Evaluation of Therapeutic Equivalence

Guidance for Industry

DRAFT GUIDANCE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)

July 2022
Generics

Contains Nonbinding Recommendations

Draft — Not for Implementation

Evaluation of Therapeutic Equivalence

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U.S. Department of Health and Human Services
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I. INTRODUCTION

This guidance explains FDA's therapeutic equivalence evaluations, including the assignment of therapeutic equivalence codes (or TE codes). As defined in 21 CFR 314.3(b), *therapeutic equivalents* are

> approved drug products that FDA has determined are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

FDA's therapeutic equivalence evaluations are listed for multisource[2] prescription drug products approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) in the active section of the *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly known as the Orange Book)[3]. As FDA explained when it first proposed to make available a list of all approved drug products, together with therapeutic evaluations of listed products that are available from more than one manufacturer, therapeutic equivalence 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.[4] For example, the Orange Book can assist in the establishment of formularies that States and other entities may use in determining when drug products may be substituted for one another. If lower-cost, therapeutically equivalent drug products are available, American consumers are more likely to receive savings on these

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For purposes of therapeutic equivalence evaluations, "multisource" drug products are, in most instances, pharmaceutical equivalence available from more than one manufacturer. In contrast, "single-source" drug products are those products for which there is only one approved product available for that active ingredient, dosage form, route of administration, and strength. See Orange Book Preface (42nd edition 2022) at xii.

[3] The electronic version of the Orange Book can be found at https://www.fda.gov/drugs/informationondrugs/ucm129662.htm.

[4] See, e.g., 44 FR 2932 (January 12, 1979) and 45 FR 72582 (October 31, 1980).

products.[5] Therapeutic equivalence evaluations are a scientific judgment based upon evidence, while generic substitution may involve social and economic policy administered by the states, e.g., reducing the cost of drugs to consumers. 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.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidance means that something is suggested or recommended, but not required.

II. THERAPEUTIC EQUIVALENCE EVALUATIONS

A. The Fundamentals of Therapeutic Equivalence

The scientific and regulatory foundation for the evaluation of therapeutic equivalence of prescription drug products involves:

- Pharmaceutical equivalence,
- Bioequivalence, and
- Same clinical effect and safety profile for the conditions of use specified in the labeling.[6]

Therapeutic equivalence can be evaluated only for products that are (or will become upon approval) multisource prescription drug products.[7] FDA approval includes, among other things, a determination that the drug product is adequately labeled, and that the methods used in, and the facilities and controls used for, the manufacture, processing, and packaging of a drug product are adequate to preserve its identity, strength, quality, and purity.[8]

FDA believes 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 when administered to patients under the conditions specified in the labeling.

1. Pharmaceutical Equivalence

To be therapeutically equivalent, drug products must be pharmaceutically equivalent.[9] As defined in 21 CFR 314.3(b), *pharmaceutical equivalents* are drug products:

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[5] Id.

[6] See 21 CFR 314.3(b).

[7] See id; see also Orange Book Preface (42nd edition 2022) at vii and xii. Prescription drug products are considered multisource when pharmaceutical equivalents are available (i.e., are not on the Discontinued Drug Product list in the Orange Book) from more than one manufacturer.

[8] See 21 CFR 314.127(a).

[9] 21 CFR 314.3(b).

- in identical dosage form and route(s) of administration;

- Contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period;

- Do not necessarily contain the same inactive ingredients; and

- Meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.[10]

2. Bioequivalence

To be therapeutically equivalent, drug products must also be bioequivalent.[11] *Bioequivalence* is, in pertinent part:

> the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[12]

For drug products that are not intended to be absorbed into the bloodstream, applicants may assess bioequivalence by conducting scientifically valid measurements that are intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.[13] FDA has promulgated regulations regarding demonstrating bioequivalence,[14] and the Agency routinely publishes guidances for industry and product-specific guidances to assist applicants and sponsors in demonstrating bioequivalence.[15]

3. Same Clinical Effect and Safety Profile

[10] 21 CFR 314.3(b) (bullets added).

[11] Id.

[12] Id.

[13] Id.

