Adherence, Inc.

Ohio Pharmacy Laws & Generic substitution

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The Ohio State Board of Pharmacy has approved Adherence Inc. as a provider of Pharmacy Continuing Education. This program is approved for 0.1 CEUS of jurisprudence continuing education

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Objectives and Goals

1. The pharmacist will be familiar with Ohio law and state board of pharmacy rules related to generic substitution.

2. The pharmacist will be familiar with the history of both the prohibition of substitution and its revival as a cost savings factor in the delivery of prescription drug benefits to the public.

3. The pharmacist will become familiar with the development of the Orange Book and how to utilize its contents.

4. The pharmacist will learn that all drugs are not listed in the Orange Book and that state law does not rely only on the Orange Book to determine generic equivalency.

5. The pharmacist will come to appreciate the special responsibility that he or she individually has in respect to the choice of drugs to be utilized in prescription drug substitution.

Health professionals: We believe the material presented in this educational module to be accurate and current at the time of publication. We would remind the reader, however, that he or she is responsible for using professional judgment and for confirming or interpreting the findings presented here before utilizing the information.

Substitution laws may vary from state to state. In some cases pharmacists are confused by what appears in professional literature, what is promoted by various manufacturers or formularies, and what is actually stated in pharmacy board rules. This module is to clarify the subject of substitution for Ohio pharmacists.

History:

For centuries pharmacists could dispense whatever brand they chose when a physician prescribed a drug, even if a physician specified a certain product by brand name. During the 1950s, restrictions on dispensing became tighter and states adopted antisubstitution rules to require that pharmacists dispense exactly what the doctor prescribed. Antisubstitution laws were enacted for various reasons:

1. To prevent unscrupulous manufacturers from marketing counterfeit drugs of popular brands.

2. To protect the public from receiving substituted drugs that might be inferior to branded versions.

3. To satisfy the outrage of the public, citizens groups, governmental agencies, and professionals against the availability of possibly inferior products.

The antisubstitution laws also acted effectively to prevent pharmacists from exercising professional judgment in the selection of drug products for their patients. It may seem odd that pharmacists actually took a leading role in having their boards of pharmacy enact the first antisubstitution laws. As a result for a number of years pharmacists were unable to substitute comparable brands of the same product even though one could be proven to be equally effective to the others but much less expensive. As time passed it was not pharmacists who voiced opposition to the illogical restriction of their professional judgment but the same consumer groups and governmental agencies who were initially outraged by potentially dangerous substitution of drug products at the consumer level. Over the years the perceived threat of unscrupulous substitution diminished for a number of reasons while the specificity of drug activity, and supply costs, increased significantly. Eventually concern became focused on the cost and potential cost savings in allowing less expensive alternatives of brand name drugs to be freely dispensed to patients who desired them. This was especially true with the advent of Medicare.

Eventually (1970) the American Pharmaceutical Association endorsed a policy seeking repeal of state antisubstitution laws. The first state to do so was Kentucky and the last was Indiana. Over a six year period (1972-1978), however, all but ten states had repealed their antisubstitution laws.

A viable rating system for generics evolved not so much from professional initiative as it did through the requirements of government regulators. An important emphasis of the Medicare program was cost-containment. This led to the conception of (1973) and implementation (1978) of the maximum allowable costs (MAC) regulations by the federal Department of Health,

Education and Welfare which set upper limits on reimbursement for certain multi-source drugs.

Early on, quality issues in respect to available drugs were largely ignored. Quality (bio-equivalence) became a pressing issue, however, as states began to develop formularies that conformed to MAC guidelines. The states (first New York) asked the Food and Drug Administration (FDA) to assist in developing their formularies. Knowing this would be only the first of many requests the FDA determined to prepare a list of all marketed prescription drug products that had been approved for safety and efficacy by the FDA. The list was first published in 1980, had a distinctive orange cover, and was called the Approved Drug Products with Therapeutic Equivalence Evaluations. It became known, however, as simply the Orange Book. Updated monthly, the Orange Book remains the definitive reference guide on bioequivalence for single and multi-source prescription drugs.

In the Orange Book drugs that do appear are categorized into one of two groups, either in the "A" or the "B" group:

"A" drug products: are considered therapeutically equivalent to other pharmaceutically equivalent products.

"**B"** drug products: are not at time of publication considered to be therapeutically equivalent to other pharmaceutical products.

These ratings will be discussed in more detail later.

