Overview of *in vivo* Bioavailability (BA) and Bioequivalence (BE) Studies Supporting NDAs and ANDAs

Yiyue Zhang, Ph.D., RAC

Senior Staff Fellow
Office of Study Integrity and Surveillance
Office of Translational Sciences
CDER | US FDA

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Learning Objectives

- Familiarize with the relevant law and regulations
- Familiarize with the regulatory pathways
- Understand basis for measuring in vivo BA or demonstrating BE
- Understand various types of evidence to measure BA or establish BE

Outline

- Relevant law and regulations
- Regulatory pathways
- Basis for measuring in vivo BA or demonstrating BE
- Types of evidence to measure BA or establish BE
- Challenge questions

Relevant Law and Regulations

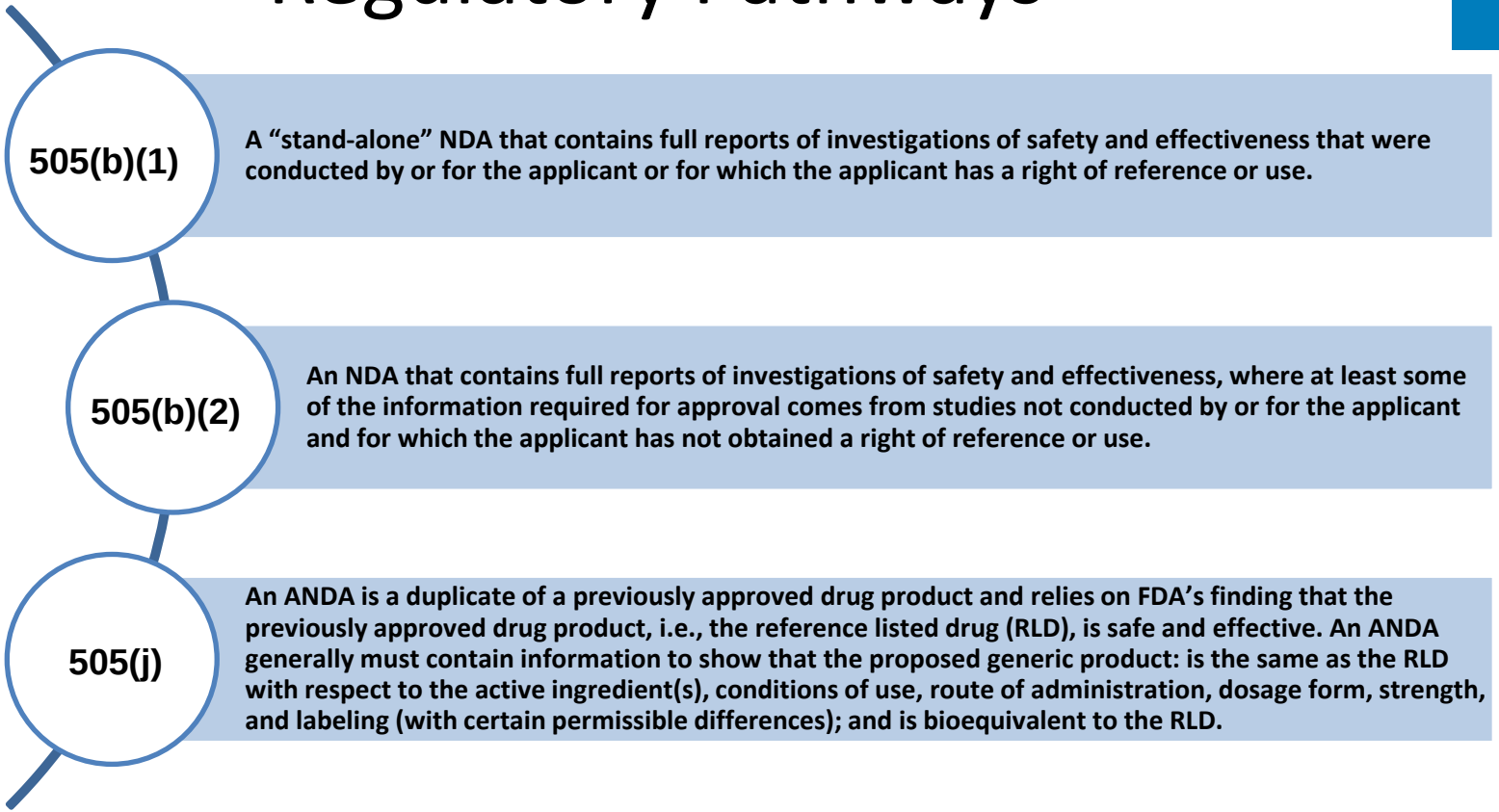
The Federal Food, Drug, and Cosmetic Act (*FD&C Act*)

- The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman Amendments)
  - Section 505(b)(2), New Drug Application (NDA)
  - Section 505(j), Abbreviated New Drug Application (ANDA)

