FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
APPROVED DRUG PRODUCTS
with
Therapeutic Equivalence Evaluations

PREFACE TO THIRTY SEVENTH~~SIXTH~~ EDITION

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). ~~Drugs on the market approved only on the basis of safety (covered by the ongoing Drug Efficacy Study Implementation [DESI] review [e.g., Donnatal® Tablets and Librax® Capsules] or pre-1938 drugs [e.g., Phenobarbital Tablets]) are not included in this publication.~~ The main criterion for the inclusion of any product is that the product is the subject of an application with an ~~effective~~ approval that has not been withdrawn for safety or efficacy reasons. Inclusion of products in~~on~~ the Orange Book~~List~~ is independent of any current regulatory action through administrative or judicial means against a drug product. In addition, the Orange Book~~List~~ 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 stating 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~~List~~ was distributed as a proposal in January l979. 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.

The therapeutic equivalence evaluations in the Orange Book~~List~~ reflect FDA's application of specific criteria to the multisource prescription drug products listed in~~on~~ the Orange Book and~~List~~ 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 code 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, October 1980, of the final version of the Orange Book~~List~~ incorporated appropriate corrections and additions. Each subsequent edition has included the 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~~1984~~ Amendments). The Hatch-Waxman~~1984~~ Amendments require that FDA, among other things, make publicly available a list of approved drug products with monthly supplements. The Orange Book~~The *Approved Drug Products with Therapeutic Equivalence Evaluations* publication~~ and its monthly Cumulative Supplements satisfy this requirement. The *Addendum* to this publication identifies drugs that qualify under the FD&C Act for periods of exclusivity~~1984 Amendments for periods of exclusivity (during which ANDAs or applications described in Section 505(b) (2) of the FD&C Act for those drugs may not be submitted for a specified period of time and, if allowed to be submitted, would be tentatively approved)~~ and provides patent information concerning the listed drugs which also may delay the approval of ANDAs or ~~Section~~ 505(b)(2) applications. The *Addendum* also provides additional information that may be helpful to those submitting a new drug application 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 Director, Division of Legal and~~&~~ Regulatory Support, Office of Generic Drug Policy, Office of Generic Drugs, Center for Drug~~ and~~ Evaluation and Research, 7620 Standish Place, Rockville, MD 20855-2773. Comments received are publicly available to the extent allowable under the Freedom of Information Act and FDA regulations.

1. INTRODUCTION

1.1 Content and Exclusion

The Orange Book~~List~~ 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 for safety or effectiveness reasons, or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing.[11] This publication also includes indices of prescription and OTC drug products by trade name (proprietary name)or established name (if no trade name exists) and by applicant name (holder of the approved application). All established names for active ingredients generally conform to official compendial names or *United States Adopted Names* (USAN) as described in (21 CFR 299.4(e)). The latter list includes applicants' names as abbreviated in this publication; in addition, a list of uniform terms is provided in Appendix C.

An *Addendum* contains ~~drug~~ 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~~1984~~ 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~~List~~. Tentative approval lists are available on FDA's website at Drug Approval Reports. When the tentative approval becomes a final~~full~~ approval through a subsequent action letter to the applicant, the Agency will list the drug product and the date of~~final~~ approval ~~date~~ in the appropriate approved drug product list.

Distributors or repackagers of products listed in~~on~~ the Orange Book~~List~~ are not identified. Because distributors or repackagers are not required to notify FDA when they shift their sources of supply from one approved manufacturer to another, it is not possible to maintain complete information linking product approval with the distributor or repackager handling the products.

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[1] Newly approved products are added to parts 1, 2, or 3, of the Orange Book, depending on the dispensing requirements (prescription or OTC) or approval authority, unless the Orange Book staff is otherwise notified before publication.

1.2 Therapeutic Equivalence-Related Terms

Pharmaceutical Equivalents. Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are ~~identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules). Pharmaceutically equivalent drug products are~~ formulated to contain the same amount of active ingredient~~, in the same dosage form~~ and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity~~), but t~~). They may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.

Pharmaceutical Alternatives. Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules). Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate-release or standard-release formulations of the same active ingredient.

Therapeutic Equivalents. Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents for which bioequivalence has been demonstrated, and~~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.