The Orange Book is widely used in selecting drug products for substitution. However, health professionals and states are under no mandate to accept therapeutic equivalency recommendations made in the Orange Book. Additionally, the FDA takes no stand on state regulation of drug product selection by pharmacists licensed by their states to practice within their boundaries. Some states explicitly enforce the criteria that only "A" rated drugs may be substituted. Some imply the same, while others allow more flexibility on the part of the practitioner. In the opinion of the author flexibility is warranted since many available drugs are not listed in the Orange Book. As one can see, it is critical that the pharmacist fully understand the pharmacy board rules that define substitution criteria for their particular state.

It should be noted that the Orange Book provides no other ratings than A and B. Pharmacists may encounter ratings such as ZA, ZB and ZC and need to understand the source of these ratings. First, they are not orange book ratings. The so-called Z ratings are found in a pricing tool published by the Defense Medical Logistics Standard Support Program to aid purchasers in the Military Health Services System. A ZA rated drug is one that has been evaluated by the FDA, but the particular labeled product has not been evaluated. A recent example might be Greenstone's azithromycin. This product is marketed under Pfizer's NDA and not based on an approved ANDA. Generally speaking, such products are marketable and can be dispensed as a substitute for the brand but they have not been independently approved by the FDA and will not appear in the orange book. They are considered so-called "authorized generics" in the industry. This topic will be considered momentarily. A ZB drug is a nonprescription or prescription drug that does not have a therapeutic equivalency rating in the orange book (an example might be aspirin 325mg). A ZC drug is a single source drug that does not have a therapeutic equivalency

rating in the orange book (an example is divalproex sodium 250mg tablets). Only Abbott's divalproex products are listed in the orange book and since no other manufacturer has filed an approved new drug application (ANDA) to market generic versions the Abbott products are not assigned a rating. In short, the Z ratings are used for price comparison only and cannot be used to make assumptions about equivalency. This is important if individual state laws specify that legal substitution requires that products be listed in the orange book. It is important, too, because a pharmacist's computer software program may link an orange book rated drug to a Z rated drug and lead the pharmacist to naively think the two drugs are therapeutically equivalent and substitutable.

Authorized generics:

A number of research oriented companies, especially as patents are due to expire, partner with generic manufacturers to develop "authorized generic" versions of their branded products. In such partnerships "authorized generics" are manufactured by the NDA holder or under a license granted by the NDA holder to another company. The term "authorized generic" is an industry term not one used by the FDA. The advantage in such partnerships is that the generic version is brought to market faster since no ANDA is required or filed with the FDA. The "authorized generic" is thus generally on the market first, ahead of competitors, and may insure the NDA holder of some profit even after the patent on the brand product expires. Another consideration is even more important: Under the Hatch-Waxman Act the generic to be marketed first under an approved ANDA receives 180 days of market exclusivity. This time may allow the company to establish its generic version as the market leader against versions approved later. To some extent the "authorized generic", though receiving no such exclusivity, may negate any advantage the ANDA holder might gain due to the 6 months exclusivity because it can be marketed before or very shortly after patent expiration. Thus a possible disadvantage to the consumer, as maintained by non-partnered generic manufacturers, is that the practice of marketing "authorized generics" may limit generic competition and inflate costs. This argument however has not faired well in the courts. Examples of "authorized generics", as mentioned previously include Greenstone's generic azithromycin (Z-Pak). Greenstone is a subsidiary of Pfizer and none of their products are listed in the orange book. Another example is Teva's generic version of clomiphene is not found in the orange book because it is marketed under license from Serono. The pharmacist will find numerous examples of "authorized generics" on the market. A last example will illustrate how confusing the issue with authorized generics can be. Most pharmacists don't like the idea of substituting generic digoxin. However, Bertek Pharmaceuticals Inc. markets AB rated digoxin (0.125 and 0.25 mg) popularly known as Digitek ® based on the ANDA approved for Amide Pharmaceuticals. The Amide digoxin products are listed in the orange book but there is no listing for Bertek.

If the pharmacist has any doubt whether a product is marketed based on an approved ANDA or due to partnership with the holder of the NDA he or she should call the marketing company. In either case the generic version can be substituted for the brand name product.

Working definitions:

It is critical that the pharmacist understands the significance of stating that two drugs are "therapeutically equivalent" versus being "pharmaceutically equivalent". An additional term that must also be considered is "bioequivalence". Therapeutic equivalent products are considered therapeutically equivalent only if they are "pharmaceutically equivalent" and if they can be expected to have the same clinical effect when administered to patients under the conditions in the product labeling.