Code of Federal Regulations (CFR), Title 21

- Part 314.54, Procedure for submission of a 505(b)(2) application requiring investigations for approval of a new indication for, or other change from, a listed drug
- Part 314.92, Drug products for which abbreviated applications may be submitted
- Part 320, Bioavailability and Bioequivalence Requirements

Regulatory Pathways



** An ANDA may not be submitted if clinical investigations are necessary to establish the safety and effectiveness of the proposed drug product.*

ANDA [505(j)] **or NDA** [505(b)(2)]**?**

- **Regulatory Considerations**
  - Duplicates
  - Petitioned ANDAs
  - Bundling

- **Scientific Considerations**
  - Type of studies, data, and information submitted
  - Active ingredient sameness evaluation
  - Intentional differences between the proposed drug product and the RLD in formulation, BA/BE, conditions of use, and other differences

Title 21 Part 320

	Part / Section
Title 21 Food and Drugs	
Chapter I Food and Drug Administration, Department of Health and Human Services	1 – 1299
Subchapter D Drugs for Human Use	300 – 499
Part 320 Bioavailability and Bioequivalence Requirements	320.1 – 320.63
Subpart A General Provisions	320.1
§ 320.1 Definitions.	
Subpart B Procedures for Determining the Bioavailability or Bioequivalence of Drug Products	320.21 – 320.63
§ 320.21 Requirements for submission of bioavailability and bioequivalence data.	
§ 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.	
§ 320.23 Basis for measuring in vivo bioavailability or demonstrating bioequivalence.	
§ 320.24 Types of evidence to measure bioavailability or establish bioequivalence.	
§ 320.25 Guidelines for the conduct of an in vivo bioavailability study.	
§ 320.26 Guidelines on the design of a single-dose in vivo bioavailability or bioequivalence study.	
§ 320.27 Guidelines on the design of a multiple-dose in vivo bioavailability study.	
§ 320.28 Correlation of bioavailability with an acute pharmacological effect or clinical evidence.	
§ 320.29 Analytical methods for an in vivo bioavailability or bioequivalence study.	
§ 320.30 Inquiries regarding bioavailability and bioequivalence requirements and review of protocols by the Food and Drug Administration.	
§ 320.31 Applicability of requirements regarding an "Investigational New Drug Application."	
§ 320.32 Procedures for establishing or amending a bioequivalence requirement.	
§ 320.33 Criteria and evidence to assess actual or potential bioequivalence problems.	
§ 320.34 Requirements for batch testing and certification by the Food and Drug Administration.	
§ 320.35 Requirements for in vitro testing of each batch.	
§ 320.36 Requirements for maintenance of records of bioequivalence testing.	
§ 320.38 Retention of bioavailability samples.	
§ 320.63 Retention of bioequivalence samples.	

Definitions

Bioavailability (BA):

The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action.

- For drug products that are not intended to be absorbed into the bloodstream, BA may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action.

21 CFR 314.3, 320.1

Definitions

Bioequivalence (BE):

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.

- Where there is an intentional difference in rate, certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action.

21 CFR 314.3, 320.1

Definitions

- **Pharmaceutical Equivalent**: Identical dosage forms and route(s) of administration with identical amounts of the identical active drug ingredient.

- **Pharmaceutical Alternative**: Identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form, or the same salt or ester.

- **Therapeutic Equivalents**:

Pharmaceutical Equivalent + Bioequivalence

Basis for Measuring BA

Comparison of measured parameters for a drug product that does not indicate a significant difference from the reference material in its **rate** and **extent of absorption**.

- **Drug products intended to be absorbed into the bloodstream**:
  - measured concentrations of the active drug ingredient in the blood, urinary excretion rates, or pharmacological effects

- **Drug products NOT intended to be absorbed into the bloodstream**:
  - scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action

Basis for Demonstrating BE

Two drug products (Test and Reference) are considered bioequivalent if they are **pharmaceutical equivalents** or **pharmaceutical alternatives; And**:

- their **rate and extent of absorption** do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.
- their **extent of absorption** do not show a significant difference with different **rates of absorption** because such differences in the rate of absorption are intentional and are reflected in the labeling.