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., meperidine hydrochloride vs. morphine sulfate for the treatment of pain)*. Any drug product in the Orange Book~~List~~ 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).** Also, distributors or repackagers of an applicant's drug product are considered to have the same code as the applicant~~. Therapeutic equivalence determinations are not made for unapproved, off-label uses~~.

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 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 will produce the same clinical effect and safety profile as the prescribed product.

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). ~~***Strength***. Strength refers to the amount of drug substance (active ingredient) contained in, delivered, or deliverable from a drug product.~~ 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~~List~~, but rather intends to apply the criteria prospectively to drug products added to the Orange Book~~List~~.

The strength of drug products in the Orange Book~~List~~ is generally expressed in terms of the amount of drug substance (active ingredient) in the drug product, but is sometimes expressed in terms of the amount of the active moiety. For example, certain drug products included in the Orange Book~~List~~ 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 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 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.

Bioequivalent Drug Products This term describes pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions. Section 505 (j)(8)(B) of the FD&C Act describes one set of conditions under which a test and reference listed drug (see Section 1.4) shall be considered bioequivalent:

> the rate and extent of absorption of the [test] drug do not show a significant difference from the rate and extent of absorption of the [reference] drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or
>
> the extent of absorption of the [test] drug does not show a significant difference from the extent of absorption of the [reference] drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the [reference] drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

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.

1.3 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.[22]

1.4 Reference Listed Drug and Reference Standard

A reference listed drug (21 CFR 314.~~94(a) (~~3(b)) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. 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. 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. FDA generally selects a single reference standard that ANDA applicants must use in *in vivo* bioequivalence testing. Ordinarily, FDA will select

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[2] We note that prior editions of the Preface to the Orange Book included a section entitled "Statistical Criteria for Bioequivalence." Please see FDA's regulations and guidance documents for additional information regarding bioequivalence and bioavailability. See FDA Drugs guidance Web page athttp://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm; FDA Drugs guidance (Product-Specific Recommendations for Generic Drug Development) Web page athttp://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm; see generally 21 CFR part 320.

the reference listed drug as the reference standard. However, in some instances (e.g., where the reference listed drug has been withdrawn from sale and an ANDA is selected as the reference standard), the reference listed drug and the reference standard may be different.

FDA has identified reference listed drugs in the Prescription Drug Product and OTC Drug Product Lists. Forthcoming, FDA will identify ~~those~~ reference listed drugs in the Discontinued Drug Product List. These identified reference listed drugs represent drug products upon~~to~~ 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.

FDA also has identified in the Prescription Drug Product and OTC Drug Product Lists reference standards to which the *in vivo* bioequivalence ~~(reference standard) and, in some instances, the *in vitro* bioequivalence of the applicant's product~~ is compared. These identified~~By designating a single~~ reference standards represent~~listed drug as~~ the FDA's best judgment at this time as~~standard to which all generic versions must be shown~~ to the appropriate comparator for purposes of in vivo bioequivalence testing~~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 drugs~~.

~~However, i~~In some instances when a listed drug is not designated as a~~the reference listed drug and/or not shown to be bioequivalent to the~~ reference listed drug, such listed drug may be shielded from generic competition. If FDA has not ~~An applicant wishing to market a generic version of a listed drug that is not~~ designated ~~as the reference listed drug may petition the Agency through the citizen petition procedure (see 21 CFR 10.25(~~a reference listed drug for a drug product the applicant intends to duplicate, the potential applicant may ask FDA to designate a reference listed drug for that drug product. Potential applicants should consult agency guidance related to referencing ~~) and CFR 10.30). If the citizen petition is~~ approved drug products in ANDA submissions for information on submitting such a request. If the request is granted, the listed drug will be designated as a~~an additional~~ reference listed drug, in which case an ANDA citing the designated reference listed drug may be submitted. 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 reference listed drugs.

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 potential applicants have adequate information required for *in vivo* bioequivalence studies, e.g., in the event that the listed drug currently selected as the reference standard has been withdrawn from sale for other than safety and efficacy reasons. Historically~~In addition~~, there we~~a~~re two situations in which two listed drugs that had~~ve~~ been shown to be bioequivalent to each other had~~ve~~ both been identified by the symbol "+" in the Orange Book.~~designated as reference listed drugs.~~ The first situation was~~is~~ when the in vivo determination of bioequivalence is self-evident and a waiver of any *in vivo* bioequivalence may be granted. The second situation was~~is~~ when the bioequivalence of two listed products may be determined through *in vitro* methodology.

