CONTENT OF ORANGE BOOK

Food and Drug Administration
Center for Drug Evaluation and Research
Approved Drug Products with Therapeutic Equivalence Evaluations

The publication, *Approved Drug Products With Therapeutic Equivalence Evaluations* (the List, commonly known as the Orange Book), identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (the FD&C Act). The main criterion for the inclusion of any product is that the product is the subject of an application with an approval that has not been withdrawn for safety or efficacy reasons. Inclusion of products in the Orange Book is independent of any current regulatory action being taken administratively or judicially against a drug product. In addition, the Orange Book contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs. Therapeutic equivalence evaluations in this publication are not official FDA actions affecting the legal status of products under the FD&C Act.

Background of the Publication. To contain drug costs, virtually every state has adopted laws and/or regulations that encourage the substitution of drug products. These state laws generally require either that substitution be limited to drugs on a specific list (the positive formulary approach) or that it be permitted for all drugs except those prohibited by a particular list (the negative formulary approach). Because of the number of requests in the late 1970s for FDA assistance in preparing both positive and negative formularies, it became apparent that FDA could not serve the needs of each state on an individual basis. The Agency also recognized that providing a single list based on common criteria would be preferable to evaluating drug products on the basis of differing definitions and criteria in various state laws. As a result, on May 31, 1978, the Commissioner of the Food and Drug Administration sent a letter to officials of each state announcing FDA's intent to provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multisource prescription products.

The Orange Book was distributed as a proposal in January 1979. It included only currently marketed prescription drug products approved by FDA through new drug applications (NDAs) and abbreviated new drug applications (ANDAs)under the provisions of Section 505 of the FD&C Act and FDA regulations at that time.

The therapeutic equivalence evaluations in the Orange Book reflect FDA's application of specific criteria to the multisource prescription drug products listed in the Orange Book and approved under Section 505 of the FD&C Act.

These evaluations are presented in the form of code letters that indicate the basis for the evaluation made. An explanation of the codes appears in the *Introduction*.

A complete discussion of the background and basis of FDA's therapeutic equivalence evaluation policy was published in the *Federal Register* on January 12, 1979 (44 FR 2932). The final rule, which includes FDA's responses to the public comments on the proposal, was published in the *Federal Register* on October 31, 1980 (45 FR 72582). The first publication of the Orange Book in October 1980, concurrent with finalization of the rule, incorporated appropriate corrections and additions. Each subsequent edition has included new approvals and made appropriate changes in data.

On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments). The Hatch-Waxman Amendments amended the FD&C Act to establish, among other things, the 505(b)(2) and 505(j) approval pathways. The Hatch-Waxman Amendments require that FDA, among other things, make publicly available a list of approved drug products with monthly supplements. The Orange Book and its monthly Cumulative Supplements satisfy this requirement. The *Addendum* to this publication identifies drugs that have qualified under the FD&C Act for periods of exclusivity and provides patent information concerning the approved drug products in the Orange Book. The *Addendum* also provides additional information that may be helpful to those submitting an NDA under section 505(b) of the FD&C Act or an abbreviated new drug application (ANDA) under section 505(j) of the FD&C Act to the Agency.

The Agency intends to use this publication to further its objective of obtaining input and comment on the publication itself and related Agency procedures. Therefore, if you have comments on how the publication can be improved, please send them to the Central Document Room, Attn: Director, Division of Legal and Regulatory Support, Office of Generic Drug Policy, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266. Comments received are publicly available to the extent allowable under the Freedom of Information Act and FDA regulations.

INTRODUCTION

Content and Exclusion

The Orange Book is composed of four parts: (1) approved prescription drug products with therapeutic equivalence evaluations; (2) approved over-the-counter (OTC) drug products for those drugs that may not be marketed without NDAs or ANDAs because they are not covered under existing OTC monographs; (3) drug products with approval under Section 505 of the FD&C

Act administered by the Center for Biologics Evaluation and Research; and (4) a cumulative list of approved products that have never been marketed, are for exportation, are for military use, have been discontinued from marketing and we have not determined that they were withdrawn from sale for safety or effectiveness reasons, or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing.[1] This publication also includes indices of prescription and OTC drug products by proprietary name (brand name or trade name) or, if no proprietary name exists, established name of the active ingredient and by applicant name, which have been abbreviated for this publication. Established names for active ingredients generally conform to compendial names or *United States Adopted Names* (USAN) as described in 21 CFR 299.4(e). A list of uniform terms is provided in Appendix C.

