



**A PHARMACY CONTINUING EDUCATION PROGRAM**

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**January 2005 "Legal Aspects of Pharmacy: Using the Orange Book for Bioequivalence Evaluations" 707-000-05-001-H03**



**THIS MONTH**  
"Pharmacy Law  
Update 2005"

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**HAVE YOU RECENTLY MOVED? PLEASE NOTIFY US.**

Drug bioequivalency is a reality that each of us consider, whether we are aware of it or not. The main resource for review of drug bioequivalence is the Orange Book. In this lesson we discuss the issues that are often regarded. This lesson provides 3.0 hours (0.3 CEUs) of credit, and is intended for pharmacists in all practice settings.

**The program ID # for this lesson is 707-000-05-001-H03.**

**Pharmacists completing this lesson by January 31, 2008 may receive full credit.**

**To obtain continuing education credit for this lesson**, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). **Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page** (for continuous participants only).

**The objectives of this lesson are such that upon completion the participant will be able to:**

1. Describe the evolution of drug product selection by pharmacists over the past 50 years.
2. Define terms used by the FDA in the Orange Book.
3. List the criteria for FDA bioequivalence evaluations.
4. Discuss the use of reference-listed drugs by the FDA.
5. Distinguish the codes used by the FDA in its bioequivalence ratings.
6. Use Orange Book listings to determine the bioequivalence of drug products.

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## BACKGROUND

Some drugs are available from several different sources and may be marketed under a generic name or trade name. These "multisource" products contain the same chemical ingredients, but they may differ in price, and they may differ in other characteristics, such as bioavailability. Physicians may make choices of which product to prescribe. Pharmacists may make choices of which product to dispense when the pharmacist is given the legal option of making that choice. Most newly developed drug products, and some products that have been on the market for many years, are "single source" products. For these products there are no issues as to similarity with any other competing product. No choice needs to be made when the drug is prescribed, because only the one product exists.

## THE HISTORY OF DRUG PRODUCT SELECTION

For many years prior to the early 1950s, pharmacists had discretion to decide which product to dispense when a physician prescribed a specific drug. The pharmacist could either dispense the particular product prescribed, or the pharmacist could select a different product, as long as the two products contained the same drug. This practice came to an end because some pharmacists were abusing the privilege and were dispensing different drugs altogether. This practice was referred to as "substitution" of one drug for another, rather than as "selection" of a product for a specified drug entity. With the passage of state "ant substitution" laws, pharmacists became obligated not only to dispense the same drug as had been prescribed by the physician, but also the same product or brand as had been prescribed. Of course, if a physician were to prescribe by generic name, the pharmacist could still select which product to dispense of that generically prescribed drug.

In the mid-1960s, consumer advocates discovered that the restriction on pharmacists imposed by the decade-old ant substitution laws was working to their economic disadvantage. Financial savings that could be realized by responsible generic substitution were being lost because pharmacists were unable to dispense a less expensive alternative product when a more expensive specific product had been prescribed. Consumer groups successfully fought for legislation that would permit (or even require) generic substitution by pharmacists, as long as specified guidelines were followed. By the mid-1970s, every state had replaced its ant substitution law with a drug product selection law. Although every state has followed a somewhat different path to the objective of cost savings without adverse effects on quality, the standard approach is to allow substitution unless the prescriber specifically forbids it. Pharmacists must select for substitution only those products that they are confident will provide an essentially identical therapeutic outcome for patients. The cost savings must be passed on to the patient.

At first there were not too many generic products from which to choose, and pharmacists had difficulty knowing which products were bioequivalent with each other. To assist pharmacists in deciding what products were bioequivalent, the FDA issued a listing of bioequivalence ratings. This list was published as a book with an orange cover, and it became known as "The Orange Book." The official title of the book is "Approved Drugs Products With Therapeutic Equivalence Evaluations." All approved drugs, either through an NDA or an ANDA, are listed in the book. Those drugs that are rated as bioequivalent with each other are so indicated in the book.

