



The Florida Senate

Interim Project Report 2000-55

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Committee on Health, Aging and Long-Term Care

Senator Charlie Clary, Chairman

REVIEW OF THE NEGATIVE DRUG FORMULARY ESTABLISHED UNDER SECTION 465.025, FLORIDA STATUTES

SUMMARY

Generic drug substitution has become an issue for both private and government insurers due to pressures from consumers, employers and taxpayers to control the growth of health care costs. Health care experts estimate that pharmacy costs for third-party payors and managed care plans will surpass hospital expenses by 2002. Pharmacy costs have become one of the fastest growing segments of overall health expenditures.

During the 1970s generic drug substitution was promoted in various states. Some states established regulatory mechanisms, however, to limit generic drug substitution for certain drugs. Florida restricts a pharmacist's professional judgment to dispense a generic equivalent drug product for a prescribed brand-name drug by prohibiting substitution of drugs identified on a negative formulary.

Since 1980, the Federal Food and Drug Administration (FDA) has published a list of approved drug products which designate therapeutic equivalence evaluations for multi-source drugs that the FDA has approved for safety and effectiveness. Although significant variation in state regulation of generic drug substitution exists and generic substitution or drug interchange occurs in numerous states without specific restriction, the FDA has not found any documented harm directly attributed to the substitution of a generic drug that the FDA has determined is therapeutically equivalent to a brand-name product.

Based on the findings of the report, staff concludes that generic drugs may be safely substituted for brand-name products in the professional judgment of the dispensing pharmacist when such drugs have met FDA's bioequivalence standards. It is recommended that the negative drug formulary be subject to repeal on July 1, 2001, unless the Board of Medicine and the Board of Pharmacy justify the continued existence of the formulary by the submission of evidence identified in this report.

BACKGROUND

During the early 1950s a number of states passed anti-substitution laws, which prohibited a pharmacist from dispensing a drug product other than the specific product identified by trade name in the prescription. The laws adopted by many states prohibited substitution, if the prescribing physician clearly directed that the prescription be filled and dispensed as written. Since the 1970s, when cost concerns increased, various states have passed laws *promoting* generic drug substitution to rein in inflationary health costs.

Before 1984, several states independently passed laws to ensure safe generic drug substitution. In 1984, FDA regulations for drug safety and efficacy were revised, resulting in expanded availability of generic drug products. Despite FDA's approval of generic drugs, debate persists around drug product selection laws that allow pharmacists to substitute drugs for which relatively small dosage changes may lead to either treatment failure or adverse effects.

State Regulation of Pharmacy and Medical Practice States regulate the practice of pharmacy and the practice of medicine and the prescribing or dispensing of medications must be done according to the applicable practice act for pharmacists and physicians. Other practitioners may be authorized under a state's law to prescribe medication, however, the physician exercises primary control and authority to prescribe drugs. Under Florida law, the following practitioners are authorized to prescribe medications: medical physicians, osteopathic physicians, podiatrists, advanced registered nurse practitioners pursuant to a protocol, dentists, and physician assistants.

A physician may prescribe a drug using the generic or common name of the active drug ingredient, or alternately, the trade or brand name. Drug products manufactured and patented by an innovator firm have

a trade name. The trade name differentiates the drug product from competing products in the same dosage form and with the same active ingredient. Other manufacturers may manufacture the drug product and use only the generic name of the drug product. The ability of a pharmacist to substitute another drug product for a prescribed product is limited by state law.

Florida's Drug Product Substitution Law

The Florida Legislature enacted an anti-substitution law in 1953. Chapter 28150, Laws of Florida (L.O.F.), codified in s. 465.061(1)(h), F.S. (1953), prohibited a pharmacist licensed in Florida from using any ingredient or article different in any manner from the ingredient or article prescribed when dispensing or compounding a prescription. The Florida pharmacy practice act contained this "anti-substitution" provision from 1953 to 1974. The law made a pharmacist subject to discipline by his or her professional board for failing to comply with this requirement and prevented a pharmacist from using his or her professional judgment to make any substitution for the drug product identified in a prescription.