For drug products NOT intended to be absorbed into the bloodstream:

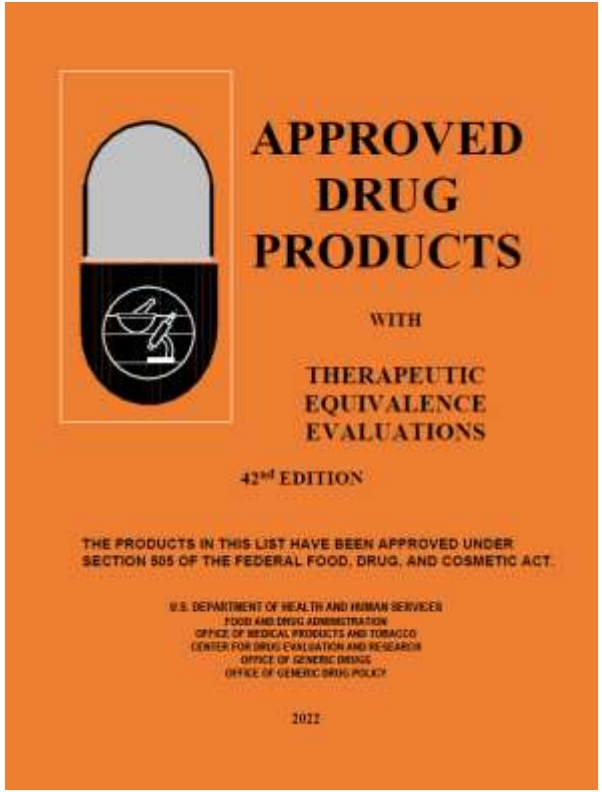
- BE may be demonstrated by scientifically valid methods that are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

Orange Book

FDA's Approved Drug Products with Therapeutic Evaluations (42nd Edition, 2022)

- **"A" CODES**: Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products.
  - AA, AN, AO, AP, AT; AB
- **"B" CODES**: Drug products that FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products.
  - BC, BD, BE, BN, BP, BR, BS, BT, BX

- *In March 2020, FDA removed from the Orange Book the listings for "biological products" that have been approved in applications under section 505 of the FD&C Act because these products are no longer "listed drugs" (see section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009).*



Types of evidence to measure BA or establish BE

BA may be measured or BE may be demonstrated by several *in vivo* and *in vitro* methods.

- FDA may require *in vivo* or *in vitro* testing, or both, to measure the BA or establish BE of drug products.
- The selection of the method used to meet requirement depends upon:
  - the purpose of the study
  - the analytical methods available
  - the nature of the drug product
- Shall use the most accurate, sensitive, and reproducible approach available.

Types of evidence to measure BA or establish BE

#1. An *in vivo* test in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time.

- Studies with pharmacokinetics (PK) endpoint in whole blood, plasma, serum
- The most accurate, sensitive, and reproducible approach
- Particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution within the body

Types of evidence to measure BA or establish BE

#2. An *in vivo* test in which the urinary excretion of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time.

- Studies with PK endpoint in urine
- The measurement intervals should be as short as possible to ensure the measured rate of elimination as accurate as possible.
- Applicable to certain category of dosage forms; not appropriate where urinary excretion is not a significant mechanism of elimination.

Types of evidence to measure BA or establish BE

#3. An *in vivo* test in which an appropriate acute pharmacological effect of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility.

- Studies with pharmacodynamics (PD) endpoint
- Particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution

Types of evidence to measure BA or establish BE

#4. Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring BA, or appropriately designed comparative clinical trials, for purposes of demonstrating BE.

- Studies with clinical endpoint
- The least accurate, sensitive, and reproducible approach
- May be considered sufficiently accurate of dosage forms intended to deliver the active moiety locally.

Types of evidence to measure BA or establish BE

- An *in vitro* test that has been correlated with and is predictive of human *in vivo* bioavailability data (IVIVC).
- A currently available *in vitro* test acceptable to FDA (usually a dissolution rate test) that ensures human in vivo bioavailability.
- Any other approach deemed adequate by FDA to measure BA or establish BE.

Guidance for Industry

- Applications Covered by Section 505(b)(2), 1999 (www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-covered-section-505b2)
- Determining Whether to Submit an ANDA or a 505(b)(2) Application, 2019 (www.fda.gov/regulatory-information/search-fda-guidance-documents/determining-whether-submit-anda-or-505b2-application)

- Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application, 2021 (www.fda.gov/regulatory-information/search-fda-guidance-documents/bioequivalence-studies-pharmacokinetic-endpoints-drugs-submitted-under-abbreviated-new-drug)
- Bioavailability Studies Submitted in NDAs or INDs – General Considerations, 2022 (www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-studies-submitted-ndas-or-inds-general-considerations)
- Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, 2003 (www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-and-bioequivalence-studies-nasal-aerosols-and-nasal-sprays-local-action)

- Product Specific Guidance (www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development)

Summary

- Relevant law, regulations and the regulatory pathways
- Understand basis for measuring in vivo BA or demonstrating BE
- Understand types of evidence to measure BA or establish BE

Challenge Question #1

True or False?

In vivo BA/BE studies may be submitted to support ANDAs under 505(j) pathway only.

A. True
B. False

Challenge Question #2

Which type of evidence may be used to measure BA or establish BE?

A. Comparative PK
B. Comparative PD
C. Comparative clinical endpoint
D. in vitro-in vivo correlation (IVIVC)
E. All of the above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