Reducing Regulatory Burden, but Maintaining the Quality of Generic Products

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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 at affordable price.**

- **Reducing Regulatory Burden →**
  Less in vivo studies
- **Quality Generic Product →**
  Safe and Effective
- **Available to Patient at Affordable Price**

Bioavailability and Bioequivalence

- 1977: BA/BE Regulations – 21 CFR 320.
- **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 …"
- **Hatch-Waxman Act of 1984:** Established a pathway for ANDA and efficient approval of generic drugs.

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

GENERIC FORMULATIONS:

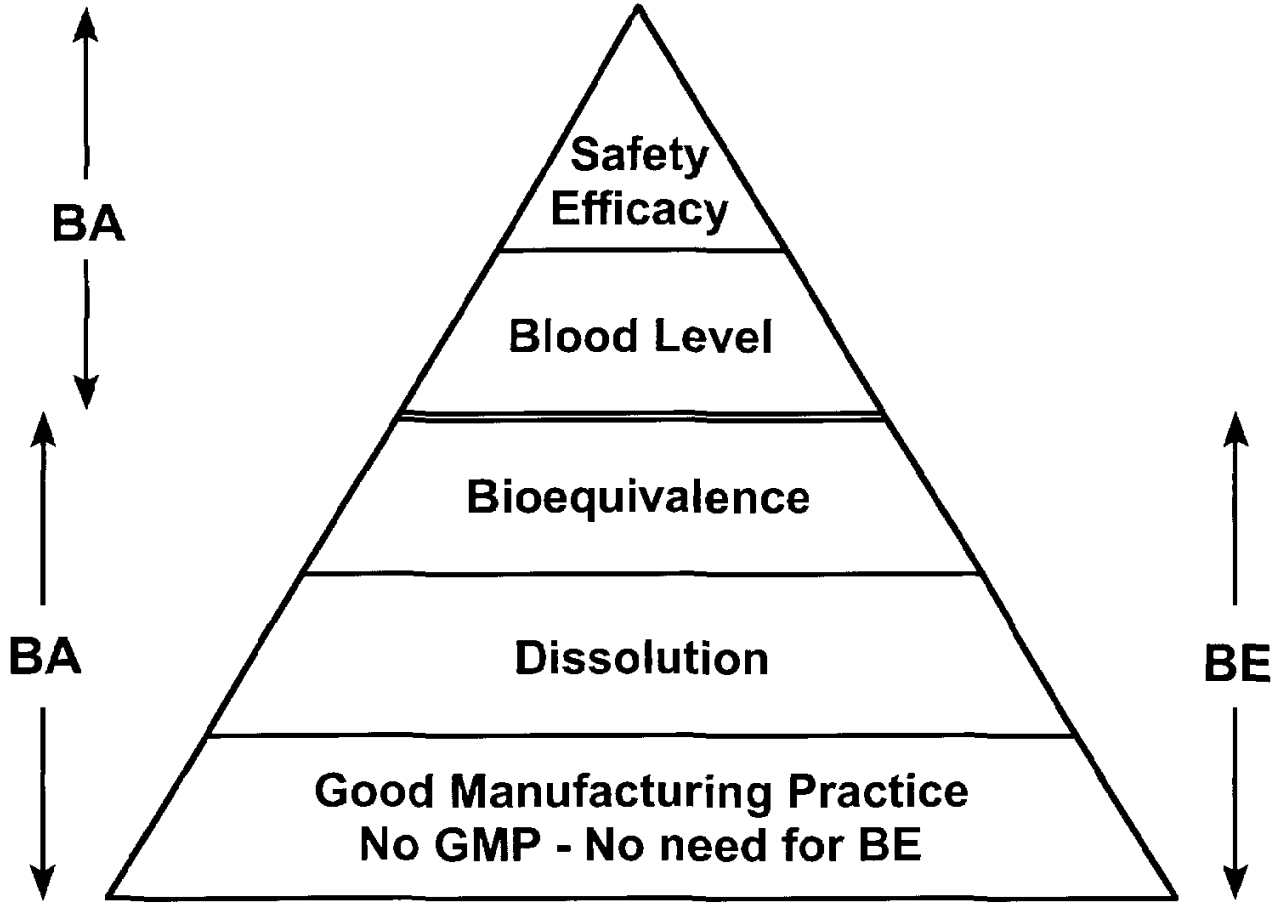
Pharmaceutical Equivalence	+	Bioequivalence	=	Therapeutic Equivalence

