

# **US FDAs Perspective on Product Quality and Bioequivalence**

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**Scientific Principles in  
Dissolution Methodology and Drug Testing**  
**Society for Pharmaceutical Dissolution Science (South  
Chapter) & JSS University Mysore, Karnataka**

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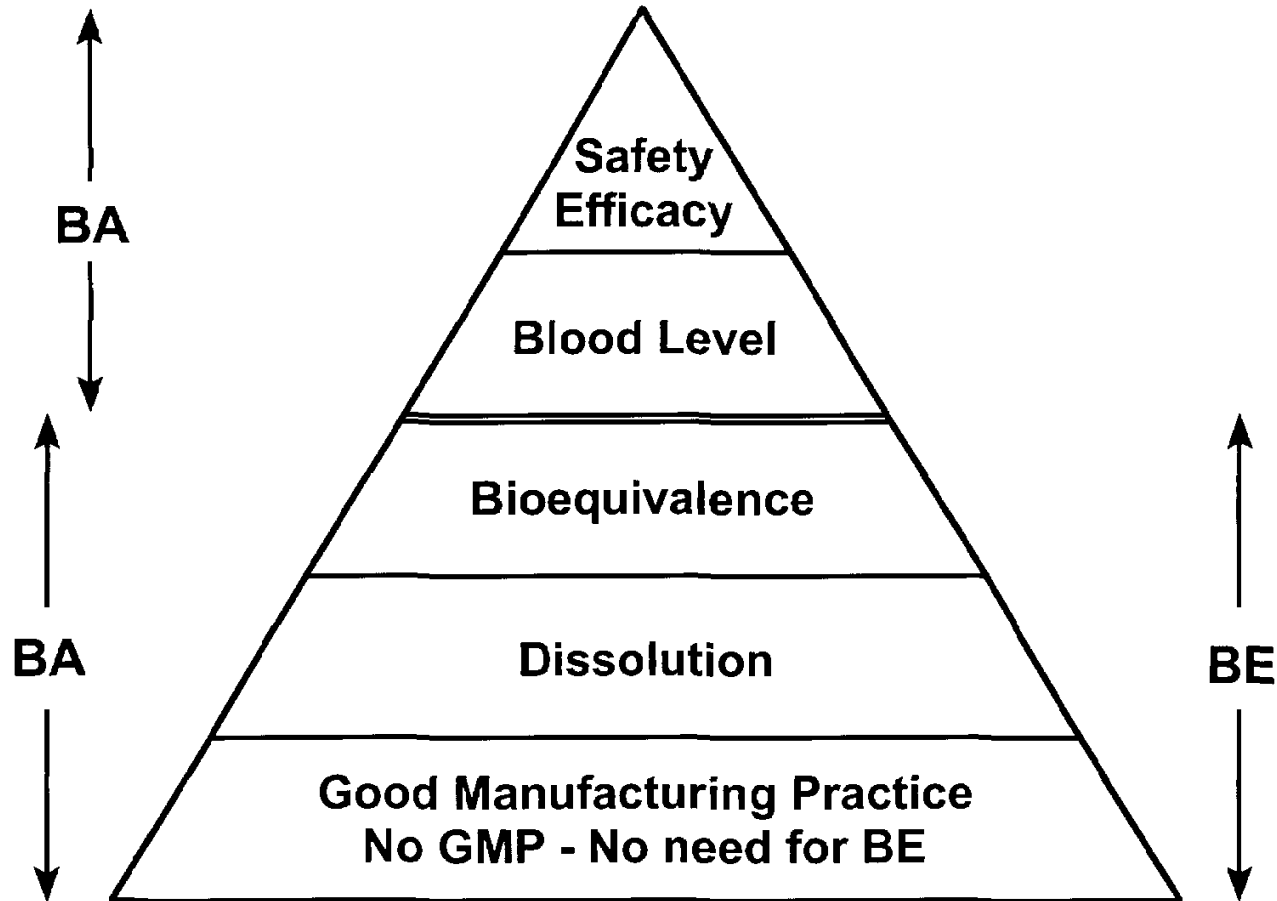
# Outline of Presentation

- Product Quality
- A generic drug approval process
  - Bioequivalence
- Product quality tests and product performance tests
  - Dissolution Testing
- Biopharmaceutics Classification System (BCS)
  - FDA and WHO Guidelines
  - Biowaiver criteria
- US FDA perspectives towards Product 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



# 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.
- 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 Drug - Standards

- Generic drugs have to meet the same rigid standards as the innovator drug. To gain FDA approval, a generic drug must:
- 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 - **cGMP** .

