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Biowaiver Approaches for Generic Drug Products in the US: Case Studies

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Topics for Discussion

- Definition of bioequivalence (BE)
- Role of BE studies in generic drug development
- Regulatory BE approaches
- Biowaivers in presence of established in vitro-in vivo (IVIVC) correlation
- Use of dissolution testing for biowaivers and as a BE approach
- In vitro tests as a BE approach

Definition of Bioequivalence (BE)

The **absence of a significant difference** in the **rate** and **extent** to which the active ingredient or active moiety in **pharmaceutical equivalents** (*same amount, same active, same dosage forms)* or **pharmaceutical alternatives** (*same active moiety, different chemical form or different dosage form or strength)* becomes available at the **site of drug action** when administered at the same molar dose under similar conditions in an appropriately designed study.

Definition from 21 CFR § 320.1

Role of BE Studies

- U.S. FDA Practice

  BE + Pharmaceutical equivalence = Therapeutic equivalence

- Therapeutically equivalent products can be substituted for each other without any adjustment in dose or additional therapeutic monitoring

Regulatory BE Approaches

Listed in 21 CRF §320.24 in descending order of accuracy, sensitivity, reproducibility:

1. (a) In vivo study in humans with pharmacokinetic (PK) endpoint;

   (b) **in vitro test correlated with in vivo data (IVIVC)**

2. In vivo study in humans in which drug excreted in urine is measured

Regulatory BE Approaches (cont.)

3. In vivo study in humans with pharmacodynamic (PD) endpoint
4. Well-controlled comparative clinical trials
5. A currently available **in vitro (usually dissolution) test that ensures human in vivo bioavailability**
6. Any **other approach deemed adequate** by the FDA to establish BE

Biowaivers (Waiver of In Vivo Testing)

Role of IVIVC in Generic Drug Development

- Pre-approval as well as certain scale-up and post-approval changes (SUPAC)
- Setting dissolution specifications
- Number of IVIVCs in generic drug submissions between January 1996 – December 2014 = 14
  - 9 IVIVCs were for pre-approval changes
  - 4 IVIVCs were for post-approval changes
  - 1 IVIVC was used to guide the development of the to-be-marketed formulation

Continued from previous slide

Purpose of IVIVC	Dosage form	Drug substance BCS classification	Dissolution apparatus and medium	Number of ANDAs with IVIVC	Number of acceptable IVIVCs
Change in dissolution method and specifications	ER tablets	Class I or III	USP apparatus II (paddle), 0.1 N HCl	1	0
Level 3 site manufacturing change		Class I	USP apparatus I (basket), 0.1 N HCl	1	0
Waiver for lower strengths		Class I	USP apparatus I (basket), phosphate buffer, pH 6.8	1	1
Waiver for higher strengths To support dissolution method	ER tablets comprised of modified-release core coated with enteric coat	Class II Class II	USP apparatus II (paddle), 0.01 N HCl followed by phosphate buffer, pH 6.8	2	0
Batch-to-batch variation in the particle size, coating weight, process changes, test product composition do not impact the BE	ER tablets comprised of controlled-release pellets	Class I	USP apparatus II (paddle), phosphate buffer, pH 6.8	3	1
Change in dissolution specifications	ER capsules	Class II	USP apparatus I (basket), water	1	1
Change in dissolution specifications	ER capsules containing beads or pellets	Class I	USP apparatus II (paddle), phosphate buffer pH 6.5	1	0
Challenge the results of a failed BE study		Class I	USP apparatus II (paddle), phosphate buffer pH 7.5	1	0
Batch-to-batch variation in pellet coating does not impact the BE		Class I	USP apparatus I (basket), simulated gastric fluid followed by simulated intestinal fluid	1	0
Change in dissolution specifications	ER oral suspension	Class I or III	USP apparatus II (paddle), phosphate buffer, pH 7.4	1	0
Exploratory to guide the development of pivotal formulation	ER tablets containing both IR and ER components	Class I	USP apparatus VII (reciprocating holder) at 30 dpm, 50 mL of acidified water, pH 3.0	1	Not applicable

IVIVC in vitro–in vivo correlation, *BCS* Biopharmaceutics Classification System, *ANDA* Abbreviated New Drug Application, *ER* extended-release, *IR* immediate-release, *BE* bioequivalence

Kaur et. al. Applications of IVIVCs in Generic Drug Development: Case Studies. The AAPS Journal (2015) 17 (4): 1035-39

IVIVC Case Studies

Case Study 1

Purpose: Support change in dissolution specifications beyond a 25% range due to a level 2 change in non-release controlling excipient

Applicant's approach	FDA's assessment
• Developed a Level A correlation using the original test product formulation and the reference product formulation • Did not access internal or external predictability	• Not appropriate to use test and reference formulations, each from a different manufacturer • Relationship between the in vivo dissolution and the in vitro dissolution is formulation dependent • In vitro dissolution is pH dependent Therefore, a minimum of 2 formulations with different release rates are required to develop IVIVC • No internal or external predictability data submitted • Developed IVIVC deemed inadequate

Case Study 1 (cont.)

