Bioequivalence Studies for Generic Drug Development

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Disclaimer

- This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Outline

- Bioequivalence (BE) of generic drug products
- Regulations that govern the bioequivalence determination of a generic drug product
- FDA guidances regarding bioequivalence
- Development of Product-Specific Guidances (PSGs)
- Bioequivalence information submitted in an Abbreviated New Drug Application (ANDA) and common issues for BE studies
- Takeaways

Regulations Governing BE

Role of BE in Therapeutic Equivalence (TE)

- Therapeutic Equivalence (21 CFR 314.3(b))
  - Pharmaceutical Equivalence (PE)
    - Generally, drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active ingredient, that deliver identical amounts of the active ingredient over the identical dosing period, and meet the identical compendial or other applicable standard of identity, strength, quality, and purity
  - **Bioequivalence (BE)**
    - 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 in an appropriately designed study.
  - Expected to have same clinical effect and safety profile when administered to patients under the conditions of use specified in the labeling

Regulations Governing BE Studies

- **21 CFR 314.94(a)(7)-***requires BE documentation in support of an ANDA.*
- **21 CFR 320.21(b)-***requires submission of evidence that the proposed drug product is bioequivalent to the reference listed drug or information supporting waiver of evidence demonstrating in vivo bioequivalence (i.e., 21 CFR 320.22).*
- **21 CFR 320.22***- contains requirements regarding the criteria for a waiver of the in vivo bioequivalence study requirement.*

Utpal Munshi, "Best Practices for Conducting Bioequivalence Studies" , SBIA, April 12, 2018

Regulations Governing BE Studies

- **21 CFR 320.23(b)-***contains requirements stating that:*
  - *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*
  - *Bioequivalence may be demonstrated by scientifically valid methods for drug products not intended to be absorbed into the bloodstream.*
- **21 CFR 320.24(a)**
  - *FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products.*
  - *Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available.*

Utpal Munshi, "Best Practices for Conducting Bioequivalence Studies" , SBIA, April 12, 2018

Regulations Governing BE Studies

- **21 CFR 320.24(b)-**Approaches for demonstrating BE
  - In vivo pharmacokinetic (PK) study in whole blood, plasma, serum or other appropriate biological fluid or a correlated in vitro study
  - In vivo urine excretion study
  - In vivo pharmacodynamic (PD) study
  - In vivo comparative clinical endpoint BE study
  - In vitro test acceptable to FDA
  - Any other approach deemed adequate by FDA to establish BE

Relevant FDA Guidances

Note: The guidance examples provided in this presentation should not be considered as an exhaustive list.

Referencing Approved Drug Products in ANDA Submissions

- This guidance provides information to potential applicants on how to identify a reference listed drug (RLD), a reference standard (RS), and the basis of submission in an ANDA submission.
  - The RLD is the listed drug to which the ANDA applicant must show its proposed generic drug is the same with respect to active ingredient(s), dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics.
  - The RS is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval of the ANDA.
- If an applicant has a question about identification of RLD or RS, the applicant may submit control correspondence to seek input from the Agency.

https://www.fda.gov/media/102360/download

BE Studies With PK Endpoints for Drugs Submitted Under an ANDA

- General recommendations in study design and data handling of bioequivalence studies with PK endpoints
- Recommendations for establishing BE for specific dosage forms
  - Oral Solutions/Suspensions/Immediate Release (IR) products/Modified Release (MR) products/Chewable Tablets/Orally Disintegrating Tablets/Sublingual/Transdermal
  - Waiver of in vivo BE requirement for additional strengths of IR drug products
  - Demonstration of BE for additional strengths of MR drug products
- Special topics that may warrant special consideration
  - E.g.: Metabolite(s); Enantiomers; Endogenous compounds; First point Cmax in a BE study; Alcohol dose dumping of MR drug products

https://www.fda.gov/media/87219/download

Bioanalytical Method Validation

- The guidance provides recommendations to bioanalytical method validation in PK BE studies.
- Recommendations of bioanalytical parameters and acceptance criteria for method validation and In-study conduct
  - Calibration Curve/Quality Controls
  - Sensitivity/Selectivity/Specificity
  - Accuracy/Precision
  - Recovery
  - Dilution
  - Stability of the analyte in the matrix
  - Incurred sample analysis/repeat analysis
- Special topics

  E.g.: Endogenous compounds
- Documentation for method validation and bioanalytical reports

https://www.fda.gov/media/70858/download

M9 Biopharmaceutics Classification System-Based Biowaivers

- This guidance provides recommendations to support the biopharmaceutic classification of drug substances and the BCS-based biowaiver of bioequivalence studies of drug products.