# 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

## 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



# Bioequivalence Studies Modified 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 MR dosage forms is not generally recommended**

# Extended Release Products

## Generics: 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.

# **Biowaiver**

## **Lower Strength(s)**

- **Conventional (Immediate) Release Tablets/Capsules**
- **Extended Release Beaded Capsules**
- **Extended Release Tablets**

**Guidance: BA and BE studies for orally administered drug products: General considerations. March 2003**

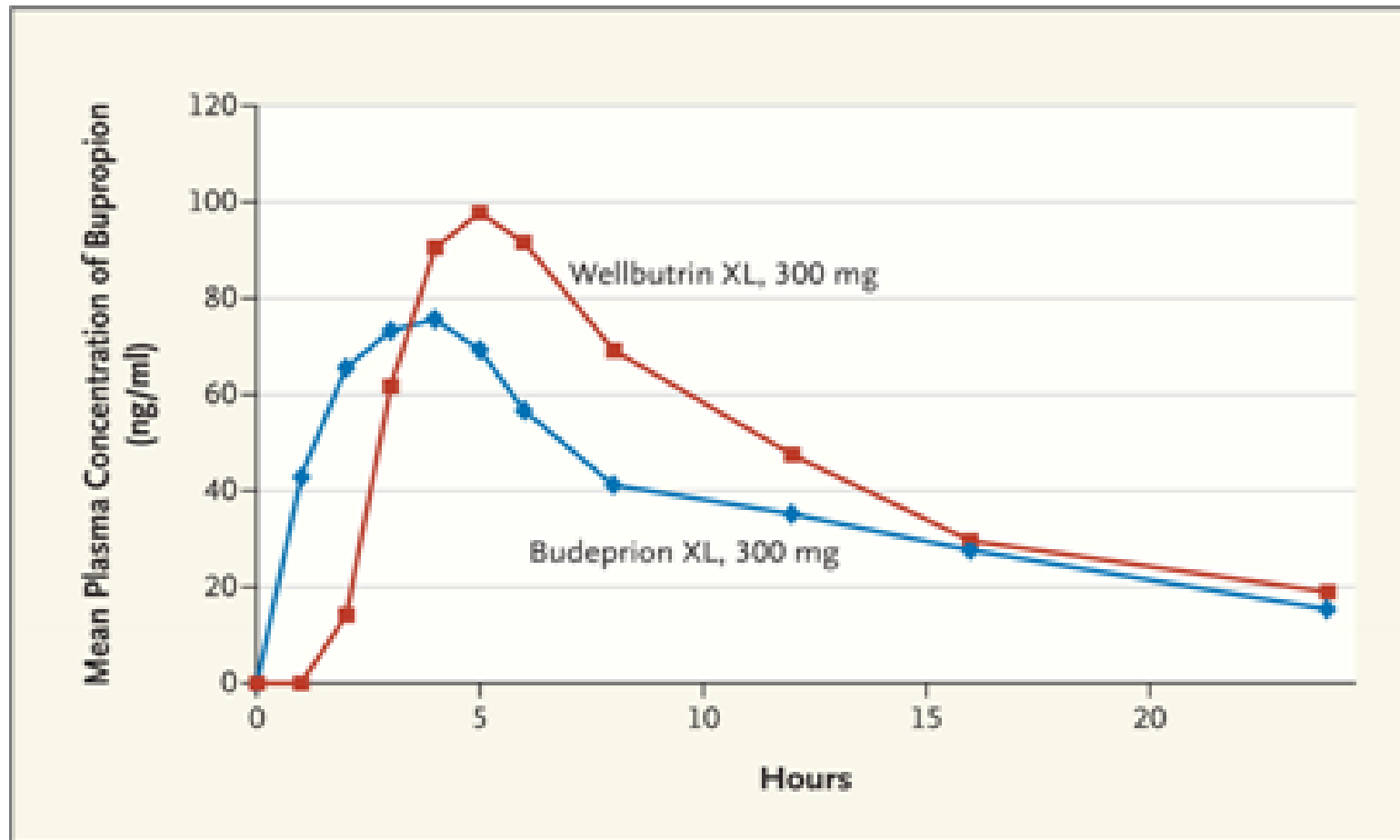
# Multiphasic Modified Release

- 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 for a generic product include:  $C_{max}$ ,  $AUC_{0-last}$  or  $AUC_{0-\infty}$  and pAUC