The *Addendum* contains patent and exclusivity information for the Prescription, OTC, Discontinued Drug Product Lists, and for the Drug Products with Approval under Section 505 of the FD&C Act Administered by the Center for Biologics Evaluation and Research. The publication may include additional information that the Agency deems appropriate to disseminate.

Prior to the 6th Edition, the publication had excluded OTC drug products and drug products with approval under Section 505 of the FD&C Act administered by the Center for Biologics Evaluation and Research. The Hatch-Waxman Amendments required the Agency to begin publishing an up-to-date list of all marketed drug products, OTC as well as prescription, that have been approved for safety and efficacy and for which new drug applications are required.

Under the FD&C Act, some drug products are given tentative approvals. The Agency will not include drug products with tentative approvals in the Orange Book because a drug product that is granted tentative approval is not an approved drug product. Tentative approval lists by month are available on FDA's website Drugs@FDA. When the tentative approval becomes a final approval through a subsequent action letter to the applicant, the Agency will list the drug product and the date of approval in the appropriate approved drug product list. In addition, we note that Section 505(x) of the FD&C Act affects the date of approval for certain drug products subject to scheduling under the Controlled Substances Act. The Agency will list the drug product in the Orange Book and the date of approval as determined under Section 505(x).

The Orange Book identifies the application holder of a drug product and does not identify distributors or repackagers.

Therapeutic Equivalence-Related Terms

Pharmaceutical Equivalents. Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where the residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.[2] They may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, within certain limits, labeling.

Pharmaceutical Alternatives. Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form, or the same salt or ester (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules).[3] Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.[4] Different dosage forms and strengths within a product line by a single manufacturer are pharmaceutical alternatives, as are extended-release products when compared with immediate-release or standard-release formulations of the same active ingredient.

Therapeutic Equivalents. Approved drug products are considered to be therapeutic equivalents if they are pharmaceutical equivalents for which bioequivalence has been demonstrated, and they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[5]

FDA classifies as therapeutically equivalent those drug 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 identical active drug ingredient in the identical 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 applies only to drug products containing

the identical active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., meperidine hydrochloride vs. morphine sulfate for the treatment of pain). Any drug product in the Orange Book repackaged and/or distributed by other than the applicant is considered to be therapeutically equivalent to the applicant's drug product even if the applicant's drug product is single source or coded as non-equivalent (e.g., **BN**). Distributors or repackagers of an applicant's drug product are not identified in the Orange Book.

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, certain 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 specific product 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 can be expected to have the same clinical effect and safety profile as the prescribed product when administered to patients under the conditions specified in the labeling.

Strength. Strength refers to the amount of drug substance contained in, delivered, or deliverable from a drug product, which includes: (1)(a) the total quantity of drug substance in mass or units of activity in a dosage unit or container closure (*e.g.*, weight/unit dose, weight/volume or weight/weight in a container closure, or units/volume or units/weight in a container closure); and/or, as applicable, (b) the concentration of the drug substance in mass or units of activity per unit volume or mass (*e.g.*, weight/ weight, weight/volume, or units/volume); or (2) such other criteria the Agency establishes for determining the amount of drug substance contained in, delivered, or deliverable from a drug product if the weights and measures described in clause (1)(a) do not apply (*e.g.*, certain drug-device combination products for which the amount of drug substance is emitted per use or unit time).[6] Note that if the criteria the Agency establishes for determining and expressing the amount of drug substance in a product evolves over time, the Agency generally does not intend to revise the expressions of strength for drug products already included in the Orange Book, but rather intends to apply the criteria prospectively to drug products added to the Orange Book.