Pharmaceutical equivalent products

1. contain the same active ingredient(s).

2. do not differ in dosage form.

3. are identical in strength or concentration, and route of administration.

According to the orange book the FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a)they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations. *The concept of therapeutic equivalence, as used to develop the List, applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., propoxyphene hydrochloride vs. pentazocine hydrochloride for the treatment of pain).* Any drug product in the List repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single source or coded as non-equivalent (e.g., **BN**). Also, distributors or repackagers of an application holder's drug product are considered to have the same code as the application holder.

The above statement provides tacit approval of authorized generics.

Therapeutic equivalence determinations are not made for un-approved, off-label indications. FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring

configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions. When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

The orange book also defines ***Bioavailability*.** This term means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

Bioequivalent Drug Products. This term describes pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions. Standardized tests are used to determine bioequivalency and a drug is considered bioequivalent if the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. Thus, bioequivalency is a term that describes the criteria that must be met in order to state that the product can be expected to have the same clinical effect as the product to which it is being compared.

Discussion: When a product is "pharmaceutically equivalent" to another product and the "bioavailability" is not significantly different the two products are considered "bioequivalent". And the FDA considers a product that is both pharmaceutically equivalent and bioequivalent to be therapeutically equivalent. One has to be careful in how the term "therapeutic equivalency" is used, however, since in common usage today, especially in managed care, the term can be referring to two products that do not contain the same "active" ingredients. For instance, one will often see in the literature that all ACE inhibitors are considered "therapeutically equivalent".

Another term often encountered is **"pharmaceutical alternative"** and products so described are not, according to FDA language, "therapeutically equivalent". A **pharmaceutical alternative** is generally taken to refer to two products with the same active ingredient <u>but are different dosage forms or strengths, or different salts, esters, or complexes.</u> FDA language technically does not sanction, for example, the substitution of two 250 mg capsules of tetracycline for one 500 mg capsule. Nor would quinine capsules be substitutable for quinine tablets.

As mentioned earlier the states are free to accept, modify or simply reject FDA determinations of equivalency among various products. Most states, however, recognize the value of the Orange Book and at least incorporate its guidelines implicitly or explicitly into pharmacy board rules on substitution.

Ohio pharmacy board rules and substitution

The Ohio Revised Code (ORC) represents laws that have been enacted by the legislative bodies of the state. The legislature also authorizes the existence of regulatory boards, e.g. the board of pharmacy, to promulgate rules to ensure that professionals for whom the board has oversight practice in such a way to conform with relevant state laws. The rules of the board are contained in the Ohio Administrative Code (OAC). Professionals are expected to be knowledgeable in respect to the ORC laws and OAC rules relevant to their practice within the state. This is a necessary since the basis for both laws and rules are supposedly to protect the public interest.

ORC 3715.01 (A) (paragraph 16)

This law is modeled after federal law and provides a working definition of the term "generically equivalent drug". Familiarity with this definition is absolutely essential since drugs considered for substitution, according to the state board's OAC 4729.38 which is discussed later, must be generically equivalent.

A "Generically equivalent drug" means a drug that contains identical amounts of the identical active ingredients, but not necessarily containing the same inactive ingredients, that meets the identical compendial or applicable standard of identity, strength, quality, and purity, including potency, and where applicable, content uniformity, disintegration times or dissolution rates, as the prescribed brand name drug and the manufacturer or distributor holds, if applicable, either an approved new drug application or an approved abbreviated new drug application unless other approval by law or from the federal food and drug administration is required. No drug shall be considered a generically equivalent drug for the purposes of chapter (3715.01) if it has been listed by the federal food and drug administration as having proven bioequivalence problems.

Discussion: The definition of a generically equivalent drug stated in ORC 3715.01 does not differ significantly from what has been discussed previously in respect to the FDA term "therapeutically equivalent". The law makes no reference to the Orange Book nor to the ratings used in the Orange Book. On the other hand, the last paragraph states that a product cannot be considered generically equivalent " if it has been listed by the FDA as having proven bioequivalence problems". This strongly implies reference to the Orange Book since so-called "B" rated drugs listed in the Orange Book are those the FDA suggests can present real potential bioequivalency problems. It is appropriate at this point to generally discuss the rating system used in the Orange Book.

More Orange Book Rating Discussion

It should be remembered that the Orange Book is a listing of all drugs for which a new drug application (NDA) or an abbreviated new drug application (ANDA) has been approved. Some drugs in the Orange Book will be innovator products (as mentioned earlier in discussing Abbott's divalproex) and rating them does not occur until generic competition occurs.