Chapter 74-108, L.O.F., revised the law to allow a pharmacist to substitute a less expensive generic *or* brand-name drug of the same active ingredients, dosage form and strength, for any prescribed drug. The prescribing practitioner had to affirmatively indicate approval of the substitution on the prescription form. If a pharmacist made a substitution, the pharmacist had to provide the prescribing practitioner with written or verbal notice of the substitution within a reasonable time. Pharmacies had to display a notice advising consumers to: "CONSULT YOUR PHYSICIAN CONCERNING THE AVAILABILITY OF THE LEAST EXPENSIVE DRUG FOR YOUR USE."

Chapter 76-47, L.O.F., expanded the 1974 law to *promote* generic drug substitution. Disclosures to consumers referring to generic drug substitution were expanded to state: "FLORIDA LAW REQUIRES A LESS EXPENSIVE GENERICALLY EQUAL DRUG BE SUBSTITUTED FOR A BRAND NAME DRUG UNLESS YOU OR YOUR PHYSICIAN REQUEST OTHERWISE. CONSULT YOUR PHYSICIAN CONCERNING THE AVAILABILITY OF THE LEAST EXPENSIVE DRUG FOR YOUR USE."

The law also imposed a requirement on the prescribing practitioner to affirmatively prohibit a community pharmacy from dispensing a generic drug for a brand-name drug product when the prescriber deemed it "medically necessary." A pharmacist who received prescriptions for brand-name drugs had to substitute a less expensive generically equivalent drug product identified in a formulary established by the community pharmacy, unless the prescriber wrote the words "medically

necessary" on the written prescription or expressly stated so when giving an oral prescription, or unless the consumer of the drug objected to the substitution. The law defined "generically equivalent drug product" to mean a drug product with the same active ingredient, finished dosage form, and strength.

The law, as amended in 1976, only applies to drugs that are prescribed by brand name. If the prescription is written for a drug identified by its generic name, the pharmacist may use his or her professional judgment to select any drug product with the same active ingredients, including a brand-name drug product. The pharmacist must notify the customer of the substitution and any savings which may result from the substitution, and must notify the customer that he or she may refuse the substitution. The full amount of any savings resulting from a substitution must be passed on to the consumer. The pharmacist must maintain a record of any drug substitution.

The law also establishes a standard of care for pharmacists when substituting a generic drug product for a brand-name product. The standard of care to be applied to the acts of any pharmacist performing professional services in compliance with Florida law for drug product selection is the same standard of care that applies to the performance of professional services in the dispensing of a prescribed drug identified by generic name.

Florida's anti-substitution law (s. 465.016(1)(g), F.S.) has been amended by ch. 79-226, L.O.F., to provide two exceptions for pharmacists to interchange drugs: to authorize pharmacists to make drug product selections pursuant to s. 465.026, F.S., relating to generic drug substitution and s. 465.019(6), F.S., relating to Class II institutional (hospital) formularies.

Creation of Florida's "Negative" Drug Formulary

A formulary is a list of drug products. A formulary may set conditions for the prescription or dispensing of drugs identified in the formulary or may exclude some drugs. A negative formulary identifies drugs which may not be prescribed or dispensed. Under the 1976 law codified in s. 465.025, F.S. (1976), the Board of Pharmacy and the Board of Medicine were required to establish by rule a "negative" formulary of generic and brand-name drugs which pose a threat to the health and safety of the public and which could not be substituted.

The Board of Pharmacy and the Board of Medicine were authorized, after the initial "negative" formulary was adopted, to add or delete drugs from the

formulary as they deem appropriate. Subsequent additions or deletions of a generic drug type or brand-name product may be requested by any person who can show cause why the change should be made. The Board of Pharmacy must mail a copy of the “negative” formulary, including any changes, to the manager of each community pharmacy. Each board regulating practitioners who may prescribe medicinal drug products must incorporate the “negative” formulary into its rules and regulations.

Other Drug Formularies Used in Florida

In addition to the “negative” drug formulary, ch. 76-47, L.O.F., required each community pharmacy to independently establish a formulary of generic and brand-name products which, if selected as the drug product of choice, would not pose a threat to the health and safety of patients. The pharmacist dispensing in a community pharmacy, must compile the formulary in reliance on drug product research, testing, information and formularies compiled by other pharmacies, states, the U. S. Department of Health, Education and Welfare and any other source which the pharmacist deems reliable in his or her professional judgment. Each community pharmacy must make its formulary available to the public, the Florida Board of Pharmacy, or any physician requesting it.