Although the strength of drug products in the Orange Book is generally expressed in terms of the amount of drug substance (active ingredient) in the drug product, it is sometimes expressed in terms of the amount of the active moiety. For example, certain drug products included in the Orange Book include a designation of "EQ" next to their expression of strength. This "EQ" designation generally is used in connection with salt drug products to indicate

that the strength of such drug product is being expressed in terms of the equivalent strength of the active moiety (e.g., "EQ 200MG BASE"), rather than in terms of the strength of the active ingredient.

Bioavailability. Bioavailability is 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 drug action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action.[7]

Bioequivalence. Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[8] Section 505(j)(8)(B) of the FD&C Act describes certain conditions under which a test drug and reference listed drug (see Section 1.4) shall be considered bioequivalent:

1. 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] listed 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

2. the extent of absorption of the [test] drug does not show a significant difference from the extent of absorption of the [reference] listed 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] listed 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 scientifically valid *in vivo* or *in vitro* test methods to demonstrate bioequivalence may be appropriate.

For example, 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.[9]

Further Guidance on Bioequivalence

FDA's regulations and guidance documents provide additional information regarding bioequivalence and bioavailability, including methodologies and statistical criteria used to establish the bioequivalence of drug products.[10]

Reference Listed Drug and Reference Standard

A reference listed drug is the listed drug[11] identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.[12] Generally, a reference listed drug is a drug product approved in a new drug application under Section 505(c) of the FD&C Act based on full reports of investigations of safety and effectiveness. For an ANDA based on an approved suitability petition (a petitioned ANDA), the reference listed drug generally is the listed drug referenced in the approved suitability petition.[13]

A reference standard is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an *in vivo* bioequivalence study required for approval.[14] FDA generally selects a single reference standard that ANDA applicants must use in *in vivo* bioequivalence testing. Ordinarily, FDA will select the reference listed drug as the reference standard. However, in some instances, the reference listed drug and the reference standard may be different. For example, where the reference listed drug has been withdrawn from sale FDA may select an ANDA as the reference standard.

FDA identifies reference listed drugs in the Prescription Drug Product, OTC Drug Product, and Discontinued Drug Product Lists. Listed drugs identified as reference listed drugs represent drug products upon which an applicant can rely in seeking approval of an ANDA. FDA intends to update periodically the reference listed drugs identified in the Prescription Drug Product, OTC Drug Product, and Discontinued Drug Product Lists, as appropriate.

In some instances when FDA has not designated a listed drug as a reference listed drug, such listed drug may be shielded from generic competition. If FDA has not designated a reference listed drug for a drug product the applicant intends to duplicate, the potential applicant may submit a controlled correspondence to the Office of Generic Drugs to ask FDA to designate a reference listed drug for that drug product. Section 1.7, *Therapeutic Equivalence Evaluations Codes* (*products meeting necessary bioequivalence requirements*) explains the character coding system (e.g.,**AB, AB1, AB2, AB3**...) for multisource drug products listed under the same heading with two or more reference listed drugs.

FDA also identifies reference standards in the Prescription Drug Product and OTC Drug Product Lists. Listed drugs identified as reference standards represent FDA's best judgment at this time as to the appropriate comparator for purposes of conducting any *in vivo* bioequivalence studies required for approval.

A potential applicant should consult Agency guidance related to referencing approved drug products in ANDA submissions for information on submitting a request for selection of a reference standard. FDA may, on its own initiative, select a new reference standard when doing so will help to ensure that applications for generic drugs may be submitted and evaluated, e.g., in the event that the listed drug currently selected as the reference standard has been withdrawn from sale.

If an applicant has a question related to the appropriate reference standard, it is recommended that an applicant planning to conduct an *in vivo* bioequivalence study submit a controlled correspondence to the Office of Generic Drugs.