If an applicant has a question related to the appropriate reference standard, ~~Reference listed drugs are identified by the symbol "+" in thePrescription and Over-the-Counter (OTC) Drug Product Lists. These identified reference listed drugs represent the best judgment of the Office of Bioequivalence at this time. The Prescription and OTC Drug Product Lists identify reference drugs for approved drug products.~~ It is recommended that an applicant planning to conduct an *in vivo* bioequivalence study~~, or planning to manufacture a batch of a drug product for which an *in vivo* waiver of bioequivalence will be requested,~~ submit a controlled correspondence to the Office of Generic Drugs~~ to confirm the appropriate reference listed drug~~.

1.5 General Policies and Legal Status

The Orange Book~~List~~ 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~~List~~ 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, intended to reduce the cost of drugs to consumers. To the extent that the Orange Book~~List~~ 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~~List~~ does not necessarily mean that the drug product is either in violation of Section 505 of the FD&C Act, ~~or~~ 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 is based on the fact that FDA has not evaluated the safety, effectiveness, and quality of the drug product.

1.6 Practitioner/User Responsibilities

Professional care and judgment should be exercised in using the Orange Book~~List~~. 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 equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling. However, these products may differ in other characteristics 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 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. For example, there may also be allergic reactions in rare cases due to a coloring or a preservative ingredient, as well as differences in cost to the patient.

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 physician's specification of that product is appropriate. Pharmacists must also be familiar with the expiration dates/times and labeling directions for storage of the different products, particularly for reconstituted products, to assure that patients are properly advised 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 is included and, in addition, 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~~on~~ the Orange Book~~List~~, but no therapeutic equivalence code is included with such products. Any drug product in the Orange Book~~List~~ repackaged and/or distributed by other than 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 nonequivalent~~non-equivalent~~ (e.g., **BN**). Also, although not identified in the Orange Book~~List~~, distributors or repackagers of an applicant's drug product are considered to have the same code as the applicant. The details of these codes and the policies underlying them are discussed in Section 1.7, *Therapeutic Equivalence Evaluations Codes*.

Products in~~on~~ the Orange Book~~List~~ 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. 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 many 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.

Although the products in~~on~~ the Orange Book~~List~~ are identified by the names of the applicants, circumstances, such as changing corporate ownership, have sometimes made identification of the applicant difficult. The Agency believes, based on continuing document review and communication with firms, that the applicant designations in the Orange Book are, in most cases, correct.

To relate firm name information on a product label to that in~~on~~ the Orange Book~~List~~, the following should be noted: the applicant's name always appears in~~on~~ the Orange Book~~List~~. This applies whether the applicant (firm name on the Form FDA 356h in the application) is the marketer (firm name in largest letters on the label) or not. However, the applicant's name may not always appear on the label of the product.

If the applicant is the marketer, its name appears in~~on~~ the Orange Book~~List~~ and on the label; if the applicant is not the marketer, and the Agency is aware of a corporate relationship (e.g., parent and subsidiary) between the applicant and the marketer, the name of the applicant appears in~~on~~ the Orange Book~~List~~ and both firm names may appear on the label. Firms with known corporate relationships are displayed in Appendix B. If there is no known corporate relationship between the applicant and the marketer, the applicant's name appears in~~on~~ the Orange Book~~List~~; however, unless the

applicant is the manufacturer, packager, or distributor, the applicant's name may not appear on the label. In this case, the practitioner, from labeling alone, will not be able to relate the marketed product to an applicant cited in the Orange Book~~List~~, and hence to a specific approved drug product. In such cases, to assure that the product in question is the subject of an approved application, the firm named on the label should be contacted.

To relate trade name (proprietary name) information on a product label to that in~~on~~ the Orange Book~~List~~, the following should be noted: if the applicant is the marketer, its name appears in~~on~~ the Orange Book~~List~~ and on the label; if the Agency is aware of a corporate relationship between the applicant and the marketer, the trade name (proprietary name) of the drug product (established name of the active ingredient, if no trade name exists) appears in~~on~~ the Orange Book~~List~~. If a corporate relationship exists between an applicant and a marketer and both firms are distributing the drug product, the FDA reserves the right to select the trade name of either the marketer or the applicant to appear in~~on~~ the Orange Book~~List~~. If there is no known corporate relationship between the applicant and the marketer, the established drug name (i.e., non-proprietary name) appears in~~on~~ the Orange Book~~List~~.