Section 465.019(6), F.S., requires a facility with a Class II institutional pharmacy to establish policies and procedures for the development of an institutional formulary system in accordance with the joint standards of the American Hospital Association and the American Society of Hospital Pharmacists. A Class II institutional formulary must be approved by the medical staff and list drugs which may be dispensed by the pharmacists employed in such an institution.

Section 465.186, F.S., requires a seven-member committee to establish a formulary of medicinal drug products and dispensing procedures for a pharmacist to *order and dispense* drug products to the public. The committee may include specified products on the formulary. The Board of Pharmacy, the Board of Medicine, and the Board of Osteopathic Medicine must adopt by rule the formulary of drugs that pharmacists may order.

Section 154.10(1)(c) 4., F.S., requires the Department of Health to establish a formulary from which prepackaged and pre-labeled medications with dosage instructions may be ordered by a registered nurse or licensed physician assistant in county health departments. The Medicaid program maintains an open formulary and the 1999 Appropriations Act prohibits the program from establishing a restrictive formulary without specific statutory authorization.

Generic Drug Substitution/Federal Requirements

The FDA regulates the *marketing* of generic drugs. If a brand-name drug product was initially marketed before 1938, there was, and still is, no requirement for FDA approval before marketing. If a brand-name drug product was initially marketed between 1938 and 1962, the manufacturer of the generic drug product was required to demonstrate that the generic and the brand-name drug had comparable *bioavailability* and did not have to replicate the extensive clinical trials that had been done by the brand-name drug manufacturer. The FDA defines “*bioavailability*” to mean the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action. “*Bioequivalence*” is a related concept which makes a scientific comparison of the rates of absorption between two drug products. “Bioequivalent drug products” are defined to mean pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions.

If the brand-name drug product was initially marketed after 1962, the manufacturer of the generic drug product had to reestablish the efficacy and safety of the active ingredient and then demonstrate that the generic drug product and the brand-name drug product had comparable bioavailability. The manufacturer of the generic drug product could reestablish safety and efficacy for the drug by submission of published studies or by conducting further studies and submitting results of the required studies which were not in the published studies.

Congress amended the Federal Food, Drug, and Cosmetic Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Waxman-Hatch Act), to require any generic drug for which FDA approval was being sought and that was a copy of a brand-name drug that was initially marketed after 1938 to be *bioequivalent* with the brand-name drug product. The Waxman-Hatch Act allowed FDA approval through an “Abbreviated New Drug Application” (ANDA) procedure for chemically equivalent generic copies of drug products approved and marketed after 1962 and directly granted FDA authority for all generic drug approvals through an ANDA. Generic drug applicants under an ANDA are generally not required to provide FDA any preclinical (animal) and clinical (human) data to establish safety and effectiveness. The safety and effectiveness that was established upon the approval of the brand-name drug product is sufficient under an ANDA. The Waxman-Hatch Act provides that no generic product will be approved by FDA that is not bioequivalent to the reference listed drug which is the

drug product chosen by FDA to serve as the basis for an ANDA. The FDA requires an applicant to provide detailed information to establish bioequivalency. Once an application is approved, the applicant may manufacture and market the generic drug product, if all issues related to the brand-name drug's patent have been resolved.

Federal Standards for Therapeutic Equivalence

Since October 1980, FDA has published equivalency ratings in the *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*. The *Orange Book* initially included only currently marketed prescription drug products approved by FDA through new drug applications and ANDAs. Today the *Orange Book* lists therapeutic evaluations for approved multi-source prescription drug products and provides public information and advice to state health agencies, prescribers, and pharmacists in the area of drug product selection.

According to the *Orange Book*, FDA considers drug products to be therapeutically equivalent only if those drug products are pharmaceutically equivalent and if such drug products are expected to have the same clinical effect and safety when administered to patients under the conditions noted on the product's labeling. Drug manufacturers seeking FDA approval to market a generic drug must submit data demonstrating that the drug product is *bioequivalent* to the innovator or reference listed drug. A drug product and the reference listed drug are considered *bioequivalent* when the rate and extent of absorption of the test drug do not show significant difference from the rate and extent of absorption of the reference drug when administered at the same dose of the therapeutic ingredient under similar experimental conditions in a single dose or multiple doses. The FDA has established statistical criteria for determining bioequivalence between a generic drug product seeking approval and the reference drug.