[14] See, e.g., 21 CFR 314.94(a)(7) and 21 CFR part 320.

[15] For example, as an initial step for selecting a methodology for generic drug development, applicants may refer to the draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. Product-specific guidances are available at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

Therapeutic equivalents are expected to have the same clinical effect and safety profile when administered to patients under the conditions of use specified in the labeling.[16] Labeling plays a critical role in the therapeutic equivalence evaluation. FDA evaluates the labeling to determine whether the drug products have the same clinical effect and safety profile under the conditions of use that the labeling specifies. As a result, pharmaceutically equivalent products with differences in labeling may not be considered therapeutically equivalent to one another.

The evaluation of whether drug products have the same clinical effect and safety profile is product-specific. For example, whether a proposed generic drug-device combination product with a user interface that contains differences from that for the RLD[17] can be substituted with the full expectation that the generic combination product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling is a product specific determination, and additional information and/or data relating to the user interface may be appropriate to support approval and to perform this evaluation.

B. Products Evaluated for Therapeutic Equivalence

FDA only evaluates certain drug products approved under section 505 of the FD&C Act for therapeutic equivalence. Section 505 establishes the following approval pathways for drug products: "stand-alone" new drug applications (NDAs); 505(b)(2) applications; and abbreviated new drug applications (ANDAs), which include petitioned ANDAs.[18]

1. Drug Products Approved Under Section 505(c) of the FD&C Act

A "stand-alone NDA" is an application submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act that contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use.

A 505(b)(2) application is an NDA submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., the Agency's finding of safety and/or effectiveness for a listed drug,

[16] 21 CFR 314.3(b).

[17] The *RLD* "is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA." 21 CFR 314.3(b).

[18] Prescription drug products that have been approved by FDA are generally listed in the Orange Book. See section 505(j)(7)(A) and (B) of the FD&C Act; 21 CFR 314.3(b). The Orange Book includes drug products whose applications became effective before the 1962 Amendments to the FD&C Act (and were deemed approved upon enactment of the 1962 amendments) on the basis of a demonstration of safety, where the effectiveness for their intended use was determined through the Drug Efficacy Study Implementation (DESI) process. Drugs marketed prior to the enactment of the Federal Food, Drug & Cosmetic Act of 1938 were not subject to premarket approval procedures and are excluded from the Orange Book.

published literature).[19] FDA generally will refuse to file a 505(b)(2) application for a drug that is a duplicate[20] of a listed drug and eligible for approval under section 505(j) of the FD&C Act.[21]

FDA generally does not conduct therapeutic equivalence evaluations upon approval of drug products in stand-alone NDAs. In most cases, a stand-alone NDA drug product would not be pharmaceutically equivalent—and thus not therapeutically equivalent—to another approved stand-alone NDA drug product. Drug products approved in stand-alone NDAs are generally designated as reference listed drugs upon which prospective generic drug applicants can rely in developing their ANDA drug products.

FDA does not routinely conduct therapeutic equivalence evaluations for every product approved in a 505(b)(2) application. 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).[22] When therapeutic equivalence is evaluated, the differences between a product approved in a 505(b)(2) application and another listed drug may preclude a finding that the products are therapeutically equivalent. These differences may include, for example, a different active ingredient or a new indication, dosage form, strength, or route of administration, or certain formulation differences.[23] See question and answer 3, 4, and 5 for more information specifically on 505(b)(2) applications and TE codes, including information on requesting a therapeutic equivalence evaluation for a drug product that is the subject of an approved or pending 505(b)(2) application. Like those in stand-alone NDAs, drug products approved in 505(b)(2) applications are generally designated as reference listed drugs upon which prospective generic drug applicants can rely in developing their ANDA drug products.

2 Drug Products Approved Under Section 505(j) of the FD&C Act

An ANDA[24] generally is an application submitted and approved under section 505(j) of the FD&C Act for a drug product that is a duplicate of a previously approved drug product, the

[19] For more information on 505(b)(2) applications, see the guidance for industry *Determining Whether to Submit an ANDA or 505(b)(2) Application* (May 2019) and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999). When final, this guidance will represent the FDA's current thinking on this topic.