**The Orange Book is now usually accessed online at the FDA website ([www.fda.gov](http://www.fda.gov)).**

The Orange Book is useful to pharmacists in making decisions about bioequivalence, but pharmacists still must decide themselves about the substitutability of one product for another. State laws vary on how

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pharmacists may make decisions about substitutability, given bioequivalence ratings provided in the Orange Book. Simply because two products are rated as bioequivalent does not necessarily mean they can be substituted under state law. And the failure to carry a bioequivalence rating does not necessarily mean two products cannot be substituted under state law. Yet, despite the variations in rules for substitution at the state level, the federal bioequivalence ratings are very useful to pharmacists in making decisions, and it is important to review the meaning of these ratings. The appropriate use of the ratings is likewise an appropriate subject for review.

## ORANGE BOOK DEFINITIONS

**Therapeutic Equivalents:** Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents, and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

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; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations. The concept of therapeutic equivalence, as used to develop the Orange Book 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).

The 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, and for pharmacists to honor this request. 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.

**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 alternative products that display comparable bioavailability when studied under similar experimental conditions. The Food, Drug and Cosmetic Act describes one set of conditions under which a test and reference listed drug (RLD) shall be considered bioequivalent: the rate and extent of absorption of the test drug does 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.

Where these above methods are not applicable (e.g., for drug products that are not intended to be absorbed into the bloodstream), other *in vivo* or *in vitro* test methods to demonstrate bioequivalence may be

appropriate.

Bioequivalence may sometimes be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human *in vivo* bioavailability data. In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies.

Bioequivalence is based on a statistical assumption that if two products are essentially identical, and if one product is known to be safe and effective, then the other product can be assumed to be safe and effective. It is also based on the reasoning that if Product B is essentially identical to Product A, and if Product C is essentially identical to Product A, then Product B is essentially identical to Product C.

### STATISTICAL CRITERIA FOR BIOEQUIVALENCE

Under the Drug Price Competition and Patent Term Restoration Act of 1984, manufacturers seeking approval to market a generic drug product must submit data demonstrating that the drug product is bioequivalent to the pioneer (innovator) drug product. A major premise underlying the 1984 law is that bioequivalent drug products are therapeutically equivalent and, therefore, interchangeable.

Bioavailability refers to the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action. Bioequivalence refers to equivalent release of the same drug substance from two or more drug products or formulations. This leads to an equivalent rate and extent of absorption from these formulations. Underlying the concept of bioequivalence is the thesis that, if a drug product contains a drug substance that is chemically identical and is delivered to the site of action at the same rate and extent as another drug product, then it is equivalent and can be substituted for that drug product. Methods used to define bioequivalence include (1) pharmacokinetic (PK) studies, (2) pharmacodynamic (PD) studies, (3) comparative clinical trials, and (4) *in vitro* studies. The choice of study used is based on the site of action of the drug and the ability of the study design to compare drug delivered to that site by the two products.

The standard bioequivalence (PK) study is conducted using a two-treatment crossover study design in a limited number of volunteers, usually 24 to 36 adults. Alternately, a four-period, replicate design crossover study may also be used. Single doses of the test and reference drug products are administered and blood or plasma levels of the drug are measured over time. Pharmacokinetic parameters characterizing rate and extent of drug absorption are evaluated statistically. The PK parameters of interest are the resulting area under the plasma concentration-time curve (AUC), calculated to the last measured concentration ( $AUC_{(0-t)}$ ) and extrapolated to infinity ( $AUC_{(0-inf)}$ ), for extent of absorption; and the maximum or peak drug concentrations ( $C_{max}$ ), for rate of absorption. Crossover studies may not be practical in drugs with a long half-life in the body, and a parallel study design may be used instead. Alternate study methods, such as *in-vitro* studies or equivalence studies with clinical or pharmacodynamic endpoints, are used for drug products where plasma concentrations are not useful to determine delivery of the drug substance to the site of activity (such as inhalers, nasal sprays and topical products applied to the skin).

The statistical methodology for analyzing these bioequivalence studies is called the two one-sided test procedure. Two situations are tested with this statistical methodology. The first of the two one-sided tests determines whether a generic product (test), when substituted for a brand-name product (reference) is significantly less bioavailable. The second of the two one-sided tests determines whether a brand-name product when substituted for a generic product is significantly less bioavailable. Based on the opinions of FDA medical experts, a difference of greater than 20% for each of the above tests was determined to be significant, and, therefore, undesirable for all drug products. Numerically, this is expressed as a limit of test-product average/reference-product average of 80% for the first statistical test and a limit of reference-product average/test-product average of 80% for the second statistical test. By convention, all data is expressed as a ratio of the average response (AUC and  $C_{max}$ ) for test/reference, so the limit expressed in the second statistical test is 125% (reciprocal of 80%).