The *Orange Book* classifies drug products as "pharmaceutical equivalents" if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration. In contrast, the *Orange Book* classifies drug products as "pharmaceutical alternatives" if they contain the same "therapeutic agent" or "therapeutic moiety," but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths. Even though pharmaceutical alternatives may be bioequivalent, FDA does not consider them to be therapeutically equivalent.

The *Orange Book* states that drug products are classified by FDA as therapeutically equivalent when they meet five criteria: (1) are approved as *safe and effective*; (2) are

pharmaceutical equivalents in that the drug products contain *identical amounts of the same active ingredient* in the *same dosage form and route of administration*; (3) are *bioequivalent* in that the drug products do not present a known or potential problem, and they meet an acceptable *in vitro* standard, or, if the drug products do present such a known or potential problem, the drug products are shown to meet an appropriate bioequivalence standard; (4) are **adequately labeled**; (5) and are manufactured in compliance with **Current Good Manufacturing Practice** regulations. When these criteria are met, therapeutically equivalent drug products may be substituted for each other because the safety and effectiveness are met.

Drugs are not listed in the *Orange Book* if a final determination on their regulatory or legal status has not been made. Drugs that were on the market before the passage of the 1938 Food, Drug, and Cosmetic Act received an exemption from the requirement for a New Drug Application (NDA) if the drug's labeling was unchanged. Drug products that have not been evaluated by FDA for safety and efficacy and are not FDA approved do not appear in the *Orange Book*. A certain number of drug products containing one or more active ingredients first introduced into the marketplace before 1962 are not covered by an NDA. Pre-1962 prescription drugs not covered by an NDA are marketed based on their manufacturers' belief that such products are not subject to the new drug provisions. Therapeutic equivalence determinations are not made for unapproved, off-label indications.

Drug products listed in the *Orange Book* are assigned therapeutic equivalence codes: the "A" rating indicates drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products because they have no known or suspected bioequivalence problems, or actual bioequivalence problems have been resolved by *in vivo* or *in vitro* data confirming bioequivalence; and the "B" rating indicates drug products that FDA considers not to be therapeutically equivalent to other pharmaceutical drug products; or the "B*" rating indicates drug products that require further FDA investigation and review to determine equivalence. All generic drugs approved after 1984 must have "A" equivalency ratings. Drug products rated "B" include products approved before 1984, with FDA's assessment of bioequivalence deferred. Drug products rated "B*" include products that are the subjects of full new drug applications that have not been evaluated as bioequivalent.

Although the term “therapeutic equivalence” may have a different meaning to health care practitioners who may regard different drugs in the same therapeutic category as equivalent in therapeutic effect, FDA does not consider pharmaceutical alternatives to be therapeutically equivalent. The therapeutic equivalence evaluations of multi-source drug products listed in the *Orange Book* represent FDA’s scientific judgment regarding which drug products may be substituted generically for one another and are intended to be used by government agencies and health care providers to save costs through drug product selection.

Generic Drug Substitution/Other States

States have taken different regulatory approaches to generic drug substitution. Some states use a positive formulary for generic drug products which identifies generic drug products and notes whether the products may be substituted for the brand-name or innovator drug product, based on specified criteria such as an “AB” equivalency rating in the *Orange Book* or other available data (Illinois, Maryland, New Jersey, and New York). Some states use a negative formulary for generic drug products (Arkansas, Florida, Kentucky, Minnesota, Missouri, and Rhode Island). The products in the negative formulary are usually identified by that state’s Board of Pharmacy and Board of Medicine. The determination by the state boards is usually based on a finding that the drugs are biologically or therapeutically inequivalent and if substituted would be harmful to the public. States may opt for a combination of positive and negative formularies to regulate generic drug substitution. Some states do not use either a negative or positive formulary, but impose other restrictions on drug product selection, such as a procedure that clarifies when substitution is authorized by the prescriber on the face of a prescription (Alabama, Arizona, North Carolina, Pennsylvania, and Texas).

Narrow Therapeutic Index Drugs

Although FDA has not formally established a category of “narrow therapeutic index” drugs, FDA has referred to such drugs as those that require careful dose titration and clinical monitoring and that may exhibit dose-related adverse effects. “Narrow therapeutic index” (NTI) drugs include the following drugs on Florida’s negative drug formulary: phenytoin; quinidine gluconate; theophylline; and warfarin. A debate has taken place in a number of states (Texas, Massachusetts, Ohio, North Carolina, Virginia, and Illinois) as to whether additional restrictions are necessary for NTI drugs. In response to such initiatives, FDA indicates that if one therapeutically equivalent drug is substituted for another, the physician, pharmacist and patient have FDA’s assurance that the physician should see the same clinical results and safety profile. The FDA supports good communication between

the patient and health care provider regarding medications that require frequent monitoring.