Generally speaking there are two rating categories into which a given product may fall, category A or category B. The reader should be aware, however, that many available drugs are not listed in the Orange Book at all since they have, for one reason or another escaped the authority of the FDA. Products assigned to Category A are considered bioequivalent while category B products, for any of several reasons are considered to not be bioequivalent. An "A" rating is granted to the manufacturer of the product who holds an approved NDA or ANDA or Form 5S or 6S (approved applications for antibiotics). One can see that it is far more important to know who manufactured a product than who distributes the product, and this helps explain why many products on the market are not listed in the Orange Book.

In certain instances, a number is added to the end of the **AB** code to make a three character code (i.e., **AB1, AB2, AB3, etc.**). Three-character codes are assigned only in situations when more than one reference listed drug of the same strength has been designated under the same heading. Two or more reference listed drugs are generally selected only when there are at least two potential reference drug products which are not bioequivalent to each other. **If a study is submitted that demonstrates bioequivalence to a specific listed drug product, the generic product will be given the same three-character code as the reference listed drug it was compared against.** For example, Adalat® CC (Miles) and Procardia XL® (Pfizer), extended-release tablets, are listed under the active ingredient nifedipine. These drug products, listed under the same heading, are not bioequivalent to each other. Generic drug products deemed by FDA to be bioequivalent to Adalat® CC and Procardia XL® have been approved, Adalat® CC and Procardia XL® have been assigned ratings of **AB1** and **AB2**, respectively. The generic drug products bioequivalent to Adalat® CC would be assigned a rating of **AB1** and those bioequivalent to Procardia XL® would be assigned a rating of **AB2**. (<u>The assignment of an **AB1** or **AB2** rating to a specific product does not imply product preference.)</u>

The rating system is far from perfect and can be a source of confusion to pharmacists:

1. The Orange Book will not list a product that is marketed under another company's NDA or ANDA and whose product is listed in the Orange Book.

2. It can be extremely difficult to determine the reference product listed in the Orange Book. For instance, Proventil ® metered inhalation spray is rated "BN" in the orange book while Ventolin ® is rated "AB". Since there are many generic albuterol metered inhalers also rated "AB" it is obvious the ANDA filed by these companies compared their products to Ventolin ®. The first interpretation is that one cannot not substitute Proventil for Ventolin, since one is rated BN and the other AB. Secondly, the pharmacist can freely choose to substitute one of several generics rated AB for Ventolin but not for Proventil. Technically, the prescriber would have to authorize

substitution for Proventil. Similarly, the newer Ventolin HFA product and Proventil HFA are rated “BX”. Though Ivax markets albuterol HFA in the same strength as cannot be substituted for these products at this time.

The pharmacist needs to be aware that the orange book rating on any given product can change and should be checked periodically.

OHIO LAW

ORC 4729.38 describes the conditions for substitution of a "generically equivalent drug", and the first paragraph (A) illustrates the importance of the pharmacist being familiar with ORC 3715.01(16) and the definition of "generically equivalent drug".

(A) Unless instructed otherwise by the person receiving the drug pursuant to the prescription, a pharmacist filling a prescription for a drug prescribed by its brand name may select a generically equivalent drug, as defined in section 3715.01 of the Revised Code, subject to the following conditions .....(discussed later)

There is no reference in ORC 4729.38 or 3715.01(20) to the fact that substitution requires an Orange Book rating. On the other hand, as discussed, <u>if the product is listed in the Orange Book and has not been granted an "A" rating it should not be substituted</u>. This leaves to be answered whether the pharmacist is free to substitute products not listed in the Orange Book.

There are a number of reasons why a drug might not be listed in the Orange Book

1. They may be drugs marketed prior to 1938 and not subject to pre-marketing clearance procedures of today. An example might be chloral hydrate which has been on the market prior to 1938. A generic manufacturer is free to market chloral hydrate dosage forms that do not differ from those already on the market.

2. As mentioned earlier, the drug may be marketed on authority of an NDA or ANDA issued to another company. By law a distributor who is not the manufacturer of the drug must list the manufacturer's name on the label. In turn, the manufacturer might be listed as the source company in the Orange Book. *

* This can get tricky. A parent company holding the NDA could potentially create a subsidiary, transfer manufacturing rights to the subsidiary while holding onto the NDA. If the subsidiary then supplies the drug to other distributors the subsidiary would be listed as the manufacturer, but not be listed in the Orange Book since the parent company retains the NDA. This is for instance the case with Greenstone’s azithromycin.