- 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



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)**

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

Extended Release Products
ANDA: BE Studies

- A single dose fasted study comparing the highest strength of test and reference product
- A food-effect study comparing highest strength of Test and Reference Product
- Must meet BE requirements (criteria)
- In vitro drug release

Draft - Guidance for Industry

Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA

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

December 2013

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

Dissolution Test

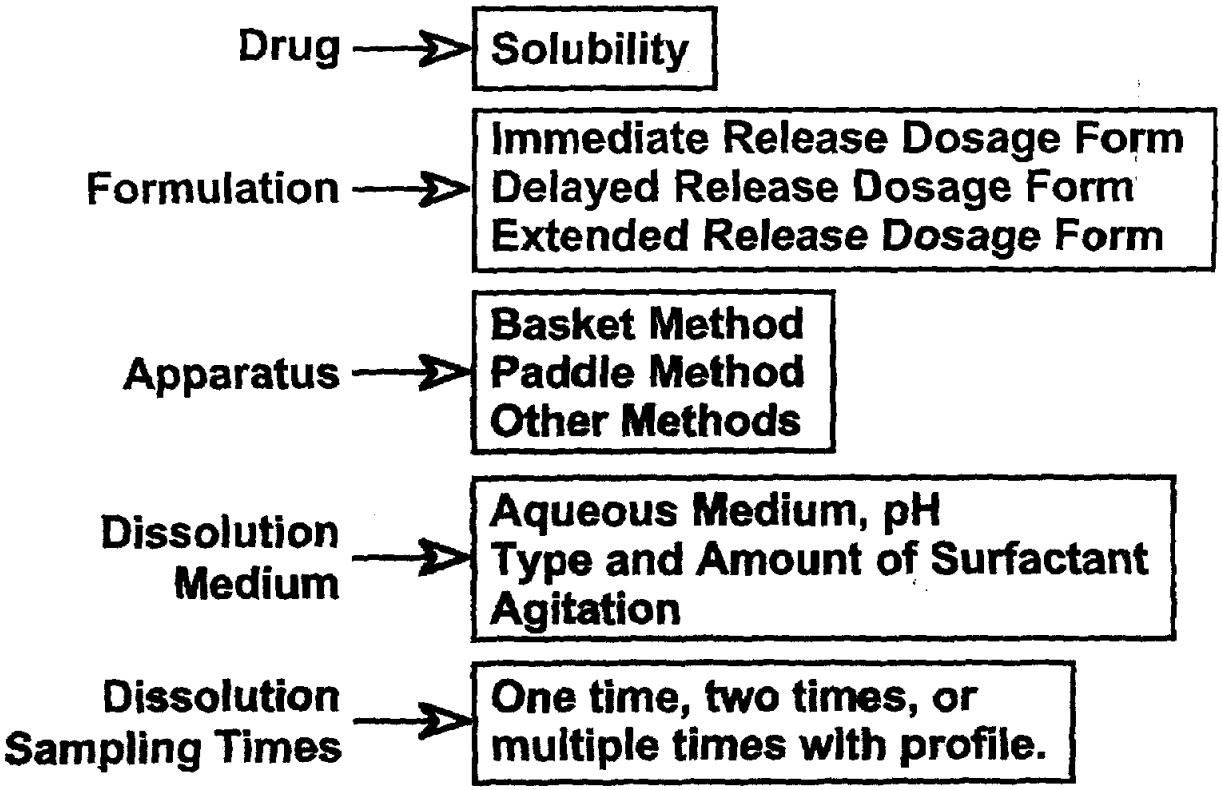
Dissolution Test

- 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

Dissolution Test

- **Mild enough to detect manufacturing and process variables that may affect in vivo performance of the product**
- **Should not be overly discriminative**

Dissolution



Dissolution - *In Vitro* Release

Apparatus:

- **Standard dissolution apparatus**
  - **Apparatus 1: Basket**
  - **Apparatus 2: Paddle**
  - **Apparatus 3: Reciprocating Cylinder**
  - **Apparatus 4: Flow-through**
  - **Apparatus 5: Paddle over Disk (Essentially same as Paddle)**
- **Need to avoid unnecessary proliferation of dissolution apparatus**

Immediate Release Drug Products

- **Single Point**
  - **For routine quality control test**
- **Two Points**
  - **For characterizing the quality of the drug product (also for use as a QC test)**
- **Profile**
  - **Profile for drug approval (12 units)**
  - **Profile comparison for biowaivers**
  - **For accepting product “sameness” under scale-up and post-approval changes**