[20] The term *duplicate* generally refers to a "drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug." See 54 FR 28872 at 28877 (July 10, 1989). However, the term *duplicate*, as used in this context, does not mean identical in all aspects to the listed drug.

[21] 21 CFR 314.101(d)(9) (noting that FDA may refuse to file an NDA if the "NDA is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the [FD&C] Act").

[22] See Orange Book Preface (42nd edition 2022) at xxiv.

[23] For examples of applications that may be submitted under section 505(b)(2) of the FD&C Act see the draft guidance for industry *Applications Covered by Section 505(b)(2)* (December 1999). When final, this guidance will represent the FDA's current thinking on this topic.

[24] For purposes of this guidance, the terms "generic", "abbreviated new drug application", and "ANDA" refer to products submitted and approved under section 505(j) of the FD&C Act. The Orange Book also refers to certain products approved under pre-Hatch-Waxman abbreviated applications (PANDAs) as ANDAs. In general, the

RLD. An ANDA generally must contain information to show that the proposed generic product (1) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and (2) is bioequivalent to the RLD. If the statutory requirements are met, an ANDA may rely on FDA's finding that the previously approved drug product, the RLD, is safe and effective.

A "petitioned" ANDA is a type of ANDA for a drug product that differs from the RLD in its dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient) and for which FDA has determined, in response to a petition submitted under section 505(j)(2)(C) of the FD&C Act (suitability petition), that studies are not necessary to establish the safety and effectiveness of the proposed drug product. For approval, the drug product approved in a petitioned ANDA may rely on the finding of safety and effectiveness for the RLD that was the basis of the suitability petition, but would not be therapeutically equivalent to its RLD because the differences permissible in a petitioned ANDA would render the product not pharmaceutically equivalent to the RLD.

In general, with the exception of a drug product approved in a petitioned ANDA, when FDA approves a drug product under an ANDA it is therapeutically equivalent to its RLD because the requirements for ANDA approval include the data and information that establish therapeutic equivalence. Accordingly, an ANDA applicant does not need to request a therapeutic equivalence evaluation from the Agency. In contrast to FDA's general practice to designate stand-alone NDAs and 505(b)(2) applications as reference listed drugs upon approval, FDA's general practice has not been to designate ANDAs as reference listed drugs upon approval because ANDAs do not contain independent findings of safety and effectiveness upon which other ANDAs can rely. [25]

C. The Therapeutic Equivalence Coding System[26]

FDA lists its therapeutic equivalence evaluations in the Orange Book using a system of multi-letter codes assigned to multi-source drug products. The coding system is designed to allow users to determine quickly whether the Agency has evaluated a particular approved drug product as therapeutically equivalent to another approved pharmaceutically equivalent drug product. Generally, the first letter of the code indicates whether the Agency has determined that a particular approved drug product is therapeutically equivalent to another drug product. The coding system also uses additional specific letters to provide further information based on FDA's evaluations.

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discussion of ANDAs and generics in this document do not include such products. For more information on PANDAs, see Notice: Drug Products Approved in Abbreviated New Drug Applications Before the Enactment of the Hatch-Waxman Amendments; Establishment of a Public Docket; Request for Comments (referred to as PANDA Notice), Docket No. FDA-2020-N-1245, available at: https://www.govinfo.gov/content/pkg/FR-2021-08-13/pdf/2021-17378.pdf, and Pre-Hatch-Waxman Abbreviated New Drug Applications in the Orange Book, available at: https://www.govinfo.gov/content/pkg/FR-2021-08-13/pdf/2021-17378.pdf.

[25] We note that PANDAs have been designated as RLDs even though they are described in the Orange Book as ANDAs (see PANDA Notice).

[26] The Preface to the Orange Book explains therapeutic equivalence codes in greater detail. See the Orange Book Preface (42nd edition 2022) discussion beginning at p. xii.

1. A *Codes*

Drug products are assigned an *A* as the first letter of their therapeutic equivalence code if FDA considers them to be therapeutically equivalent to other pharmaceutically equivalent products. Drug products considered to be therapeutically equivalent are grouped together in the Orange Book.