Every product in~~on~~ the Orange Book~~List~~ 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~~on~~ the Orange Book~~List~~. The main criterion for inclusion of a product is that it has an application that has been approved and~~with an effective approval~~ that has not been withdrawn for safety or efficacy reasons. FDA believes that retention of a violative product in~~on~~ the Orange Book~~List~~ 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 ~~data upon which the~~ Agency's assessment of whether a product meets the criteria for therapeutic equivalence~~ was made~~.

1.7 Therapeutic Equivalence Evaluations Codes

The coding system for therapeutic equivalence evaluations is constructed to allow users to determine quickly whether the Agency 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 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 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

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 presumed and considered self-evident based on other data in the application for some dosage forms (e.g., solutions) or satisfied 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 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 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 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 rare instances, there may be variations among therapeutically equivalent products in their use or in conditions of administration. Such differences may be due to patent or exclusivity rights associated with such use. 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.

Also, 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 may differ among some therapeutically equivalent drug products. Differences in preservatives and other inactive ingredients 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

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 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. Two or more reference listed drugs are generally selected only when there are at least two potential reference listed drug products that are not identified as 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 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~~List~~, 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~~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 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~~on~~ the Orange Book~~List~~ (e.g., dextrose injection 5%, dextrose injection 10%, sodium chloride injection 0.9%) since these products are on the market without FDA approval and the 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.[33] 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 xmg/mL. Generally, ~~T~~the amount of dry powder or lyophilized~~freeze dried~~ powder in a container is~~has always been~~ identified as the strength, expressed as xmg/vial.

With the finalization of the Hatch-Waxman~~1984~~ Amendments that characterized each strength of a drug product as a listed drug, it became evident that the format of the Orange Book should be changed to reflect each strength of a parenteral solution. To this end, the Orange Book now displays the strength of all new approvals of parenteral solutions. Previously, we would have displayed only the concentration of an approved parenteral solution, e.g. 50mg/mL. If this drug product had a 20 mL and 60 mL container approved, we would now display two product strengths for this product, listing both total drug content and concentration of drug substance in the relevant approved container, e.g. 1Gm / 20mL (50mg/mL) and 3Gm / 60mL (50mg/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 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.

[3] The strengths of certain parenteral drug products, including contrast agents, may be expressed as a percentage.

"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~~medicament~~ 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 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 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.

1.8 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 considered therapeutically equivalent.

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. Because there are multiple reference listed drugs of 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 TE codes may be potentially confusing and inadequate for these drug products. Accordingly, FDA provides the following explanation and chart of therapeutic equivalence evaluations for levothyroxine sodium drug products.

Levothyroxine Sodium (Mylan ANDA 076187), Levoxyl (King Pharms NDA 021301), Synthroid (Abbvie NDA 021402), and Levo-T (Alara NDA 021342) tablets have been determined to be therapeutically equivalent to corresponding strengths of Unithroid (Jerome Stevens NDA 021210) tablets.[4]

Levo-T (Alara NDA 021342), Levothyroxine Sodium (Mylan ANDA 076187), and Unithroid (Jerome Stevens NDA 021210)~~,~~ tablets have been determined to be therapeutically equivalent to corresponding strengths of Synthroid (Abbvie NDA 021402) tablets.

Levo-T (Alara NDA 021342), Unithroid (Jerome Stevens NDA 021210), and Levothyroxine Sodium (Mylan ANDA 076187)~~,~~ tablets have been determined to be therapeutically equivalent to corresponding strengths of Levoxyl (King Pharms NDA 021301) tablets.

Levothyroxine Sodium (Mylan ANDA 076187) tablets have been determined to be therapeutically equivalent to corresponding strengths of Levothroid (Lloyd NDA 021116) tablets.[4] The chart outlines TE codes for all 0.025 mg products in the active section of the Orange Book. Other product strengths may be similar. Therapeutic equivalence has been established between products that have the same AB+number TE code. More than one TE code may apply to some products. One common TE code indicates therapeutic equivalence between products.