For statistical reasons, all data are log-transformed prior to conducting statistical testing. In practice, these

statistical tests are carried out using an analysis of variance procedure (ANOVA) and calculating a 90% confidence interval for each pharmacokinetic parameter (C<sub>max</sub> and AUC). The confidence interval for both pharmacokinetic parameters, AUC and C<sub>max</sub>, must be entirely within the 80% to 125% boundaries cited above. Because the mean of the study data lies in the center of the 90% confidence interval, the mean of the data is usually close to 100% (a test/reference ratio of 1). Different statistical criteria are sometimes used when bioequivalence is demonstrated through comparative clinical trials, pharmacodynamic studies, or comparative in-vitro methodology.

The bioequivalence methodology and criteria described above simultaneously control for both, differences in the average response between test and reference, as well as the precision with which the average response in the population is estimated. This precision depends on the within-subject (normal volunteer or patient) variability in the pharmacokinetic parameters (AUC and C<sub>max</sub>) of the two products, and on the number of subjects in the study. The width of the 90% confidence interval is a reflection in part of the within-subject variability of the test and reference products in the bioequivalence study. A test product with no differences in the average response when compared to the reference might still fail to pass the bioequivalence criteria if the variability of one or both products is high and the bioequivalence study has insufficient statistical power (i.e., insufficient number of subjects). Likewise, a test product with low variability may pass the bioequivalence criteria, when there are somewhat larger differences in the average response.

The primary concern from the regulatory point of view is the protection of the patient against approval of products that are not bioequivalent. The current practice of carrying out two one-sided tests at the 0.05 level of significance ensures that there is no more than a 5% chance that a generic product that is not truly equivalent to the reference will be approved.

### REFERENCE LISTED DRUG (RLD)

A reference listed drug is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. A common misconception is that an applicant for an ANDA can choose any listed product against which it can compare its own product to obtain ANDA approval. This is not correct. The ANDA applicant must compare its own product with a RLD listing.

The FDA has identified in the Prescription Drug Product and OTC Drug Product Lists those reference listed drugs to which the *in vivo* bioequivalence and, in some instances, the *in vitro* bioequivalence of the applicant's product is compared. By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference listed drugs. However, in some instances when listed drugs are approved for a single drug product, a product not designated as the reference listed drug and not shown to be bioequivalent to the reference listed drug may be shielded from generic competition. A firm wishing to market a generic version of a listed drug that is not designated as the reference listed drug may petition the FDA through the Citizen Petition procedure. When the Citizen Petition is approved, the second listed drug will be designated as an additional reference listed drug, and the petitioner may submit an Abbreviated New Drug Application citing the designated reference listed drug. Products meeting necessary bioequivalence requirements explains the **AB**, **AB1**, **AB2**, **AB3** coding system for multisource drug products listed under the same heading with two reference listed drugs.

In addition, there are two situations in which two listed drugs that have been shown to be bioequivalent to each other may both be designated as reference listed drugs. The first situation occurs when the *in vivo* determination of bioequivalence is self-evident and a waiver of *in vivo* determination of bioequivalence may be granted. The second situation occurs when the bioequivalence of two listed drugs may be determined through *in vitro* methodology. The reference listed drug is identified by a "Yes" in the Prescription and Over-the-Counter (OTC) Drug Product Lists and is identified in the printed version by a "+". These identified reference listed drugs represent the best judgment of the Division of Bioequivalence at this time. The Prescription and OTC Drug Product Lists identify reference drugs for oral dosage forms, injectables, ophthalmics, otics, and topical products.

**Multisource and single-source drug products:** The FDA has evaluated for therapeutic equivalence

only multisource prescription drug products, which in most instances means those pharmaceutical equivalents available from more than one manufacturer. A therapeutic equivalence code is included for such products. Those products with approved applications that are single-source (i.e., there is only one approved product available for that active ingredient, dosage form and route of administration) are also included on the List, but no therapeutic equivalence code is included with such products.