For products that are therapeutically equivalent (i.e., those codes in which an *A* is the first letter), the second letter in the code identifies that either:

(1) actual or potential bioequivalence problems have been resolved with adequate evidence, or
(2) there are no known or suspected bioequivalence problems.

In the former case, for pharmaceutically equivalent products that have raised questions of bioequivalence and for which in vivo and/or in vitro methods were used to establish bioequivalence, FDA assigns them an *AB* code. In the latter case (when there are no known or suspected bioequivalence problems), the second letter in the therapeutic equivalence code (i.e., the *A*, *N*, *O*, *P*, or *T* in *AA*, *AN*, *AO*, *AP*, or *AT*) identifies the dosage form.[27] For active ingredients or dosage forms for which no in vivo bioequivalence issue is known or suspected, the information necessary to show bioequivalence (between pharmaceutically equivalent products) is either presumed and considered self-evident (based on other information in the application for some dosage forms (e.g., solutions)),[28] or satisfied by a showing that an acceptable in vitro approach is met.

2. B *Codes*

Drug products are assigned a *B* as the first letter of their therapeutic equivalence code if, at this time, actual or potential bioequivalence problems have not been resolved with adequate evidence of bioequivalence. Until actual or potential bioequivalence questions are resolved, FDA considers such products not to be therapeutically equivalent to other pharmaceutically equivalent products.

For such products, the second letter in the therapeutic equivalence code (i.e., the *C*, *D*, *E*, *N*, *P*, *R*, *S*, *T*, *X*, and *B** in *BC*, *BD*, *BE*, *BN*, *BP*, *BR*, *BS*, *BT*, *BX*, or *BB**) either identifies the dosage form or provides further general information regarding why the product is not considered to be

[27] At a high level, the *A* codes, other than *AA*, indicate the following things. A solution or powder for aerosolization that is therapeutically equivalent to another such approved product and for which there are no known or suspected bioequivalence problems would be coded *AN*. *AA* identifies products in conventional dosage forms, e.g., tablets or capsules, not presenting bioequivalence problems. All oral dosage forms nonetheless must meet an appropriate bioequivalence standard for approval. *AO* identifies injectable oil solutions. *AP* identifies injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions. *AT* identifies topical products. See the Orange Book Preface (42nd edition 2022) discussion beginning at p. xiii.

[28] See 21 CFR 320.22 for a discussion on when bioequivalence may be self-evident.

therapeutically equivalent.[29] In its description of the *B* codes, the Orange Book describes circumstances under which FDA may find that a drug product is not therapeutically equivalent to another approved pharmaceutically equivalent drug product.[30]

3. Three-Character Codes

In some instances, a number is added to certain codes to make a three-character code. Three-character codes generally are assigned only in situations in which more than one RLD of the same strength has been designated under the same product heading (i.e., same active ingredient(s), dosage form, route(s) of administration, and strength) in the Orange Book. For example, for the listing for Diltiazem Hydrochloride Capsule, Extended Release, multiple RLDs are designated, including Tiazac (NDA 020401 for 120, 180, 240, 300, 360, and 420 milligrams (mg)), Cardizem CD (NDA 020062 for 120, 180, 240, 300, and 360 mg), and Dilacor XR (NDA 020092 for 120, 180, and 240 mg). ANDAs that reference Tiazac have the *AB4* rating, ANDAs that reference Cardizem CD have the *AB3* rating, and ANDAs that referenced Dilacor XR have the *AB2* rating.

D. Revisions to Therapeutic Equivalence Evaluations

FDA may revise its therapeutic equivalence evaluation for a particular drug product if, based on data or information FDA receives or becomes aware of, FDA determines that such a revision is warranted. FDA may revise either the first or second letter of the therapeutic equivalence code. The following is a non-exhaustive list of examples:

- FDA will revise a therapeutic equivalence code if it decides that another therapeutic equivalence code would be more accurate than the current one.
- FDA will remove any associated therapeutic equivalence code for a drug product that is moved from the Active section to the Discontinued Drug Product List section of the Orange Book.
- FDA will remove the therapeutic equivalence code for a drug product listed in the Active section of the Orange Book if that drug product becomes a single-source product.

