Pharmacokinetic Studies
Pilot Study

- Generally performed in a smaller number of subjects, e.g., six.
- To validate the analytical methodology, assess variability, and to optimize sample collection time intervals.
- In the case of MR to determine sampling times to assess lag time and dose dumping.

Pharmacokinetics Study

- BE Study - Crossover study design (T and R products)
- Study protocol, adequate washout period (generally 5 half lives of the drug)
- Sampling Time - 12 to 18 samples (3 or more terminal half lives)
- Sample Analysis - (Bioanalytical Method Validation)
- PK Data Analysis - Total exposure (AUC) and peak exposure (Cmax)
Pharmacokinetic study

Study population

- Should be ≥ 18 years of age and capable of giving informed consent, representing the general population (age, gender and race).
- If the drug product is intended for both genders, the sponsor should attempt to include equal number of males and females.
- If the drug product is to be used predominantly in the elderly, the sponsor should attempt to include subjects of 60 years or older in the study, with a target of 40% elderly subjects analyzed.
- No subgroup analysis is needed for statistical procedures.
- Restriction on admission into the study should be based on safety considerations.

Study Design and Analysis

Single dose, crossover study design

- T and R Products
- Analysis - Average Bioequivalence (ABE)

Single Dose, replicate study design

- TT and RR Products
- Analysis - Average Bioequivalence (ABE)

Bioequivalence

- Average Bioequivalence (ABE) is traditionally based on 2-product, 2-period, 2-sequence cross-over study design.
- Log transformed AUC and Cmax data analyzed by ANOVA.
- 90% CI on the geometric mean ratio of Test and Reference products must fall within fixed BE limits of 80-125%.
- ABE determines whether average responses to the two formulations are similar between individuals.

Modified Release Dosage Form

MR = Delayed Release Dosage Form
+ Extended Release Dosage Form
ER: Extended Release Dosage Form
Controlled Release Dosage Form
Sustained Release Dosage Form
Prolonged Release Dosage Form
IR and MR Drug Products

Product marketed as

- single strength
- multiple strengths

Do all strengths need to be studied for BE?

- BE study need to be carried out only for the highest strength,
- Lower strengths can get biowaiver, based on dose proportional formulations and dissolution profile comparisons

Immediate Release Products

- A single dose fasted study comparing the highest strength of test and reference product
- Food effect study, if required (labeling)
- Must meet BE requirements - criteria
- In vitro drug release

Biowaivers

Proportionally Similar

- All active and inactive ingredients are exactly in the same proportion
- Total weight remains nearly the same for all strengths (within ± 10% of total weight of the strength on which a bio study was performed) and the change in strength is obtained by altering the amount of the active ingredient and one or more of the inactive ingredients.

Dissolution

Immediate Release Drug Products

- Single Point
  - Using Apparatus 1 (Basket) or 2 (Paddle)
  - For routine quality control test
- Two Points
  - For characterizing the quality of the drug product (also for use as a QC test)
- Profile
  - Profile comparison for granting biowaivers
  - For accepting product “sameness” under scale-up and post-approval changes
Bioequivalence Studies
Extended Release Drug products

• Single dose study is considered more sensitive in assessing the drug product quality - release of the drug substance from the drug product into circulation
• A multiple-dose BE study for ER dosage forms is not generally recommended

Extended Release Products

• A single dose fasted study comparing the highest strength of test and reference product
• A multiple dose study is NOT required
• A food-effect study comparing highest strength of Test and Reference Product
• Must meet BE requirements (criteria)
• In vitro drug release

Extended Release Drug Products

• Profiles
  – In multimedia, different pHs
  – Influence of agitation
• Specifications
  – Profiles with at least 3 to 4 points
  – Range of dissolution at all points
  – Time: 1 or 2 Hrs, around 50 % dissolution and around 80% dissolution

ER Products - Dissolution Studies in Alcohol

• Due to concerns of dose dumping when taken with alcohol, additional dissolution testing using various concentrations of ethanol in the dissolution medium is required:
  T and R product, 12 units in each case, data collected every 15 minutes for 2 hours
• Proposed method (without alcohol)
• 5% (v/v) alcohol
• 20% (v/v) alcohol
• 40% (v/v) alcohol
(e.g., Oxycodone, Trazodone, Bupropion, Venlafaxine, Lamotrigine, Quetiapine Fumarate, Ropinirole)
Lower Strengths - Biowaiver

Waiver based on dissolution profile similarity

- **Conventional (Immediate) Release**
  - Formulation proportional
  - Dissolution profile comparison with highest strength under one condition.