Outcome: Applicant conducted new BE studies on the reformulated test product. The dissolution specifications were then recommended based on dissolution testing conducted on the bio-lot (reformulated test product) used in the new BE studies.

Case Study 2

Purpose: Support the claim that batch to batch variation in the test product composition does not impact the BE

Applicant's approach	FDA's assessment
Used IVIVC data from summary basis of approval (SBOA) for the reference listed drug (RLD) product	Use of IVIVC data from SBOA for the RLD is not acceptable.

Outcome: Applicant conducted new BE studies on the reformulated test product

Case Study 3

Purpose: Support a Level 3 site change

Applicant's approach	FDA's assessment
• In vitro dissolution profiles and in vivo plasma concentration profiles were obtained from three test formulations with different release-rates (slow, medium, and fast) to develop Level A correlation • Assessed internal and external predictability	• The fast- and slow-releasing formulations had similar dissolution profiles, despite the fact that these two formulations showed marked differences in Cmax and AUC • PK parameters could not be accurately predicated using developed IVIVC • Internal and external predictability were not confirmed

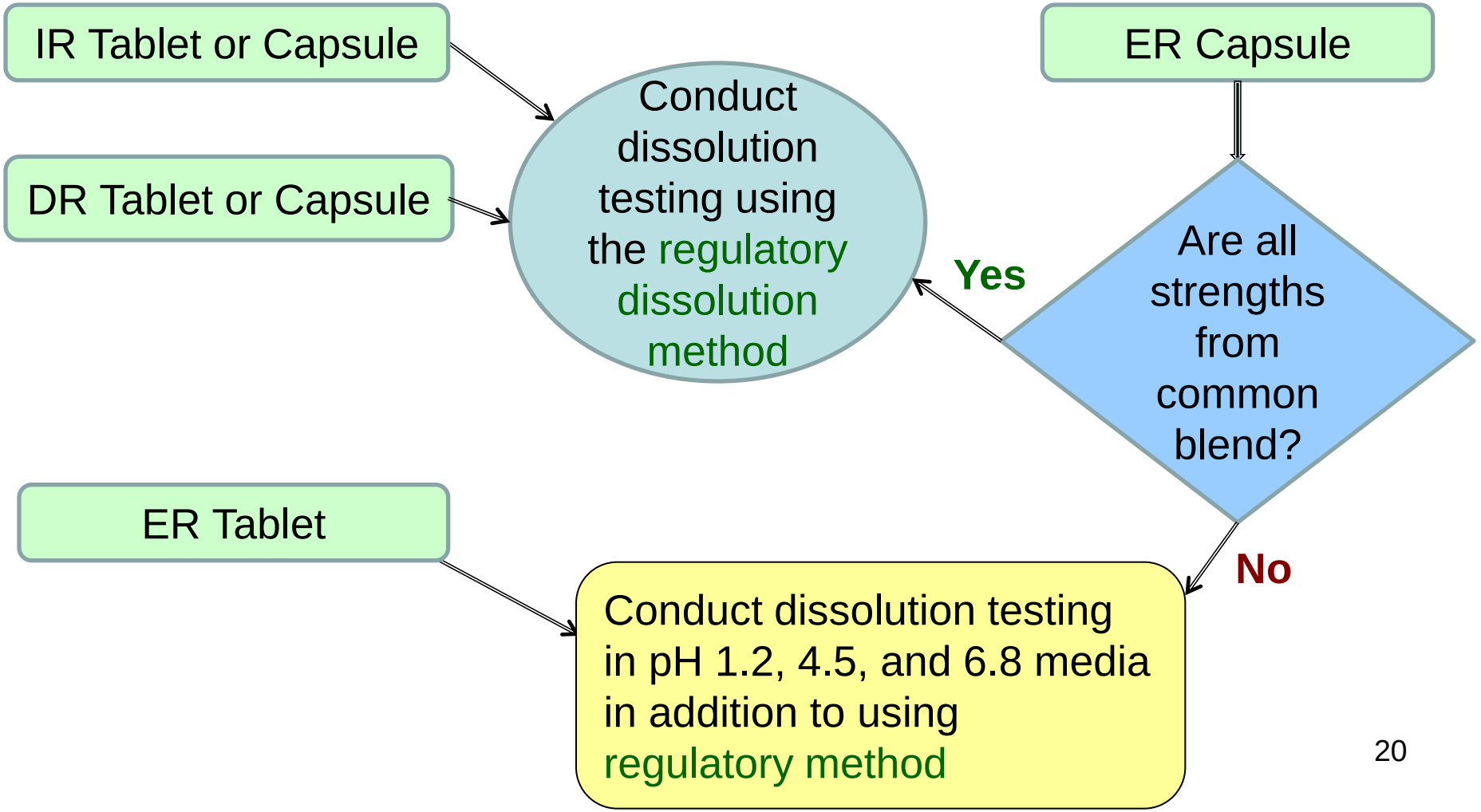
Outcome: Applicant conducted an in vivo study to support the Level 3 site change