General Policies and Legal Status

The Orange Book contains public information and advice. It does not mandate the drug products that are purchased, prescribed, dispensed, or substituted for one another, nor does it, conversely, mandate the products that should be avoided. To the extent that the Orange Book sets forth FDA's evaluations of the therapeutic equivalence of drug products that have been approved, it contains FDA's advice to the public, to practitioners, and to the states regarding drug product selection. These evaluations do not constitute determinations that any product is in violation of the FD&C Act or that any product is preferable to any other. Therapeutic equivalence evaluations are a scientific judgment based upon evidence, while generic substitution may involve social and economic policy administered by the states, e.g., reducing the cost of drugs to consumers. To the extent that the Orange Book identifies drug products approved under Section 505 of the FD&C Act, it sets forth information that the Agency is required to publish and that the public is entitled to under the Freedom of Information Act. Exclusion of a drug product from the Orange Book does not necessarily mean that the drug product is in violation of Section 505 of the FD&C Act, that such a product is not safe or effective, or that such a product is not therapeutically equivalent to other drug products. Rather, the exclusion may be based on the fact that FDA has not evaluated the safety, effectiveness, and quality of the drug product.

Practitioner/User Responsibilities

Professional care and judgment should be exercised in using the Orange Book. Evaluations of therapeutic equivalence for prescription drugs are based on scientific and medical evaluations by FDA. Products evaluated as therapeutically equivalent can be expected, in the judgment of FDA, to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. However, these products may differ in other characteristics that are not required by statute or regulation to be the same, such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, in some instances, labeling. If products with such differences are substituted for each other, there is a potential for patient confusion, e.g., due to differences in color or shape of tablets, inability to provide a given dose using a partial tablet if the proper scoring configuration is not available, or decreased patient acceptance of certain products because of flavor. There may also be patient-specific allergic reactions in rare cases due to a coloring or a preservative ingredient.

FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing such products with due care and with appropriate information to individual patients. In those circumstances where the characteristics of a specific product, other than its active ingredient, are important in the therapy of a particular patient, the practitioner's prescribing of that product may be appropriate. Pharmacists must also be familiar with the different characteristics of therapeutically equivalent products, e.g., expiration dates/times and labeling directions for storage of the different products (particularly for reconstituted products), so they can properly advise patients when one product is substituted for another.

Multisource and single-source drug products. In the Orange Book, FDA has evaluated for therapeutic equivalence only multisource prescription drug products approved under Section 505 of the FD&C Act, which in most instances means those pharmaceutical equivalents available from more than one manufacturer. For such products, a therapeutic equivalence code generally is included and product information is highlighted in bold face and underlined. Those products with approved applications that are single-source (i.e., there is only one approved product available for that active ingredient, dosage form, route of administration, and strength) are also included in the Orange Book, but no therapeutic equivalence code is included with such products. Any drug product in the Orange Book repackaged and/or distributed by the applicant or some other person authorized by the applicant (e.g., an authorized generic) is considered to be therapeutically equivalent to the applicant's drug product even if the applicant's drug product is single source or coded as non-equivalent (e.g., **BN**). Distributors or repackagers of an applicant's drug product are not identified in the Orange Book. The details of therapeutic equivalence codes and the policies underlying them are discussed in Section 1.7, *Therapeutic Equivalence Evaluations Codes*.

Products in the Orange Book are identified by the names of the holders of approved applications (applicants) who may not necessarily be the manufacturer of the product. There are numerous entities other than the applicant that may be involved in the development, manufacturing, and/or marketing of a product. Products listed in the Orange Book are identified by the applicant's name (firm name on the Form FDA 356h in the application). Where the applicant's name does not appear on the label, a person wishing to relate a specific product to the applicant name in the Orange Book may refer to FDA's NDC Directory[15] and match its search terms to information on the label, such as the NDC Code if available.

