Bioequivalence and Drug Product Quality

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Outline of Presentation

• Bioequivalence
  – A generic drug approval process
• Biopharmaceutics Classification System (BCS)
  - Biowaiver criteria
• Product quality tests and product performance tests
  - Dissolution Testing
• Quality system and QbD
Bioavailability and Bioequivalence

1977: 21 CFR 320 - BA/BE Regulations

- **Bioavailability:**
  “... the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action ... “

- **Bioequivalence:**
  “... as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in the pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions ...”
Generic Drug Products

• The mission of a regulatory authority is to assure that safe and effective drugs are marketed in the country and are available to the people.

• The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and efficacy. This applies to drugs marketed after 1962.

• Generic drugs have to meet the same rigid standards as the innovator drug.
Generic Drug - Standards

- FDA ensures that the generic drug products are safe and effective, are pharmaceutically equivalent and bioequivalent to the brand-name.
- Contain the same active ingredient as the innovator drug (inactive ingredients may vary)
- Be identical in strength, dosage form, and route of administration as the innovator drug
- Have the same use indications (labeling)
- Be bioequivalent
- Meet the same batch requirements for **identity, strength, purity and quality**
- Be manufactured under the same strict standards of FDA’s good manufacturing practice regulations required for innovator products.
BE and DPQ

• **BE**: Bioequivalence focuses on the release of the drug substance from the drug product and its absorption into the systemic circulation.

• BE is a comparative test that uses specified criteria for comparisons and predetermined BE limits.

• **DPQ**: What do we mean by this term? Drug product of acceptable performance, i.e., Drug product of acceptable safety, efficacy and quality.
Generic Drug Products

• **Safety**
  - Same API, no need to re-establish toxicity studies

• **Efficacy**
  - Established thru BE study

• **Quality**
  Specifications
  - Product Quality Tests
    Identity, quality, purity, strength, assay, potency, content uniformity
  - Product Performance Tests
    Dissolution
Drug Product Standards - Quality

SAFETY EFFICACY
BLOOD LEVEL
BIOEQUIVALENCE
Dissolution
Good Manufacturing Practice
No GMP - No need for BE
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.
Immediate Release Drug Products

Generic - BE Studies

- A single dose fasted study in 24-36 healthy subjects comparing the highest strength of Test and Reference Product

- Lower strengths approved based upon formulation proportionality and dissolution profile comparison.

- Food effect study, if required (labeling)

- In vitro release
Extended Release Products

Generic: BE Studies

• A single dose fasted study in 24-36 healthy subjects comparing the highest strength of Test and Reference Product

• A food-effect study in 24-36 healthy subjects comparing highest strength of Test and Reference Product

• Lower strengths of tablets approved based on formulation proportionality, use of same drug release mechanism and dissolution profile similarity.
Immediate Release Products (Conventional Release Products)

Drug Product: BA/BE

Preapproval
- New Drug
  - BA Study

Generic Drug
- Class 1
  - HS/HP/RD
  - Dissolution
- Class 1: HS/HP
  - Class 2, 3, 4

Postapproval
- Dissolution Profile
- BE Study

Higher Strength
- BE Study

Lower Strength
- Dissolution Study
Modified Release Dosage Forms

Drug Product: BA/BE

Preapproval

New Drug
- BA Study each strength
- Food effect study
- Multiple dose study at highest strength

Generic Drug

Higher Strength

Lower strength

Postapproval

Dissolution Profile, $f_2$
- BE Study

BE Study at higher strength
- Food effect study

Tablets
- Formulation proportional
- Dissolution profile $f_2$ in 3 media

Beaded capsule
- Dissolution Profile $f_2$ in one medium
Multiphasic Modified Release

- For MR 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, $\text{AUC}_{0-\infty}$ or $\text{AUC}_{0-\infty}$ and pAUC
Biopharmaceutics Classification System (BCS)
Biopharmaceutics Classification System

• It is a framework for classifying drug substance based on its solubility and permeability

• Drug Substance (API) classified into 4 classes:
  – Class 1: Highly Soluble / Highly Permeable (HS/HP)
  – Class 2: Low Solubility / Highly Permeable (LS/HP)
  – Class 3: Highly Soluble / Low Permeability (HS/LP)
  – Class 4: Low Solubility / Low Permeability (LS/LP)

• It is a drug development tool to justify ‘biowaiver’ in conjunction with the dissolution of the drug product.


