Bioequivalence Recommendations for Generic Drug Products in the US FDA

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Topics for discussion

- General considerations for bioequivalence (BE) study with pharmacokinetic (PK) endpoints
- BE approaches for locally acting drugs
- Use of pAUC as a BE metric
- Summary and conclusion

Role of BE studies

- The proposed generic must be shown to be pharmaceutically equivalent and bioequivalent to the reference listed drug (RLD) to establish that the two are therapeutically equivalent (TE)
- TE products can be substituted for each other without any adjustment in dose or additional therapeutic monitoring
- The most efficient method of assuring therapeutic equivalence is to assure that the formulations of two pharmaceutically equivalent drug products perform in an equivalent manner

General consideration for BE study with PK endpoints

BE approaches

Listed in 21 CFR §320.24

1. Pharmacokinetic study in which drug concentrations are measured in plasma
2. PK study in which drug concentrations are measured in urine
3. Acute pharmacological effect measured as a function of time - BE study with pharmacodynamic (PD) endpoints
4. Well-controlled clinical trial in humans (BE study with clinical endpoints)
5. Currently available *in vitro* test, acceptable to FDA, that ensures bioavailability (BA)
6. Any other approach deemed adequate by FDA to establish BA or BE

BE study with PK endpoints

- Most drugs reviewed by the Divisions of Bioequivalence are
  - Absorbed into the systemic circulation
  - Systemically active
- For such drugs, BE is best demonstrated in a study in human subjects with pharmacokinetic endpoints

BE study with PK endpoints

- Most studies use **healthy normal subjects**
  - FDA asks that both **males and females** be enrolled
  - Can use **patients**, if there are safety issues
- The number of subjects is based on pharmacokinetic variability
- A BE study of a highly variable drug (HVD) may require enrollment of a larger number of subjects
- Applicants may also consider using a reference-scaled average bioequivalence approach

BE study with PK endpoints

- Use ANOVA with two one-sided tests procedure to statistically analyze BE study data (Schuirmann DJ, *J Pharmacokinet Biopharm.* 1987 Dec;15(6):657-80)
- BE criteria are that the 90% confidence intervals of geometric mean AUC_{0-t}, AUC_{∞} and C_{max} Test/Reference ratios must fall within 0.800 to 1.250
  - Rounding up or down is not permitted
- T_{max} may also be evaluated, if rapid onset of effect is necessary for efficacy
- If there are marked differences between test and reference T_{max} values, OGD will request an evaluation from appropriate CDER clinical division

BE study with PK endpoints

- Two PK studies usually recommended:
  - One in the fasting state
    - The most sensitive and accurate way to evaluate the formulation
  - One is in the fed state
    - Assures the drug product performs the same way in the presence of food
- Sometimes fasting sprinkle study
  - if RLD is labeled to be taken with a soft food, such as applesauce
  - Only applies to modified-release drugs

Reference-scaled average BE (ABE) approach for highly variable drug products

- Studies should use at least 24 subjects
- The reference product is administered twice in the BE study
  - TRR, RTR, RRT
  - A fully-replicated design is also acceptable
- The protocol should specify the intention to use the reference-scaled ABE approach
- Please see progesterone capsule product guidance for more details

Reference-scaled ABE analysis: mixed scaling approach

- The scaling is mixed
  - If $s_{WR} < 0.294$, use the two one-sided tests procedure to determine BE
  - If $s_{WR} \geq 0.294$, use the reference-scaled ABE procedure to determine BE
- Where
  - s_{WR}^2 is the within-subject variance for the reference, estimated in the BE study
  - s_{WR} is the within-subject SD