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[4] Lloyd's Levothroid tablets (NDA 021116) is currently listed in the Discontinued Drug Product List section of the Orange Book and Mylan's levothyroxine product (ANDA 076187) has been selected as the reference standard for ANDA applicants to use to establish bioequivalence to Levothroid. If an ANDA that uses Mylan's levothyroxine product as its reference standard is approved, the ANDA will receive an AB4 rating. The ANDA applicant also may obtain an AB rating for its product to the other reference listed drugs (i.e., Unithroid, Synthroid, and Levoxyl) by submitting supplements that demonstrate that the generic product is bioequivalent to these other reference listed drugs and satisfies all other therapeutic equivalence criteria with respect to these reference listed drugs. See Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA to Teri Nataline, Principal Consultant, Lachman Consultant Services, Inc., Docket No. FDA-2015-P-0403 (May 27, 2016).

Trade Name	Applicant	Strength	TE Code	Appl No	Product No
UNITHROID	STEVENS J	0.025MG	AB1	021210	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB1	076187	001
LEVOXYL	KING PHARMS	0.025MG	AB1	021301	001
SYNTHROID	ABBVIE	0.025MG	AB1	021402	001
LEVO-T	ALARA PHARM	0.025MG	AB1	021342	001
SYNTHROID	ABBVIE	0.025MG	AB2	021402	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB2	076187	001
LEVO-T	ALARA PHARM	0.025MG	AB2	021342	001
UNITHROID	STEVENS J	0.025MG	AB2	021210	001
LEVOXYL	KING PHARMS	0.025MG	AB3	021301	001
LEVO-T	ALARA PHARM	0.025MG	AB3	021342	001
UNITHROID	STEVENS J	0.025MG	AB3	021210	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB3	076187	001
LEVOTHROID	LLOYD	0.025MG	N/A[5]	021116	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB4	076187	001

Patent Certification(s) and Reference Standard~~Listed Drug~~ based upon a suitability petition. An ANDA that utilizes as~~refers to~~ a reference standard a product~~listed drug~~ approved pursuant to a suitability petition must demonstrate that the proposed product can be expected to have the same therapeutic effect as the reference listed drug.~~, and~~ I~~i~~t must include appropriate patent certification(s) and an exclusivity statement with respect to the reference listed drug that served as the basis for the approved suitability petition. (This concept also generally applies to an ANDA applicant that utilizes a reference standard that is not~~cites~~ a reference listed drug, i.e., such~~ that was based upon~~ an application must include appropriate~~NDA that is still covered by~~ patent certification(s) and an~~/or~~ exclusivity statement with respect to the reference listed drug.)~~, e.g. a second RLD selected for use in conducting bioequivalence studies.~~

Waived exclusivity. If an NDA submitted under section 505(b) of the FD&C Act qualifies for exclusivity under the FD&C Act, the exclusivity is generally listed in the Patent and Exclusivity Section of the Orange Book. If a drug product has received this exclusivity, the FDA will not accept for review and/or will not approve~~delay the approval of~~ a 505(b)(2) application or an ANDA under section 505(j) of the FD&C Act, as applicable, in accordance with the relevant exclusivity. If the listed drug is also protected by one or

[5] Levothroid is in the Discontinued Drug Product List and therefore no longer is assigned a TE code.

more patents, the approval date for the ANDA or 505(b)(2) application ~~or ANDA~~ will be determined by~~based on an~~ analysis of the applicant's patent certification(s) or statement(s) for each relevant patent and the effect of relevant exclusivity listed in the Orange Book. However, the holder of the NDA may waive its exclusivity as to any or all ANDAs and 505(b) (2) ~~and ANDA~~ applications that might otherwise be blocked by such exclusivity~~NDA~~. If an NDA sponsor waives its right to the exclusivity protection, qualified ANDAs or 505(b)(2) ~~or ANDA~~ applications may be accepted for review and/or approved, as applicable, pursuant to the NDA holder's exclusivity being waived. An NDA for which the holder has waived its exclusivity as to all ANDAs and 505(b)(2) ~~and ANDA~~ applications will be coded with a "W" in the Patent and Exclusivity Section of the Orange Book. The applicant whose product might otherwise be blocked by this exclusivity~~listed drug~~ should indicate in the exclusivity statement in its application that the holder of the listed drug has waived its exclusivity.