FDA also may change a drug product's therapeutic equivalence code from an *A*-rating to a *B*-rating if FDA becomes aware of information that raises questions about the data and information that the Agency relied on in approving that product. For example, if FDA discovers significant issues at a facility where a drug product was used in testing to support its approval and those

[29] At a high level, the *B* codes indicate the following things. *BC* identifies extended-release dosage forms (e.g., capsules, injectables, and tablets). *BE* identifies delayed-release oral dosage forms. *BN* identifies products in aerosol-nebulizer drug delivery systems. *BR* identifies suppositories or enemas that deliver drugs for systemic absorption. *BT* identifies topical products with bioequivalence issues. *BD* indicates active ingredients and dosage forms with documented bioequivalence problems. *BS* indicates that products have drug standard deficiencies. *BP* indicates active ingredients and dosage forms with potential bioequivalence problems. *B** indicates that a drug product requires further FDA investigation and review to determine therapeutic equivalence, and *BX* indicates that the data available to FDA are insufficient to determine therapeutic equivalence. See the Orange Book Preface (42nd edition 2022) discussion at pp. xviii-xx.

[30] See the Orange Book Preface (42nd edition 2022) discussion beginning at p. xviii.

issues are relevant to the underlying therapeutic equivalence evaluation, FDA may change an *AB* therapeutic equivalence code to a *BX* code until the related facility issues and questions about their impact on the application are resolved.

III. FREQUENTLY ASKED QUESTIONS

1. When are therapeutic equivalence codes for ANDAs listed in the Orange Book?

Because the approval standards for a drug product in an ANDA (other than a drug product in a petitioned ANDA) require in general, among other things, a demonstration that the proposed drug product has the same dosage form, route of administration, strength, and active ingredient as its RLD, is bioequivalent to its RLD, and generally has the same labeling as its RLD, with limited exceptions,[31] a generic drug is considered therapeutically equivalent to its RLD upon approval. In general, the therapeutic equivalence code for an approved ANDA will be listed with the approved ANDA at the time that ANDA is added to the Orange Book,[32] and the ANDA holder does not need to request a therapeutic equivalence evaluation to its RLD.

2. Are there any instances in which an approved ANDA drug product would not have a therapeutic equivalence code?

Yes. Generally, FDA assigns a therapeutic equivalence code for an ANDA drug product at the time of the drug's approval, and this code is included in the listing for that drug product in the Orange Book. However, there are limited instances in which a drug product approved under section 505(j) would not have a therapeutic equivalence code. For example:

- If an RLD is discontinued or withdrawn from sale for reasons other than safety or effectiveness[33] and a drug product approved under the ANDA that references that RLD becomes a single-source product, then any assigned therapeutic equivalence codes for the RLD and the ANDA are removed from the Orange Book; the ANDA will not have a TE code until it becomes a multisource product, for example through the approval of a therapeutically equivalent ANDA or 505(b)(2) application.[34]

- If FDA approves an ANDA based on an approved suitability petition for a change permissible under section 505(j)(2)(C) of the FD&C Act (including a change in dosage form, route of administration, and strength), the approved ANDA would not be pharmaceutically equivalent to its RLD and, therefore, would not be therapeutically equivalent to the RLD or have a therapeutic equivalence code to the

[31] As noted in section II.B.2.c of this guidance, approval of ANDAs under a suitability petition would not constitute a finding of therapeutic equivalence because the ANDA products are not pharmaceutical equivalents to their RLDs.

[32] The Orange Book Staff provides daily updates to the electronic Orange Book for new generic drug approvals.

[33] See 21 CFR 314.161.

[34] If an RLD is discontinued or withdrawn and there are multiple ANDAs that reference that RLD, the remaining ANDAs retain their existing therapeutic equivalence codes. Subsequently approved ANDAs that are pharmaceutical equivalents to the RLD would be assigned the same therapeutic equivalence code.

RLD. If a second ANDA is approved for the petitioned change, that second ANDA and the first ANDA would be designated as therapeutically equivalent to each other.