- Eligibility for a BCS waiver
  - Eligible: IR Solid Oral Dosage Forms and Suspension
  - Ineligible: MR drug products/Narrow therapeutic range drugs/Dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets)

BCS-1 Waiver	BCS-3 Waiver
❖ High solubility ❖ High permeability ❖ Rapid dissolution ❖ The test formulation does not contain excipients in amounts that will affect absorption	❖ High solubility ❖ Very rapid dissolution ❖ Test formulation is qualitatively the same and quantitatively very similar to that of the RLD product

https://www.fda.gov/media/148472/download

Additional Guidances

- Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c) (August 2020) https://www.fda.gov/media/141218/download
- SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (November 1995) https://www.fda.gov/media/70949/download
- SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation(October 1997) https://www.fda.gov/media/70956/download
- Statistical Approaches to Establishing Bioequivalence (February 2001) https://www.fda.gov/media/70958/download
- **Guidance Document Search Webpage: https://www.fda.gov/regulatory-information/search-fda-guidance-documents**

Product-Specific Guidance (PSG) Development

PSGs for Generic Drug Development

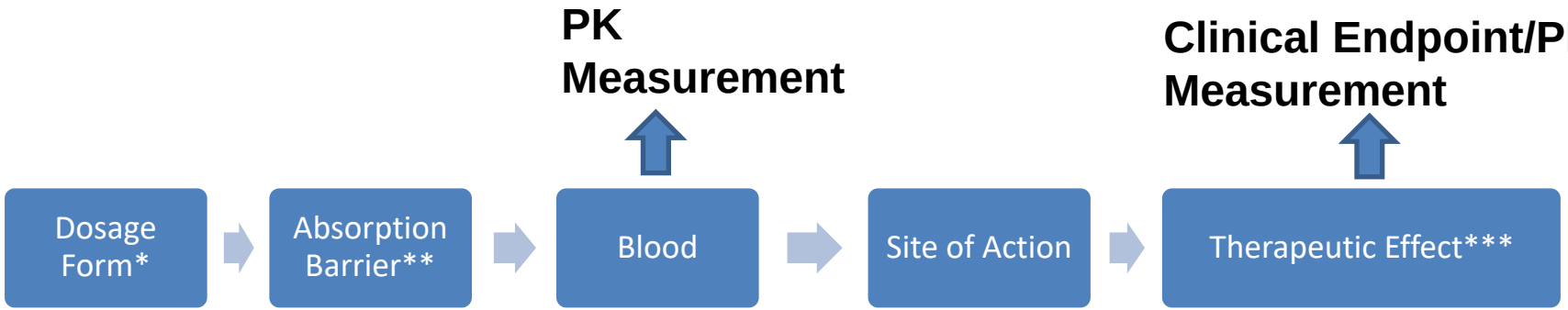
- Office of Generic Drugs (OGD) leads PSG development in collaboration with multiple disciplines and offices within the FDA.
- Describe the Agency's current thinking on the evidence needed to demonstrate that a generic drug is therapeutically equivalent to the corresponding RLD product.
- Assist the generic pharmaceutical industry in identifying the most appropriate methodology and approaches for developing generic drugs and generating the evidence needed to support ANDA approval.

The ABCs of Product Specific Guidances, CDER SBIA Chronicles, September 2nd, 2021, https://www.fda.gov/media/151949/download

PSGs for Generic Drug Development

- As of July 2022, a total of 2003 PSGs have been published.
  - Generally published quarterly
- PSG database for specific products arranged by active ingredient
  - Product-Specific Guidances for Generic Drug Development (fda.gov)
- Upcoming PSG for Complex Generic Drug Product Development webpage
  - Upcoming Product-Specific Guidances for Complex Generic Drug Product Development | FDA

