

# Guidance for Industry

## Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling

### *DRAFT GUIDANCE*

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
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## **Guidance for Industry<sup>1</sup>**

### **Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling**

#### **I. INTRODUCTION**

This draft guidance is intended to clarify for drug product applicants, repackers, and distributors FDA's position regarding placing the therapeutic equivalence code on approved FDA drug product labels and labeling. Using therapeutic equivalence codes to describe equivalence or inequivalence will contribute to the accurate and safe selection of drug products by health care practitioners.

This draft guidance (1) provides an historical perspective on therapeutic equivalence, (2) describes how the Agency advises the public on the therapeutic equivalence or inequivalence of approved drug products, and (3) advises applicants, repackers, and distributors of the preferred format and placement of such information on product labels. Although inclusion of a therapeutic equivalence code on prescription drug labels/labeling is voluntary, in certain cases where safety issues are raised, the Agency may ask that a therapeutic equivalence code be included.

#### **II. BACKGROUND**

The approval of generic versions of multiple-source, inequivalent,<sup>2</sup> reference listed drug products, with identical active ingredient(s), dosage form, strength, and route(s) of administration has raised potential safety concerns for the Agency. When multiple reference listed products exist with the same established names and strengths, chances increase that a generic product will be dispensed to a patient that is not therapeutically equivalent to the one intended or previously prescribed. For

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<sup>1</sup> This draft guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This draft guidance represents the Agency's current thinking on placing the therapeutic equivalence code on the labels and labeling of prescription drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

<sup>2</sup> The term *multiple source* refers to innovator products that are produced by multiple manufacturers and are *inequivalent* for any one of a number of reasons (e.g., the products have different release times).

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example, four inequivalent reference listed products exist for Diltiazem extended-release capsules, each of which has overlapping strengths with the same established name.

In the *Federal Register* of January 12, 1979 (44 FR 2932), the Agency proposed making publicly available the *Approved Prescription Drug Products with Therapeutic Equivalence Evaluations List* (hereinafter referred to as the *Orange Book*), which lists approved FDA drug products together with the therapeutic equivalence evaluations of prescription products that are available from more than one source. Two comments received on this proposal questioned the legality of using therapeutic equivalence evaluations from the *Orange Book* to indicate in drug product labeling and advertising that one drug product may be safely interchanged with another drug product. In addition, the Agency received an inquiry from a drug manufacturer who expressed interest in including such a claim on a drug product's label and/or labeling. In response to each of these questions, the Agency explained at the time that it had not yet developed a position on the issue.

Because the Agency believes that drug products in the *Orange Book* evaluated as therapeutically equivalent can be expected to have the same therapeutic effect when administered under the conditions specified in the labeling, the Agency announced in the *Federal Register* of October 31, 1980 (45 FR 72582) that it was making the *Orange Book* publicly available.

In 1984, the Drug Price Competition and Patent Term Restoration Act (the 1984 amendments) authorized the submission of abbreviated new drug applications (ANDAs) for generic versions of *innovator* or *pioneer* drugs that were first approved after 1962. The 1984 amendments authorized FDA to approve generic versions of approved drug products that have been shown through the ANDA review process to be the same as the pioneer drug product. For most drug products, the 1984 amendments require each ANDA applicant to provide information demonstrating, among other things, that (1) the conditions of use prescribed, recommended, or suggested in the labeling for its proposed product have been previously approved for the pioneer product; (2) the active ingredient in the proposed drug product is the same as that in the pioneer product, or, if the product has more than one active ingredient, that the active ingredients are the same as the active ingredients in the pioneer drug; (3) the route of administration, dosage form, and strength of the proposed drug product are the same as those of the pioneer product; (4) the proposed drug product is bioequivalent to the pioneer product; and (5) the labeling for the proposed drug product is the same as that for the pioneer product (21 U.S.C. 355(j)(2)(A)). The 1984 amendments did not specifically require the labeling of a generic product to contain information as to the product's therapeutic equivalence evaluation.