Use of Dissolution Testing for Biowaivers

Dissolution Testing for Biowaivers of Multiple Strength Products

- In vivo BE to the RLD established for one or more strengths of the test
- All strengths must be proportionally similar
- Dissolution profiles of other strengths (non-bio strengths) must be comparable to the strength that underwent in vivo BE testing.
- Dissolution approach differs depending on whether product is immediate-release (IR), delayed-release (DR), or extended-release (ER), capsule or tablet

Dissolution Approaches for Biowaivers of Multiple Strength Products



Dissolution Profile Comparison using f2 metric

- The similarity factor f2 measures the similarity in % dissolution of two curves

- Acceptable f2 value ≥ 50 on comparing mean dissolution data for non-biostudy strength (s) vs. biostudy strength (s)

Case Study

- Multiple strengths of an IR drug product
- In vivo BE to the RLD established for the highest strength (biostudy strength)
- Active ingredient has low solubility. The FDA-recommended dissolution method recommend use of surfactant in the dissolution medium and USP Apparatus II

Case Study (cont.)

	F2 value
Test biostudy strength vs. lowest strength	**< 50**
Reference strength used in BE study vs. lowest strength	**< 50**

- When dissolution testing data generated using 2 tablets of lowest strength in dissolution apparatus was compared with 1 tablet of biostudy strength, f2 value > 50.

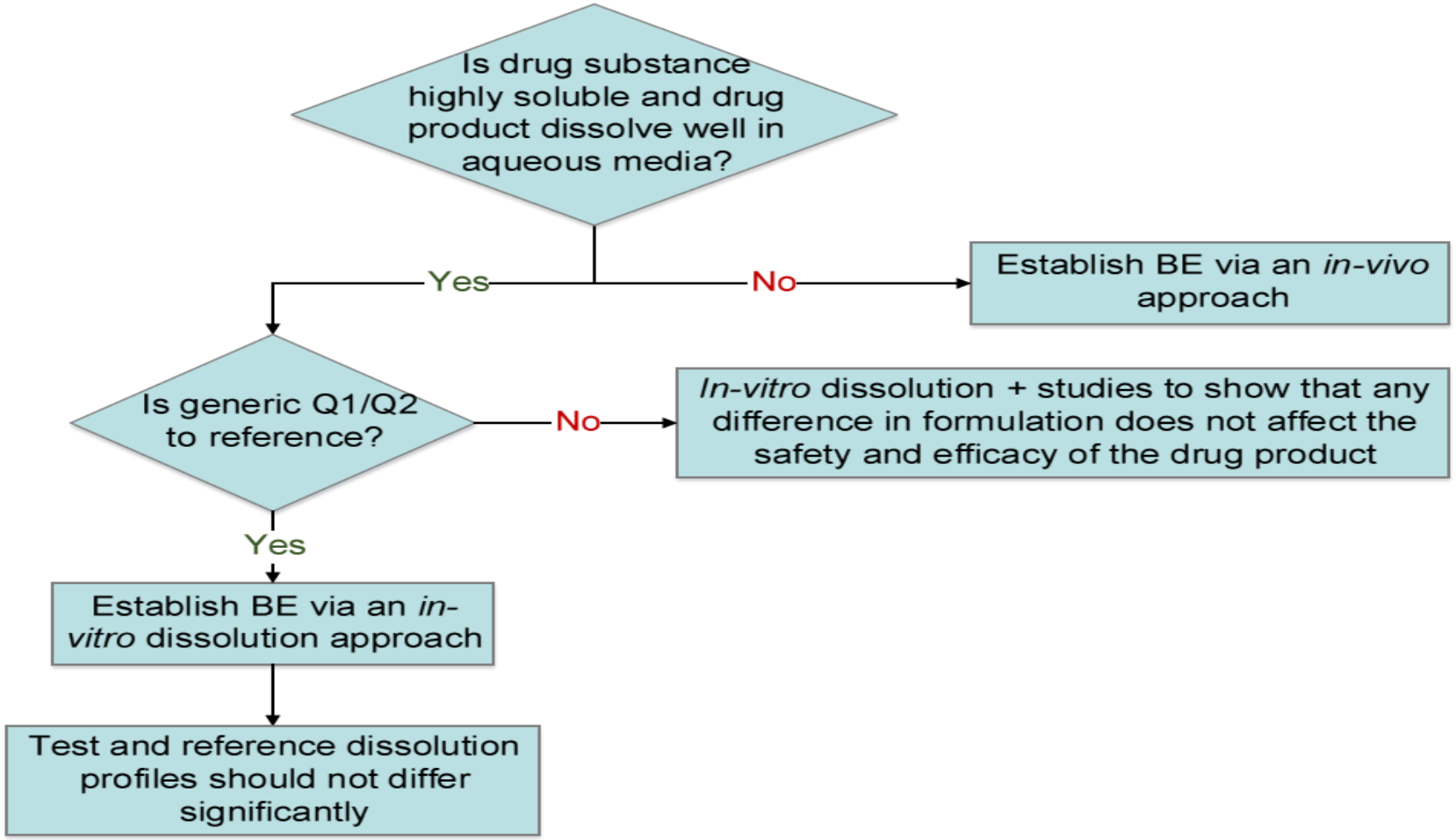
- **Outcome**: Waiver request for in vivo testing of lowest strength was deemed acceptable