Products on the List are identified by the names of the holders of approved applications (applicants) who may not necessarily be the manufacturer of the product. The applicant may have had its product manufactured by a contract manufacturer and may simply be distributing the product for which it has obtained approval. In most instances, however, the manufacturer of the product is also the applicant. The name of the manufacturer is permitted by regulation to appear on the label, even when the manufacturer is not the marketer.

## THERAPEUTIC EQUIVALENCE EVALUATIONS CODES

The two-letter coding system for therapeutic equivalence evaluations is constructed to allow users to determine quickly whether the FDA has evaluated a particular approved product as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter). With few exceptions, the therapeutic equivalence evaluation date is the same as the approval date.

The two basic categories into which multisource drugs have been placed are indicated by the first letter as follows:

**"A"**—Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products, i.e., drug products for which:

- (1) there are no known or suspected bioequivalence problems. These are designated **AA, AN, AO, AP, or AT**, depending on the dosage form; or
- (2) actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. These are designated **AB**.

**"B"**—Drug products that FDA, at this time, considers NOT to be therapeutically equivalent to other pharmaceutically equivalent products, i.e., drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. Often the problem is with specific dosage forms rather than with the active ingredients. These are designated **BC, BD, BE, BN, BP, BR, BS, BT, BX, or B\***.

Individual drug products have been evaluated as therapeutically equivalent to the reference product in accordance with the definitions and policies outlined below.

### "A" CODES

**"A"** products are those for which actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. Drug products designated with an **"A"** code fall under one of two main policies:

- (1) for those active ingredients or dosage forms for which no *in vivo* bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is presumed and considered self-evident based on other data in the application for some dosage forms (e.g., solutions) or satisfied for solid oral dosage forms by a showing that an acceptable *in vitro* dissolution standard is met. A therapeutically equivalent rating is assigned such products so long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications (these are designated **AA, AN, AO, AP, or AT**, depending on the dosage form, as described below); or
- (2) for those drug products containing active ingredients or dosage forms that have been identified by FDA as having actual or potential bioequivalence problems, and for post-1962 drug products in a dosage form presenting a potential bioequivalence problem, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through *in vivo* and/or *in vitro* studies the bioequivalence of the product to a selected reference product (these products are designated as **AB**).

There are some general principles that may affect the substitution of pharmaceutically equivalent products in specific cases. Prescribers and dispensers of drugs should be alert to these principles so as to deal appropriately with situations that require professional judgment and discretion.

There may be labeling differences among pharmaceutically equivalent products that require attention on the part of the health professional. For example, pharmaceutically equivalent powders to be reconstituted for administration as oral or injectable liquids may vary with respect to their expiration time or storage conditions after reconstitution. An FDA evaluation that such products are therapeutically equivalent is applicable only when each product is reconstituted, stored, and used under the conditions specified in the labeling of that product.

The specific sub-codes for those drugs evaluated as therapeutically equivalent and the policies underlying these sub-codes follow.

**“AA”—Products in conventional dosage forms not presenting bioequivalence problems:**

Products coded as **AA** contain active ingredients and dosage forms that are not regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues. However, all oral dosage forms must, nonetheless, meet an appropriate *in vitro* bioequivalence standard that is acceptable to the FDA in order to be approved.

**“AB, AB1, AB2, AB3”—Products meeting necessary bioequivalence requirements:**

Multisource drug products listed under the same heading (i.e., identical active ingredient(s), dosage form, and route(s) of administration) and having the same strength generally will be coded **AB**, if a study is submitted demonstrating bioequivalence.

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 that 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. (The assignment of an AB1 or AB2 rating to a specific product does not imply product preference.) Even though drug products of distributors and/or repackagers are not included in the List, they are considered therapeutically equivalent to the application holder's drug product, if the application holder's drug product is rated either with an AB or three-character code, or is single source in the List. Drugs coded as AB under a heading are considered therapeutically equivalent only to other drugs coded as AB under that heading. Drugs coded with a three-character code under a heading are considered therapeutically equivalent only to other drugs coded with the same three-character code under that heading.