**Mean Plasma Concentration of Bupropion (Budeprion XL and Wellbutrin XL)  
as a Function of Time in 24 Fasting Healthy Volunteers.**



Ref: Woodcock J et al. N Engl J Med 2012. DOI: 10.1056/NEJMp1212969

# 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.

# Dissolution Test

- It is the most useful physicochemical test for assessment of drug product quality
- To assess batch to batch quality
- The release specifications (QC test) allows batch release into the market place
- Functions as a signal of **BioInequivalence**
- Application in granting Biowaiver

# QbD Guiding Principles

## Drug Release Testing

- Dissolution testing is a tool for
  - Product development and optimization
  - Product characterization
  - Establishing performance test
- A clear distinction of the purpose for which this tool is to be used is necessary
  - QC tool vs. waiver of in vivo studies



# Immediate Release Drug Products

- **Apparatus**
  - Apparatus 1 (Basket), 50/120 rpm
  - Apparatus 2 (Paddle), 50-75 rpm
- **Medium**
  - Aqueous Medium, pH 1.2 – 6.8
  - For sparingly water soluble drugs – use surfactant - must be justified, lowest amount must be used
  - 500-1000 ml at  $37 \pm 0.5^{\circ}\text{C}$
- **Sampling Times**
  - 15 minute intervals until 85 % dissolution

# **Dissolution**

## **Sparingly Water Soluble Drug products**

### **Dissolution medium**

- **Use of surfactant must be justified**
- **Lowest amount of surfactant must be used.**

# Extended Release Drug Products Dissolution Data

- **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)

# Dissolution Science

## *Where are we today?*

- Increased knowledge and understanding of the science behind the test methodology
- Availability of precise, rugged and reliable dissolution test equipment
- Dissolution test is used as a surrogate in vitro bioequivalence test and

# Role of Dissolution Testing in Regulating Pharmaceuticals

- Increasingly, in vitro dissolution testing is relied on to assure product performance.
- An appropriate dissolution test procedure is a simple and economical method that can be utilized effectively to assure acceptable drug product quality.
- Appropriate dissolution test can be used as a surrogate marker for Bioequivalence.

# **Biopharmaceutics Classification System (BCS)**

# **Biopharmaceutics Classification System**

- **It is based on solubility and permeability of the drug substance and dissolution of the drug product.**
- **It also takes into consideration**
  - **Gastric pH, gastric fluid volume and gastric emptying time**
  - **Intestinal pH, intestinal fluid volume, intestinal transit time and permeability**



# **Biopharmaceutics Classification System**

## **View on Bioequivalence**

**If two drug products, containing the same drug, have same concentration time profiles at the intestinal membrane surface then they will have the same rate and extent of absorption**

- **Same in vivo dissolution profiles under all luminal conditions**
- **Formulation components do not affect the membrane permeability and/or intestinal transit.**