In the past several years, the Agency has received a number of requests from manufacturers of generic products to place the therapeutic equivalence rating and the name of the therapeutically equivalent reference listed product on the label of the product. The Agency has considered these requests and has concluded that using therapeutic equivalence ratings in the label and labeling is in the best interest of the public health.

### **III. WHAT IS THERAPEUTIC EQUIVALENCE?**

As described in the *Orange Book*, FDA considers products to be therapeutically equivalent if they meet the criteria outlined below, even though they may differ in certain other characteristics such as shape, scoring configuration, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information). When such differences are important in the care of a particular patient, the prescribing physician may want to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product as labeled will produce the same clinical effect and safety profile as the prescribed product. For an additional discussion of therapeutic equivalence, see the introduction to the 18th edition of the *Orange Book*.

The FDA classifies drug products to be therapeutically equivalent if they meet the following criteria:

1. They are approved as safe and effective.
2. They are pharmaceutically equivalent in that they
  - contain identical amounts of the same active ingredient in the same dosage form and route of administration, and
  - meet compendial or other applicable standards of strength, quality, purity, and identity.
3. They are bioequivalent in that they
  - do not present a known or potential bioequivalence problem and they meet an acceptable in vitro standard, or
  - if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard.
4. They are adequately labeled.
5. They are manufactured in compliance with current good manufacturing practice regulations.

The concept of therapeutic equivalence, as used in the *Orange Book*, applies only to drug products containing the same active ingredients and does not encompass a comparison of different therapeutic agents used for the same condition. As the introduction to the *Orange Book* explains, any drug product in the *Orange Book* repackaged and/or distributed by someone other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single source or is coded as inequivalent (e.g., *B* - see discussion below).

### **IV. THE EQUIVALENCE CODING SYSTEM**

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The coding system used in the *Orange Book* for therapeutic equivalence evaluations is designed 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).

If FDA considers a drug product to be therapeutically equivalent to other pharmaceutically equivalent drug products, the first letter in the two-letter coding system will be *A*. If there is no known or suspected bioequivalence problem, the second letter will be *A*, *N*, *O*, *P*, or *T*, depending on the dosage form involved or whether actual or potential bioequivalence problems have been resolved. For example, an *AA* code denotes therapeutically equivalent products in conventional dosage forms that do not present actual or potential bioequivalence problems or drug quality or standards issues. An *AN* code denotes therapeutically equivalent solutions and powders for aerosolization. An *AT* code denotes therapeutically equivalent topical products. If actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence, the second letter will be *B*, resulting in a two-letter code of *AB*.

If FDA does not consider the drug product to be therapeutically equivalent to other pharmaceutically equivalent drug products, the first letter in the two-letter code will be *B*. The second letter may be *C*, *D*, *E*, *N*, *P*, *R*, *S*, *T*, or *X*, depending on the dosage form involved. For example, a *BC* code denotes an extended-release tablet, capsule, or injectable product that FDA does not consider to be therapeutically equivalent. A *BD* code denotes a product that FDA does not consider to be therapeutically equivalent because the active ingredients or dosage forms have documented bioequivalence problems, and adequate studies demonstrating bioequivalence have not been submitted to the FDA. A *BN* code denotes a product in metered dose aerosol-nebulizer drug delivery systems that FDA does not consider to be therapeutically equivalent.

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.

Multiple-source drug products listed under the same heading (i.e., identical active ingredient(s), dosage form, and route(s) of administration) and having the same strength generally will be coded *AB* if data 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*). Three-character codes are assigned only in situations when more than one reference listed drug of the same strength have been designated under the same heading.

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**V. AGENCY POSITION**

The Agency believes it is legally permissible<sup>3</sup> to allow the therapeutic equivalence code linked to the proprietary name of the reference listed drug product to be placed on container labels and/or drug product labeling. Although nothing would prohibit the placing of the therapeutic equivalence rating in the package insert labeling, we believe that the most appropriate placement is on the immediate container and carton labeling where it is easy to see. This information may assist the health professional in determining whether a specific drug product is therapeutically equivalent to another pharmaceutically equivalent drug product.