**“AN”—Solutions and powders for aerosolization:**

Uncertainty regarding the therapeutic equivalence of aerosolized products arises primarily because of differences in the drug delivery system. Solutions and powders intended for aerosolization that are marketed for use in any of several delivery systems are considered to be pharmaceutically and therapeutically equivalent and are coded **AN**. Those products that are compatible only with a specific delivery system or those products that are packaged in and with a specific delivery system are coded **BN**, unless they have met an appropriate bioequivalence standard. Solutions or suspensions in a specific delivery system will be coded **AN**, if the bioequivalence standard is based upon *in vitro* methodology. If bioequivalence needs to be demonstrated by *in vivo* methodology then the drug products will be coded **AB**.

**“AO”—Injectable oil solutions:**

The absorption of drugs in injectable (parenteral) oil solutions may vary substantially with the type of oil employed as a vehicle and the concentration of the active ingredient. Injectable oil solutions are, therefore,

considered to be pharmaceutically and therapeutically equivalent only when the active ingredient, its concentration, and the type of oil used as a vehicle are all identical.

**“AP”—Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions:**

It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences among the products in the general category, *Injectable; Injection*. For example, some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are all considered to be pharmaceutically and therapeutically equivalent provided they are designed to produce the same concentration prior to injection and are similarly labeled. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product’s labeling to assure that it is given only by the route(s) of administration stated in the labeling.

The strength of parenteral drug products is defined as the total drug content of the container. Until recently, the strengths of liquid parenteral drug products in the Orange Book have not been displayed. The concentration of the liquid parenteral drug product in the Orange Book has been shown as xmg/ml. The amount of dry powder or freeze dried powder in a container has always been identified as the strength.

**“AT”—Topical products:**

There are a variety of topical dosage forms available for dermatologic, ophthalmic, otic, rectal, and vaginal administration, including solutions, creams, ointments, gels, lotions, pastes, sprays, and suppositories. Even though different topical dosage forms may contain the same active ingredient and potency, these dosage forms are not considered pharmaceutically equivalent. Therefore, they are not considered therapeutically equivalent. All solutions and DESI drug products containing the same active ingredient in the same topical dosage form for which a waiver of *in vivo* bioequivalence has been granted and for which chemistry and manufacturing processes are adequate to demonstrate bioequivalence, are considered therapeutically equivalent and coded **AT**. Pharmaceutically equivalent topical products that raise questions of bioequivalence, including all post-1962 non-solution topical drug products, are coded **AB** when supported by adequate bioequivalence data, and **BT** in the absence of such data.

**“B”CODES**

“**B**” products, for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence, often have a problem with specific dosage forms rather than with the active ingredients. Drug products designated with a “**B**” code fall under one of three main policies:

- (1) the drug products contain active ingredients or are manufactured in dosage forms that have been identified by the FDA as having documented bioequivalence problems or a significant potential for such problems and for which no adequate studies demonstrating bioequivalence have been submitted to FDA; or
- (2) the quality standards are inadequate or FDA has an insufficient basis to determine therapeutic equivalence; or
- (3) the drug products are under regulatory review.

The specific coding definitions and policies for the “**B**” sub-codes are as follows:

**“B\*”—Drug products requiring further FDA investigation and review to determine therapeutic equivalence:**

The code **B\*** (referred to as “B Star”) is assigned to products previously assigned an **A** or **B** code when FDA receives new information that raises a significant question regarding therapeutic equivalence that can be resolved only through further FDA investigation and/or review of data and information submitted by the applicant. The **B\*** code signifies that the FDA will take no position regarding the therapeutic equivalence of the product until the FDA completes its investigation and review.

**“BC”—Extended-release dosage forms (capsules, injectables and tablets):**

An extended-release dosage form is defined by the official compendia as one that allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g., as a solution or a prompt drug-releasing, conventional solid dosage form).

Although bioavailability studies have been conducted on these dosage forms, they may be subject to bioavailability differences, primarily because firms developing extended-release products for the same active ingredient rarely employ the same formulation approach. FDA, therefore, does not consider different extended-release dosage forms containing the same active ingredient in equal strength to be therapeutically equivalent unless equivalence between individual products in both rate and extent has been specifically demonstrated through appropriate bioequivalence studies. Extended-release products for which such bioequivalence data have not been submitted are coded **BC**, while those for which such data are available have been coded **AB**.