3. Are there any instances in which an approved NDA drug product would not have a therapeutic equivalence code?

Yes, there are instances in which an approved NDA drug product listed in the Orange Book would not have a therapeutic equivalence code. For example, if an NDA drug product does not have a therapeutic equivalence code, it could indicate that:

- The drug product is one for which there are no therapeutically equivalent products listed in the Active Section of the Orange Book.

- The drug product was approved in a 505(b)(2) application and is not therapeutically equivalent to the listed drug it references because it is not a pharmaceutical equivalent (for example, it is for a strength that was not approved for the listed drug).

- The drug product was approved in a 505(b)(2) application and is pharmaceutically equivalent to a "stand-alone" NDA, but the 505(b)(2) application holder has not made a request for, and FDA has not conducted, a therapeutic equivalence evaluation for the 505(b)(2) application.

4. What is an example of a 505(b)(2) application for which a request for an *A* rating may be granted?

As noted in Section II.B.1, a drug product approved in a 505(b)(2) application may have differences from other listed drugs which may preclude a finding of therapeutic equivalence. However, a drug product approved in a 505(b)(2) application that meets the criteria for therapeutic equivalence as described in 21 CFR 314.3(b) may receive an appropriate therapeutic equivalence code.

For example, FDA may determine that an injectable solution drug product submitted under a 505(b)(2) application is therapeutically equivalent to the listed drug it references if that drug product is pharmaceutically equivalent and bioequivalent to the listed drug but because of a difference in excipients from the listed drug[35] it references it could not have been approved in an ANDA.

5. How do I request therapeutic equivalence evaluation of a drug product submitted in a 505(b)(2) application?

The holder of an approved 505(b)(2) application drug product may request a therapeutic equivalence evaluation in a citizen petition submitted under 21 CFR 10.25(a) and 10.30. FDA will evaluate whether a therapeutic equivalence code for a 505(b)(2) application is appropriate,

[35] See 21 CFR 314.94(a)(9)(ii) – (v) for a discussion on permissible differences in exception excipients.

after the drug product is approved and FDA has received a therapeutic equivalence code request from the 505(b)(2) application holder.

In many cases, FDA will assess therapeutic equivalence for a 505(b)(2) application utilizing information supporting the safety, effectiveness, and quality of the drug product that is already contained in the NDA file. If the applicant for a product submitted in a 505(b)(2) application intends to request a therapeutic equivalence evaluation upon approval, we recommend that the applicant contact the regulatory project manager for the division to discuss how the applicant's presentation of data and information will facilitate a therapeutic equivalence evaluation and/or to discuss which additional information (if any) may be needed.[36]

6. Does FDA assign a therapeutic equivalence code to tentatively approved[37] drug products?

A drug product that is tentatively approved is not an approved drug product and cannot be marketed.[38] Accordingly, FDA does not list that drug product in the Orange Book and does not give it a therapeutic equivalence code.

7. If a drug product is repackaged and distributed by either the applicant or a party other than the applicant, will it be given its own therapeutic equivalence code?

No. In the Orange Book, FDA would not include a separate listing with separate TE code for a product that has been repackaged and distributed.

8. How do instructions in the labeling regarding reconstitution, dilution, or other manipulation(s) before dispensing or administration affect FDA's determination of dosage form?

The labeling for a drug product may include instructions for reconstitution, dilution, or other manipulation(s) of the drug product before use. FDA evaluates the dosage form of such a drug product before such reconstitution, dilution, or other manipulation(s). Thus, for example, a

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[36] For more information on contacting the appropriate Office of New Drugs review division, see https://www.fda.gov/drugs/regulatory-science-research-and-education/reorganization-office-new-drugs-corresponding-changes-office-translational-sciences-and-office.