Extended Release Drug Products

- **Profiles**
  - In multimedia, different pHs
  - Influence of agitation
- **Specifications** (12 Units)
  - 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

Policy Related Dissolution, BA/BE and SUPAC Guidances

- IR Dissolution Guidance
- ER (IVIVC) Dissolution Guidance
- BCS (Waiver) Guidance
- General BA/BE Guidance
- SUPAC-IR Guidance
- SUPAC-MR Guidance

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

Dissolution and Drug Release Tests

- General Chapters in USP
  - <701> Disintegration
  - <711> Dissolution
  - <724> Drug Release
  - <1092> The Dissolution Procedure: Development and Validation

Dissolution in Alcohol Media

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., Morphine, Cyclobenzaprine, Methylphenidate HCl, Dexmethylphenidate HCl, Oxycodone, Trazodone, Bupropion, Venlafaxine, Lamotrigine, Quetiapine Fumarate, Ropinirole)

Dissolution Profile Comparison

$$f_1 = \{[\sum_{t=1}^{n} | R_t - T_t |]/[\sum_{t=1}^{n} R_t]\} \bullet 100$$

$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

- R_t and T_t are the cumulative % dissolved at each of the selected n time points
- f_1 is proportional to the average difference between the two profiles (difference factor)
- f_2 is inversely proportional to the average squared difference between the two profiles and measures the closeness between the two profiles (similarity factor).

Dissolution Based Biowaivers

- **Conventional Release Products**
  - Lower strengths, proportional formulations, f_2
  - BCS Class 1: HS/HP/RD
  - BCS Class 3: HS/LP/Very Rapidly dissolving
- **Extended Release Products**
  - Lower strengths, proportional formulations and same release mechanism
  - Beads in a capsule - Profile comparison in one medium
  - Tablets - Profile comparison in pH 1.2, 4.5, 6.8

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 BA/BE.

Dissolution Test
Impact

- Assures Product Quality
- Useful as a Bioequivalence Test
- Establishes Procedure for Granting Biowaiver
  - New Drug Application and Abbreviated New Drug Application
  - Higher Strength
  - Lower Strength(s)
- Assures Product Sameness Under SUPAC Related Changes

Biopharmaceutics Classification System (BCS)

- BCS Guidance
- BCS Class 1 and 3 Biowaivers
- Update on BCS related Guidance
- BCS Monographs

Biopharmaceutics Classification System

- **BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, BCS takes into account three major factors that govern the rate and extent of absorption from IR solid oral dosage forms: dissolution, solubility and intestinal permeability.**

BCS Guidance:

