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Evaluation of Therapeutic Equivalence Guidance for Industry

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Introduction

The Food and Drug Administration (FDA or Agency) recently (June 2020) announced the availability of a draft guidance for industry entitled "Evaluation of Therapeutic Equivalence." The draft guidance explains the FDA's proposed approach to therapeutic equivalence evaluations, including the assignment of therapeutic equivalence codes, if finalized as written. Historically, draft guidance's from FDA have been close the final guidance.

The FDA's therapeutic equivalence evaluations help state health agencies, prescribers, and pharmacists decide which drug products may be substituted for one another. These evaluations are based on scientific evidence and do not constitute determinations that any product is preferable to any other. Understanding these considerations can be invaluable to organizations contemplating development and manufacturing of applicable new therapies.

Therapeutic Equivalence Evaluations

The Fundamentals of Therapeutic Equivalence

Therapeutic equivalence is the scientific and regulatory framework used to evaluate whether two prescription drugs are equivalent in terms of their clinical effect and safety profile. This evaluation can only be done for drugs that are multi-source prescription drugs. FDA approval of a drug includes a determination that the drug is adequately labelled and that the manufacturing, processing, and packaging methods used for the drug are adequate to preserve its identity, strength, quality, and purity. The FDA believes that products classified as therapeutically equivalent can be substituted for each other with the expectation that the product will produce the same clinical effect and safety profile as the prescribed product.

Pharmaceutical Equivalence

To be therapeutically equivalent, drug products must be pharmaceutically equivalent. This means that the products must be in the same dosage form and route of administration and contain the same amount of the active drug ingredient. They may not contain the same inactive ingredients but must meet the same standards of identity, strength, quality, and purity.

Bioequivalence

The FDA requires that for a drug to be therapeutically equivalent, it must also be bioequivalent. Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions. For drug products not intended to be absorbed into the bloodstream, applicants may assess bioequivalence by conducting scientifically valid measurements that reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action. The FDA has promulgated regulations regarding demonstrating bioequivalence, and the Agency routinely publishes guidance for industry and product-specific guidance to assist applicants and sponsors in demonstrating bioequivalence.

Same Clinical Effect and Safety Profile

The FDA evaluates the labelling of proposed generic drugs to determine whether they have the same clinical effect and safety profile as the reference drug. If the labelling of the proposed generic drug

differs from that of the reference drug, the FDA may require additional information to determine whether the generic drug can be substituted with the expectation that it will produce the same clinical effect and safety profile.

Products Evaluated for Therapeutic Equivalence

The FDA only evaluates certain drug products approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for therapeutic equivalence. A "stand-alone new drug application" (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. 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. 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 a therapeutic equivalence rating for a drug product approved in a 505(b)(2) application may petition the Agency through the citizen petition procedure. 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, route of administration, or certain formulation differences. 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.

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

The FDA's approval of a drug product under an ANDA generally means that the product is therapeutically equivalent to its reference-listed drug (RLD). An ANDA applicant must not request a therapeutic equivalence evaluation from the Agency. However, if a drug product is approved in a petitioned ANDA, it may 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.

The Therapeutic Equivalence Coding System

The FDA has a system of codes to indicate whether two drugs are therapeutically equivalent. The codes help users quickly determine whether the FDA has evaluated a particular drug as equivalent to another. The first letter of the code indicates whether the FDA has determined that a particular drug is therapeutically equivalent to another drug. The coding system also uses additional letters to provide further information based on FDA's evaluations.

A Codes

The FDA assigns therapeutic equivalence codes to drugs in order to group drugs that are considered to be therapeutically equivalent. The first letter of the code (A) indicates that the FDA considers the drug therapeutically equivalent to other drugs. The second letter of the code (AB) indicates that the FDA has resolved any potential bioequivalence issues with the drug. The second letter of the code (A, N, O, P, or T) also indicates the drug's dosage form.

B Codes

The FDA has assigned a "B" letter code to drug products that have not yet been determined therapeutically equivalent to other similar products. This code is used to identify products that may have potential bioequivalence issues that have not yet been resolved. Products with this code are not considered therapeutically equivalent to other products until the potential bioequivalence issues have been resolved.

Three-Character Codes

According to the FDA, there are three different ratings for generic drugs: AB1, AB2, and AB3. AB1 drugs are considered the most similar to the brand-name drug, while AB3 drugs are the least similar. In some cases, a fourth rating, AB4, is given to generic drugs that are considered to be equivalent to multiple brand-name drugs.

