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

Implementation of BABE Requirements at the FDA: Lessons Learned

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Regulatory Authority Mission

"Assure that SAFE and EFFECTIVE Quality drugs are marketed in the country and are available to the People"

FDA Regulations - History

- 1906 – Original Food and Drug Act
- 1938 – Federal Food, Drug and Cosmetic Act (Safety)
- 1962 – Kefauver – Harris Amendments (Efficacy, IND, GMPs)
- 1974 – Office of Technology Assessment (BA/BE, Dissolution)
- 1977 – CFR 320.1 defined BA, BE, PE and TE.
  OTC monograph approach, DESI for 1938-1962.
- 1984 – Drug Price Competition and Patent Restoration Act (Waxman-Hatch Act)
- 1997 – FDA Modernization Act
- 2002 – Best Pharmaceuticals Act for Children

Bioavailability and Bioequivalence

- 1977: BA/BE Regulations – 21 CFR 320.1
- **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 …"

Bioequivalence – Drug Regulations

Pharmaceutical Sciences

- Provided the scientific basis for the 1984 **"Drug Price Competition and Patent Term Restoration Act"**
  - Provided the statutory authority to FDA for BE based approval of new generic drugs,
  - Provided scientific basis for accepting BE studies as a surrogate for clinical studies.
- Established present system of generic drug approval process, ANDA - FDCA 505(j)
- **Principles of BCS**
  - Provided justification for drug approval based on in vitro dissolution studies.

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.
- FDA ensures that the generic drug products are safe and effective, are pharmaceutically equivalent and bioequivalent to the brand-name counterparts – the same dose of the same active ingredient, delivered in the same way, and manufactured according to the same standards of quality.
- FDA encourages manufacturing using QbD principles, with emphasis on maintaining Quality and data integrity.

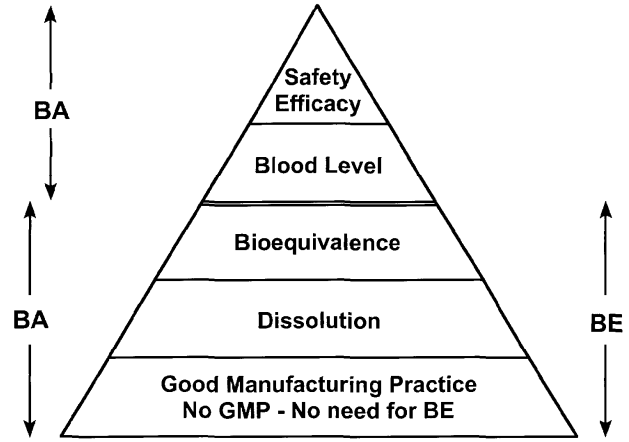
Generic Drug Product

- 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.
- Same standards are enforced for brand name drugs and generic drugs.

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

Drug Product Standards - Quality



Bioequivalence

What is Bioequivalence?

- **Comparison of two products with respect to rate and extent of drug availability.**

Why do Bioequivalence?

- **For product approval, and to use as a substitute for brand name product.**

When do you do Bioequivalence?

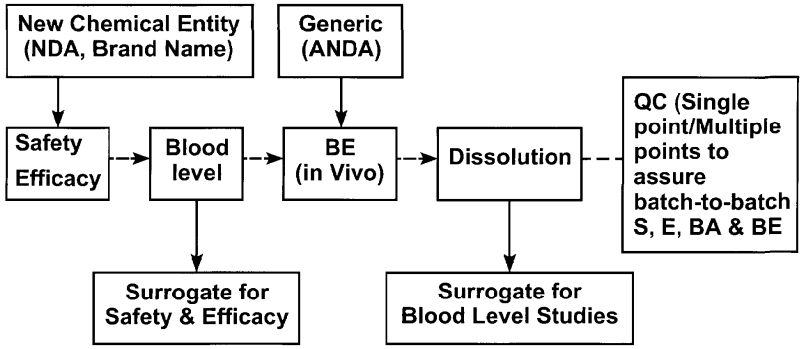
- **To establish BE between clinical batch and to-be-marketed formulation/batch**
- **To compare BE between test product and reference product**
- **To compare pre-change and post-change products in certain SUPAC related changes**

Drug Products

Drug Approval

New Drug Application (NDA)	*Abbreviated New Drug Approval (ANDA)*
Safety: Toxicity Studies	
Efficacy: Clinical Studies • Bioavailability Studies • Pharmacokinetic studies	• Bioequivalence Studies
• Manufacturing Controls	• Manufacturing Controls
• *In Vitro* Dissolution	• *In Vitro* Dissolution

Drug Product Approval



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.

Thank You for Your Attention