The use of therapeutic equivalence evaluations in drug product labeling will help promote the purpose of the *Orange Book*, to assist the health professional in product selection, and to serve state health agencies in the administration of their drug product selection laws. A statement on the container label and carton labeling that one product is therapeutically equivalent (or inequivalent, as the case may be) to another will help ensure that the therapeutic equivalence evaluations in the *Orange Book* reach the audiences that need to receive the information. Pharmacists and other health professionals who practice drug product selection for patients will become more knowledgeable about which product may be safely substituted for another. This information will also assist pharmacists and other health professionals in those states that use the *Orange Book's* therapeutic equivalence ratings in carrying out their state's drug product selection law and increase public education in the area of drug product selection.

The applicant, repacker, or distributor is responsible for ensuring that the therapeutic equivalence claim in labeling is accurate and current. Section 502(a) of the Federal Food, Drug, and Cosmetic Act states that a drug shall be deemed to be misbranded if its labeling is false or misleading in any particular. Labeling would be false or misleading if it states that a drug product is therapeutically equivalent to another drug product when in fact it is inequivalent.

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<sup>3</sup> Prior to the enactment of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act), section 301(1) of the Federal Food, Drug and Cosmetic Act prohibited the use on the labeling of any drug or device of any representation or suggestion that approval of an application with respect to such drug or device is in effect. With the repeal of section 301(1) in the Modernization Act, the Agency believes that any legal arguments that therapeutic equivalence ratings should not be used in the labeling are moot. Certain trademark law has established that “[a] manufacturer does not commit unfair competition merely because it refers to another's product by name in order to win over customers interested in a lower cost copy of that product if the reference is truthful and does not likely confuse consumers into believing that the copy is from the same source as the original.” *Calvin Klein Cosmetics v. Parfumes de Coeur Ltd.*, 824, F.2d 655, 668, 3 USPQ2d 1498, 1500 (8th Cir. 1987). See also: *Societe Comptoir de L'Industrie v. Alexander's Department Stores, Inc.*, 299 F.2d 33 (2d. Cir. 1962); *G.D. Searle & Co. v. Hudson Pharmaceutical Corp.*, 715 F.2d 837, 841, 220 USPQ 496, 500-501 (3rd. Cir. 1983) [wherein the court stated that the defendant could continue to use the brand name METAMUCIL® on its generic product provided the trademark appeared in the same size type as the other words on the label, the trademark registration symbol “®” was used with the METAMUCIL® trademark and a disclaimer was added stating that there is no association between the generic product and METAMUCIL®]; *The Upjohn Co. v. American Home Products Corp.*, 598 F. Supp. 550, 561, 225 USPQ 109, 117 (S.D.N.Y. 1984) [wherein the court allowed the defendant to use the trademark MOTRIN® in its advertising provided that a disclaimer was added stating the MOTRIN® trademark was owned by another company].

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Drug information, as presented by the *Orange Book*, is dynamic and complex and is subject to changing conditions. As explained in the preface to the *Orange Book*, when a change occurs in the information contained in FDA files concerning a multiple-source product that is in the *Orange Book*, the potential exists that the drug product will no longer meet the criteria for therapeutic equivalence as initially evaluated. In such an instance, FDA will reevaluate the drug and, if the listed evaluation is no longer accurate, the evaluation will be revised accordingly. Revisions to the *Orange Book* are shown in monthly supplements, which are mailed to all subscribers and are available on the Internet (<http://www.fda.gov/cder/drug.htm>). Thus, when an applicant, repacker, or distributor chooses to include therapeutic equivalence evaluations in drug product labeling, it is that applicant's or labeler's responsibility to be certain that the evaluation is accurate and current in accordance with the *Orange Book* and its supplements. An inaccurate statement in the labeling regarding therapeutic equivalency could result in that product being subject to regulatory action.