1.9 Therapeutic Equivalence Code Change for a Drug Entity

The Agency will use the following procedures when, in response to a petition or on its own initiative, it is considering a change in the therapeutic equivalence code for approved multisource drug products. Such changes will generally occur when the Agency becomes aware of new scientific information affecting the therapeutic equivalence of an entire category of drug products in the Orange Book~~List~~ (e.g., information concerning the active ingredient or the dosage form), rather than information concerning a single drug product within the category. These procedures will be used when a change in therapeutic equivalence code is under consideration for all drug products found in the Prescription Drug Product List under a specific drug entity and dosage form. The change may be from the code signifying that the drug does not present a bioequivalence problem (e.g., **AA**) to a code signifying an actual or potential~~a~~ bioequivalence problem (e.g., **BP**), or vice versa. This procedure does not apply to a change of a particular product code (e.g., a change from **BP** to **AB** or from **AB** to **BX**).

Before making a change in a therapeutic equivalence code for an entire category of drugs, the Agency will announce in the *Introduction* to the Cumulative Supplement that it is considering the change and will invite comment. Comments, along with scientific data, may be sent to the Director, Office of Bioequivalence, Office of Generic Drugs, Center for Drug Evaluation and Research, HFD-650, 7620 Standish Place, Rockville, MD 20855.

The comment period will generally be 60 days in length, and the closing date for comments will be listed in the description of the proposed change for each drug entity.

The most useful type of scientific data submitted to support comments is an *in vivo* bioavailability/bioequivalence study conducted on batches of the subject drug products. These submissions should present a full description of the analytical procedures and equipment used, a validation of the analytical methodology, including the standard curve, a description of the method of calculating results, and a description of the pharmacokinetic and statistical models used in analyzing the data. Anecdotal or testimonial information is the least useful to the Agency, and such submissions are discouraged. Copies of supporting reports published in the scientific literature or unpublished material, however, are welcome.

1.10 Change of the Therapeutic Equivalence Evaluation for a Single Product

The aforementioned procedure described in Section 1.9 does not apply to a change in a single drug product code. For example, a change in a single drug product's code from **BP** to **AB** as a result of the submission of an acceptable bioequivalence study ordinarily will not be the subject of notice and comment in the Cumulative Supplement. Likewise, a change in a single drug product's code from **AB** to **BX** (e.g., as a result of new information raising a significant question as to bioequivalence) does not require notice and comment. The Agency's responsibility to provide the public with the Agency's most current information related to therapeutic equivalence may require a change in a drug product's code prior to any formal notice and opportunity for the applicant to be heard. The publication in the *Federal Register* of a proposal to withdraw approval of a drug product will ordinarily result in a change in a product's code from **AB** to **BX** if this action has not already been taken.

We recognize that certain drug products approved in 505(b) (2) applications may not have therapeutic equivalence codes, and that FDA may undertake therapeutic equivalence evaluations with respect to such drug products. A person seeking to have a therapeutic equivalence rating for a drug product approved in a 505(b) (2) application may petition the Agency through the citizen petition procedure (see 21 CFR 10.25(a) and 21 CFR 10.30).

1.11 Discontinued Section

Those drug products in the discontinued section of the Orange Book (Discontinued Drug Product List) for which a determination has already been made that the products were not withdrawn for safety or effectiveness reasons have “**Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**” following the product strength. The determinations listed in Orange Book~~Those drug products~~ are only reflective of determinations made since 1995 and published in the Federal Register. The identification of these drug products in the Discontinued Drug Product List should avoid the submission of multiple citizen petitions for the same drug product. ~~FR notices no longer applicable are removed from the Annual Edition (i.e., there is a currently marketed reference listed drug and no applicable patent or exclusivity).~~ The Orange Book FR Safety or Effectiveness Determinations List, available on FDA’s website, lists products that have ~~current and removed~~ notices. The list is updated quarterly. Notices issued during the year routinely are added to the Electronic Orange Book Query ~~–~~on FDA’s website~~ in the month they become effective~~.

Generally, approved products are added to the Discontinued Drug Product List when the applicant notifies the Orange Book staff of the products’~~'~~ not-marketed status. Products may also be added to the Discontinued Drug Product List if annual reports indicate the product is no longer marketed or as a result of other Agency administrative actions. Changes to the Orange Book are not affected by the drug registration and listing requirements of Section 510 of the FD&C Act.