3. The product may be approved but not yet listed in the Orange Book.

4. The drug may be termed a "DESI" drug, which are not controlled by the FDA but through the Drug Efficacy Study Process.

The term "DESI" drug is very confusing to many pharmacists and should be discussed at this point.

DESI

Prior to 1962 manufacturers were not required to have their drug products approved for efficacy, only for safety. In that year, however, the Kefauver-Harris Amendment to the Food, Drug and Cosmetic Act required that manufacturers prove efficacy in addition to safety. The amendment also required that the new proof of efficacy be retroactive to drugs approved by the FDA between 1938 and 1962. This would have been an exceptional burden for the FDA so they asked the National Academy of Sciences/ National Research Council to assist in the review of the older drugs. There was approximately 15,000 drug products reviewed between 1966 and 1969 and only about 12 % of these were judged effective for all claimed uses by the NAS/NRC expert panels. This phase of the initial inquiry was termed the **Drug Efficacy Study Implementation** (DESI) process and those drugs reviewed became known as DESI drugs. Manufacturers of ineffective drugs were given time to submit data to dispute panel determinations, or to file for a hearing before an administrative law judge. There are some DESI drugs still on the market and fall primarily into the following categories:

1. Those which have not yet demonstrated efficacy but have been issued a notice of opportunity by the FDA for a hearing to withdraw approval of the application, e.g. Librax ® or Donnatal ®.

2. Those for which clinical efficacy studies are being conducted but are not yet completed. e.g. nitroglycerin transdermal patches.

3. Those that have never been approved but are similar and related to a DESI drug product that was raised to the effective status, e.g. Naldecon ®.

Because of efficacy questions and because most DESI drugs are obsolete due to the marketing of more effective medications many drug plans exclude some or all DESI drugs from coverage. This includes many of the state Medicaid programs.

In substituting DESI drugs the pharmacist will want to carefully consider the inactive ingredients. Say, for instance, that the dyes differ significantly between the two choices. The pharmacist want to make sure the patient is free of any known dye allergies. Another important consideration might be the Na+ content of the products or the choice of preservatives used in the products.

The federal Health Care Financing Administration (HCFA) generally considers DESI drugs to be ineffective for the conditions indicated on the label or in the information packet. Thus, for most government programs DESI drugs are not reimbursable.

DESI drugs are classified by Health Care Financing Administration (HCFA) and the

manufacturers of combination products into five groups numerically identified beginning with Group 2. The groups are:

Group 2 Drugs for which Medicaid will receive federal matching funds for the drug program and the indications for product use have been proven effective.

Group 3 Drugs classified as largely effective for indicated uses and for which federal matching funds are available.

Group 4 Drugs classified as possibly effective for indicated uses and for which federal matching funds are occasionally (perhaps) available.

Group 5 Drugs classified as not effective for indicated uses and for which federal matching funds are not available.

Group 6 New drugs not classified and for which federal matching funds are not available.

In most states as a rule Medicaid reimburses drugs in Groups 2 and 3 only. Drugs in groups 4, 5, and 6 are considered DESI drugs and are NOT covered by Medicaid. A list of DESI drugs is available from the Medicaid Pharmacy Unit. Each calendar quarter, the Centers for Medicaid and Medicare (CMS) publishes a list of LTE/IRS drugs which has been reviewed for accuracy by the FDA. It is available at: http://www.cms.hhs.gov/medicaid/drugs/desi.pdf.

OHIO LAW CONTINUED

§ 4729.38. Generically equivalent drugs.

(A) Unless instructed otherwise by the person receiving the drug pursuant to the prescription, a pharmacist filling a prescription for a drug prescribed by its brand name may select a generically equivalent drug, as defined in section 3715.01 of the Revised Code, subject to the following conditions:

(1) The pharmacist shall not select a generically equivalent drug if the prescriber handwrites "dispense as written," or "D.A.W.," on the written prescription, or, when ordering a prescription electronically or orally, the prescriber specifies that the prescribed drug is medically necessary. These designations shall not be preprinted or stamped on the prescription. Division (A)(1) of this section does not preclude a reminder of the procedure required to prohibit the selection of a generically equivalent drug from being preprinted on the prescription.

(2) The pharmacist shall not select a generically equivalent drug unless its price to the patient is less than or equal to the price of the prescribed drug.