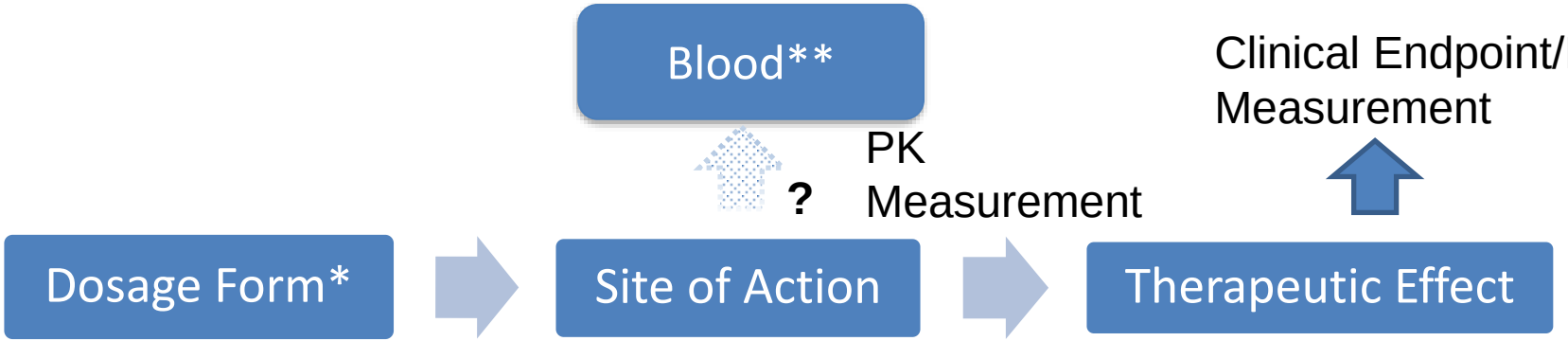
Considerations in Developing BE Recommendations for Systemically Available Drugs



* E.g.: Oral Dosage Forms, Transdermal Drug Delivery System, Injectable Suspension, etc.
**E.g.: Gut wall, Buccal Mucosa, Skin, Nose, Lung, etc.
*** Some products may need both PK and clinical endpoint or PD studies to establish BE; E.g.: some inhalational drug products

Route of administration: E.g.: Enteral tube feeding; Sprinkle in applesauce;
Formulation design: E.g.: Abuse deterrent opioid; Liposomal injectable;
Properties of drug substance: E.g.: highly variable; endogenous compound;
Mechanism of drug delivery: E.g.: Drug-Device combination product such as Dry Powder Inhaler

Considerations in Developing BE Recommendations for Locally Acting Drugs



* E.g.: Drugs of Oral Dosage Forms, Topical Dermatological/Ophthalmic Product, Nasal and Orally Inhalation Product, etc.
**May or may not have systemic absorption

- Mechanism of Action and Site of Action-E.g.:
  - Topical Corticosteroids (Vasoconstrictor Assay)
  - Sevelamer Carbonate Tablets (In vitro binding studies)
  - Mesalamine Extended-Release Tablets (Multi-pH dissolution testing)
- Availability and feasibility of testing-E.g.:
  - Many in vitro tests such as particle size distribution, In vitro release test/In vitro permeation study (IVRT/IVPT) as alternative BE approaches

Key Elements of PK BE Study Recommendations

- Study Design
  - Single-Dose vs. Steady State
  - Cross-over vs. Parallel
  - Partial or Fully replicated
- Study Subjects
  - General Population, patients
- Study Type
  - Fasting, fed, fasting sprinkle
- Analyte to Measure
  - Parent drug vs. metabolite
  - Biological matrix: whole blood, serum, plasma, or urine
  - Analyte(s) pivotal for BE determination vs. analyte(s) considered supportive
- Waiver Criteria for additional strengths (if applicable)

Key Elements of PK BE Study Recommendations

- Additional comments for some special considerations, for example:
  - Endogenous compounds
  - Subject inclusion/exclusion criteria
  - Safety measurements during study conduct
  - Partial AUC

BE-Related Information in ANDA Submissions and Common Deficiencies

Generic Drug Application

- ANDA
  - An ANDA contains data which is submitted to FDA for the review and potential approval of a generic drug product.
  - Guidance for Industry: ANDA Submissions-Content and Format (June 2019)
    - https://www.fda.gov/media/128127/download
  - Guidance for Industry: Good ANDA Submission Practices (January 2022)
    - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-anda-submission-practices-guidance-industry

BE Information Included in an ANDA Submission

Module 1	Module 2	Module 3	Module 5
• Basis of Submission	• Summary Tables of BE data	• Component and Composition Table	• Study reports and Protocols of BE studies

BE Information Included in an ANDA Submission

- An ANDA applicant should submit data from all BE studies the applicant conducts on the drug product formulation submitted for approval
  - https://www.fda.gov/files/drugs/published/Submission-of-Summary-Bioequivalence-Data-for-Abbreviated-New-Drug-Applications.pdf
  - A complete or summary report for each individual study conducted on the same formulation as the exhibit batch
  - Include studies that did not show the product met BE criteria