- **Extended Release**
  - Formulation proportional
  - Same drug releasing mechanism
  - Beaded capsules – dissolution profile comparison with highest strength under one condition
  - Tablets - dissolution profile comparison with highest strength in pH 1.2, 4.5 and 6.8

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Bioequivalence Studies

Why do they fail?

- Bioinequivalent products
- Not sufficient subjects/power (highly variable drug products)
- Highly variable formulation
- Problems with bioanalytical method
- Problems with multiple parameter measurements
- Outliers
- S x F interaction

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Immediate Release Products (Conventional Release Products)

- Drug Product: BA/BE
  - Preapproval
  - New Drug
  - BA Study
  - Class 1: HS/HP
  - Dissolution
  - Higher Strength
  - BE Study
  - Lower Strength
  - Dissolution Study
  - Postapproval
  - Dissolution Profile BE Study

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Modified Release Dosage Forms

- Drug Product: BA/BE
  - Preapproval
  - New Drug
  - BA Study each strength
  - Food effect study
  - Multiple dose study at highest strength
  - Higher Strength
  - BE Study at higher strength
  - Food effect study
  - Lower strength
  - Tablets
  - Formulation proportional
  - Dissolution profile f in 3 media

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Drug Approval Process

- **ANDA - Generic Drugs**
- **Orange Book**
  - RLD
  - Product rating, AB, BA

**Therapeutic Equivalence**
The products are considered TE when they meet regulatory criteria of PE and BE.
TE = Interchangeability between generic product and reference product.

Narrow Therapeutic Index Drugs

- For generic (ANDA) - Two BE Studies:
  - 1. 4-way fully replicated crossover design – fasting
  - 2. 4-way fully replicated crossover design – fed
  - Study design: Sequence 1: T R T R Sequence 2: R T R T
- BE based on 90% CI
  Scale BE limits to the variability of reference product.
  Compare T & R product within-subject variability.
  Method of statistical analysis using Reference-Scaled ABE (RSABE) approach.
- BE study using highest strength – 10 mg.
  Biowaiver for lower strengths
- Assayed potency specifications: 95-105%


Highly Variable Drugs

- Highly variable drugs are defined as drugs in which the within subject variability is 30% or greater.
- BE study:
  RSABE approach where reference product is administered twice (either 3-way or 4-way study design).
  Acceptance limits scale based on the within-subject variability of the reference product.
  The AUC and $C_{max}$ GMRs should be within 0.80-1.25.
  RSABE approach applied to AUC and $C_{max}$.
Deeply concerned about the growing epidemic of opioid abuse, dependence and overdose in US. In response to this crisis, agency has developed a comprehensive action plan:

• Expand use of advisory committees.
• Develop warnings and safety information for IR opioid labelling.
• Strengthen post-market requirements.
• Update Risk Evaluation and Mitigation Strategy (REMS) Program.
• Expand access to abuse-deterrent formulations (ADFs) to discourage abuse.
• Support better treatment.
• Reassess the risk-benefit approval framework for opioid use.

Special considerations for multiphasic MR dosage forms
Multiphasic Modified Release

- For multiphasic modified release products designed to have a rapid onset of drug action followed by sustained response, an additional metric of partial AUC is required. e.g., for Zolpidem Tartrate Extended Release - (Ambien CR)
  - The cutoff for partial AUCs may be determined on the basis of the PK/PD or PK/response characteristics of the product.
  - BE requirement for a generic product include: \(C_{\text{max}}\), \(AUC_{0-\text{last}}\) or \(AUC_{0-\infty}\) and \(pAUC\)

Selection of time for calculating first pAUC for multiphasic MR products

- Sampling time (T) for first pAUC is based on time at which 90-95% of subjects are likely to achieve optimal early onset of response
- May use other information on the absorption rate of the drug to supplement the information above

BE metrics requested for some multiphasic MR products

- Four BE metrics are calculated
  \(- C_{\text{max}} \quad AUC_{0-T} \quad AUC_{T-t} \quad AUC_{\infty}\)
- \(AUC_{0-T}\) should compare T & R exposure responsible for early onset of response
- \(AUC_{T-t}\) should compare T & R exposure responsible for sustained response
- All metrics should meet BE limits (80-125)

Where T is product-specific time, t is last PK sampling time
Conclusions

• Immediate (Conventional) Release Products
  – In vivo Requirements
  – Special cases – NTI and HVD
  – Biowaivers
  – In vitro requirements
• Extended Release Products
  – In vivo requirements
  – Special cases – Multiphasic systems
  – In vitro requirements
  – Special cases – Dissolution in alcoholic media

Thank You for Your Attention