Dissolution Testing as a BE Approach

Dissolution Testing as a BE Approach

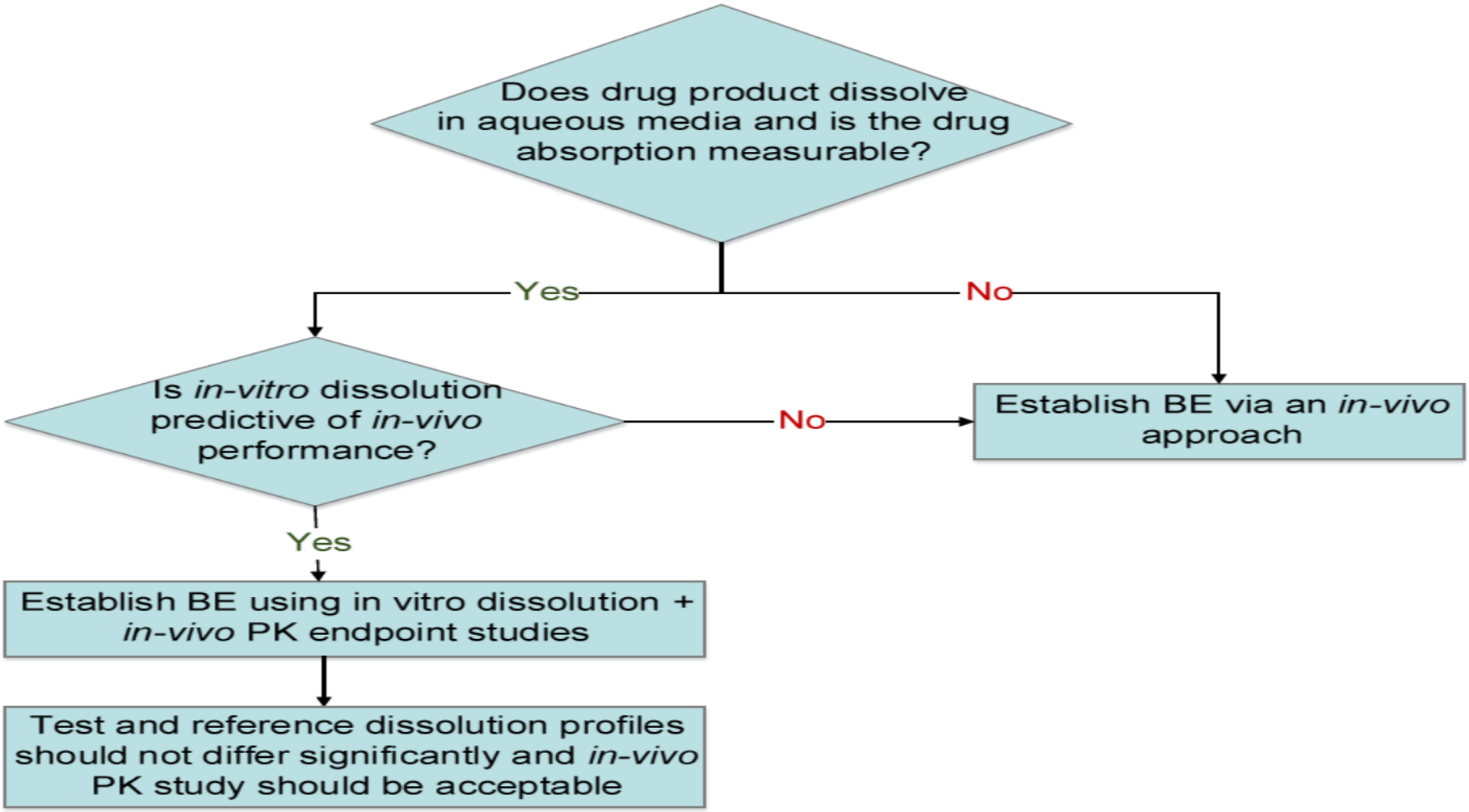
- FDA has used this approach for some locally-acting drug products indicated to treat diseases of the gastrointestinal (GI) tract
- Dissolution testing as a standalone BE approach for IR drug products, if formulation is qualitatively (Q1) and quantitatively (Q2) same to the reference
  - Examples: Vancomycin Capsules and Acarbose Tablets
- In vitro dissolution testing along with in vivo study to establish BE for MR drug products
  - Examples: Mesalamine DR Tablets and ER Capsules