BE Information Included in an ANDA Submission

- Summary Tables Webpage
  - https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/abbreviated-new-drug-application-anda-forms-and-submission-requirements
  - Summary tables are available and include, but are not limited, to those for in vivo PK BE studies, BCS-based biowaivers, in vitro feeding tube testing, comparative clinical endpoint studies, topical dermatologic corticosteroids in vivo BE studies, in vitro binding studies, studies for nasal spray products, and studies for pressured metered dose inhaler products

BE Information Included in an ANDA Submission (In Vivo and In Vitro)

- Analytical Study Data
  - Pre-study method validation report
  - Analytical report for BE studies
  - Analytical raw data from the study runs (accepted and rejected) of all subjects
  - Serially selected chromatograms for 20% of the study subjects
  - Analytical standard operating procedures (SOPs) used in the application
- Study Site information
  - Clinical and Analytical Sites
  - Street address for all CROs who conduct BE studies

BE Information Included in an ANDA Submission

- In vivo BE studies
  - Study protocols
  - Study reports
    - Study information; Product information; Study design
    - Demographic profiles of subjects, Dropout Information, Study adverse events and Protocol Deviation
    - Statistical results
  - Study datasets in appropriate CDISC format
  - Case report forms for all subjects (CRFs)

BE Information Included in an ANDA Submission

- In vitro BE study
  - Method development report
    - E.g.: IVRT, IVPT, Quantitative Capsule Rupture Test (QCRT)
  - Method validation report
    - Accuracy and Precision of the method
    - Method robustness
    - Discriminatory power of the method
  - Pivotal BE study report

Common BE Deficiencies
(In Vivo and In Vitro)

- Analytical
  - Inadequate dilution integrity data
  - Inadequate stability data
  - Incomplete or missing numerical raw data
  - Incomplete or missing standard operating procedures (SOPs)
  - Missing rejected and/or accepted chromatograms
  - Inconsistencies between summary tables and reports

- Statistical Analysis
  - No pre-specified statistical plan
  - Incorrect model used
  - Missing justification for method used

Tian Ma, Common Deficiencies for Study Sample Reanalysis in Pharmacokinetic Bioequivalence Studies Submitted in Abbreviated New Drug Applications (ANDAs), SBIA, June 30, 2020
Utpal M. Munshi, Best Practice for Conducting Bioequivalence Studies, SBIA, April 12, 2018
Dongmei Lu et al, Common Deficiencies of in vitro Binding Bioequivalence (BE) Studies Submitted in Abbreviated New Drug Applications (ANDAs), The AAPS Journal 2018, 20: 26

Common BE Deficiencies
(In Vitro)

- Missing study details including study procedures, study dates, apparatus information, number of replicates, individual data of each replicate and drug product information
- Missing study site name and address
- Discrepancies within submission, e.g., information not consistent between summary tables and study report
- Missing or inadequate rationale for selecting method parameters in method development report
- Inadequate method validation

Tian Ma, Expectations for In Vitro Release Test (IVRT) Data and Information Submitted in ANDAs, IVRT IVPT Workshop, August 20, 2021
Archana A. Manerikar, Considerations for In Vitro Permeation Test (IVPT) Data and Information Submitted in ANDAs, IVRT IVPT Workshop, August 20, 2021

Takeaways

- Generic drug products approved via an ANDA submission are considered therapeutically equivalent to the RLD based on the demonstration of bioequivalence and pharmaceutical equivalence.
- The general guidances and PSGs reflect FDA's current thinking for generic drug product development.
- Depending on the site of action, route of delivery, dosage form, formulation design, etc., BE approaches utilizing in vivo or in vitro methods or a combination thereof, may be recommended.
- A detailed, well-organized ANDA submission can reduce the number of deficiencies and review cycles.

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Challenge Question-1

- Which of the following should be considered when making BE recommendations during PSG development?
  a) Route of administration
  b) Formulation design
  c) Site of action
  d) Feasibility to measure systemic bioavailability
  e) All of the above

Challenge Question-2

- Which of the following BE-related information should be included in an ANDA submission?
  a) Basis of submission
  b) Composition and component table of the test formulation
  c) Summary tables of BE data
  d) Reports of failed BE studies on the same formulation as the exhibit batch
  e) All of the above


THANK YOU