



Generic and Therapeutic Substitution

Pharmacists are often faced with decisions about whether to substitute one drug product for another. These decisions can have important clinical, economic, and legal ramifications. Until the 1970s, virtually every state had either a statute or an administrative rule strictly forbidding prescription drug substitution. Today, the situation is very different. All 50 states have drug product selection laws that allow, encourage, or mandate some form of substitution.

Two types of substitution are addressed in state statutes: generic and therapeutic. Generic substitution is the act of dispensing a different brand or unbranded drug product than the one prescribed. Generic substitution can only be done legally when the substituted products contain the **same** chemical entity and are bioequivalent to one another. Therapeutic substitution is the act of dispensing a therapeutic alternate (different chemical entity) to the drug product prescribed. Therapeutic substitution, unlike generic substitution, **always** requires prescriber approval. This approval may be *a priori* in the form of a formulary system or prescribing protocol.

The basic tenet of generic therapeutic substitution is that patients will receive products that are therapeutically equivalent. The primary reference guide for pharmacists on the therapeutic equivalence of drugs is the so-called Orange Book, the Food and Drug Administration's (FDA) *Approved Drug Products With Therapeutic Equivalence Evaluations*. The Orange Book has been available for nearly 20 years and is regarded as the most reliable source for determining therapeutic equivalence. Unfortunately, many health care providers, including pharmacists, are not familiar with its existence, much less the policies surrounding its development and use.

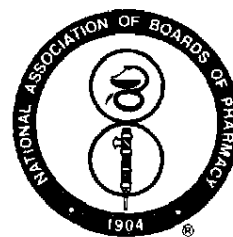
Starting with the passage of the Food, Drug, and Cosmetic Act (FD&C Act) in 1938, the FDA began to evaluate the safety of drug products before they were to be marketed. It was not until the passage of the 1962 amendments to the FD&C Act that manufacturers were also required to demonstrate the efficacy of their products before FDA approval was granted. Manufacturers were also required under the 1962 amendments to file a new drug application (NDA) for any "innovator drug" or an abbreviated new drug application (ANDA) for any new generic drug. In 1984, the ANDA process was revised as part of the Drug Price Competition and Patent Term Restoration Act. As the law now stands, an ANDA is required to include information on product chemistry and manufacturing controls similar to that found in an NDA but does not have to include the preclinical or clinical safety and effectiveness data from studies in laboratory animals and humans, as is required for an NDA. An ANDA submission must include, however,

evidence that the generic drug is therapeutically equivalent to the innovator drug product, which means that it must be both pharmaceutically equivalent (ie, have the same active ingredients in the same dosage form and strength, and use the same administration route), and bioequivalent (ie, have more or less the same rate and extent of absorption). Under the 1984 Act, bioequivalence must be confirmed in a small (24 to 36 subjects) standardized crossover bioequivalence study.

The FDA assigns therapeutic equivalence codes to generic products when the products meet both the aforementioned requirements, are approved as safe and effective, are adequately labeled, and are manufactured in compliance with current Good Manufacturing Practice regulations. An underlying principle of the therapeutic equivalence code designation is that the drug products are pharmaceutical equivalents that are expected to produce the same clinical benefits when administered for the conditions approved in the product labeling. Drug products that are determined to be therapeutically equivalent to innovator drugs are assigned an "A" for the first letter of their therapeutic equivalence code. A second letter provides additional information regarding the particular dosage form of that product (eg, aerosol = AN, injectable oil = AO, iv aqueous = AP, topical = AT). The AB-rating assigned to equivalent drug products indicates that bioequivalence requirements have been met with adequate in vivo or in vitro evidence. In contrast, drugs that are assigned a "B" for the first letter of the therapeutic equivalence code (BN, BT, etc), are not considered therapeutically equivalent to other products because bioequivalence problems have not been resolved to the satisfaction of the FDA.

"I've seen quite a bit of confusion regarding the substitutability of certain drugs, most recently between Premarin (conjugated estrogens tablets, USP) and Cenestin (synthetic conjugated estrogens, A)," says Ronald Maddox, Dean of the Campbell University School of Pharmacy. "The FDA determined that these two drugs are not therapeutically equivalent and, therefore, has not listed the products with a therapeutic equivalence code."