1.12 Changes to the Orange Book

Every effort is made to ensure the Annual Edition is current and accurate. Applicants are requested to inform the FDA Orange Book staff of any changes or corrections, including any change in a product’s marketing status that would result in the product being moved to the Discontinued Drug Product List. FDA notes that 21 CFR 314.81(b)(3)(iv) requires an applicant to submit

a notice to the Agency within fifteen working days of the withdrawal from sale of a drug product. In addition, a request to include a newly approved product in the Discontinued Drug Product List, rather than parts 1, 2 or 3 of the Orange Book~~List~~ (as discussed in Section 1.1), must be submitted to the Orange Book staff by the end of the month in which the product is approved to ensure that the product is not included in the "active" portions of the next published Orange Book update. To the extent that conventions for describing product identification information (i.e., active ingredients, dosage forms, routes of administration, product names, applicants, strengths) evolve over time, the Agency generally does not intend to revise such information for drug products already included in the Orange Book~~List~~, but rather intends to apply the change prospectively to drug products added to the Orange Book~~List~~.

We can be contacted by email at orangebook@fda.hhs.gov. Send Changes by mail to:

FDA/CDER Orange Book Staff
Office of Generic Drug Policy
Office of Generic Drugs
7620 Standish Place
Rockville, MD 20855-2773

1.13 Availability of the Edition

Commencing with the 25th edition, the Annual Edition and current monthly Cumulative Supplement are available in a Portable Document Format (PDF) at the EOB home page, Electronic Orange Book~~ Query~~, by clicking on Publications. The PDF annual format duplicates previous paper versions except for the Orphan Products Designations and Approvals List. An annual subscription of the PDF format may be obtained from the U.S. Government Publishing~~Printing~~ Office, 866-512-1800.

PATENT AND EXCLUSIVITY INFORMATION ADDENDUM

This *Addendum* identifies drugs that qualify under the Drug Price Competition and Patent Term Restoration Act of ~~(~~1984 (Hatch-Waxman Amendments) for periods of exclusivity and provides patent information concerning the listed drug products. During exclusivity periods, certain~~,~~ ~~during which~~ abbreviated new drug applications (ANDAs) and applications described in Section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act (~~the~~ FD&C Act) (505(b)(2) applications) for those drug products ~~may,~~ in some instances may~~,~~ not be submitted or approved~~made effective~~ as described below~~, and provides patent information concerning the listed drug products~~. Those drugs that have qualified for Orphan Drug Exclusivity pursuant to Section 527 of the FD&C Act, those drugs that have qualified for Pediatric Exclusivity pursuant to Section 505A of the FD&C Act, and those drugs that have qualified for Generating Antibiotics Incentives Now (GAIN) exclusivity pursuant to Section 505E of the FD&C Act are also included in this *Addendum*. This section is arranged in alphabetical order by active ingredient name followed by the trade name. Active ingredient headings for multiple ingredient fixed-~~(~~combination~~)~~ drug products are arranged alphabetically. For an explanation of the codes used in the *Addendum*, see the *Patent and Exclusivity Terms* Section. The exclusivity codes are general shorthand descriptions and do not necessarily identify, with specificity, the actual scope of exclusivity. These exclusivities do ~~Exclusivity prevents the submission or effective approval of ANDAs or applications described in Section 505(b) (2) of the FD&C Act. It does~~ not prevent the submission or approval of an ~~a second 505(b) (1)~~ application submitted pursuant to Section 505(b)(1) of the FD&C Act that would otherwise be blocked if it had been submitted pursuant to Section 505(b)(2) or 505(j), except in the case of Orphan Drug exclusivity. Drugs that may qualify~~Applications qualifying~~ for periods of exclusivity include:

(1) A new chemical entity, submitted in~~(1)~~ A new drug application under section 505(b) of the FD&C Act and approved after September 24, 1984. A new chemical entity is an active ingredient that contains "no active ingredient~~, for a drug product~~ (including any ester or salt of the active ingredient)" that~~) of which~~ has ~~never~~ been approved by FDA in any other ~~new drug~~ application submitted under Section 505 (b) of the FD&C Act. No subsequent ANDA or 505(b) (2) application for a drug that contains~~described in Section 505(b) (2) of the FD&C Act for~~ the same "active ingredient (including any ester or salt of the active ingredient)"~~drug~~ may be *submitted* for a period of *five years* from the date of approval of the original application, except that such an application may be *submitted* after *four years* if it contains a certification that a patent claiming the drug is invalid or will not be infringed by the product for which approval is sought. See sections 505(j)(5)(F)(ii) and 505(c)(3)(E)(ii) of the FD&C Act.

