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Bioequivalence Testing in the U.S. for Generic Drug Products

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Topics for Discussion

- Why FDA requests bioequivalence (BE) studies
- Regulatory authority on BE
- General BE study considerations
- BE approaches: IVIVC, Urine, PD, Clinical, *in vitro*
- Bio-waivers: IV solutions, Oral solutions, Solid oral dosage forms, BCS class I, DESI
- Dissolution
- Special Cases: Specific examples of actual BE requirements for certain drug products
Why FDA requests BE studies

• To determine rate/extent of absorption of each therapeutic moiety for
  – Potential generic products for which there is a reference listed drug (RLD) approved for marketing in US
  – Potential new drug products (new salts, dosage forms) for which adequate clinical studies have already been conducted
  – Reformulated drug products
• Effective July 15, 2009: FDA is requiring all BE studies conducted on a drug product formulation submitted for approval i.e. fasting, fed, sprinkle, failed, etc.
Regulatory authority on BE

• The United States Food, Drug, and Cosmetic Act (FDCA), enacted by Congress in 1938, gives authority to FDA
  – Provisions for generic drugs added in 1984
• FDCA (§505(j)) states that rate and extent of drug absorption must be compared to establish bioequivalence between two products
• The FDA’s regulations are codified in Title 21 of the Code of Federal Regulations (21 CFR)
• Under 21 CFR, Part 320 is for “Bioavailability and Bioequivalence Requirements”
  – $C_{\text{max}}$ as index of rate of absorption
  – $\text{AUC}$ as index of extent of absorption
General BE study considerations

- Most studies use healthy normal subjects
  - FDA asks that both males, females be enrolled
  - Can use patients, if there are safety issues
- The number of subjects is based on pharmacokinetic (PK) variability
- A BE study of a highly variable drug may require enrollment of a larger number of subjects
General BE study considerations (cont.)

• If drug poses a safety risk to healthy normal subjects, must study in patients

• Examples
  – Clozapine: Evaluate BE in a steady-state study in schizophrenic patients on established regimens (see FDA guidance on Clozapine Tablets)
  
  – Etoposide: Evaluate BE as the first dose of a treatment cycle in cancer patients
General BE study considerations (cont.)

- Bioanalytical methods must be validated
- Pre-study Bioanalytical Method Validation should determine the following
  - Assay selectivity
  - Assay precision and accuracy
  - Stability of stored analyte(s) (i.e. drug and metabolite, if applicable) in various matrices
  - Recovery of analyte(s) and internal standard
  - Assay limit of quantitation (LOQ)
General BE study considerations (cont.)

- AUC is determined by the trapezoidal method
- $C_{\text{max}}$ (and corresponding $T_{\text{max}}$) is determined numerically
- FDA requests that $AUC_{0-t}$, $AUC_{\infty}$ and $C_{\text{max}}$ meet BE criteria
- Applicants should also report $K_{\text{el}}$ and $T_{1/2}$
- If drug has a long $T_{1/2}$, then not necessary to calculate $AUC_{\infty}$ (also $K_{\text{el}}$ and $T_{1/2}$)
General BE study considerations (cont.)

• Use ANOVA with two one-sided tests procedure to statistically analyze BE study data (Schuirmann DJ, *J Pharmacokin et Biopharm.* 1987 Dec;15(6):657-80)

• BE criteria are that 90% confidence intervals of geometric mean AUC$_{0-t}$, AUC$_\infty$ 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
  – Example: Naproxen Sodium ER Tablets (RLD Naprelan® CR Tablets)
Single-dose fasting BE study

- Most sensitive and discriminating form of BE study design
- FDA requests single-dose fasting BE study for all systemically available/active drugs unless precluded for safety reasons
  - Example: Mefloquine Tablets, 250 mg
  - For reasons of safety, label recommends that patients take on full stomach
  - Long half-life drug
- FDA requests
  - Single dose, parallel design fed BE study only
  - Use a truncated AUC at 72 hours
Single-dose fed BE study

- For most solid oral dosage forms, sponsor should conduct both fasting & fed BE studies
- Drug is given within 30 minutes of consuming a high-fat meal
- Meal should provide 800-1000 Kcal in total and at least 50% of the total Kcal from fat
- FDA publishes a standardized meal description
  - Non-standardized meal is acceptable if meets total Kcal and fat Kcal criteria
  - FDA discourages using vegetarian meals - may not produce same effects as non-vegetarian meals
When FDA requests fed BE studies

• For immediate-release (IR) products, dictated by FDA-approved label for the RLD

  - If label contains statements about effect of food on absorption or administration

  - If drug cannot be given on an empty stomach (for safety reasons)
When FDA requests fed BE studies (cont.)