It must be emphasized, however, that the Orange Book is merely a guide. It provides advice regarding generic substitution to health care professionals and states, but does not mandate on a federal level, which drug products to use when performing generic substitution. Generic substitution mandates are found in individual state laws and regulations. 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 or formularies. Pharmacists are encouraged to review the laws



and regulations in their states to determine the appropriate and legal methods by which to perform generic substitution.

Why review this information? Each day, pharmacists must use their professional judgment when making decisions about drug product selections or substitutions, decisions that can have an important impact on their patients' health. Pharmacists should make such decisions with a clear understanding of the above standards.

Fee Increase for Licensure Transfer, MPJE, and NAPLEX Effective January 1

The National Association of Boards of Pharmacy (NABP) has announced fee increases for three of its programs; the transfer of pharmaceutical licensure, the Multistate Pharmacy Jurisprudence Examination™ (MPJE™), and the NAPLEX® (North American Pharmacist Licensure Examination™).

Effective January 1, 2001, the fee for processing a Preliminary Application for Pharmaceutical Licensure Transfer will increase from \$250 to \$300 per state for the first state to which the applicant is requesting licensure transfer. This increase, the first since NABP's Electronic Licensure Transfer Program (ELTP) was implemented in 1996, covers the average annual cost of living between 1996 and 2003.

The fee to request licensure transfer to additional states on the same application form as the first state will remain at \$50 per state. In addition, the current \$50 fees for changing the transferring state, referred to as "Change of State," and extending the life of an Official Application for Transfer of Pharmaceutical Licensure, known as "Extension of Time," will remain unchanged.

Candidates taking the MPJE will pay a new \$45 administrative fee, beginning January 2001, to cover increased seating fees charged to NABP by the Chauncey Group International, Ltd, the testing vendor for the MPJE and NAPLEX. Similarly, candidates sitting for the NAPLEX will be required to pay an additional administrative fee of \$110. Like the MPJE, this new charge is being implemented to offset higher seating fees charged to NABP by the Chauncey Group International, Ltd.

Base testing fees for both the NAPLEX and MPJE are not expected to increase for the next several years. The MPJE fee will remain \$85 and the NAPLEX fee will stay at \$250.

Eight More Sites Earn VIPPS Certification

Since awarding the first three Verified Internet Pharmacy Practice Sites™ (VIPPS™) certification in September 1999, NABP has issued eight new site certifications. Currently, eleven

pharmacy sites have earned VIPPS certification, including the eight most recent recipients (in order of certification):

CVS.com www.cvs.com
FamilyMeds.com www.familymeds.com
Tel-Drug, Inc www.teldrug.com
HealthScript Pharmacy Services www.healthscript.com
Rx.com www.rx.com
Caremark www.rxrequest.com
DrugEmporium.com www.DrugEmporium.com
PrescriptionOnline.com www.PrescriptionOnline.com

As VIPPS-certified sites, the online pharmacies may display the VIPPS hyperlink seal of approval on their Web sites. By clicking on the VIPPS seal, consumers are able to find the verified information they need to make informed decisions regarding their choice of online pharmacies. Consumers may also access the VIPPS database directly via NABP's Web site at www.nabp.net.

"Each certified pharmacy practice site was able to satisfy VIPPS' rigorous 17-point Internet pharmacy practice criteria, demonstrate appropriate licensure, and pass an on-site criteria review by a VIPPS inspection team," says NABP President Jerry Moore, RPh, JD. "These pharmacies have demonstrated consumers can use their Internet services with confidence."

The VIPPS certification process begins with the submission of a completed VIPPS Application Form and supporting documentation. Submitted materials include essential information such as the applicant's business name, ownership, address and phone number, Web site address, and documentation of adherence to VIPPS criteria. Such criteria include maintaining and following written policies and procedures for drug utilization review, patient counseling, patient confidentiality, and quality improvement programs.

After an evaluation of the applicant's submitted materials, a written evaluation is issued to the applicant and a site inspection is scheduled. Upon completion of the site visit, inspectors submit a report of their findings to NABP, including deficiencies and recommended corrective actions. A written report is then issued to the applicant. If deficiencies are noted, the report includes recommendations for VIPPS criteria compliance. If the review is satisfactory, the report confirms VIPPS certification.

VIPPS applications continue to be received at NABP headquarters, and more pharmacy sites are expected to be certified soon. For more information about VIPPS, please contact NABP at 847/698-6227, or visit the NABP Web site at www.nabp.net.