Bioavailability Determination: Special Topics

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Overview

- Discuss special topics in the guidance
- Approach to determine bioavailability (BA)
  - Examples and case study

Special Topics

- Combination and co-administered drug products
- Endogenous substances
- Drugs with long half-lives
- Narrow therapeutic index drugs
- Drug products with complex Mixtures as the active ingredients
- Orally administered drugs intended for local action
- Enantiomers versus Racemates
- Effect of alcoholic beverages on MR drug products

Combination and Co-administered Drug Products

Combination and Co-administered Drug Products

- Fixed combination product – two or more active ingredients formulated as a single product.
- Purpose of BA study – compare each active drug ingredient in the combination versus single-ingredient drug products administered concurrently as separate, single ingredient preparations
- A two-treatment, single dose, crossover, fasted study
- Highest strength of the fixed combination

Case Study # 1

- NOPANE® is a combination product (X/Y) of two approved drugs (Drug X and Drug Y).
  - Drug Y is recommended to be given with food for tolerability reasons.
  - Drug X can be given with or without food.
- If a relative BA study is needed, should the sponsor conduct study under fasting or fed condition?
- Fed

Fixed Combination Products

- Include appropriate measurement of systemic concentration of each active ingredient
- Confidence interval approach for BA assessment should be applied to each measured entity of the fixed combination and its reference product(s)
- Evaluation of effect of high-fat meal on the new combination drug product

Example: Immediate Release Fixed Dose Combination (FDC) Tablets

- 2 drug combination; 505 (b) (2) pathway
- 4 strengths of the FDC immediate release tablets (co-formulated)
- Approved reference products for each drug with corresponding strengths

Example: Immediate Release FDC Tablets

- 2 Relative BA studies
- Open label, randomized 2-treatment, 2-period, 2-sequence, crossover, single dose study.
  - Single dose of FDC highest strength and single doses of coadministration of 2 reference products given concurrently
  - Single dose of FDC lowest strength and single doses of coadministration of 2 reference products given concurrently
- Measured of systemic concentrations of each active ingredient
- Confidence interval approach for BA assessment applied for each measured entity
- Demonstrated comparable BA of the 2 active components of the FDC

Case Study # 2

- Drug AB is a FDC tablet of two approved products – Drug A and Drug B
- There is potential for drug interaction between Drug A and Drug B
- Which relative BA study design is appropriate?
  - Design 1: Two-arm design of the FDC vs. A+B 
  - Design 2: Three-arm study FDC vs. A vs. B

Two Drugs given in Combination (not co-formulated)

- Given in combination to increase exposure of one of the drugs (i.e., Subject drug + booster drug)
- If both drugs are new molecular entities (NMEs)
  - BA of each determined individually and when administered in combination
- If combination includes a NME with an approved booster drug
  - Only the BA of the NME (subject drug) should be assessed

Case Study # 3

- Drugs S and Y are two NMEs where, Drug Y is given to boost the exposure of Drug S
- Drug S product formulation is changed post-approval and there is a need for a BA study
- Should the BA study for Drug S include the booster?
- Yes

Endogenous Compounds

Endogenous Compounds

- Naturally present in the body
    - Hormones (e.g., estrogen, progesterone, growth hormone, insulin, thyroid hormones, calcitonin, testosterone, etc.)
    - From diet (Omega-3-fatty acids, vitamins)

Endogenous Substances: Challenges for BA determination

- Existing baseline levels of the target analyte without administering the test compound
- Baseline of the endogenous substances are not constant during the experimental period – affected by circadian rhythm, dietary intake etc.
  - Enroll individuals with low or no production of endogenous substance instead of healthy subjects
  - Inhibition of production/down regulation of hormone by treatment
  - Dietary restriction of the substance before and during the study

Case Study # 4

- NOGEN® is an endogenous product. Subjects have pre-dose level of the drug. Are there any unique study design considerations for such a product?
- Adjust for the baseline levels

Endogenous Substances: Approach for BA determination

- Measure baseline concentrations in the body prior to study drug administration
- Subtraction of the time-averaged baseline or time-matched baseline from the post-dose concentration for each subject may be recommended in some indications
- Baseline concentrations should be determined for each dosing period and baseline corrections should be period-specific
- Pharmacokinetics and statistical analysis on both uncorrected and corrected data.