**“BD”—Active ingredients and dosage forms with documented bioequivalence problems:**

The **BD** code denotes products containing active ingredients with known bioequivalence problems and for which adequate studies have not been submitted to FDA demonstrating bioequivalence. Where studies showing bioequivalence have been submitted, the product has been coded **AB**.

**“BE”—Delayed-release oral dosage forms:**

A delayed-release dosage form is defined by the official compendia as one that releases a drug (or drugs) at a time other than promptly after administration. Enteric-coated articles are delayed-release dosage forms.

Drug products in delayed-release dosage forms containing the same active ingredients are subject to significant differences in absorption. Unless otherwise specifically noted, the FDA considers different delayed-release products containing the same active ingredients as presenting a potential bioequivalence problem and codes these products **BE** in the absence of *in vivo* studies showing bioequivalence. If adequate *in vivo* studies have demonstrated the bioequivalence of specific delayed-release products, such products are coded **AB**.

**“BN”—Products in aerosol-nebulizer drug delivery systems:**

This code applies to drug solutions or powders that are marketed only as a component of, or as compatible with, a specific drug delivery system. There may, for example, be significant differences in the dose of drug and particle size delivered by different products of this type. Therefore, the FDA does not consider different metered aerosol dosage forms containing the same active ingredient(s) in equal strengths to be therapeutically equivalent unless the drug products meet an appropriate bioequivalence standard.

**“BP”—Active ingredients and dosage forms with potential bioequivalence problems:**

FDA's bioequivalence regulations contain criteria and procedures for determining whether a specific active ingredient in a specific dosage form has a potential for causing a bioequivalence problem. It is FDA's policy to consider an ingredient meeting these criteria as having a potential bioequivalence problem even in the absence of positive data demonstrating inequivalence. Pharmaceutically equivalent products containing these ingredients in oral dosage forms are coded **BP** until adequate *in vivo* bioequivalence data are submitted. Injectable suspensions containing an active ingredient suspended in an aqueous or oleaginous vehicle have also been coded **BP**. Injectable suspensions are subject to bioequivalence problems because differences in particle size, polymorphic structure of the suspended active ingredient, or the suspension formulation can significantly affect the rate of release and absorption. FDA does not consider pharmaceutical equivalents of these products bioequivalent without adequate evidence of bioequivalence; such products would be coded **AB**.

**“BR”—Suppositories or enemas that deliver drugs for systemic absorption:**

The absorption of active ingredients from suppositories or enemas that are intended to have a systemic effect (as distinct from suppositories administered for local effect) can vary significantly from product to product. Therefore, FDA considers pharmaceutically equivalent systemic suppositories or enemas bioequivalent only if *in vivo* evidence of bioequivalence is available. In those cases where *in vivo* evidence is available, the product is coded **AB**. If such evidence is not available, the products are coded **BR**.

**“BS”—Products having drug standard deficiencies:**

If the drug standards for an active ingredient in a particular dosage form are found by FDA to be deficient so as to prevent an FDA evaluation of either pharmaceutical or therapeutic equivalence, all drug products containing that active ingredient in that dosage form are coded **BS**. For example, if the standards permit a wide variation in pharmacologically active components of the active ingredient such that pharmaceutical equivalence is in question, all products containing that active ingredient in that dosage form are coded **BS**.

**“BT”—Topical products with bioequivalence issues:**

This code applies mainly to post-1962 dermatologic, ophthalmic, otic, rectal, and vaginal products for topical administration, including creams, ointments, gels, lotions, pastes, and sprays, as well as suppositories not intended for systemic drug absorption. Topical products evaluated as having acceptable clinical performance, but that are not bioequivalent to other pharmaceutically equivalent products or that lack sufficient evidence of bioequivalence, will be coded **BT**.

**“BX”—Drug products for which the data are insufficient to determine therapeutic equivalence:**

The code **BX** is assigned to specific drug products for which the data that have been reviewed by the FDA are insufficient to determine therapeutic equivalence under the policies stated in this document. In these situations, the drug products are presumed to be therapeutically inequivalent until the FDA has determined that there is adequate information to make a full evaluation of therapeutic equivalence.