Reference-scaled ABE study: acceptance criteria

- The 95% upper confidence bound for

$$\left(\bar{Y}_T - \bar{Y}_R \right)^2 - \theta s_{WR}^2$$

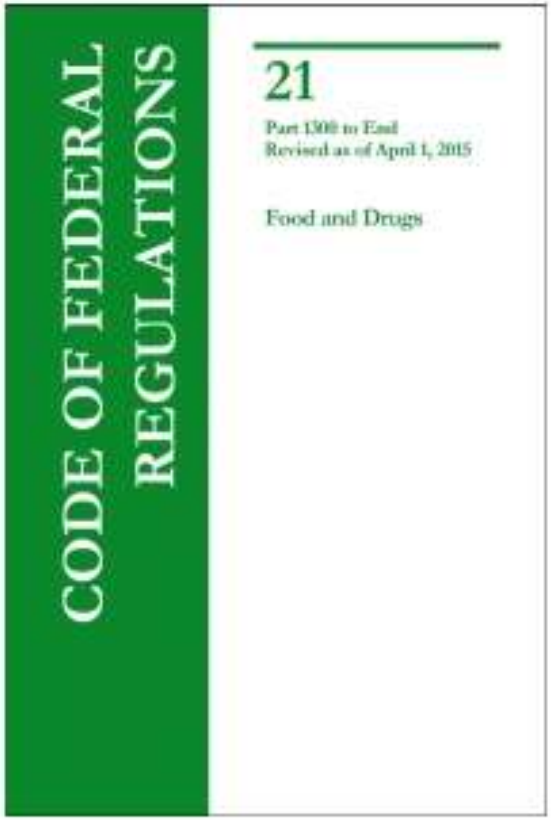
must be ≤ 0;

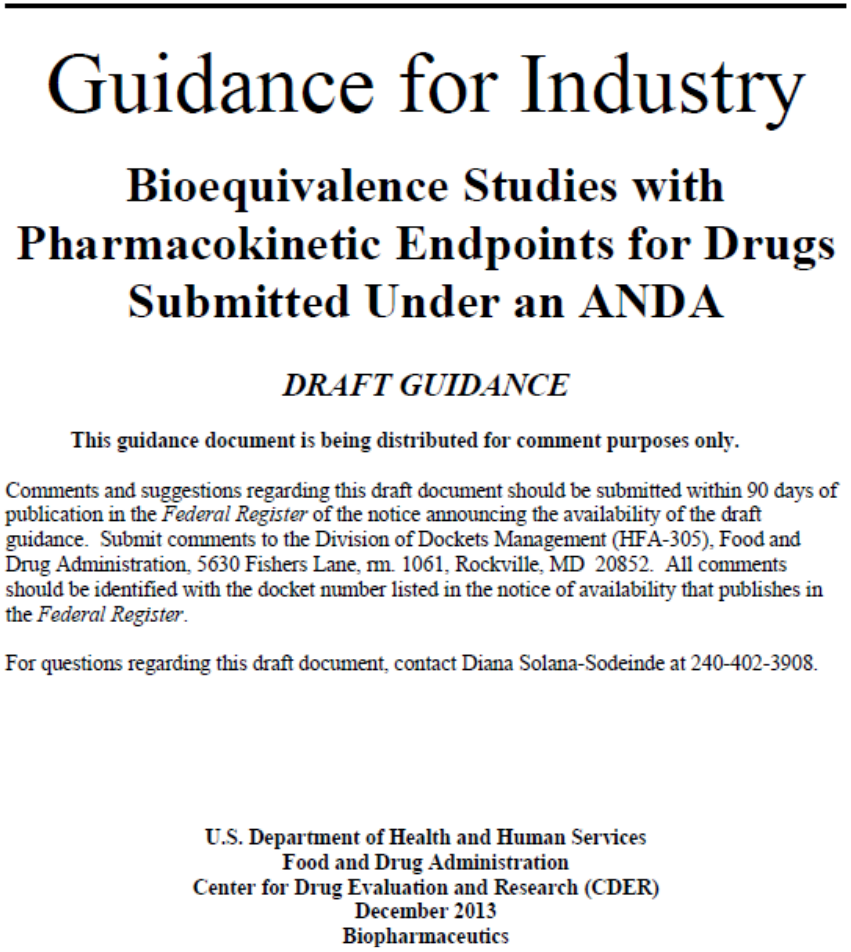
AND

- The limits on $Y_T - Y_R$ are ln(0.8) to ln(1.25)
  - Point estimate (PE) constraint

How do you know the **best current** BE approach?

- **Regulations (**21 CFR 320)
- **General Guidances**





Guidance for Industry

Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Diana Solana-Sodeinde at 240-402-3908.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 2013
Biopharmaceutics

Product-specific guidances for generic drug development

Contains Nonbinding Recommendations

Draft Guidance on Progesterone

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Progesterone

Form/Route: Capsule/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Partial or fully replicated crossover design *in-vivo*
   Strength: 200 mg
   Subjects: Healthy males and postmenopausal females, general population. As many postmenopausal women as possible should be included in the study.
   Additional Comments: Please measure baseline progesterone levels at -1.0, -0.5, and 0

Recommended Apr 2010; Revised Feb 2011

BE approaches for locally acting drugs

Examples of locally acting drugs

- Topical drugs applied to skin
- Nasal spray products
- Inhalation drug products
- Drugs to treat GI disease