FDA Guidance - Waiver for Class 1 and class 3 Drugs
BCS Based Biowaivers

• **BCS Class 1: HS/HP - VRD or RD**
  – Quantity of excipients should be consistent with intended function
  – When new excipient or atypically large amount of excipient is used, additional information documenting the absence of an impact on BA may be needed

• **BCS Class 3: HS/LP - VRD**
  – contains no inactive ingredients that are known to alter GI motility and/or absorption
  – Inactive ingredients must be Q1 and Q2 (compared with RLD)

For biowaivers Test (multisource) and Reference (comparator) products must have similar dissolution profile ($f_2$) in all 3 media, pH 1.2, 4.5 and 6.8.
Dissolution Tests

Drug Product Quality Test

• Immediate Release
  – Tablets and capsules (Water soluble drugs)
  – Water insoluble drugs

• Capsules

• Delayed Release

• Extended Release
  – ER Dissolution in alcohol
Drug Products – Quality Tests

Quality Tests and Performance Test

• Compendial requirements
  – Monographs

• Product Quality Tests
  – Identity, quality, purity, strength, assay, potency, content uniformity

• Product Performance Test
  Dissolution
  – IR dosage forms; S1, S2, S3
  – MR dosage forms 12 Units – Ranges; L1, L2, L3
Drug Product Quality Tests and Drug Product Performance Test

- Drug product tests are divided into two categories:
  1. Those that assess general quality attributes and
  2. Those that assess product performance, i.e., in vitro release of the drug substance from the drug product.

- Quality tests assess the integrity of the dosage form, whereas performance test assess drug release and other attributes that relate to in vivo drug performance. Taken together, quality and performance tests assure identity, strength, quality, and purity of the drug product.
Quality System


• Quality: To build your reputation and trust. Q is the basis of the public’s confidence in pharmaceuticals. Q is the foundation on which everything must rest. Q must be built into every aspect

• FDA’s pharmaceutical quality initiative for the 21st century and Quality by Design programs.

• Considering meaningful manufacturing quality metrics

• FDA/CDER/ New Office of Pharmaceutical Quality

• Continual quality surveillance.
Quality System Model

- Six-system inspection approach – The quality system and the five manufacturing systems
  - Quality System
  - Production System
  - Facilities and Equipment System
  - Laboratory Controls System
  - Materials System
  - Packaging and Labeling System

- The quality system provides the foundation for the manufacturing systems that are linked and integrated.

- The model provides ability to assess whether each of the system is in a state of control.

- Implementing effective quality system in manufacturing requires a significant investment of time and resources, but has long term benefits
Quality by Design

Use of QbD concept

• Demonstrates knowledge of the product
• Identifies possible sources of variability and risk
• Allows assessment of product quality attributes
• Forms the basis of continuous improvement
Generic Drug Product

• The drug product safety and efficacy for the generic product is established by it being pharmaceutically equivalent and bioequivalent, and thus **therapeutically equivalent**.

• The **quality** of the product is ensured thru product identity, strength, purity, assay, potency, content uniformity, dissolution (for solid oral dosage forms) and being manufactured under FDA’s good manufacturing practice.

• The approved drug product should also conform to the drug product **performance** criteria.
Conclusion

Generic Drugs (which) are

• Pharmaceutically Equivalent and Bioequivalent
  and (which) are

• Prepared under GMP conditions and meet Quality and Performance Standards
  are Therapeutically Equivalent and
  Therapeutically Interchangeable
Thank You for Your Attention