**AN UNCOMPLICATED EXAMPLE**

Although the Orange Book listing for dexamethasone is lengthy, it addresses relatively straightforward issues of bioequivalence. You can easily get the listing on the Internet. Refer to that listing for the following discussion. On the Internet, go to [www.fda.gov](http://www.fda.gov). In the upper left corner, under SEARCH, type in ORANGE BOOK & click on GO. Then click on ELECTRONIC ORANGE BOOK HOME PAGE. Click on SEARCH BY ACTIVE INGREDIENT. Type in DEXAMETHASONE, and click on SUBMIT. **DISCUSSION.** All of the oral elixirs are rated as bioequivalent. The oral solution and ophthalmic suspension are single source products, and they are each listed as the RLD for the drug and dosage form, and they have no bioequivalence rating because there is no additional product with which to be bioequivalent. For each strength of oral tablet there are some products that are rated as “AB” and are, therefore, rated as bioequivalent with each other. There are also oral tablets that are rated as “BP” and are, therefore, not rated as bioequivalent with any other product. The one and two mg. strengths of oral tablets are single source, thus they have no bioequivalence rating. Each product listed as “yes” under the column labeled “RLD” is a reference listed drug for that strength of dexamethasone oral tablet.

**A SOMEWHAT COMPLICATED EXAMPLE**

On the Internet, again go to the Orange Book Site, and do a SEARCH for the active ingredient CYCLOSPORINE. **DISCUSSION.** This is a drug for which there are products that have not been shown to be bioequivalent (and are therefore “B” rated), and for which there is more than one RLD, thus there are multiple “A” ratings (“AB1” and “AB2”). Only those “A” rated products with the same rating are considered by the FDA to have been shown to be bioequivalent. The other products may in fact all be bioequivalent, but they have not been rated as bioequivalent by the FDA.

- (1) The 100 mg. and 25 mg. strengths of Abbott’s Gengraf are coded as “AB1” and are rated as bioequivalent with Eon’s product, Novartis’ product neural, and Pliva’s product.
- (2) The 50 mg. strength of Abbott’s Gengraf is coded as “BX” and is not rated as bioequivalent with any other product.
- (3) The 25 mg. and 100 mg. strengths of Novartis’ product Sandimmune are coded as “AB2” and are rated as bioequivalent with Torpharm’s products.

**A VERY COMPLICATED EXAMPLE**

The most difficult to understand listing in the Orange Book is usually considered to be that for levothyroxine sodium. On the Internet, go to the Orange Book Site, and do a SEARCH for the active ingredient LEVOTHYROXINE SODIUM. **DISCUSSION.** This is a drug that was introduced to the market in 1962 and was thought at the time to not be a “new drug.” Since only new drugs require approval, levothyroxine was never approved by the FDA. Perhaps the original manufacturer believed that since levothyroxine was essentially the same as thyroid extract, and because thyroid extract was not the subject of an approval, levothyroxine did not require approval either. In any event, the FDA did not object to the unapproved marketing of levothyroxine until the late 1990s, when the agency notified manufacturers that approval would be required for continued marketing of the drug. Some sponsors obtained approval through a shortened version NDA submission, and they do not have bioequivalence listing, since their products were not compared to other products.

Some sponsors obtained approval through an ANDA, by comparing their product to a RLD. These products approved through the ANDA process do have bioequivalence listings. To make matters more complicated, there are three RLDs for levothyroxine. Thus, for those products rated as bioequivalent there are ratings AB1, AB2 and AB3. Some manufacturers have more than one rating listed for their products. Again, here are a few clarifications of the Orange Book Listing:

- (1) All Abbott products are coded as "AB2" and are rated as bioequivalent with those other products similarly rated (Alara Pharm and Mylan).
- (2) All Alara Pharm products are coded both "AB2" and "AB3" and are rated as bioequivalent with all other products rated either "AB2" or "AB3" (Abbott, Jones Pharma, Mylan and Stevens J).
- (3) All Genpharm products are coded as "BX" and are not rated as bioequivalent with any other product.
- (4) All strengths of Jones Pharma's product, except for the 0.137 mg. Strength, are coded as both "AB1" and "AB3" and are rated as bioequivalent with other products rated as either "AB1" or "AB3" (Alara Pharm, Mylan, Stevens J). The 0.137 mg. strength is coded as "AB3" and is rated as bioequivalent only with other products rated as "AB3" that market a 0.137 mg. strength (Alara Pharm).
- (5) Lloyd's product is coded as "BX" and is not rated as bioequivalent with any other product. The 0.3 mg. strength of Lloyd's product is a reference listed drug for the strength.
- (6) Mylan's product is coded as "AB1" and "AB2" and "AB3" and is rated as bioequivalent with all other products coded as either "AB1" or "AB2" or "AB3" (Abbott, Alara Pharm, Jones Pharma, Stevens J).
- (7) Note that Stevens J's Unithroid brand of levothyroxine is rated as bioequivalent only with the other products that are also given the therapeutic equivalence code AB1 and AB3. The 0.3 mg. strength of Unithroid is a reference listed drug.
- (8) Vintage's products are coded as "BX" and are not rated as bioequivalent with any other products.