[37] *Tentative approval* is notification that an NDA or ANDA otherwise meets the requirements for approval under the FD&C Act, but cannot be approved because there is a 7-year period of orphan exclusivity for a listed drug under section 527 of the FD&C Act and 21 CFR 316.31, or that a 505(b)(2) application or ANDA otherwise meets the requirements for approval under the FD&C Act, but cannot be approved until the conditions in 21 CFR 314.107(b)(1)(iii), (b)(3), or (c) are met; because there is a period of exclusivity for the listed drug under 21 CFR 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the FD&C Act; because there is a period of exclusivity for the listed drug under section 505E of the FD&C Act; or because a court order pursuant to 35 U.S.C. 271(e)(4)(A) orders that the NDA or ANDA may be approved no earlier than the date specified. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval letter after any necessary additional review of the NDA or ANDA. 21 CFR 314.3(b).

[38] Id. See section 505(j)(5)(B)(iv)(II)(dd)(BB) of the FD&C Act (stating that a "drug that is granted tentative approval by the Secretary is not an approved drug and shall not have an effective approval until the Secretary issues an approval after any necessary additional review of the application"); see also 21 CFR 314.105(d).

powder for oral solution drug product[39] would have a different dosage form from a ready-to-use oral solution drug product.[40] As a result, a powder for oral solution drug product and a ready-to-use oral solution drug product would not be pharmaceutically equivalent and therefore not therapeutically equivalent to each other.

9. Can a drug product be therapeutically equivalent if it has different packaging from the listed drug it references?

Drug products that vary in packaging may or may not be therapeutically equivalent to each other. For example, if the packaging difference results in a different clinical effect or safety profile of one drug product to the other or precludes the two products from being pharmaceutical equivalents, they will not be considered therapeutically equivalent.

10. Can an ANDA drug product receive an A code if its labeling omits an indication(s) or other condition(s) of use, or other aspect(s) of labeling that is approved for the RLD but protected by patent or by exclusivity?

Yes. An ANDA drug product can be determined to be therapeutically equivalent to its RLD even if the drug product, due to listed patents or exclusivity for the RLD, is approved for fewer than all of the indications or other conditions of use for the RLD, or omits, due to listed patents or exclusivity for the RLD, other aspects of labeling currently approved for the RLD. ANDA drug products are permitted by statute and FDA's regulations to omit or "carve out," for patent or exclusivity reasons, an indication(s) or other condition(s) of use, or other aspect(s) of labeling approved for the RLD.[41] In making a therapeutic equivalence determination, FDA evaluates whether the two drug products are pharmaceutical equivalents for which bioequivalence has been demonstrated, 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.[42]

Because the approval standards for a drug product in an ANDA (other than a drug product with a permissible change in a petitioned ANDA) mean that, among other things, demonstrations of pharmaceutical equivalence to its RLD, bioequivalence to its RLD, and generally the same labeling as its RLD (with limited exceptions, including to allow for the omission, for patent or

[39] For purposes of this guidance, FDA uses the term "powder for oral solution" drug product to describe a product in a powder dosage form for oral administration with instructions in the labeling for reconstitution as a solution before administration.

[40] For purposes of this guidance, FDA uses the term "ready-to-use oral solution" drug product to describe a drug product in an oral solution dosage form for oral administration that does not include instructions for further manipulation, reconstitution, dilution, etc., before administration.

[41] See section 505(j)(2)(A)(v) and (viii) of the FD&C Act and 21 CFR 314.94(a)(8)(iv); see also 21 CFR 314.127(a)(7).

[42] Prior to approval of an ANDA, FDA will determine the specific language in the labeling of the RLD that describes the protected use and will assess whether an ANDA that omits the protected information from its labeling will be rendered less safe or effective than the RLD for the remaining non-protected conditions of use. 21 CFR 314.127(a)(7). FDA will not approve an ANDA that omits protected information from its labeling if that omission renders the ANDA less safe or effective for the remaining non-protected conditions of use.

exclusivity reasons, of an indication(s) or other condition(s) of use, or other aspect(s) of labeling), an approved ANDA drug product is considered therapeutically equivalent to its RLD and will receive an A code at approval, even if its labeling omits certain indications or other conditions of use, or other aspects of labeling approved for the RLD but protected by patent or exclusivity.