IR drug products

non-NTI drug products

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

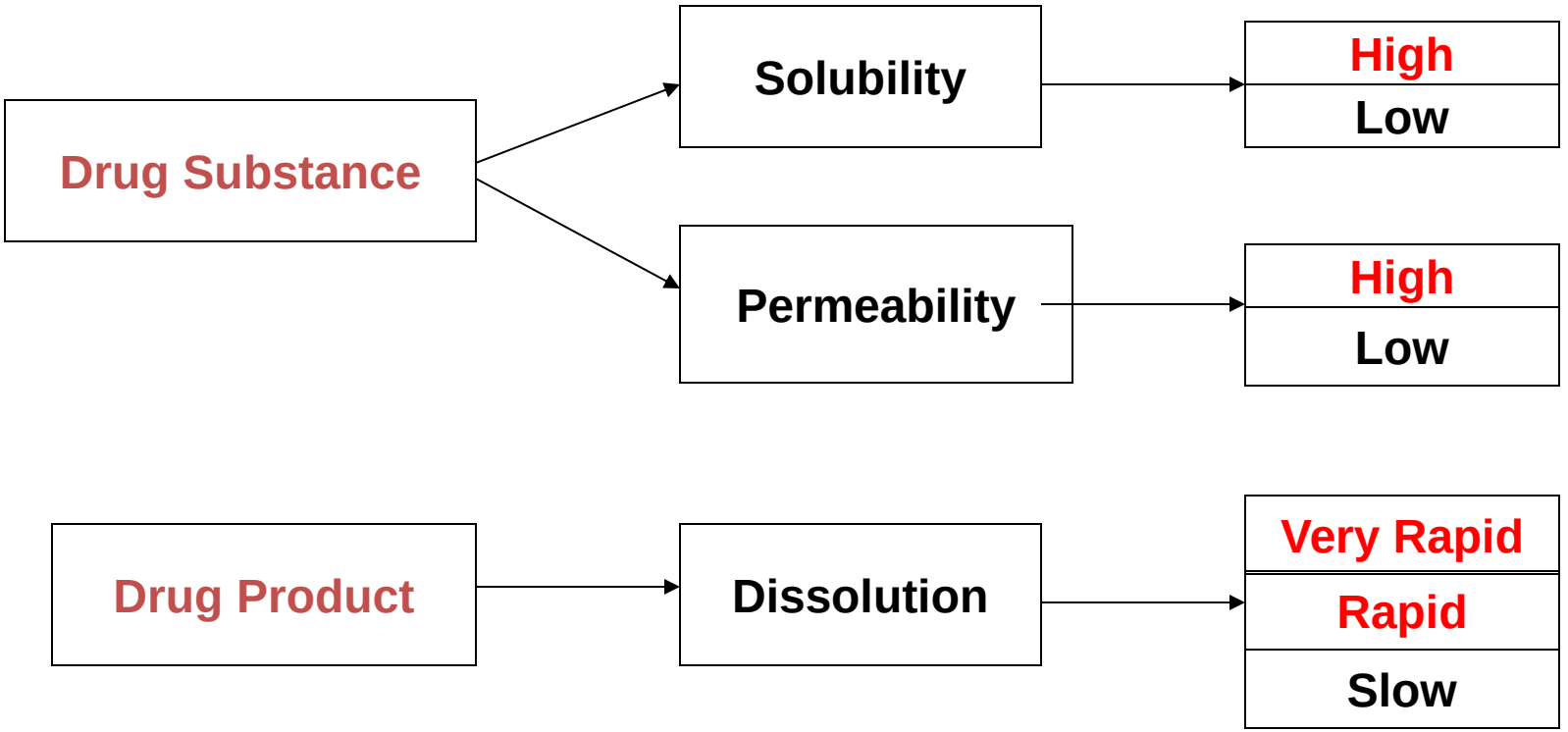
Solubility

- Solubility is defined in terms of dose solubility, highest dose strength solubility in 250 ml of aqueous medium, pH 1.0-6.8.
- Classified as either high or low
  - High defined as dose/solubility volume less than or equal to 250 ml
  - Low defined as dose/solubility volume greater than 250 ml for any pH

Permeability

- Permeability is defined in terms of human permeability, absolute bioavailability (comparison with intravenous dose) or in terms of jejunum permeability.
- Highly permeable when the extent of drug absorption in human is >85% of an administered dose (compared to iv).
- Measurements:
  - In Vitro method: Caco 2
  - In Vivo method: In human

Biopharmaceutics Classification System



World Health Organization

Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

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

Dissolution Test (BCS)

Test and Reference product -

- Paddle method at 50rpm (FDA) or 75rpm (WHO)
  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**
  - 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**
  - **c**ontains 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.

*** Based on draft BCS Guidance, May 2015**

BCS Related Guidance

- **BCS Guidance:** Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on a biopharmaceutics classification system - August 2000.
- **Draft Guidance:** Update on the (above) BCS biowaiver guidance - May 2015
- **Draft Guidance:** Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and Class 3 Drugs - August 2015.

