Bioavailability Studies Submitted in NDAs and INDs – General Considerations

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Outline

- Importance of bioavailability (BA) studies
- When BA studies should be performed
- Study design
- Appropriate PK measurements for a BA study
- Alternative approaches to assessing BA
- Fed vs fasted studies

What is this guidance about?

- BA studies conducted for INDs and NDAs
  - Study conduct
    - IR Products
    - MR products
  - Documenting BA for various dosage forms
  - Other approaches to demonstrate BA
  - Special Topics
- Not for biosimilar products
- Not for generic products

Why are BA studies important?

BA/BE a Requirement for Submission (CFR 320.21….Subpart B)

- New Drug Application (NDA):
  - Evidence demonstrating in vivo BA of drug product
  - Information to permit FDA to waive BA
  - Relative BA between clinical trial formulation (CTF) vs to-be-marketed (TBM) formulation

- Abbreviated New Drug Application (ANDA)
  - Evidence demonstrating BE to reference listed drug
  - Information to permit FDA to waive BE

- Supplemental Application
  - Change in the manufacturing site or process, including formulation or strength, beyond the variations provided for in approved application
  - Change in labeling to provide for a new indication for use of the drug product, if clinical studies are required to support new indication
  - Change in the labeling to provide for a new dosage regimen or for an additional dosage regimen for a special population e.g. infants, if clinical studies are required to support the new or additional dosage regimen

Why are BA studies Important?

BA studies can provide useful PK information related to

- Dosage regimens and to support drug labeling
  - Relative fraction of dose absorbed into systemic circulation
- Linearity and non-linearity in PK
- Effects of food or other nutrients on absorption of drug
- Provide information indirectly about the properties of a drug substance before entry into the systemic circulation, such as permeability and the influence of presystemic enzymes and/or transporters

When are BA studies conducted?

- To determine the absolute or relative BA (i.e., comparing the formulation vs. an IV or another oral formulation [e.g., solution])

- To compare 2 formulations during drug development
  - Pre-approval
  - Post-approval

BA Studies– General Features

- Type of study
  - crossover/parallel design

- Pilot study
  - validate analytical methodology
  - assess PK variability
  - determine sample size to achieve adequate power
  - optimize sample collection time intervals
  - determine length of the washout period

BA Studies – General Features

- Study populations
  - healthy subjects, 18 years or older
  - male and female subjects should be enrolled in BA studies unless there is a specific reason to exclude one gender

- Single dose evaluation under fasted conditions (after an overnight fast)
  - more sensitive

- Moieties to be measured
  - Parent or the active moiety rather than metabolites unless the measurement of the parent or active moiety is impractical

BA Study Conduct

- An adequate washout period (e.g., ≥5 half-lives or pre-dose < 5% of C_{max} in all subjects)
- 12 to 18 samples per subject per dose
- If the pre-dose concentration is > 5 percent of C_{max}, then the subject should be dropped from all PK evaluations

BA Study Conduct

For emesis:

- Exclude data for subject from statistical analysis
  - For IR Products- if vomiting occurs at or before 2 times median T_{max}
  - For MR products- if vomiting occurs at any time during the dosing interval

- Plasma concentration data from subjects who vomited during the study should be reported even though they were excluded from the analysis

BA Study– Measures of Systemic Exposure

- Peak exposure : C_{max}
- Total exposure : AUC_{0-t} or AUC_{0-inf}
- Partial exposure : pAUC
  - used in some specific therapeutic areas
    - pAUC product specific

      - e.g., ADHD, Pain

      - e.g., AUC(0-3), AUC (3-7), AUC (7-12)
- BE Criteria: 90% CI falls within the 80.00- 125.00% interval

Other approaches to support BA

- IVIVC :
  - describes the relationship between in vitro attribute and a relevant in vivo response
  - e.g., the rate or extent of drug release to plasma drug concentration or amount of drug absorbed
- PD Studies:
  - When PK is not possible
  - Should be well-justified PD endpoint

Other approaches to support BA

- Comparative Clinical Studies:
  - When measurement in an accessible biological fluid (PK approach) or PD approach is not possible

- In Vitro Studies: In vitro Dissolution
  - F2 comparison

New MR Product Given an Approved IR Product

- For drugs with linear PK
  - Compare highest strength ER to IR over ER dosing interval
    - 100 mg ER QD vs 50 mg IR BID
- For drugs with non-linear PK
  - SD highest and lowest strengths ER vs. respective IR strengths over ER dosing interval
- SD dosage strength proportionality study for ER
- SD food effect study on highest ER strength
- Steady state study on the highest strength ER vs. IR

BA for MR Products

New ER product (ER_{new}) comparison to an approved ER product (ER_{old}) with a **different dosing interval** (i.e., where ER_{new} and ER_{old} have unequal dosing intervals)

- The recommendations are the same as outlined in the previous scenario. In this case, the reference product could be either the approved ER_{old} or IR product

BA for MR Products

New ER product (ER_{new}) comparison to an approved ER product (ER_{old}) with **the same dosing interval**

- A single-dose fasting study on the highest strength of the ER_{new} product compared to the ER_{old} product
- If ER_{new} and ER_{old} are of different strengths, compare equivalent dose using the highest strengths
- Food-effect study should be conducted on the highest ER_{new} strength.
- When the ER_{new} strengths are **not proportionally** similar in composition, conduct:
  - SD fasting, dosage strength equivalence assessment study
  - or a dosage strength proportionality study for the ER_{new} product

Fasted vs. Fed Studies

- For new IR drug products developed via the pathway under section 505(b)(1) of the FD&C Act for which BA is determined using a solution, IV, or a previously developed formulation as a reference, the BA study should be conducted under fasted conditions except when tolerability issues are anticipated in the fasted state.

- Additionally, the effect of food on the BA of the new drug product should be evaluated using a high-fat and high-calorie meal. If the objective is to evaluate the effect of other meal types, then other meals with different compositions can also be assessed in addition to the high-fat and high-calorie meal.

Fasted vs. Fed Studies

- If the reference drug product is labeled to be taken without regard to meals, then the test and reference drug product should be compared under fasted conditions.
- In addition, the effect of a high-fat meal on the new drug product should be evaluated.
- Alternatively, the BA of the new drug product under fed conditions can be established by comparing the test product to the reference drug product both administered with a high-fat meal

Fasted vs. Fed Studies

- If the reference drug product is labeled to be taken with food, then the test drug product should be compared under fed conditions. The fed conditions in this study should be the same as described in the labeling for the reference product.

- In addition, the evaluation of the effect of a high-fat meal on the new drug product (test fed versus test fasted) can be useful to inform and support labeling of the test product.

- Three-way crossover study can be considered because it allows for the relevant comparisons to be made directly (e.g., test fed vs reference fed and food-effect assessment).

Fasted vs. Fed Studies

If the reference drug product is labeled to be taken with food to avoid tolerability issues in the fasted state, then the BA for the test drug product should be evaluated under fed conditions according to the labeling instructions for the reference product

Questions