(3) The pharmacist, or the pharmacist's agent, assistant, or employee shall inform the patient or the patient's agent if a generically equivalent drug is available at a lower or equal cost, and of the

person's right to refuse the drug selected. Division (A) (3) of this section does not apply to any:

(a) Prescription that is billed to any agency, division, or department of this state which will reimburse the pharmacy;

(b) Prescriptions for patients of a hospital, nursing home, or similar patient care facility.

(B) Unless the prescriber instructs otherwise, the label for every drug dispensed shall include the drug's brand name, if any, or its generic name and the name of the distributor, using abbreviations if necessary. When dispensing at retail a generically equivalent drug for the brand name drug prescribed, the pharmacist shall indicate on the drug's label or container that a generic substitution was made. The labeling requirements established by this division are in addition to all other labeling requirements of Chapter 3715. of the Revised Code.

(C) A pharmacist who selects a generically equivalent drug pursuant to this section assumes no greater liability for selecting the dispensed drug than would be incurred in filling a prescription for a drug prescribed by its brand name.

(D) The failure of a prescriber to restrict a prescription by specifying "dispense as written," or "D.A.W.," pursuant to division (A) (1) of this section shall not constitute evidence of the prescriber's negligence unless the prescriber had reasonable cause to believe that the health condition of the patient for whom the drug was intended warranted the prescription of a specific brand name drug and no other. No prescriber shall be liable for civil damages or in any criminal prosecution arising from the interchange of a generically equivalent drug for a prescribed brand name drug by a pharmacist, unless the prescribed brand name drug would have reasonably caused the same loss, damage, injury, or death.

It is important to remember that generically equivalent drugs can differ in respect to inactive ingredients. The pharmacist should consider the inactive ingredients of the generic drug against the patient’s profile, especially in respect to any possible allergy to the inactive ingredients, e.g. dyes and preservatives

A QUESTION OF LIABILITY:

An important statement in ORC 4729.38 (C) is as follows:

A pharmacist who selects a generically equivalent drug pursuant to this section assumes no greater liability for selecting the dispensed drug than would be incurred in filling a prescription for a drug prescribed by its brand name.

Here again, the emphasis is on the pharmacist understanding just what the state board intends by

the term "generically equivalent". This rule, too, was intended to encourage substitution by assuring the provider that no additional liability would be incurred.

PATIENT'S RIGHT OF REFUSAL

Another extremely important statement is that found in ORC 4729.38 (A) (3):

The pharmacist, or the pharmacist's agent, assistant, or employee shall inform the patient or the patient's agent if a generically equivalent drug is available at a lower or equal cost, and of the person's right to refuse the drug selected. Division (A) (3) does not apply to any:

(a) Prescription that is billed to any agency, division, or department of this state which will reimburse the pharmacy.

(b) Prescriptions for patients of a hospital, nursing home, or similar care facility.

The right of refusal is especially important in the retail setting:

The rule of law is that the patient has the right to refuse generic substitution. **This is a rule that one routinely sees violated in retail pharmacy practice, yet it is very important on ethical grounds.** This right of refusal remains true even if, for instance, the patient's drug plan requires substitution. It will probably be unusual under such circumstances for the patient to refuse generic substitution but it is important to remember whether to accept a generic remains his or her individual choice. If this right is not observed, the pharmacist is not allowing the patient to act as an autonomous agent and this is an important breach in professional ethics.

Another important consideration in this respect is that the pharmacist must bear in mind that the patient, since he or she never fully relinquishes the right to reject generic substitution, is always to be included in the decision making process involved in generic substitution. A patient, if he or she decides not to accept generic substitution, may have to pay a much higher price for the drug that is prescribed; but, on the other hand, may have a completely rational reason in doing so. To not allow the patient to be part of the decision making is, as mentioned above, to restrict their autonomy or their ability to act as a free agent. Such acts lead health care providers, perhaps due to pressure from third-party payers, to act paternalistically.

Generic substitution and formularies

A law that became effective in 1984 and needs revision provides some protection to the dispensing pharmacist when he or she is required to conform to an established formulary.

ORC 4729.381 states:

No licensed pharmacist shall be liable for civil damages or in any criminal prosecution arising from the dispensing of a drug based upon a formulary established by a practitioner in a hospital, health maintenance organization, or long-term care facility and requiring the pharmacist to dispense the particular drug.