BE approaches for locally acting drug products

- For drug products which are locally-acting, plasma concentrations may not be measurable or reflect rate and extent of absorption at site of action
- FDA determines the optimal BE approach for each proposed generic locally acting products on a case-by-case basis
- Approach may be PK, PD, clinical, or in vitro

In vivo BE approaches for locally acting drugs

BE Study Endpoint(s)	Examples
Pharmacodynamic	Acarbose tablets (if not formulated same as reference) Corticosteroid creams Orlistat tablets
Clinical	Clotrimazole cream Tretinoin cream 5-fluorouracil cream

In vitro BE approaches for locally acting drugs

BE Study Endpoint(s)	Examples
Rates of binding to substrate	Ca Acetate Sevelamer Cholestyramine Colestipol
Dissolution rates in media of varying pH	Acarbose * Vancomycin *
Antimicrobial kill rates	Tobramycin in ophthalmic suspensions

* Generic formulation must be qualitatively and quantitatively same as reference

Combined in vivo and in vitro approaches for locally acting drugs

BE Study Endpoint(s)	Examples
PK In vitro dissolution rates in media of varying pH	Balsalazide capsules Sulfasalazine capsules Mesalamine MR tablets and capsules (pAUC)
PK Clinical In vitro tests related to device performance	Fluticasone propionate nasal spray

Use of partial AUC as a BE metric

FDA proposes to use pAUC for some specialized dosage forms

- Initiation: In 2008, following the posting of the Bioequivalence Recommendations Guidance for Zolpidem ER Tablets
- Objectives: To provide additional assurance of therapeutic equivalence for some complex generic products
  - Formulation contains an IR portion and a delayed- or extended-release (DR, ER) portion
  - Most recently, proposed for locally-acting systemically absorbed MR drug products indicated to treat GI disease
- Outcome: Approval of generic versions of multiphasic modified release formulations of zolpidem, methylphenidate, and mixed amphetamines

Products for which pAUC is used

Product	Description	Indication
Zolpidem ER Tablet	Tablet consists of an IR layer & an ER layer	Treatment of insomnia
Methylphenidate ER Capsule	Capsules contains mix of IR and ER beads, or mix of IR and enteric-coated beads	Stimulant used to treat attention deficit hyperactivity disorder
Methylphenidate ER Tablet	Tablet consists of an IR layer & an ER layer	
Mixed Amphetamines ER Capsule	Capsule contains two types of beads, designed to give double-pulsed delivery	
Mesalamine DR Tablet	Enteric-coated tablet	Treatment of patients with ulcerative colitis
Mesalamine ER Capsule	Capsule containing ER beads	

Example: pAUC as a BE metric

	Ambien CR®, zolpidem ER tablet
Formulation	Bilayer tablet, IR and ER components
Indication	Short-term treatment of insomnia
Mechanism	•In IR phase, gives comparable input rate to that of IR product alone •In ER phase, maintains zolpidem plasma concentrations
Reference	BE metrics: C_{max}; $AUC_{0-1.5h}$; $AUC_{1.5h-t}$; AUC_{∞} AUC_{0-T} should compare T & R exposure responsible for early onset of response AUC_{T-t} should compare T & R exposure responsible for sustained response

Example: pAUC for mesalamine MR products

- Mesalamine acts locally in the GI tract; It is well absorbed, but not necessarily at the site of action;
- Comparing pAUC values should confirm that test and reference provide drug at the same rate and extent at the site of action;
- In addition, test and reference dissolution profiles are to be compared at pH values representative of GI tract conditions.

Product	In vivo BE metrics	Rationale for pAUC values
Mesalamine DR Tablets	$AUC_{8\text{-}48}$, $AUC_{0\text{-}t}$, C_{max}	$AUC_{8\text{-}48}$ is clinically relevant
Mesalamine ER Capsules	$AUC_{0\text{-}3}$, $AUC_{3\text{-}t}$, $AUC_{0\text{-}t}$, C_{max}	$AUC_{0\text{-}3}$ and $AUC_{3\text{-}t}$ best characterize GI absorption from this dosage form

Summary and conclusions

- The Food, Drug and Cosmetic Act and FDA regulations give the FDA the legal authority to request BE studies
- FDA posts guidances on BE approaches; make sure to follow the most updated guidance:

  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
- For most systemically available/active generic drugs, FDA requests a single-dose fasting and a single-dose fed BE study
- For locally acting drug product, the BE approach can be different considering the drug's mechanism of action, site of action, complexity of the RLD formulation and feasibility, sensitivity of an approach.

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Thank You!

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