Every product in the Orange Book is subject at all times to regulatory action. From time to time, approved products may be found in violation of one or more provisions of the FD&C Act. In such circumstances, the Agency may commence appropriate enforcement action to correct the violation, if necessary, by securing removal of the product from the market by voluntary recall, seizure, or other enforcement actions. Such regulatory actions are, however, independent of the inclusion of a product in the Orange Book. The main criterion for inclusion of a product is that it has an NDA or ANDA that has been approved and that has not been withdrawn for safety or efficacy reasons. FDA believes that retention of a violative product in the Orange Book will not have any significant adverse health consequences, because other legal mechanisms are available to the Agency to prevent the product's actual marketing. FDA may, however, change a product's therapeutic equivalence rating if the circumstances giving rise to the violation change or otherwise call into question the Agency's assessment of whether a product meets the criteria for therapeutic equivalence.

Therapeutic Equivalence Evaluations Codes

Generally, drug products that the Agency considers multisource have been assigned a therapeutic equivalence code. The coding system for therapeutic equivalence evaluations is designed to allow users to determine quickly whether the Agency has evaluated a particular approved product (e.g., a particular strength of an approved drug) 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 some exceptions (e.g., therapeutic equivalence evaluations for certain 505(b)(2) applications), 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 of the relevant therapeutic equivalence code as follows:

A Drug products that FDA considers to be <u>therapeutically equivalent</u> 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 <u>not to be therapeutically equivalent</u> 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

Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products.

"**A**" products are those for which there are no known or suspected bioequivalence problems or 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 either presumed and considered self-evident (based on other information in the application for some dosage forms (e.g., solutions)), or satisfied by a showing that an acceptable *in vitro* approach 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 Efficacy Study Implementation (DESI) 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 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 (e.g., 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). FDA's determination that such products are therapeutically equivalent is applicable only when each product is reconstituted, stored, and used under the conditions specified in its labeling.

The Agency may use notes in this publication to point out special situations, such as potential differences between two drug products that have been evaluated as bioequivalent and otherwise therapeutically equivalent, when they should be brought to the attention of health professionals. These notes are contained in Section 1.8, *Description of Certain Special Situations*. For example, in certain instances, there may be variations among therapeutically equivalent products in their use or in conditions of administration. When such variations may, in the Agency's opinion, affect prescribing or substitution decisions by health professionals, a note may be added to Section 1.8.

For example, occasionally a situation may arise in which changes in a listed drug product after its approval (for example, a change in dosing interval) may have an impact on the substitutability of already approved generic versions of that product that were rated by the Agency as therapeutically equivalent to the listed product. When such changes in the listed drug product are considered by the Agency to have a significant impact on therapeutic equivalence, the Agency will change the therapeutic equivalence ratings for other versions of the drug product unless the manufacturers of those other versions of the product provide additional information to assure equivalence under the changed conditions. Pending receipt of the additional data, the Agency may

add a note to Section 1.8, or, in rare cases, may even change the therapeutic equivalence rating.

In some cases (e.g., Isolyte® S w/ Dextrose 5% in Plastic Container and Plasma-Lyte® 148 and Dextrose 5% in Plastic Container), closely related products are listed as containing the same active ingredients, but in somewhat different amounts. In determining which of these products are pharmaceutically equivalent, generally the Agency has considered products to be pharmaceutically equivalent with labeled strengths of an ingredient that do not vary by more than 1%.

Different salts, esters or other noncovalent derivatives (such as a complex, chelate, or clathrate) of the same active moiety are regarded as different active ingredients. For the purpose of this publication, products containing such different active ingredients are considered pharmaceutical alternatives and, thus, not therapeutically equivalent. Anhydrous and hydrated entities, as well as different polymorphs, are considered to be the same active ingredient and are expected to meet the same standards for identity to be considered pharmaceutical equivalents and therapeutic equivalents.

The codes in this book are not intended to preclude health care professionals from converting pharmaceutically different concentrations into pharmaceutical equivalents using accepted professional practice.

Where package size variations have therapeutic implications, products so packaged have not been considered pharmaceutically equivalent. For example, some oral contraceptives are supplied in 21-tablet and 28-tablet packets; the 28-tablet packets contain 7 placebo or iron tablets. These two packaging configurations are not regarded as pharmaceutically equivalent; thus, they are not designated as therapeutically equivalent.