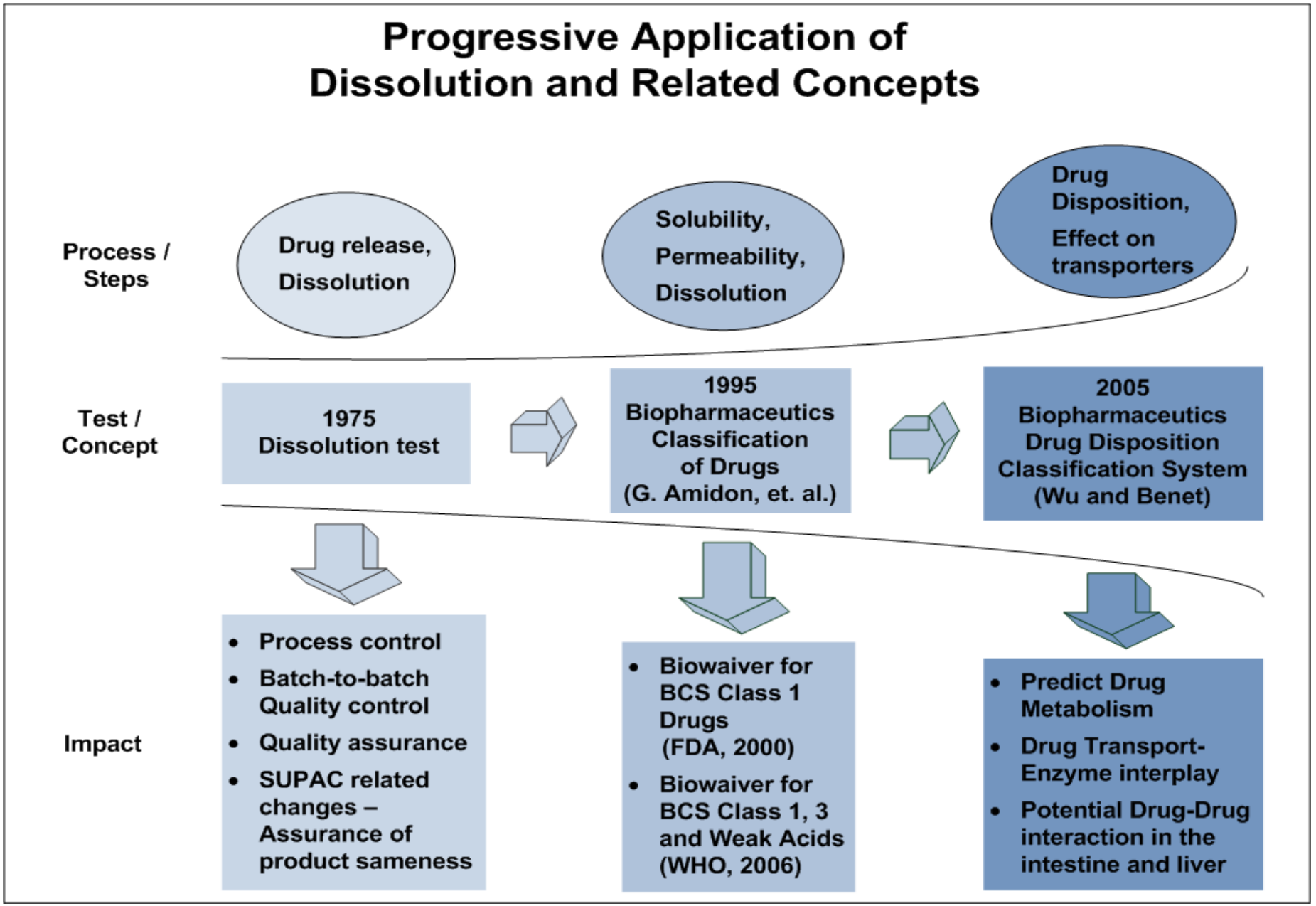
BCS-based Biowaiver Monographs Project - Overview

- **Genesis of biowaiver monographs**
- Project initiated by FIP/SIG - BCS;
  Now FIP/SIG Regulatory Science/FG - BCS and Biowaiver.
- No direct implication, no formal regulatory status, but represents best scientific judgment about eligibility for BCS based biowaiver. It provides a good starting point for the applicant. It is also used as a source of information by regulators.
- Drug substances selected based on WHO's List of Essential Medicines + other important drugs

Biowaiver Monographs

- Literature review - Solubility, permeability, dissolution, pharmacokinetic and bioequivalence data
  - Document summarizing all known relevant information
  - Review can suggest feasibility of biowaiver for a generic formulation
  - Indicates criteria for in vitro equivalence test.
  - Review can also indicate when biowaiver is not recommended, e.g., ciprofloxaxin, furosemide, mefloquin
- Published as a commentary in J Pharm Sci after peer review process. Also on virtual special issue of J Pharm Sci.
- Available on FIP web page: www.fip.org
- More than 35 biowaiver monographs, ranging from BCS class 1- 4 have been prepared and published.

Progressive Application of Dissolution and Related Concepts



Ref: VP Shah. J Pharm Sci. 102: 2895-2897, 2013.

Conclusions

- **Reducing Regulatory Burden -**
  No in vivo studies, biowaiver,
  Appropriate dissolution procedure and standards
- **Maintaining Generic Product Quality -**
  Manufactured under GMP conditions
  Product is PE and BE (thru in vitro standards)
- **Dissolution standards -**
  Assure safety and efficacy

Thank you for your Attention