As a hypothetical example, suppose that a drug, Drugex, is approved for three indications: treatment of type 2 diabetes mellitus, treatment of hypertension, and prevention of heart disease. A method-of-use patent is listed in the Orange Book, and the use code describes the approved method of use claimed by the patent as "treatment of hypertension." The Orange Book also lists a period of three-year exclusivity for Drugex with the exclusivity code of "prevention of heart disease." In this case, an ANDA applicant could seek approval of a generic drug that relies on Drugex as its RLD with labeling that retains the type 2 diabetes mellitus indication but "carves out" the indications for treatment of hypertension and prevention of heart disease, which are protected by patent and exclusivity, respectively. If FDA found that the omissions did not render the ANDA drug product less safe or effective than Drugex for the remaining, non-protected conditions of use, and the ANDA met all other requirements for approval, it would be approved. The Orange Book would list an A code for the ANDA drug product, reflecting that it is therapeutically equivalent to Drugex and thus can be expected to have the same clinical effect and safety profile as Drugex when administered to patients under the conditions specified in the ANDA drug product's labeling.

11. How do inactive ingredients affect a therapeutic equivalence evaluation?

Differences in inactive ingredients between an ANDA and its RLD of the type permissible in ANDA products, e.g., preservatives, generally do not affect FDA's evaluation of therapeutic equivalence for the ANDA product. FDA evaluates the inactive ingredients in a generic product as part of the ANDA approval process,[43] and, as noted earlier, in general upon approval, an ANDA product is considered to be therapeutically equivalent to its RLD.

Therapeutic equivalence evaluations for a product approved through the 505(b)(2) pathway consider differences in inactive ingredients between that product and the listed drug to which a TE code is sought. Inactive ingredients that may be in drug products approved through the 505(b)(2) pathway and that may differ from the inactive ingredients in the listed drug to which a therapeutic equivalence evaluation is sought, may influence the bioequivalence, route of administration, safety profile, dosage form, or labeled indications of the drug products. Because 505(b)(2) applications are not required to demonstrate pharmaceutical equivalence or bioequivalence, differences in inactive ingredients may be part of FDA's therapeutic equivalence evaluation for 505(b)(2) products.

12. How is therapeutic equivalence evaluated for drug/device combination products submitted in an ANDA?

[43] See Section 505(j)(2)(A)(vi) of the FD&C Act (cross-referencing section 505(b)(1)(C)); 21 CFR 314.94(a)(9).

Therapeutic equivalence evaluations are made between an ANDA and its RLD at the time of approval, including for ANDAs for drug/device combination products. A generic combination product classified as therapeutically equivalent to the RLD can be expected to produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling. This does not mean, however, that the proposed generic combination product and its RLD need to be identical in all respects. FDA recognizes that an identical design may not always be feasible and, in certain instances, differences in the design of the user interface for a generic combination product as compared to the RLD may exist without precluding approval of the generic combination product under an ANDA. Any differences in device and labeling identified between a proposed generic combination product and its RLD should be adequately analyzed, scientifically justified, and otherwise not preclude approval under an ANDA.[44] The extent to which differences between the proposed generic combination product and the RLD affect the approvability of the ANDA product will be evaluated on a case-by-case basis.[45] In some instances in which differences exist, certain additional information and/or data relating to the user interface of the generic combination product may be appropriate to support approval of the proposed generic combination product in an ANDA. Such additional information and/or data are intended to confirm that the differences in device and labeling for the proposed generic combination product are acceptable and that the proposed generic combination product can be substituted with the full expectation that the generic combination product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.

13. What are "special situations" in the Orange Book?

Section 1.8 of the Orange Book Preface, "Description of Certain Special Situations," identifies, among other things, "special situations" where a more comprehensive explanation of equivalence scenarios beyond the two- or three-character therapeutic equivalence codes in the Orange Book may aid healthcare professionals and other interested parties.

14. How does an interested party comment on or contest a therapeutic equivalence evaluation?

An interested party who wishes to comment on or contest a therapeutic equivalence evaluation may submit a citizen petition under 21 CFR 10.25(a) and 10.30 or, in general, if a relevant citizen petition has already been submitted, an interested party may submit a comment to the docket for that citizen petition.

[44] See draft guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[45] See the Office of Combination Products guidance for industry and FDA staff *Principles of Premarket Pathways for Combination Products* (January 2022).