School of Pharmacy

Faculty of Medicine

The Chinese University of Hong Kong

Workshop in Celebration of 25th Anniversary of the School of Pharmacy

Biopharmaceutics of Modified Release Products and Challenging Drug Molecules

Immediate Release and Modified Release Bioequivalence Requirements

Vinod P. Shah, Ph.D.
Pharmaceutical Consultant
(Formerly with US FDA)

GENERIC FORMULATIONS:

Pharmaceutical Equivalence	+	Bioequivalence	=	Therapeutic Equivalence

- Same active ingredient
- Same strength
- Same dosage form and route of administration
- Comparable labeling

- *In vivo* measurement of active moiety (moieties) in biologic fluid
- *In vivo* pharmacodynamic comparison
- *In vivo* clinical comparison
- *In vitro* comparison

- Switchable under labelled conditions of use

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**

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 biostudy 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.**

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

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 dost 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

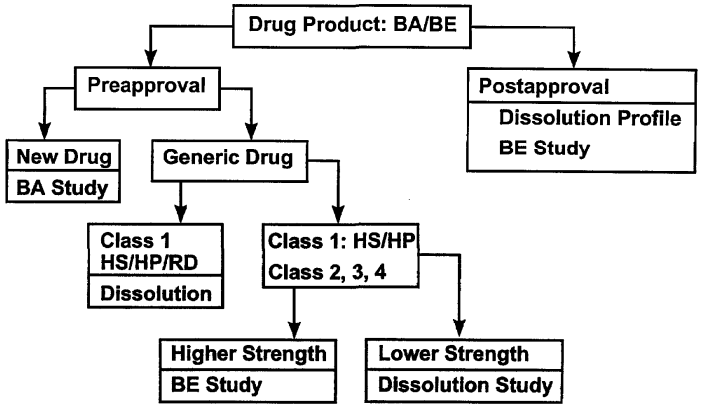
Bioequivalence Studies

Why do they fail?

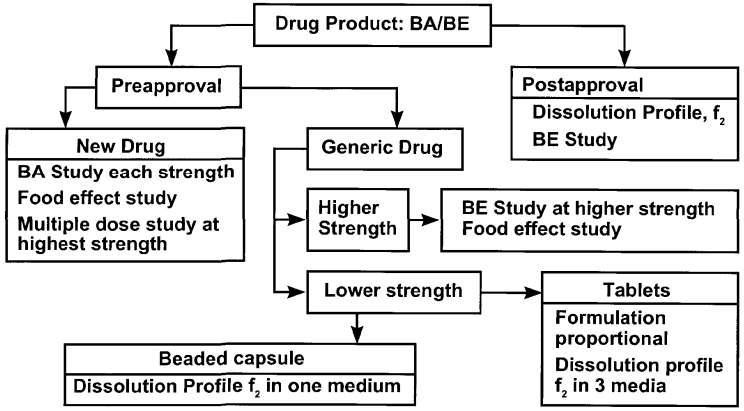
- **Bioinequivalent products**
- **Not sufficient subjects/power (highly variable drug products)**
- **Highly variable formulation**
- **Problems with bioanalytical method**
- **Problems with multiple parameter measurements**
- **Outliers**
- **S x F interaction**

Immediate Release Products

(Conventional Release Products)



Modified Release Dosage Forms



Guidance for Industry

Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General Considerations

http://www.fda.gov/cder/guidance/index.htm

March 2003

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%

Ref: FDA/OGD Draft Guidance on Warfarin Sodium, December 2012.

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}.

FDA Opioids Action Plan

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.
  - Fact Sheets/UCM484743.pdf

FDA – Opioids Action Plan

- **FDA Draft Guidance**: General Principles or Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products – March 2016
  - R product to describe abuse-deterrent properties.
  - Comparative evaluation of abuse T and R product.
  - Tier-based approach: starting with simple and gentle manipulation of the product in in vitro studies to more destructive and chemical manipulation
  - Evaluation of abuse deterrence.
  - Routes of abuse: injection; ingestion; insufflative (nasal route); smoking (inhalation)

FDA – Opioids Action Plan

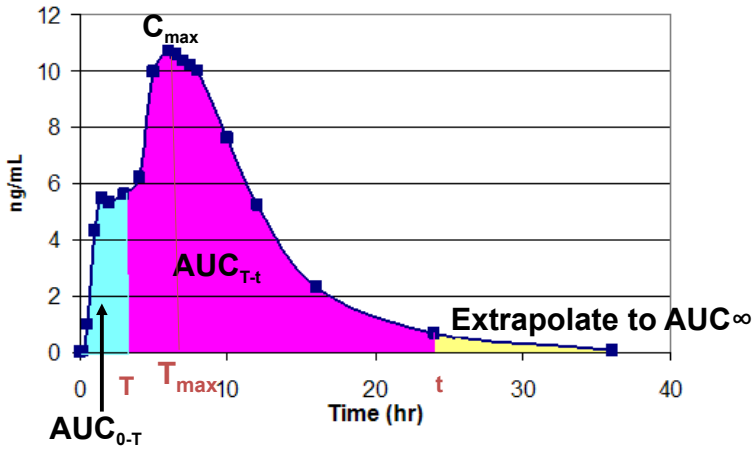
- **FDA Draft Guidance**:
- The guidance is intended to assist a potential applicant who plans to develop, and submit an ANDA to seek approval of a generic version of a solid oral opioid drug product that has the potential for abuse and which references an opioid drug product with abuse-deterrent properties described in its labeling.
- It recommends comparative in vitro studies that should be conducted and submitted to demonstrate that T product is no less abuse-deterrent than R with respect to all potential routes of abuse.

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 fir a generic product include: Cmax, $AUC_{0\text{-last}}$ or $AUC_{0\text{-}\infty}$ and pAUC

Illustrating BE metrics for some multiphasic MR products



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_{max} $AUC_{0\text{-}T}$ $AUC_{T\text{-}t}$ AUC∞*
- $AUC_{0\text{-}T}$ should compare T & R exposure responsible for early onset of response
- $AUC_{T\text{-}t}$ 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