### **CONCLUSION**

The exercise of judgment by pharmacists in the selection of a product when generic substitution is permitted under state law can be guided by the science underlying the Orange Book listings. While substitutability continues to be a matter regulated by state law and left to the pharmacist's professional discretion, bioequivalence is an issue that has been squarely addressed by the FDA through the Orange Book. Access to the Orange Book is available through the Internet. Pharmacists should learn how to use this valuable resource and rely on it as they pursue their drug product selection practices.

Fill in the information below, answer questions and return **Quiz Only** for certification of participation to: CE PRN<sup>®</sup>, 400 Lake Cook Road, Suite 207, Deerfield, IL 60015.

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**LESSON EVALUATION**

Please fill-out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Please rate each of the following from 1 to 7. Circle your choices. (1 is the lowest rating; 7 is the highest).

	Poor			Average			Excellent
1. Relevance of topic to practice.	1	2	3	4	5	6	7
2. Author's ability to communicate.	1	2	3	4	5	6	7
3. Author's knowledge of topic.	1	2	3	4	5	6	7
4. Appropriateness of topic.	1	2	3	4	5	6	7
5. Do you have any further comments about this lesson?	_____						

**Please Select the Most Correct Answer**

1. During what decade were the ant substitution laws passed?
  - A. 1930s
  - B. 1940s
  - C. 1950s
  - D. 1960s
2. The concept of bioequivalence as used by the FDA in its Orange Book ratings, encompasses a comparison of products with what similarities?
  - A. Same dosage form
  - B. Same strength
  - C. Same molecular entity
  - D. All of these
3. Against what standard may an applicant for an ANDA base a comparison of the sponsored new product?
  - A. Any listed drug
  - B. Any marketed drug
  - C. The reference listed drug
  - D. Any previous ANDA sponsored drug
4. Which of the following parameters are those consistently used by the FDA in making decisions about bioequivalence?
  - A. AUC only
  - B. Cmax only
  - C. Tmax only
  - D. AUC & Cmax
5. A physician prescribes Decadron 0.75 mg oral tablets. Which of the following products is rated as bioequivalent with Decadron 0.75 mg oral tablets?
  - A. Par Pharm's product
  - B. Organon's product
  - C. Roxane's product
  - D. None of these
6. Two products listed together in the Orange Book are both rated as 'BX.' What does this mean about the two products?
  - A. They are rated as bioequivalent
  - B. They are not bioequivalent
  - C. They are not rated as bioequivalent
  - D. They are not bioavailable
7. Two products listed together in the Orange Book are both rated as 'AB2.' What does this mean about the two products?
  - A. They are rated as bioequivalent
  - B. They are not bioequivalent
  - C. They are not rated as bioequivalent
  - D. They are not bioavailable
8. Two products listed together in the Orange Book are both rated as 'AB.' What does this mean about the two products?
  - A. They are rated as bioequivalent
  - B. They are not bioequivalent
  - C. They are not rated as bioequivalent
  - D. They are not bioavailable
9. A physician prescribes Sandimmune 50 mg oral capsules. Which of the following products is rated as bioequivalent with Sandimmune 0.75 mg oral tablets?
  - A. Abbott's product
  - B. Pliva's product
  - C. Torpharm's product
  - D. None of these
10. Which of the following products is rated as bioequivalent with Levoxyl 0.15 mg oral tablets?
  - A. Mylan's product
  - B. Lloyd's product
  - C. Abbott's product
  - D. None of these

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