- For all orally-administered modified-release (MR) oral drug products
  - Delayed-release (DR)
  - Extended-release (ER)
  - To compare potential for dose-dumping
  - Not necessary to conduct fed BE studies for all strengths of MR products
When FDA does not request fed BE study

- When the label advises that the drug must be taken on an empty stomach

- When the label makes no statements about effect of food on absorption or administration of an IR product

- When the drug is classified as BCS Class I drug (applies only to IR products)
BE Approaches

- Listed in 21 CFR §320.24, in descending order of accuracy, sensitivity, reproducibility

1. Pharmacokinetic (PK) study in which drug concentrations are measured in plasma
   - *In vitro-in vivo* correlation (IVIVC)

2. PK study in which drug concentrations are measured in urine
BE Approaches (cont.)

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 Approaches: IVIVC

• The *in vitro*/*in vivo* correlation (IVIVC)
  – Develop formulations with differing release rates and correlate *in vitro* dissolution with *in vivo* absorption

  – If an IVIVC is established, can waive *in vivo* studies in some circumstances

  – Evaluate both internal and external predictability
BE Approaches: Urine

• Urine measurements are appropriate when drug cannot be reliably measured in plasma

• Example: potassium chloride

• Baseline in blood is too high to permit accurate measurement
Special Case: IR tablet, drug cannot be detected accurately in plasma

- Alendronate Sodium tablets, available in strengths of 5, 10, 35, 40, 70 mg
- Problems with plasma detection because of low concentrations and redistribution from bone
- Food markedly reduces bioavailability
- FDA requests
  - single-dose fasting study on the 70 mg strength; measurement of alendronate in urine
  - FDA will consider granting biowaivers on the lower strengths
BE Approaches: Pharmacodynamic (PD)

• The FDA accepts PD effect methods to approve generic topical corticosteroid drug products

• This approach is based on ability of corticosteroids to produce vasoconstriction or blanching in skin

• FDA has a guidance on this approach
Special Case: Topical Corticosteroid

- Mometasone Furoate Cream, 0.1%
- Mometasone is a medium potency steroid
- In pilot study, applying the RLD to arm, an ED50 value of X minutes was obtained, which should confirm that mometasone is a medium-potency corticosteroid
- In pivotal study, investigators do the following
  - Apply test and reference drug to both arms (multiple sites) for X minutes, and reference drug for 0.5 X and 2X minutes
  - Monitor blanching response of skin for 24 hours after removing drug
  - Perform BE statistics on the AUEC metric
BE Approaches: Clinical

- BE studies with clinical endpoints
- For drug products that are not systemically absorbed
- Examples
  - Topical drug products
  - Some locally acting GI drug products
- Designs are randomized, blinded, balanced, parallel
- Patients receive test, reference, placebo
- Placebo group used to ensure that patients respond to test and reference product
Special Case: Topical Acne Gel

- Tretinoin gel, available in strengths of 0.025, 0.05, and 0.1%
- FDA requested BE studies with clinical endpoints on the 0.025% and 0.1%
  - Endpoint related to healing of lesions
- FDA granted a biowaiver on the 0.05% strength
  - Based on the fact that all strengths were proportionally similar
BE Approaches: *In Vitro*

- *In vitro* approaches are also used with locally acting drug products
  - Oral cholestyramine suspensions, tablets, capsules
  - Nasal sprays and suspensions
BE Approaches: Highly Variable Drugs

New Proposal

• Reference-scaled average BE approach
• Three-period BE study
  – Administer reference product twice
  – Administer test product once
  – Sequences: TRR, RTR, RRT
• BE criteria scaled to reference variability
• Both AUC and C_{max} should meet BE acceptance criteria
• Point estimate constraint (0.8-1.25) will impose a limit on the difference between test and reference means

1. Bioequivalence Approaches for Highly Variable Drugs and Drug Products. Haidar et. al. 
2. Highly Variable Drugs: Observations from Bioequivalence Data Submitted to the FDA for New 
Waivers of *in vivo* testing (biowaivers)

- Set forth in 21 CFR Part 320
- IV solutions
- Oral solutions
- Non-BE strengths of solid oral dosage forms
- BCS Class I drugs
- DESI drugs with no bioequivalence problems
Biowaivers – IV solutions

- Set forth in 21 CFR §320.22(b)(1) - A *parenteral solution intended for injection*, or an otic or ophthalmic solution
- Must contain the same active and inactive ingredients in the same amounts as the RLD
  - Qualitatively (Q1) and quantitatively (Q2) the same
- Example: Levocarnitine for injection, 200 mg/mL
  - FDA requests
    - Composition should be the same as that of the RLD
    - Sponsors should submit CMC, labeling, and formulation data in support of biowaiver request
Biowaivers – Oral solutions

- Set forth in 21 CFR §320.22(b)(3)
- A generic oral solution can contain different excipients than the RLD
- Formulation must not contain an excipient that will significantly affect absorption of the active ingredient
- Example: Prednisolone sodium phosphate oral solution
  - To document BE, FDA requests composition data on the generic product
  - Generic composition can be different from RLD composition (within certain limit)
  - Inactive ingredients should not have safety issues
Biowaivers – Solid oral dosage forms