Preservatives and other inactive ingredients may differ among some therapeutically equivalent drug products. These differences do not affect FDA's evaluation of therapeutic equivalence except in cases where these components may influence bioequivalence or routes of administration.

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

Multisource drug products coded as **AA** contain active ingredients and are in 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 Agency 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 ingredients(s), dosage form, and route(s) of administration) and having the same strength (see Section 1.2, *Therapeutic Equivalence-Related Terms, Strength)* generally will be coded **AB** if data and information are 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 generally are assigned only in situations when more than one reference listed drug of the same strength has been designated under the same heading. If a study is submitted that demonstrates bioequivalence to a reference 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 and Procardia XL®, extended-release tablets, are listed under the active ingredient nifedipine. These drug products, listed under the same heading, are not bioequivalent to each other. Adalat® CC and Procardia XL® have been assigned ratings of **AB1** and **AB2**, respectively. Generic drug products deemed by FDA to be bioequivalent to Adalat® CC and Procardia XL® have been approved. As a result, the generic drug products bioequivalent to Adalat® CC have been assigned a rating of **AB1** and those bioequivalent to Procardia XL® have been 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 Orange Book, they are considered therapeutically equivalent to the applicant's drug product if the applicant's drug product is rated either with an **AB** or three-character code or is single source in the Orange Book. 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 general-use 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 and are otherwise determined to be therapeutically equivalent. 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, historically 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 pharmaceutical alternative drug products. They are not rated as therapeutically equivalent (AP) to each other even if these pharmaceutical alternative drug products 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.

Certain commonly used large volume intravenous products in glass containers are not included in the Orange Book (e.g., dextrose injection 5%, dextrose injection 10%, sodium chloride injection 0.9%) since these products are on the market without FDA approval and FDA has not published conditions for marketing such parenteral products under approved NDAs. When packaged in plastic containers, however, FDA regulations require approved applications prior to marketing. Approval then depends on, among other things, the extent of the available safety data involving the specific plastic component of the product. All large volume parenteral products are manufactured under similar standards, regardless of whether they are packaged in glass or plastic. Thus, FDA has no reason to believe that the packaging container of large volume

parenteral drug products that are pharmaceutically equivalent would have any effect on their therapeutic equivalence.

Consistent with the definition of strength included in Section 1.2, *Therapeutic Equivalence-Related Terms,* the strength of parenteral drug products generally is identified by both the total drug content and the concentration of drug substance in a container approved by FDA.[16] In the past, the strength of liquid parenteral drug products in the Orange Book has not been fully displayed. Rather, the strength of liquid parenteral drug products in the Orange Book has been displayed in terms of concentration, expressed as x mg/mL. Generally, the amount of dry powder or lyophilized powder in a container is identified as the strength, expressed as x mg/vial.

However, FDA subsequently realized that the format of the Orange Book with respect to parenteral solutions should be changed to reflect that each strength of a drug is considered to be a separate listed drug. The Orange Book displays the strength of all new approvals of parenteral solutions. Previously (i.e., prior to 2003), we would have displayed only the concentration of an approved parenteral solution, e.g. 50 mg/mL. For example, if this application had a 20 mL and 60 mL container approved, we would now display two product strengths, listing both total drug content and concentration of drug substance in the relevant approved container, e.g. 1 gm/20 mL (50 mg/mL) and 3 gm/60 mL (50 mg/mL).

AT Topical products

There are a variety of topical dosage forms available for dermatologic, ophthalmic, otic, rectal, and vaginal administration, including creams, gels, lotions, oils, ointments, pastes, solutions, sprays, suppositories, and inserts. 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, or the application contains adequate scientific evidence establishing through an *in vitro* approach the bioequivalence of the product to a selected reference product, 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 and for which a waiver of *in vivo* bioequivalence has not been granted, including all post-1962 non-solution topical drug products, are coded **AB** when supported by adequate *in vivo* bioequivalence data, and **BT** in the absence of such data.

"B" CODES

Drug products that FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products.

"**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 Agency 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*** 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 Agency investigation and/or review of data and information submitted by the applicant. The **B*** code signifies that the Agency will take no position regarding the therapeutic equivalence of the product until the Agency completes its investigation and review.