Revisions to Therapeutic Equivalence Evaluations

FDA may revise its therapeutic equivalence evaluation for a particular drug product if, based on new data or information, FDA determines that such a revision is warranted. This may include revising the therapeutic equivalence code from an A-rating to a B-rating if the FDA becomes aware of information that raises questions about the data and information that the Agency originally relied on upon approving the product.

FAQs

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

A generic drug product is considered therapeutically equivalent to its reference listed drug (RLD) upon approval if it meets certain standards regarding dosage form, route of administration, strength, active ingredient, bioequivalence, and labelling. The therapeutic equivalence code for an approved ANDA will be listed in the Orange Book when the ANDA is added.

Are there any instances where an approved ANDA drug product would not have a therapeutic equivalence code?

The FDA assigns therapeutic equivalence codes to ANDA drug products at approval time. However, there are some instances where an ANDA drug product 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, 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.

What is an example of a 505(b)(2) application for which a request for an A rating maybe granted?

A drug product approved under 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.

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

The FDA may evaluate the therapeutic equivalence of a drug product submitted in a 505(b)(2) application. The holder may request this evaluation of an approved 505(b)(2) application drug product in a citizen petition submitted under 21 CFR 10.25(a) and 10.30. In many cases, the 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. Suppose the applicant for a product submitted in a 505(b)(2) application intends to request a therapeutic equivalence evaluation upon approval. In that case, it is recommended 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 or to discuss which additional information (if any) may be needed.

Does FDA assign a therapeutic equivalence code to tentatively approved drug products?

The FDA does not assign therapeutic equivalence codes to tentatively approved drug products, and this is because these products are not yet approved for marketing and thus are not listed in the Orange Book.

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

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

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

The FDA evaluates the dosage form of a drug product before it is reconstituted, diluted, or otherwise manipulated. This means that, for example, a powder for an oral solution drug product would have a different dosage form from a ready-to-use drug product. 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.

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

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

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

An ANDA drug product can receive an A code if its labelling omits an indication or other condition of use that is approved for the RLD but protected by patent or exclusivity. This is because the approval standards for an ANDA mean that the drug product must generally be equivalent to the RLD regarding pharmaceutical equivalence, bioequivalence, and labelling.

How do inactive ingredients affect a therapeutic equivalence evaluation?

Inactive ingredients in generic drugs approved through the ANDA process are generally not evaluated for therapeutic equivalence. However, for drugs approved through the 505(b)(2) pathway, differences in inactive ingredients may influence FDA's therapeutic equivalence evaluation.

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

The FDA evaluates therapeutic equivalence for drug/device combination products submitted on an ANDA case-by-case basis. Any differences in device and labelling identified between a proposed generic combination product and its RLD should be adequately analysed, scientifically justified, and otherwise not preclude approval under an ANDA. In some instances where differences exist, additional information 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.

What are "special situations" in the Orange Book?

The Orange Book Preface describes certain "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.

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

If you wish to comment on or contest a therapeutic equivalence evaluation, you may submit a citizen petition under 21 CFR 10.25(a) and 10.30, or, if a relevant citizen petition has already been submitted, you may submit a comment to the docket for that citizen petition.

In conclusion, the FDA's therapeutic equivalence evaluations help state health agencies, prescribers, and pharmacists decide which drug products may be substituted for one another. These evaluations are based on scientific evidence and do not constitute determinations that any product is preferable to any other.

Reference:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-therapeutic-equivalence

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Dr. Blackwell is a leading industry consultant with broad experience that encompasses early process development to commercial operations. His product experience includes antibodies, vaccines, recombinant proteins, small molecules, peptides, cell therapy and medical devices. Clients include virtual start-ups to multi-national pharma. Dr. Blackwell has regulatory experience with INDs, PAIs, DMFs, and leading NDA CMC submissions. He has extensive experience with CMO selection, oversight, and management. He has been involved with third party Consent Decree monitoring, organizational mentoring, and quality system remediation. He has led or actively participated in more than forty product, company, or technology due diligence projects. Dr. Blackwell was on the formative management team and led Manufacturing and Technical Operations for Shore Therapeutics in the successful recommercialization of Fenoglide. He is a member of ISPE, PDA, AAPS and RAPS. He has graduate training in chemical engineering (Ph.D.), microbiology (M.S.), and business/technology management (M.B.A./M.S.) at Northeastern University, The Ohio State University, and University of Maryland, respectively.