Example: FDC combination of two Endogenous compounds

- FDC product: Capsule
- A comparative BA study conducted
  - E 2 mg and P 200 mg as reference drugs
  - 2 mg E/200 mg P as test drug

Example: FDC Capsules

- Healthy postmenopausal female subjects
- Single dose, 3-way crossover, reference-replicated, reference-scaled study
- Samples collected at -1, -0.5, and 0 h pre-dose for baseline concentrations
  - PK parameters of baseline-adjusted and baseline-unadjusted levels of all active E and P components was determined.

Drugs with Long Half-Lives

Case Study # 5

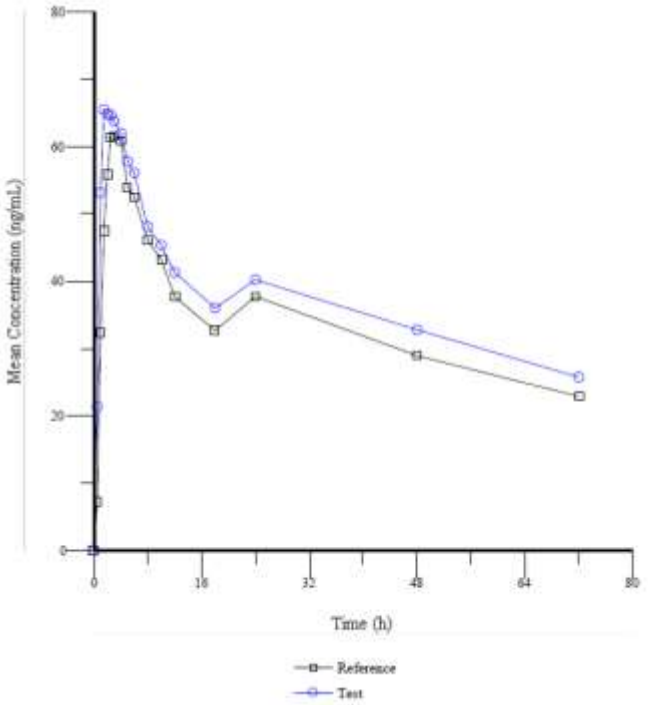
- Drug Z has a half-life of 72 h
- What study design would you choose for a relative BA study?
  - Crossover
  - Parallel

Drugs with Long Half-Life

- Crossover vs. parallel studies
  - Ensure adequate washout periods between periods in the crossover study
  - Ensure similar subject demographics in each treatment group in the parallel study
  - Sample collection time to ensure complete absorption
- Truncated AUC can be used for drugs that:
  - Do not exhibit flip-flop kinetics
  - Do not have high intra-subject variability

Example: Truncated AUC

- Drug
  - Slowly eliminated – half-life ~ 1 week
- Truncated AUC used for comparing bioavailability



High Variability Drugs

Narrow Therapeutic Index Drugs

High Variability Drugs

- High intra-subject variability (≥ 30%)
  - Variation in the same subject taking the same drug in two different occasions under similar conditions
- Generally, exhibit a wide therapeutic window
- Consider a reference scaled approach using a replicate design (subjects receive the reference product more than once)
  - Reduces sample size

Narrow Therapeutic Index Drugs (NTI)

- Example drugs -warfarin, digoxin, phenytoin, theophylline
  - Therapeutic drug monitoring is an essential for dosing
  - Knowledge of AUC or Cmax are critical for safe and effective use
- Require tighter limits for BA assessment and product quality standards
  - Criteria might need to be narrowed

Approach for BA Determination for NTI

- Determined using scaling approach
- Four-way, fully replicated, crossover design in healthy subjects
- Simultaneous comparison of the mean and within-subject variability of the test and reference
- Proposed limits for NTI drugs of 90.00% - 111.11% scaled based on the within-subject variability of reference

Yu, LX, W Jiang, X Zhang, R Lionberger, F Makhlouf, DJ Schuirmann, L Muldowney, M-L Chen, B Davit, D Conner, and J Woodcock, 2014, Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs, Clinical Pharmacol Ther, 97(3):286-291.

Case Study # 6

- NOPANE® has >50% intrasubject variability. What approach is appropriate for a relative BA study.
- Reference scaled approach

Summary

- Discussed some special topics and the approaches to determine bioavailability
  - Baseline correction for endogenous compounds
  - Bioavailability of individual components in an FDC
  - When to choose a reference scaled study design
  - Considerations for long half-life drugs, and NTI drugs
- Sponsors should consult the appropriate review division to discuss their specific situation.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