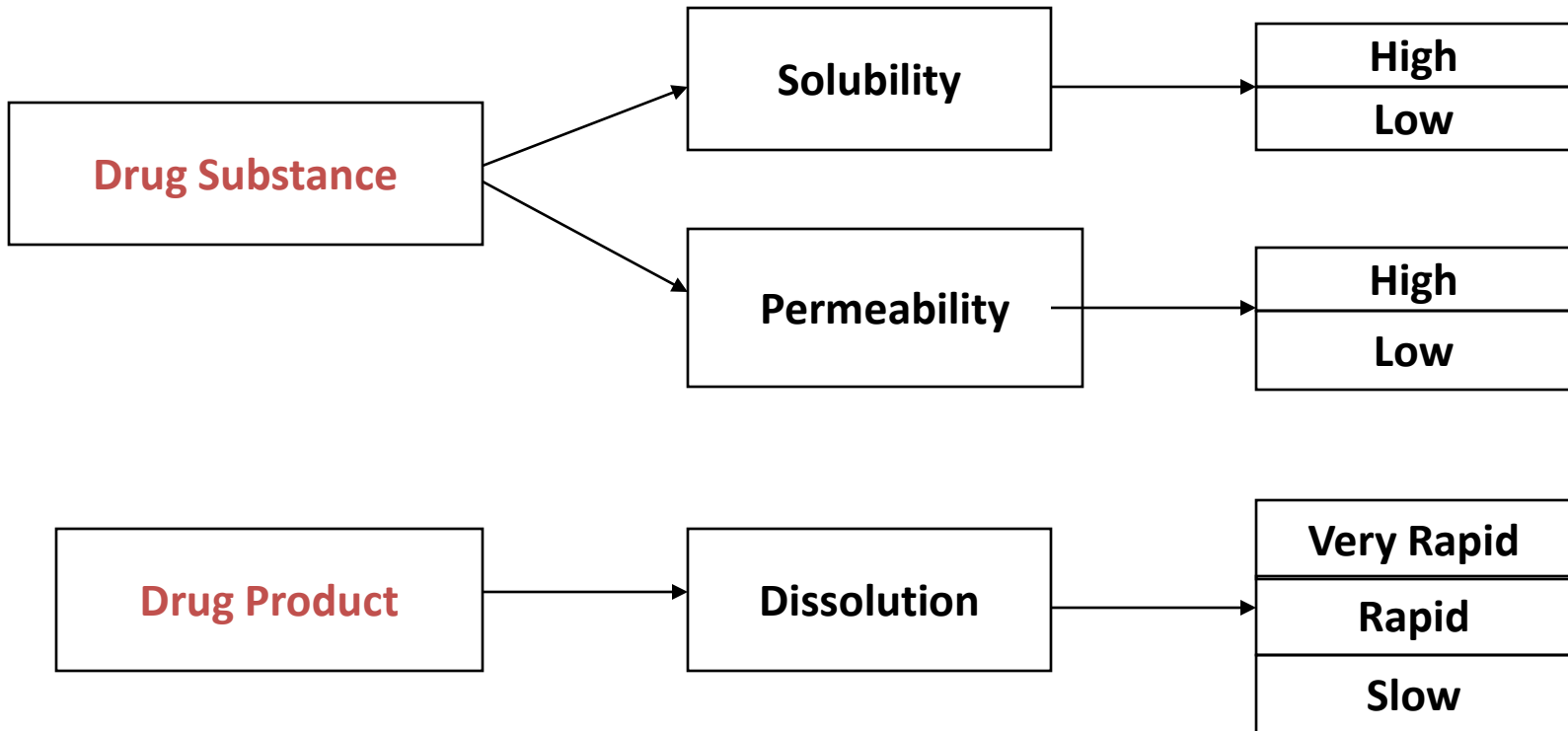
**Ref: GL Amidon, H Lennernas, VP Shah, JR Crison. A theoretical basis for a BCS: The correlation of in vitro drug product dissolution and bioavailability. Pharm. Res. 12: 413-420, 1995.**

# 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.

**GL Amidon, H Lennernas, VP Shah, JR Crison. A theoretical basis for a biopharmaceutics classification system: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 12: 413-420, 1995**

# Biopharmaceutics Classification System



# Waiver of in vivo BA & BE for IR drug products based on BCS

- **Criteria for biowaiver**
  - Highly soluble: Highest dose soluble in 250 ml in pH 1.2 – 6.8
  - Highly permeable: extent of absorption greater than 85%
  - Rapidly dissolving: 85% or greater by basket method 100 rpm or paddle method 50 rpm in 900 ml in pH 1.2, 4.5 and 6.8
- **For a waiver of BE, T and R products should exhibit similar dissolution profile**

# Biopharmaceutics Classification System

- **BCS class 1:**

- BCS is a regulatory tool in the drug approval process.
- Rate and extent of drug absorption is unlikely to be affected by drug dissolution and/or GI residence time.
- It is unlikely that absorption will be limited by efflux transporters.
- It is based on evaluation of two intrinsic properties of the drug substance (API) - permeability and solubility and one property of the dosage form - dissolution.

