Evaluating Therapeutic Equivalence

Elizabeth Giaquinto Friedman, JD, LLM
Regulatory Counsel
Division of Policy Development, Office of Generic Drug Policy, Office of Generic Drugs
CDER | U.S. FDA

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Learning Objectives

- Outline the fundamentals of therapeutic equivalence
- Describe therapeutic equivalence evaluations
- Describe therapeutic equivalence determinations

Therapeutic Equivalence

- Therapeutic equivalents can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product
- Therapeutic equivalence evaluations are listed in the Orange Book for multisource Rx drug products approved under section 505 of the FD&C Act
- Therapeutic equivalence evaluations have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists

Therapeutic Equivalence

Scientific and regulatory foundations for the evaluation of therapeutic equivalence are:

1. Pharmaceutical equivalence
2. Bioequivalence
3. Same clinical effect and safety profile

1. Pharmaceutical Equivalence

- Pharmaceutical equivalents are drug products that
  - Are identical in dosage form and route of administration;
  - Contain identical amounts of the identical active drug ingredient;
  - Do not necessarily contain the same inactive ingredients; and
  - Meet the identical compendial or other applicable standards of identity, strength, quality, and purity, including potency

2. Bioequivalence

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

3. Same clinical effect and safety profile

- 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
- This evaluation is product-specific

Therapeutic Equivalence Evaluations

- Drug products eligible for therapeutic equivalence evaluations
  - Drug products approved under abbreviated new drug applications (ANDAs)
  - Drug products approved under section 505(b)(2) applications

Therapeutic Equivalence Evaluations

- ANDAs
  - Drug products that are duplicates of previously approved drug products
  - Drug products approved in ANDAs are therapeutically equivalent to the reference listed drug (RLD)
    - The requirements for ANDA approval include the data and information that establish therapeutic equivalence
    - *Exception: Petitioned ANDAs*

Therapeutic Equivalence Evaluations

- 505(b)(2) applications
  - Contain 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, effectiveness for a listed drug, published literature

Therapeutic Equivalence Evaluations

- 505(b)(2) applications (cont'd)
  - Differences between a drug product approved in a 505(b)(2) application and a listed drug generally preclude a finding that the products are therapeutically equivalent
  - FDA may determine that an approved 505(b)(2) drug product is therapeutically equivalent to another listed drug if it is:
    - Pharmaceutically equivalent
    - Bioequivalent
    - Expected to have the same clinical effect and safety profile

Coding System

- FDA lists its therapeutic equivalence evaluations in the Orange Book using a system of lettered codes
- Codes allow users to determine whether FDA has evaluated a drug product as therapeutically equivalent to an approved pharmaceutically equivalent drug product
- The coding system uses specific letters to provide additional information based on FDA's evaluations

Coding System

	A Codes	*B* Codes
First letter	Considered therapeutically equivalent to other pharmaceutically equivalent products	Considered not to be therapeutically equivalent to other pharmaceutically equivalent products
Second letter	Identifies either: 1. Actual or potential bioequivalence problems have been resolved with adequate evidence (i.e., the *B* in *AB*) 2. Dosage form (i.e., the *A*, *N*, *O*, *P*, or *T* in *AA*, *AN*, *AO*, *AP*, or *AT*)	Identifies either: 1. Dosage form 2. Further information regarding why the product is not considered to be therapeutically equivalent

Therapeutic Equivalence Determinations

- ANDAs
  - Drug products approved in ANDAs are considered therapeutically equivalent to the RLD upon approval
  - Therapeutic equivalence codes for approved ANDAs are listed when the approved ANDA is added to the Orange Book
  - ANDA holders do not need to request therapeutic equivalence evaluations

Therapeutic Equivalence Determinations

- ANDAs (cont'd)
  - When an approved ANDA drug product would not have a therapeutic equivalence code:
    - The drug product approved becomes a single-source product
    - The drug product was approved under a petitioned ANDA

Therapeutic Equivalence Determinations

- 505(b)(2) applications
  - Applicants must demonstrate that the drug product is pharmaceutically equivalent, bioequivalent, and is expected to have the same clinical effect and safety profile as the reference drug
  - FDA assesses therapeutic equivalence using information in the NDA
  - The therapeutic equivalence code is assigned after approval and upon receipt of a request from the 505(b)(2) application holder

Therapeutic Equivalence Determinations

- 505(b)(2) applications (cont'd)
  - When an approved 505(b)(2) drug product would not have a therapeutic equivalence code:
    - The drug product is not pharmaceutically equivalent or therapeutically equivalent to the listed drug it references
    - The drug product holder has not made a request for a therapeutic equivalence evaluation

Challenge Question #1

Which of the following is not fundamental to therapeutic equivalence evaluations:

A. Pharmaceutical equivalence

B. Bioequivalence

C. Clinical effect and safety profile

D. Date of approval

Challenge Question #2

When is a therapeutic equivalence code listed in the Orange Book for a drug product approved in a 505(b)(2) application?

A. Automatically upon approval of the drug product

B. Following an FDA assessment of therapeutic equivalence upon tentative approval

C. Following an FDA assessment of therapeutic equivalence upon receipt of a request from the application holder

D. After approval of an ANDA referencing the same listed drug

Summary

- Therapeutic equivalence depends on:
  - Pharmaceutical equivalence
  - Bioequivalence
  - Same clinical effect and safety profile
- Therapeutic equivalence codes for approved ANDAs are generally listed in the Orange Book at the time of approval
- Therapeutic equivalence evaluations for approved 505(b)(2) products will be conducted upon receipt of a request from the application holder

Questions?

Elizabeth Giaquinto Friedman, JD, LLM
Regulatory Counsel
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CDER | U.S. FDA


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