Texas and North Carolina have no restriction on the original substitution of NTI drugs but have passed legislation to restrict substitution when the drugs are refilled. State NTI drug laws include: Texas (1998), which requires the Board of Pharmacy to create a list of NTI drugs in consultation with the Board of Medicine and requires a prescription for an NTI drug to be refilled only by using the same drug product by the same manufacturer, unless otherwise agreed to by the prescribing physician (if refilled with a generic equivalent, the pharmacist must notify the patient when the drug is dispensed and the prescribing physician within 72 hours); North Carolina (1997), which requires a prescription for an NTI drug to be refilled using only the same drug product by the same manufacturer that the pharmacist last dispensed under the prescription unless the prescriber and the patient give documented consent; and Virginia (1997), which prohibits a pharmacist from substituting or interchanging a NTI drug without the documented consent of the patient’s prescriber, to the extent required by regulations adopted by the Board of Pharmacy. The NTI drug restrictions have not yet been implemented in Texas and Virginia.

METHODOLOGY

Staff reviewed state and federal requirements for generic drug substitution of brand-name products and talked with state and federal agency officials, pharmacy industry representatives, representatives of professional associations for health care practitioners, and personnel with regulatory boards on several occasions to discuss issues and to gather specific information pertinent to the project. Developments in other states which are considering changes in law or regulation over generic substitution of drugs were monitored. Staff reviewed various federal publications and regulations, the minutes for the Negative Formulary Committee and technical articles. Staff performed legal research to ascertain the status of the law pertinent to the project.

FINDINGS

Operation of Florida’s Negative Drug Formulary

The initial negative drug formulary (rule 21S-5.01, Florida Administrative Code) identified 11 drugs: digoxin, digitoxin, quinidine, nitroglycerin, warfarin sodium, conjugated estrogens, erythromycin, chloramphenicol, bishydroxy coumarin, phenytoin, and nitrofurantoin. The rule was adopted by the Board of

Medical Examiners and the Board of Pharmacy after public hearings and took effect December 14, 1976.

The boards appoint members to a committee to review petitions for changes to the negative drug formulary and to make recommendations back to the boards. Historically, the negative drug formulary committee has included two appointees each from the Board of Medicine and the Board of Pharmacy, and a fifth member has been appointed jointly. The committee relies in part on recommendations from hired pharmacy consultants to make their recommendations regarding changes to the negative drug formulary rule. According to the staff of the Board of Pharmacy, since the original rule was adopted, the boards have not exercised their authority to independently revise the formulary and the formulary has only been changed in response to a petition.

The person (usually a drug manufacturer) seeking an amendment to the negative drug formulary must submit information in support of the request that meets the burden of proof to show cause why the amendment should be made. In contrast to FDA bioequivalence standards, s. 465.025, F.S., does not define “clinically significant or therapeutic inequivalence,” or suggest what evidence may be reasonable to make such a determination. A consultant or group of consultants, which may include a pharmacy consultant and a medical physician, is hired by the Board of Medicine and the Board of Pharmacy to review any information submitted with a petition for a change. The consultants make a recommendation to the negative formulary committee. The procedure for revising the negative formulary expressly requires the committee to review the formulary independent of the financial incentives of both generic and brand-name manufacturers. However, the mechanism to revise the negative formulary is susceptible to influence by drug manufacturers who have significant financial incentives to promote specific drug products. For example, on January 7, 1999, the negative formulary committee rejected (4-1) the recommendation of its pharmacy consultant when a manufacturer petitioned to have warfarin sodium deleted from the formulary.

The negative drug formulary is currently codified at 64B16-27.500, Florida Administrative Code. The drugs currently included on the negative formulary are listed along with the initial year they were added to the negative formulary: digoxin (1976); digitoxin (1976); warfarin (1976); conjugated estrogen (1976); quinidine gluconate (1976); dicumarol (1977); phenytoin (1976), chlorpromazine (1981) - limited to oral dosage forms (1982) - limited to solid oral dosage forms (1992); theophylline (controlled release) (1982); levothyroxine

sodium (1984); and pancrelipase oral capsules (1990)-limited to oral dosage forms (1992).