This law was obviously promulgated when HMOs, for instance, were essentially closed organizations, in which case the pharmacist was an employee of the organization and, for all practical purposes, probably not included in decisions involving the development of the formulary. Some HMOs now contract with community pharmacies and enforce the same formulary requirements once seen only in closed organizations. It has become common for preferred provider organizations (PPOs) and even pharmacy benefit management (PBM) organizations to establish formularies.

The author is not an attorney but it seems that this law should be restructured to protect pharmacists who must conform to a formulary imposed by a any third-party entity over which he or she can exercise no control. Other than formulary restrictions, a similar problem exists with so-called step-therapy or where drugs in the same class are assigned preference by third-party payers. This type of forced dispensing will be a very important issue in the future since formulary development and implementation are universally seen as important components of cost saving strategies. This is certainly true, for example, with the government's Part D prescription drug plan now offered to those over 65 years of age.

Summing up:

The laws in Ohio and State Board of Pharmacy rules are such that they encourage the substitution of generically equivalent drugs. The rules provide the pharmacist with guidelines to enable him or her to substitute in order:

1. To pass on cost savings to the public.

2. To maintain a profitable gross margin equal to that if substitution was not chosen.

3. To not incur additional liability if one chooses to substitute.

4. To assure that the patient is always informed that substitution of a generically equivalent drug has taken place, and that he or she always retains the right to reject substitution.

The pharmacist is required to assess the generic equivalency of the products chosen to be substituted for others. The reliance on an "A" rating in the Orange Book is not absolute. The working definition of generic equivalency can be found in ORC 3715.01 (A) (16).

The pharmacist is free to substitute on grandfathered drugs (manufactured prior to1938), DESI

drugs, and drugs marketed after 1962 provided he or she determines objectively that the substituted drug is "generically equivalent" to the drug for which the substitution is made.

Generic equivalence can generally be assumed for drugs marketed prior to 1938 provided they have identical active ingredients, meet the same compendial or other applicable standards of identity, strength, quality, and purity, including potency, and where applicable, content uniformity, disintegration times or dissolution rates.

Certainly a drug manufactured to USP or NF standards meets these criteria. On other drugs it may be necessary for the pharmacist to seek certification from the manufacturer that the product fulfills these requirements. These grandfathered drugs include some popular drugs, e.g. aspirin with codeine, chloral hydrate, codeine, digoxin, nitroglycerin sublingual, thyroid, quinine, phenobarbital, potassium chloride oral preparations, methenamine, and phenazopyridine.

The inclusion of digoxin and thyroid in this sample list brings up an interesting point. The pharmacist must stay up with current literature and not substitute drugs for which bioequivalency problems exist and when the pharmacist, based on practice standards, should know that they do. Another important point is that these older problem drugs are usually prescribed by chemical name. The drug the pharmacist chooses to initiate therapy should not be changed for the patient during therapy unless the patient and physician are informed of the change. In short, there are times when switching brands cannot be avoided during therapy (supply problems, etc.) but it should not be done capriciously.

DESI drugs should meet the same criteria as above. In addition, the manufacturer may be the best and only source of information on whether the criteria listed above are met. If the manufacturer cannot supply the needed information it should be assumed that the product in question is not generically equivalent. It is important to remember that the individual pharmacist is responsible for determining the generic equivalency of a product. In the case of an employee pharmacist, his or her employer should be able to verify that the products the pharmacist is asked to dispense are indeed generically equivalent.

Drugs marketed after 1962 through approval by the FDA of an NDA or ANDA are listed in the Orange Book. Those rated "A" in this reference book are considered generically equivalent. On the other hand, those rated "B" are not. Though Ohio law does not require that only "A" drugs can be substitution, this is implied by the admonition that " no drug shall be considered a generically equivalent drug ..... if it has been listed by the federal food and drug administration as having proven bioequivalence problems [as in ORC 3715.01 (16)].

Orange book ratings can be found in the Red Book, Blue Book, USP - DI Volume 3, and provided by the manufacturer in case the pharmacist does not have ready access to the Orange Book. Additionally, the FDA can provide the information for individual products (1-301- 594-0337). They are also available online at: http://www.fda.gov/cder/ob/default.htm

"B" does not stand for "BAD"

All drugs listed in the Orange Book, regardless of rating, have been approved by the FDA for both safety and efficacy. In other words, they should pose no significant risk to patients if used according to approved dosage, and they can generally be relied upon to provide defined pharmacological effects. There may be several reasons a drug is rated “B” in the orange book. A common reason, however, is that there is something about them that makes it difficult to duplicate them while avoiding potential bioequivalent problems. In many instances this is related to dosage form and especially how the active ingredient is released, as in products that come in sustained or controlled release dosage forms.