BC Extended-release dosage forms (capsules, injectables and tablets)

Extended-release tablets are formulated in such a manner as to make the contained drug substance available over an extended period of time following ingestion.

Although bioavailability studies have been conducted on these dosage forms, they may be subject to bioavailability differences, primarily because applicants 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

Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of "enteric" coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet has passed through the stomach. Drug products in delayed-release dosage forms containing the same active ingredients are subject to significant differences in absorption. Unless otherwise specifically noted, the Agency 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 Agency 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; such products are coded **AB**.

BP Active ingredients and dosage forms with potential bioequivalence problems

FDA's bioequivalence regulations (21 CFR 320.33) 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 bioequivalence data are submitted, after which such products are coded **AB**. 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 products are 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, gels, lotions, oils, ointments, pastes, solutions, sprays, suppositories, and inserts 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 Agency 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 Agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence.

Description of Certain Special Situations

Certain drugs listed in the Orange Book present special situations that merit further discussion. The following are descriptions of certain examples of those special situations:

Amino Acid and Protein Hydrolysate Injections. These products differ in the amount and kinds of amino acids they contain and, therefore, are not considered pharmaceutical equivalents. For this reason, these products are not considered therapeutically equivalent. At the same time, the Agency believes that it is appropriate to point out that where nitrogen balance is the sole therapeutic objective and individual amino acid content is not a consideration, pharmaceutical alternatives with the same total amount of nitrogen content may be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

Gaviscon®. Gaviscon® is an OTC product that has been marketed since September 1970. The active ingredients in this product, aluminum hydroxide and magnesium trisilicate, were reviewed by the Agency's OTC Antacid Panel and were considered to be safe and effective ingredients (Category I) by that Panel. However, the tablet failed to pass the antacid test that is required of all antacid products. The Agency, therefore, placed the tablet in Category III for lack of effectiveness. A full NDA with clinical studies was submitted by Marion Laboratories, Inc., and approved by FDA on December 9, 1983. Gaviscon®'s activity in treating reflux acidity is made possible by the physical-chemical properties of the inactive ingredients, sodium bicarbonate and alginic acid. Therefore, *all ANDAs that cite Gaviscon® tablets as the reference listed drug must contain the inactive ingredients sodium bicarbonate and alginic acid.* A full NDA will be required to support the effectiveness of the drug product if different inactive ingredients are to be substituted for sodium bicarbonate or alginic acid or if different proportions of these ingredients are to be used.

Levothyroxine Sodium.[17] Because there are multiple reference listed drugs for levothyroxine sodium tablets and some reference listed drugs' sponsors have conducted studies to establish their drugs' therapeutic equivalence to other reference listed drugs, FDA has determined that its usual practice of assigning two or three character therapeutic equivalence codes may be potentially confusing and inadequate for these drug products. Looking at the Orange Book listing alone for a product identified as a reference listed drug or reference standard, it may be difficult to determine to which therapeutic equivalence code the reference listed drugs and/or reference standard designation corresponds. For example, Unithroid 0.3 mg strength has been assigned the therapeutic equivalence codes AB1, AB2, and AB3 and it is identified as the reference listed drug and reference standard, but it is unclear that the reference listed drug and reference standard designations are associated with the AB1 therapeutic equivalence code.

Accordingly, FDA provides the following chart, which identifies (1) a reference listed drug for each therapeutic equivalence in the Orange Book and (2) and the reference standard products in the Active Section of the Orange Book.[18]

- Therapeutic equivalence has been established between products that have the same AB+number therapeutic equivalence code (i.e. AB1, AB2, AB3 or AB4).

- More than one therapeutic equivalence code may apply to some products. One common therapeutic equivalence code indicates therapeutic equivalence between products. For example, Unithroid has been assigned therapeutic equivalence codes AB1, AB2, and AB3 therefore Unithroid tablets are considered therapeutically equivalent to other levothyroxine sodium products of the same strength with these therapeutic equivalence codes.