Some drugs listed in the negative drug formulary are inconsistent with the FDA standard for bioequivalent generic drug products. Five of the eleven drugs included on the negative formulary currently have “AB” or “AP” equivalence ratings in the *Orange Book* in the following dosage forms: digoxin (injectable); warfarin (tablet); quinidine gluconate (tablet extended release); phenytoin (suspension, injectable, and capsule extended); and theophylline (capsule extended release). The “A” equivalency rating indicates drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products.

The FDA has recently advised states that its approval of a generic drug product assures that the generic drug is interchangeable with the brand-name drug under all approved indications and conditions of use. For these reasons, FDA-approved product labeling does not recommend that any additional tests need to be performed by the health care provider when a switch occurs from a brand-name product drug to a generic equivalent drug product, from a generic equivalent to a brand-name drug product, or from one generic product to another when both are deemed equivalent to a brand-name product. The negative drug formulary committee’s failure to affirmatively recommend to the boards, a revision of the formulary to delete generic drug products that have been subsequently designated in the *Orange Book* as therapeutically equivalent with a referenced brand-name product, is inconsistent with FDA bioequivalency standards.

The Florida negative drug formulary also includes drugs that are only available from a single source or which are discontinued from marketing. The negative drug formulary lists conjugated estrogen, a single source drug for which there is only one FDA-approved product available for the active ingredient, dosage form and route of administration. The negative drug formulary includes dicumarol. Dicumarol (25mg tablet, oral) is identified in the *Orange Book* without any generic equivalents. Other dosage forms and strengths of dicumarol are on the FDA discontinued drug product list which contains approved products that have never been marketed, have been discontinued from marketing, or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing. The negative drug formulary committee and the boards are not required to affirmatively and independently review the formulary in light of subsequent developments

such as the change in the status of a drug as a single source product.

The negative drug formulary includes digitoxin, digoxin, and levothyroxine sodium that have no equivalency rating available in the *Orange Book*. Digitoxin and digoxin are pre-1938 drugs not covered by a new drug application with FDA and therefore do not appear in the *Orange Book*, although digoxin injectable was approved by FDA. Levothyroxine sodium is a pre-1962 prescription drug not covered by a new drug application. In the August 14, 1997 *Federal Register*, FDA stated that no currently marketed orally administered levothyroxine sodium product has been shown to demonstrate consistent potency and stability and therefore, no currently marketed orally administered levothyroxine sodium product is generally recognized as safe and effective. The FDA announced that it will permit orally administered levothyroxine prescription drug products to be marketed without an approved new drug application only until August 14, 2000.

The manufacturer of Synthroid® recently reached a \$41.8 million settlement with 37 states, including Florida. Florida will receive \$1.7 million under the settlement. The various states' position is that Synthroid® is the dominant and most expensive brand of levothyroxine sodium on the market. A company, whose liabilities and obligations the manufacturer assumed, signed a contract with a researcher to design and perform a research study assessing the bioequivalence of Synthroid® and three other levothyroxine sodium products. The study found that all four products were bioequivalent. According to the Florida Attorney General, the manufacturer tried to stop publication of the study and made claims that no other competing brand was useful in replacement of Synthroid®. Under the terms of the settlement, the manufacturer gave an assurance that it will cease misleading or deceptive claims about its product. Florida and other states alleged that consumer protection laws were violated by claims that Synthroid was unique or superior to competing brands and that consumers were kept from obtaining information about other less costly products. The settlement in no way implies or acknowledges any wrongdoing by the manufacturer.

Although consultant pharmacists employed in Class II institutions (hospitals) must follow that institution's formulary and dispensing procedures, pharmacists who are employed by a Class II institution, such as a hospital, are not prohibited from substituting any of the drugs included in the Florida negative drug formulary. The negative drug formulary does not apply to institutions with formularies. Pharmacists who support the elimination of the negative drug formulary argue that two practice

standards exist for pharmacy, one for community pharmacy and another for institutions with formularies. Such pharmacists note that, if there were significant problems with generic substitution, the adverse patient outcomes would become apparent in the institutional setting where generic substitution is not restricted. Proponents for the elimination of the negative drug formulary note that the physician may maintain therapeutic control over the drug product by noting that the drug is "medically necessary" on the prescription. Physicians who support the negative drug formulary argue that institutional formularies are developed with the input of prescribing practitioners.