> It should be noted that if a prescription is for a drug rated “B” is ordered it is permissible to dispense a generic provided the generic is marketed under the innovator’s NDA or ANDA.

At the beginning of drug therapy any "B" rated drug can be recommended or used with equal confidence. The clinician must simply know what therapeutic end point he or she wishes to attain for the patient. This may be a given serum level, clinical response, or lack of expected side effects. The drug chosen to initiate therapy should not be changed unless the clinician and the patient are informed of the change. If possible, the pharmacist should be able to articulate what the clinician needs to know to assess any possible change in clinical response from the new drug. Additionally, the patient should be informed of any change in drug response, possible adverse effects, cautions, or additional monitoring that might result from the change.

An unfortunate situation arises when the community pharmacist is required or forced to substitute based on the formulary of a plan to which the patient has a contractual arrangement. This can involve substitution of "generically equivalent drugs" as define by the state, or for "therapeutically equivalent" drugs as define by the formulary (not necessarily "therapeutically equivalent" as defined by the FDA). A good example would be the forced substitution of a preferred NSAID. For most patients the preferred product will not pose any problems, but for a few patients the preferred product might increase the risk of certain side effects, including a higher incidence of GI bleed. The law needs to protect the pharmacist better if he or she is forced to dispense certain drugs due to decisions made by a third-party payer and, of which, the pharmacist has no recourse.

Parting comment:

The issue of substitution is a complex one and likely to become even more confusing in the future. The pharmacist should remain abreast with state laws or pharmacy board rules that provide direction on the appropriateness or legality of substitution. The pharmacist is strongly cautioned that he or she cannot be directed to substitute by any entity when the substitution is not permitted by the state. The pharmacist should be especially cautious when he or she is mandated to dispense products that a managed care entity, not the state or FDA, describes as a "therapeutic equivalent".

Adherence, Inc. **Continuing Education Questions.**

There is only one best answer for each question. Please complete the answer sheet and mail along with a $ 10.00 administrative fee to: Adherence, Inc., PO Box 42407, Cincinnati, Ohio 45242 -0407. Special note: A grade of 75% is require for CE credit. One retake without an additional fee is allowed.

1. Antisubstitution laws existed prior to 1972 for various reasons, including all but

a. to prevent unscrupulous manufacturers from marketing counterfeit drugsof popular brands.

b. to protect the gross margin of drug manufacturers and community pharmacists.

c. to protect the public from receiving substituted drugs that might be inferior

to branded versions.

d. to satisfy the outrage of the public, citizens groups, and governmental agencies.

2. By 1978 all but _____ states had repealed their antisubstitution laws.

a. 8

b. 10

c. 12

d. 15

3. Two products considered pharmaceutical equivalents

a. contain the same active ingredients

b. may differ in dosage form

c. are indentical in strength or concentration, and route of administration

d. a and c above

4. It is possible for drugs to share "A" ratings under a single drug listing in the Orange Book and not be therapeutically equivalent.

a. true

b. false

5. Drugs not listed in the Orange Book include

a. those drugs marketed prior to 1938

b. DESI drugs

c. drugs marketed under another company's NDA or ANDA

d. all the above

6. DESI drugs are by their very nature less effective than drugs listed in the Orange Book.

a. true

b. false

7. Bioequivalency means that two products can be expected to

a. have the same clinical effect

b. have similar clinical effects

c. be identical in all comparable ways

d. be pharmaceutically equivalent

8. Bioavailability and bioequivalency have essentially the same meanings.

a. true

b. false

9. Erythromycin stearate and erythromycin estolate would normally be considered

a. bioequivalent

b. therapeutically equivalent

c. pharmaceutical alternative

d. a and c above

10. ORC 3715.01 (A) (Paragraph 16) stipulates that all generic drugs have an "A" rating in the Orange Book in order to be substituted.

a. true

b. false

11. Ohio pharmacy law states clearly that "B" rated drugs not be used for substitution purposes.

a. true

b. false

12. All drugs on the market with known bioequivalency problems are listed in the Orange Book.

a. true

b. false

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3. READABILITY & PRESENTATION	1	2	3	4	5

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2.	A B C D	6.	A B C D	10.	A B C D
3.	A B C D	7.	A B C D	11.	A B C D
4.	A B C D	8.	A B C D	12.	A B C D

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