# Dissolution Test (BCS)

## *Multisource (test) and Comparator (reference) product*

- Paddle method at 75rpm (WHO) or 50rpm (FDA)  
**or** Basket method at 100 rpm in pH 1.2, 4.5, 6.8
- Dissolution profile similarity

## *Dissolution Characteristics:*

- Very rapidly dissolving – 85% in 15 min
- Rapidly dissolving – 85% in 30 min
- Slowly dissolving – more than 30 min for 85% dissolution

# BCS Based Biowaivers\*

- **BCS Class 1: HS/HP**
  - VRD or RD in pH 1.2, 4.5 and 6.8
- **BCS Class 2: LS/HP/Weak Acids**
  - Rapid dissolution in pH 6.8 and similar dissolution profile in pH 1.2, 4.5 and 6.8
- **BCS Class 3: HS/LP/VRD**
  - contains no inactive ingredients that are known to alter GI motility and/or absorption

**For biowaivers Test (multisource) and Reference (comparator) products must have similar dissolution profile ( $f_2$ ) in all 3 media**

**Ref: WHO Technical Report Series No. 937, 2006 Annex 7, p 347-390.**

# **Drug Product Quality**



# Drug Product Quality

- Aim at **modernizing Agency's (FDAs) regulation** of pharmaceutical manufacturing and product quality
  - to provide medicines of highest quality, second to none
- Pharmaceutical cGMPs for 21<sup>st</sup> century
  - A risk based approach
  - Incorporates concepts of risk management and quality systems while continuing to ensure product quality
- Science based policies and standards
- A drug quality system for the 21<sup>st</sup> century
  - Science and risk based approach to product quality regulations
- QbD

# Quality by Design (QbD)

- QbD is essential part of modern approach to pharmaceutical quality – it combines critical manufacturing process and operating parameters.
- QbD – Design space: Multi-dimensional space that encompasses combination of product design, manufacturing process parameters and component attributes that provide assurance of acceptable product quality and performance.

# Quality by Design

Quality by Design involves the following key elements:

- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessments
  - Impact of process parameters in the final product
  - Risk assessment assures product quality
- Develop design space for raw materials & finish product
- Design and implement control strategy
  - Includes starting materials, intermediates and finished product
  - Set most appropriate (realistic) parameters
- Manage product life cycle, including continual improvement

# 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

# Quality by Design



**Product Lifecycle and QbD – Pharmaceutical Quality Assessment System for the 21<sup>st</sup> Century, FDA, December 2009**

# Quality System

- Quality: To build the reputation and trust.  
Q is the basis of 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 21<sup>st</sup> century and Quality by Design programs.
- Considering meaningful manufacturing quality metrics
- FDA/CDER/ New Office of Pharmaceutical Quality
- Continual quality surveillance.