(2) A new drug application approved after September 24, 1984, for a drug product containing "an active ingredient (including any ester or salt of the~~at~~ active ingredient)"~~)~~ that has been approved in an earlier new drug application and that includes reports of new clinical investigations (other than bioavailability studies). Such investigations must have been conducted or sponsored by the applicant and must have been essential to approval of the application. If these requirements are met, a subsequent ANDA or a 505(b)(2) application may

not be approved for the exclusivity-protected "conditions of approval of such drug" before the expiration of *three years* from the date of approval of the original application. If a NDA or 505(b)(2) applicant has exclusivity only for a new indication or use, this exclusivity generally does not preclude the approval of an ANDA or 505(b) (2) application for indications and uses not covered by the exclusivity, assuming the~~the approval of a subsequent ANDA or an application described in Section 505(b) (2) of the FD&C Act may not be *made effective* for the same~~ proposed drug product will be safe and effective as labeled. See sections 505(j)(5)(F)(iii) and 505(c)(3)(E)(iii) of the FD&C Act.
~~drug or use, if for a new indication, before the expiration of *three years* from the date of approval of the original application. If an applicant has exclusivity for a new application or 505(b)(2) application for the drug product with indications or use, this does not preclude the approval of an ANDA or 505(b) (2) application not covered by the exclusivity.~~

(3) A supplement to a new drug application for a drug containing a previously approved "active ingredient (including ~~(~~any ester or salt of the active ingredient)"~~)~~ approved after September 24, 1984, that contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the applicant. ~~The approval of~~ a subsequent ANDA or 505(b)(2) application may not be approved for an exclusivity-protected change approved in the ~~505(b) (2) application for a change approved in the~~ supplement ~~may not be *made effective*~~ for *three years* from the date of approval of the original supplement. See sections 505(j)(5)(F)(iv) and 505(c)(3)(E)(iv) of the FD&C Act.

The FD&C Act requires that patent information be filed with all newly submitted Section 505(b) drug applications. No NDA may be approved after September 24, 1984, without the submission of patent information to the Agency. Effective August 18, 2003, this information must be filed using ~~FDA~~ Form FDA 3542a ~~3524a~~ "Patent Information Submitted with the Filing of an NDA, Amendment or Supplement".

Effective August 18, 2003, upon approval of an application, patent information for purposes of listing in the Orange Book must be submitted to the Agency within 30 days of the date of approval on ~~FDA~~ Form FDA 3542 "Patent Information Submitted Upon and After Approval of an NDA or Supplement." Please note that the date of approval for an NDA for which FDA recommends controls under the Controlled Substances Act is the later of the date on the approval letter for the NDA or the date of issuance of the interim final rule controlling the drug (see section 505(x)(1) and (2) of the FD&C Act). Patent information on unapproved applications or on patents beyond the scope of the FD&C Act (i.e., process or manufacturing patents) will not be published. ~~FDA~~ Form FDA 3542 will be the only form used for the purposes of this publication.

The patents that FDA regards as covered by the statutory provisions for submission of patent information are: patents that claim the active ingredient(s); drug product patents, which include formulation/composition patents; method-of-use patents that claim one or more~~for a particular~~ approved methods~~indication or method~~ of using the approved drug product; and certain other patents as detailed on ~~FDA~~ Form FDA 3542. This information, as provided by the sponsor on ~~FDA~~ Form FDA 3542, will be published as described above. As of December 5, 2016, an NDA holder submitting information on a

patent that claims both the drug substance and the drug product (and is eligible for listing on either basis) is required only to specify that the patent claims either the drug substance or the drug product.

A requirement for submission of patent information to FDA for certain old antibiotics became effective October 7, 2008 under section 4(b)(1) of the QI Program Supplemental Funding Act (Public Law 110-379) (QI Act). ~~A guidance for industry on this subject is available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080566.pdf.~~

Upon approval, patent numbers and expiration dates, in addition to certain other information on appropriate patents claiming drug products that are the subject of approved applications, will be published daily in the Electronic Orange Book ~~Query~~. The Addendum lists patent and exclusivity information up to January of the Edition year. The monthly Cumulative Supplements to the annual edition list patent and exclusivity information changes since the Annual Edition Addendum. Since all parts of this publication are subject to changes, additions, or deletions, the Electronic Orange Book, updated daily, should be consulted for the most recent patent and exclusivity information.