Variation in State Regulation

States have imposed different standards for substitution of generic drugs. Florida lists eleven drugs on its negative formulary, but a neighboring state, Georgia, provides that a pharmacist may substitute a drug with the same generic name in the same strength, quantity, dose, and dosage form as the prescribed brand-name product which is, in the pharmacist's reasonable professional opinion, pharmaceutically equivalent.

The Massachusetts Drug Formulary Commission recommends drugs that should be placed on a list of interchangeable drugs, which includes FDA "A" rated drugs, certain drugs not approved by FDA, and drugs not listed which are placed on an exception list. The Massachusetts formulary automatically incorporates FDA "A" rated drugs, but petitioners may propose to add the products to the exception list which would prohibit interchange of the drug. The exception list only includes two drugs, digoxin and levothyroxine, which are also included on Florida's negative formulary. The Massachusetts drug formulary must be independently revised at least once a year to include pertinent new information. As changes are made to the formulary, pharmacists must notify the patient and prescriber when indicated for proper care of the patient.

Lack of Evidence of Harm

Even though generic substitution occurs in numerous states without specific restriction, FDA notes that there has not been a showing of documented harm directly attributed to the substitution of a generic drug that FDA has determined is therapeutically equivalent to a brand-name product. Although there are anecdotal reports of decreased efficacy or increased toxicity after drug substitution, FDA has determined, upon investigation, that problems attributed to substitution of one approved drug for another has not occurred.

Pharmacists must exercise the appropriate standard of care when making drug product selection and such acts subject the pharmacist to liability. If harm occurs, based on generic substitution, pharmacists are liable for malpractice when alleged adverse reactions have occurred due to the interchange of a generic product for a prescribed brand-name product. A pharmacist may be liable if a consumer relied on the pharmacist’s judgment and the pharmacist knew the purpose for the use of the drug. A consumer may also hold a pharmacist liable for any injuries resulting from a lawful drug substitution. Legal scholars have noted that there are **no reported cases of a pharmacist’s liability for harm** alleged to have occurred due solely to the legal substitution of a generic drug product for another brand-name product.

Costs Associated with Negative Formulary Drugs

Cost estimates based on the wholesaler acquisition cost were obtained from Shands Hospital Pharmacy for drug products on the Florida negative drug formulary which are “AB” or “AP” rated in the *Orange Book*. The following cost savings were estimated for each drug at the same dosage and strength, if generic substitution was permitted in community pharmacies: (1) (warfarin 5mg-Barr \$0.412) vs. (Coumadin®- Dupont \$0.552) - 25 % cost savings; (2) (theophylline 300mg - Inwood \$0.0872) vs. (Theodur®- Schering \$0.329) - 73.4% cost savings; (3) (phenytoin 125mg suspension - Alparma \$24.05) vs. (Dilantin®- ParkeDavis \$27.54) - 12.7% cost savings; (4) (phenytoin 100mg - Mylan \$0.20) vs. (Dilantin®- Parke Davis \$0.212) - 5.6% cost savings. Cost estimates from Consultec, Inc. Prescription Benefits Management, Florida’s Medicaid fiscal intermediary, showed that the

average wholesale price per unit of each drug listed on the Florida negative formulary was lower if generic substitution were permitted, except the difference in price between Coumadin® and warfarin was insignificant. Although no data was available for Premarin® and dicumarol, the Florida Medicaid program estimates that it could save \$1.9 million per quarter if generic substitution was permitted.

RECOMMENDATIONS

Based on the findings of the report, staff concludes that generic drugs may be safely substituted for brand-name products in the professional judgment of the dispensing pharmacist when such drugs have met FDA’s bioequivalence standards. It is recommended that the negative drug formulary be subject to repeal on July 1, 2001, unless the Board of Medicine and the Board of Pharmacy justify the continued existence of the formulary. The boards must jointly submit a report to the Legislature by January 1, 2001, which recommends whether the negative drug formulary should be retained. If the report recommends retention of the negative drug formulary, the report must specify how further restrictions on generic drug substitution will be based solely on scientific evidence of drug equivalency, what standards and evidence are to be used in making such determinations, and estimates of the costs of making drug equivalency determinations in Florida.

COMMITTEE(S) INVOLVED IN REPORT (*Contact first committee for more information.*)
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MEMBER OVERSIGHT
Senators Silver and Myers