# Quality

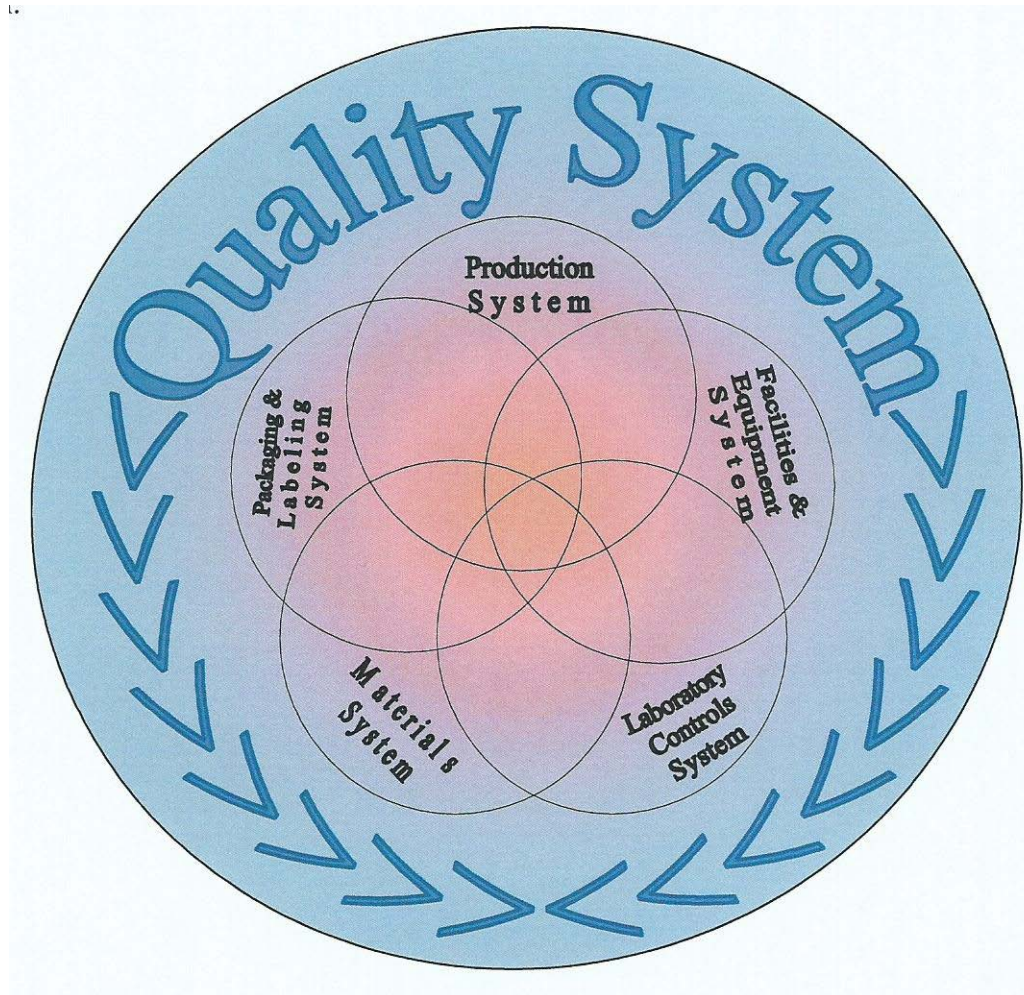
- GMP regulations – Complying with existing regulations, no new (quality) requirements.
- Industry must maintain top-quality manufacturing controls and standards, and must build robust quality and risk-management systems into all levels of operations.
- Instilling and maintaining quality is a formidable challenge.
- A Potential Promise: “In a world where quality risk management is fully embraced, we could foresee a time when enhanced regulatory flexibility might be possible.” ... **Margaret A. Hamburg, M.D.,  
Commissioner of FDA, February 22, 2013.**

# Quality

- Develop new tools, standards and approaches to assess the safety, efficacy, quality and performance of drug products.
- FDASIA: FDA Safety and Innovation Act, July 2012.
- Pharmaceutical cGMPs for the 21<sup>st</sup> Century – A Risk-Based Approach – August 2002
- To enhance and modernize the regulation of pharmaceutical manufacturing and product quality
- Guidance for Industry: Quality Systems Approach to Pharmaceutical cGMP Regulations. September 2006.



# Quality System Model



**Ref: FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical cGMP Regulations. September 2006**

# 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 System Approach to Pharmaceutical Manufacturing Practice

- Pharmaceutical cGMPs for 21<sup>st</sup> Century initiative: Encourage industry to adopt modern and innovative manufacturing technologies.
- Intended to help manufacturers implement modern quality systems and risk management approaches to meet cGMP regulations. (21 CFR parts 210 and 211)
- Describes a comprehensive quality system model
- Quality should be built into the product, and testing alone cannot be relied on to ensure product quality.
- Not intended to create new requirements
- Discusses management responsibilities, resources, manufacturing operations, evaluation activities.

# cGMPs & the Concepts of Modern Quality Systems

## Concepts as they relate to pharmaceutical manufacturing

- **Quality**
  - Identity, strength, purity and other quality characteristics designed to ensure the required levels of safety and efficacy
- **Quality by design**
  - Designing and developing a product and associated manufacturing process to ensure consistent product quality
- **Quality risk management**
  - Guide setting specifications and process parameters
- **CAPA (Corrective and Preventive Action)**
  - Focus on investigating, understanding, and correcting discrepancies; attempting to prevent their recurrence
- **Change control**
  - Managing change to prevent unintended consequences
- **The quality unit**
  - Quality control (assessment) and Quality assurance (Audit)
- **Six-system inspection model**
  - FDA's Drug Manufacturing Inspection Program

# 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 cGMP conditions and meet Quality and Performance Standards**

are

Therapeutically Equivalent and  
Therapeutically Interchangeable

***Thank You for  
Your Attention***