**VI. IMPLEMENTATION**

The following presentations illustrate how therapeutic equivalence rating should be placed on prescription drug labeling. Such minor changes in labeling can be implemented and reported at the time of the next annual report of an application. Although inclusion of a therapeutic equivalence rating on prescription product labels/labeling is voluntary, in certain cases where safety issues are raised, the Agency may ask that a rating be included. This could occur, for example, when multiple reference listed drug products exist with the same established name and/or overlapping strengths thereby making the potential for confusion high.

- A. With regard to displaying the therapeutic equivalence code on container labels and carton labeling, we recommend the following:

**GROUCHOSE®**  
(Harpose Tablets, USP)  
\_\_mg

AB to CHICOSE®\*

\*Chicose® is a registered trademark of Marx Brothers, Inc.

OR

This product is AB to CHICOSE®. Chicose® is a registered trademark of Marx Brothers, Inc.

- B. With respect to the above presentations, we also recommend the following:

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- The generic (established) name should be displayed prominently and be printed in letters that are at least half as large as the letters comprising a proprietary name.
- The trademark registration symbol “®” or “™”, as appropriate, should appear with the trademark.
- The therapeutic equivalency statement (AB to Brand X®) should be less prominent than the applicant, repacker, or distributor’s trademark and established name of the prescription drug product. The trademark, as seen in the equivalency statement, should also always be the same size type as the words surrounding the trademark.
- The label should include a disclaimer identifying the owner of the trademark (e.g., Chicose® is a registered trademark of...).

## VII. QUESTIONS AND ANSWERS

### 1. Does this guidance apply to Over-the-Counter drug products?

This guidance document applies only to approved prescription drug products. Since the Agency does not provide therapeutic codes for OTC products in the *Orange Book*, a therapeutic code should not be placed on OTC products.

### 2. Does this guidance apply to package insert labeling?

The intent of this guidance document is to assist the health care practitioner in product selection. Although nothing would prohibit the placing of the therapeutic equivalence rating in the package insert labeling, we believe that the most appropriate placement is on the immediate container and carton labeling.

### 3. Does this guidance apply to distributors of brand name prescription drug products?

Yes, it would be useful for a distributor of a brand name prescription drug product to state “AB to Brand X®”. Any drug product in the *Orange Book* repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder’s drug product even if the application holder’s drug product is single source or is coded as inequivalent.

### 4. What would happen if a product was labeled to claim therapeutic equivalence and then was downgraded to being inequivalent?

The applicant, repacker, and/or distributor is responsible for ensuring that the

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therapeutic equivalence claim in its labeling is accurate and current. Within this context, it is expected that the applicant, repacker, and/or distributor will take whatever steps are necessary to ensure that its labeling is not false or misleading in any particular. An inaccurate statement in the labeling regarding therapeutic equivalency could result in that product being subject to regulatory action.

**5. Will brand name companies be allowed to state that their drug products are *NOT* equivalent to each other?**

Yes, a brand name company could state “BX to Brand X®”.

**6. Does the placement of therapeutic equivalence codes on the label interfere with state substitution laws?**

No, the therapeutic equivalence code does not supersede any state determination of substitutability. The therapeutic equivalence code, as seen in the *Orange Book* and on prescription labels is public information and advice. It does not mandate the drug products that may be 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* and the labels/labeling set forth FDA’s evaluations of the therapeutic equivalence of drug products that have been approved, they contain 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 preferable to any other.

**7. What are the responsibilities of the practitioner/user with respect to FDA’s advice on therapeutic equivalence?**

As discussed in detail in the introduction to the 18th edition of the *Orange Book*, professional care and judgment should be exercised in using the therapeutic equivalence evaluations as a basis for product substitution. 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. There may also be better stability of one product over another under adverse storage conditions; in rare cases, allergic

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reactions due to a coloring or a preservative ingredient; or 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.