Dissolution as a BE Approach for Locally-acting IR GI Drug Products



Jiang et. al. Bioequivalence for Drug Products Acting Locally within Gastrointestinal Tract. In FDA Bioequivalence Standards. PP. 301

Dissolution as a BE Approach for Locally-acting MR GI Drug Products



Jiang et. al. Bioequivalence for Drug Products Acting Locally within Gastrointestinal Tract. In FDA Bioequivalence Standards. PP. 302

In Vitro Tests as a BE Approach

In Vitro BE Studies

- In vitro test are less variable, easier to control, and are more likely to detect differences between products

- In vitro test should be clinically relevant

Examples of In Vitro BE Studies

Drug Product	In Vitro Approach
Cholestyramine Oral Powder	Bile Acid Binding
Lanthanum Tablets	Phosphate Binding
Zolmitriptan Nasal Spray	A battery of in vitro tests*
Acyclovir Topical Ointment	Q1 and Q2 the same Comparable physico-chemical characteristics and in vitro drug release from the test and reference
Azacitidine Subcutaneous Injection	Q1 and Q2 the same Comparable physico-chemical characteristics, particle morphology, and particle diameter

*FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (April 2003)

Case 1 – Acyclovir Ointment

Product	Acyclovir Ointment, 5%
Indication	Genital herpes and limited non-life-threating mucocutaneous herpes simplex virus
Study Type	2 approaches – In vitro option, test and reference must be Q1/Q2 – In vivo option: BE study with clinical endpoint, if not Q1/Q2

Case 1 – Acyclovir Ointment (cont.)

In Vitro Tests	The test and reference must have comparable – In vitro drug release rate – Particle size – Viscosity – Active ingredient morphic form – PEG molecular weight distribution
Rationale	– In vitro BE approach more sensitive than clinical endpoint study – Due to small clinical benefits shown by topical acyclovir in clinical trials over placebo, a clinical endpoint study may not be feasible or reliable

Case 2 – Azacitidine Injection

Product	Azacitidine Injection, 100 mg/vial
Indication and Usage	For myelodysplastic syndromes administered via intravenous (IV) or subcutaneous (SC) route
How supplied	Supplied as a lyophilized powder for reconstitution as (i) solution for IV administration, and (ii) suspension for SC administration
Study Type	In vitro tests to establish BE, when reconstituted as a suspension for SC administration

Case 2–Azacitidine Injection (cont.)

In Vitro Tests	The test and reference must have comparable – Viscosity, osmolality, pH – Particle morphology – Particle size
Rationale	– In vitro BE approach more sensitive than clinical endpoint study

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