• Set forth in 21 CFR §320.22(d)(2)
  – Acceptable *in vivo* BE must be established for one strength (generally the highest strength)
  – Dissolution testing on all strengths must be acceptable
  – Strengths must be proportionally similar to the bio-strength
• For safety reasons, OGD may request an *in vivo* study on a lower strength, and grant biowaiver(s) on higher strength(s)
• Example: Terazosin Hydrochloride Tablets, 1, 2, 5, and 10 mg strength
  – Because of safety concerns, FDA requests fasting BE study on the 2 mg strength
  – FDA will consider granting biowaivers on 1, 5, and 10 mg strengths
Biowaivers - BCS Class I Drugs

• Highly soluble
  – An amount of drug comparable to the highest strength must be soluble in 250 mL of solution over wide pH range
• Highly permeable
  – Can be established by *in vivo* or *in vitro* methods
• Rapidly dissolving
  – At 0.1N HCl (pH 1.2), pH 4.5, and pH 6.8 buffers; 900 mL, using paddles at 50 rpm or basket at 100 rpm
• Example: Ofloxacin tablets, 200, 300, and 400 mg
  – Solubility > 400mg/250 mL
  – Oral bioavailability > 95%
  – Dissolution is rapid at pH 1.2, 4.5, and 6.8
  – FDA designated the drug as BCS Class I and granted biowaiver
Biowaivers – DESI

• Drug Efficacy Study Implementation (DESI) was conducted in the 1970s
• Panel of scientific experts conducted study
• In vivo BE studies can be waived for solid oral dosage forms that meet these criteria
  – Approved before 1962 in US
  – Determined to be efficacious by DESI panel
  – No bioequivalence problems
  – Dissolution data must be acceptable
• Example: Hydroxyzine Hydrochloride Tablets (meet all the above criteria)
Dissolution

• The Division of Bioequivalence (DBE) at OGD is responsible for determining optimal method and setting specifications for generic drugs
  • FDA method used for IR and DR products
  • Case-by-case method development for ER drug products
  • Use dissolution data to support requests for biowaivers of non-bio strengths
• Example: FDA requests the following for Omeprazole DR Capsules, 10, 20, and 40 mg
  – Two-stage dissolution testing
  – Acid media for two hours
    • Must test residual omeprazole in capsules
  – Buffered media for the duration of dissolution testing
  – FDA will consider granting biowaiver on 10 mg (non-bio) strength
Summary and Conclusions

• The FDCA and FDA regulations give the FDA the legal authority to request BE studies

• FDA posts guidances on BE approaches: http://www.fda.gov/cder/guidance/

• For most systemically available/active generic drugs, FDA requests a single-dose fasting and a single-dose fed BE study

• Applicants can request waivers of in vivo testing provided they meet FDA criteria
Special Case: ER Tablet, all strengths proportional

• Alprazolam ER tablets is available in 0.5, 1, 2, and 3 mg strengths
• FDA requests
  – Single-dose fasting and fed BE studies on the 3 mg strength
  – Acceptable dissolution testing in at least 3 media on all strengths
  – FDA will consider granting biowaivers for all lower strengths
Special Case: IR Tablet, all strengths *not* proportional

- Cilostazol tablets
- 50 and 100 mg strengths are not proportionally similar
- Labeling recommends taking the tablet on empty stomach
- FDA requests the following
  - Acceptable fasting BE study on the 100 mg strength
  - Acceptable fasting BE study on the 50 mg strength
  - No fed BE study needed
Special Case: DR Capsule, all strengths not proportional

- Omeprazole DR capsules, available in 10, 20, and 40 mg strengths
- The 20 and 40 mg strengths are not proportionally similar
- The label recommends opening capsule and sprinkling on applesauce
- FDA requests the following for omeprazole DR capsules
  - Single-dose fasting and fed in vivo BE studies on the 40 mg strength
  - A single-dose fasting BE study on the 20 mg strength
  - A sprinkled fasting study on the 40 mg strength
  - FDA will consider granting biowaiver for the 10 mg strength
Special Case: NTI (Narrow Therapeutic Index) drugs

- Levothyroxine Sodium Tablets
- Available in strengths of 0.025, 0.05, 0.075, 0.088, 0.1, 0.112, 0.125, 0.137, 0.15, 0.175, 0.2, and 0.3 mg
- Labeling recommends to take the tablet 0.5-1 hour before breakfast
- FDA requests fasting BE study on the 0.3 mg strength only
- FDA will consider granting biowaivers on all the lower strengths
Special Case: Oral Suspension

• Megestrol acetate oral suspension, available in strength of 40 mg/mL
• Label does not mention food effect on megestrol absorption or PK
• FDA requests only fasting BE study on a single dose of suspension (20 mL)
• Dissolution testing should be done on 12 units (from 12 individual bottles) of 20 mL suspension
  – One unit equals a full dose of the drug product
• Dissolution testing uses paddles at 25 rpm
Useful Links

• Dissolution database: http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm

• Individual product BE recommendations database: http://www.fda.gov/cder/guidance/bioequivalence/default.htm

• FDA guidances: http://www.fda.gov/cder/guidance/

• Orange book: http://www.fda.gov/cder/ob/default.htm
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