 26, 2002.

³⁷ Barbara M. Davit et. al. "Effect of Food on Absorption of Dilantin Kapseals and Mylan Extended Phenytoin Sodium Capsules [Correspondence]." *Neurology* 58(4) (February 26, 2002): 666.

³⁸ B. J. Wilder, MD. "Effect of Food on Absorption of Dilantin Kapseals and Mylan Extended Phenytoin Sodium Capsules [Correspondence]." *Neurology* 58(4) (February 26, 2002): 666-7.

³⁹ B. L. Carter, M. A. Noyes, and R. W. Demmler. "Differences in Serum Concentrations of and

Responses to Generic Verapamil in the Elderly.” *Pharmacotherapy* 13 (4) (July-August 1993): 359-68.

⁴⁰ J. J. Saseen et al. “Postabsorption Concentration Peaks with Brand-name and Generic Verapamil: A Double-Blind, Crossover Study in Elderly Hypertensive Patients.” *Journal of Clinical Pharmacology* 37 (6) (June 1997): 526-34.

⁴¹ M. C. Meyer et al. “The Relative Bioavailability and In Vivo-In Vitro Correlations for Four Marketed Carbamazepine Tablets.” *Pharmaceutical Research* 15 (11) (November 1998): 1787-91.

⁴² Philip P. Gerbino and Andrea S. Joseph. “Multi-source Drugs: Implications and Concerns in the Geriatric Population.” *Hospital Pharmacy* 28 (2) (1993): 96-8, 101-2.

⁴³ See Anthony J. Piraino. “Managing Medication in the Elderly”. *Hospital Practice* (June 15, 1995): 59-65.

⁴⁴ Teresa Floridi. *Generic/Therapeutic Substitutions*. National Conference of State Legislatures (NCSL), Health Policy Tracking Service Issue Brief, December 31, 2001.

⁴⁵ North Carolina Board of Pharmacy. *Generic and Therapeutic Substitution*. North Carolina Board of Pharmacy Newsletter on the Web. <http://www.ncbop.org/Oct2000-1.asp>, October 2000. While the term, “formulary,” is often used to denote a list of drugs that are covered under a prescription drug benefit plan, in this sense the term refers to a list of drugs that are considered interchangeable (a positive formulary) or are not considered interchangeable (a negative formulary).

⁴⁶ North Carolina Board of Pharmacy. *Item 937-Narrow Therapeutic Index Drugs*. North Carolina Board of Pharmacy Newsletter on the Web, <http://www.ncbop.org/item937.asp>, July 1997.

⁴⁷ American Academy of Family Physicians. *Drugs Generic (Position Paper)*. AAFP Policies on Health Issues, www.aafp.org/policy/issues/d-drugsgenericposition.html, March 2001.

⁴⁸ American Medical Association. *H-125.998 Generic Substitution of Prescribed Drugs*. http://www.ama-assn.org/apps/pf_online/pf_online?f_n=browse&doc=policyfiles/HOD/H-125.998.HTM

⁴⁹ American Medical Association. Report of Reference Committee E, American Medical Association House of Delegates (I-00). <http://www.ama-assn.org/meetings/public/interim00/reports/hodaction/s/annorefe.pdf>

⁵⁰ AAFP, March 2001.

⁵¹ R. Yelkur, *Generic versus brand name prescription drug choice: an empirical characterization of elderly consumers’ generic proneness*. Doctoral dissertation,

Mississippi State University, DAI, 57, no. 02A: 0772 (1995).

⁵² Author calculations from AARP. *Prescription Medication Use Among Persons Age 45+* (Power Point Presentation). Washington, DC (available from Linda L. Barrett, Ph.D., AARP, 601 E Street NW, Washington, DC 20049), April 2002.

⁵³ American College of Cardiologists/American Heart Association. *Drugs, Therapeutic Substitution, and Generic, ACC/AHA Advocacy Position*; <http://216.185.112.5/presenter.jhtml?indentifier=4526>

⁵⁴ Epilepsy Foundation. “Substitution of Generic Drugs May Cause Problems for Epilepsy Patients.” www.efa.org/epusa/generic.html, accessed March 26, 2002.

⁵⁵ According to the FDA, generic drug manufacturers can only use inactive ingredients that have already been approved by the FDA for use in a brand-name product, although not necessarily for the drug to which it is bioequivalent. Therefore, any adverse reactions would also occur if a brand-name drug with the same inactive ingredient were taken. FDA, personal communication, March 5, 2002.

⁵⁶ National Institute for Health Care Management Research and Educational Foundation. *Prescription Drug Expenditures in 2001: Another Year of Escalating Costs*. Washington, DC: National Institute for Health Care Management Research and Educational Foundation, May 2002.

⁵⁷ For example, single-source COX-2 inhibitors (such as celecoxib and rofecoxib) are comparably effective to nonsteroidal anti-inflammatory drugs (NSAIDs), many of which are multi-source, in reducing inflammatory pain. COX-2 inhibitors may be more appropriate for that sector of the population that is at risk for gastrointestinal bleeding and renal toxicity. See Bell et al. “Cox-2 Inhibitors and Other Nonsteroidal Anti-Inflammatory Drugs in the Treatment of Pain in the Elderly.” *Clinics in Geriatric Medicine* 17 (3) (2001): 489-502; Vasoo et al. “New Cyclooxygenase Inhibitors.” *Annals of Academy of Medicine* 30 (2) (2001): 164-9; D. M. McCarthy. “Prevention and Treatment of Gastrointestinal Symptoms and Complications Due to NSAIDs.” *Best Pract Res Clin Gastroenterol* 15 (5) (2001): 755-73.

⁵⁸ Ritter et al., 2002.

⁵⁹ FTC, 2001.

⁶⁰ North Carolina Board of Pharmacy. *Generic Substitution Issues*. North Carolina Board of Pharmacy Newsletter on the Web. <http://www.ncbop.org/Oct01-4.asp>, October 2001.

⁶¹ National Institute for Health Care Management Foundation (NIHCM). *Prescription Drugs and*

Intellectual Property Protection: Finding the Right Balance Between Access and Innovation, August 2000; *American Health Line*. “Politics & Policy—Pediatric Exclusivity: House Gives Final Approval,” December 19, 2001. [http://nationaljournal.com/cgi-bin/iftch4?ENG+AMERICAN_HEALTHLINE--POLL_TRACK--AD_SPOTLIGHT+7-ahindex+1022126-](http://nationaljournal.com/cgi-bin/iftch4?ENG+AMERICAN_HEALTHLINE--POLL_TRACK--AD_SPOTLIGHT+7-ahindex+1022126-REVERSE+0+0+35814+F+3+23+1+glucophage)

⁶² FTC, 2001.

⁶³ United States Senate. *S. 3051: Greater Access to Affordable Pharmaceuticals Act*, 106th Congress, 2nd Session; Julie Appleby. “Congress Asked to Tighten Drug Patent Laws.” *USA Today* (February 26, 2002). <http://www.usatoday.com/money/health/2002-02-26-generics.htm>

David Gross, AARP Public Policy Institute, May 2003. The author acknowledges the valuable technical assistance provided by Judy Xu in the preparation of this Issue Brief.

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