Emerging Trends in Biopharmaceutics Classification System and Biowaivers

Vinod P. Shah, Ph.D.,
Pharmaceutical Consultant

Southern African Regional and International Symposium
SARI 2014
MCC/AAPS Symposium

Pretoria, S Africa, March 11-13, 2014

Outline of Presentation

- FDA - BCS Biowaiver Guidance
- WHO Technical Report (Guidance)
- Emerging trends in BCS & biowaivers
- BCS data base at FDA
- BCS based research projects
- BCS-based biowaiver monographs
- Conclusions

Biowaiver

The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than in vivo bioequivalence test.

For solid oral dosage forms, Biowaiver(s) is generally based on a dissolution test.

Guidance for Industry

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

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

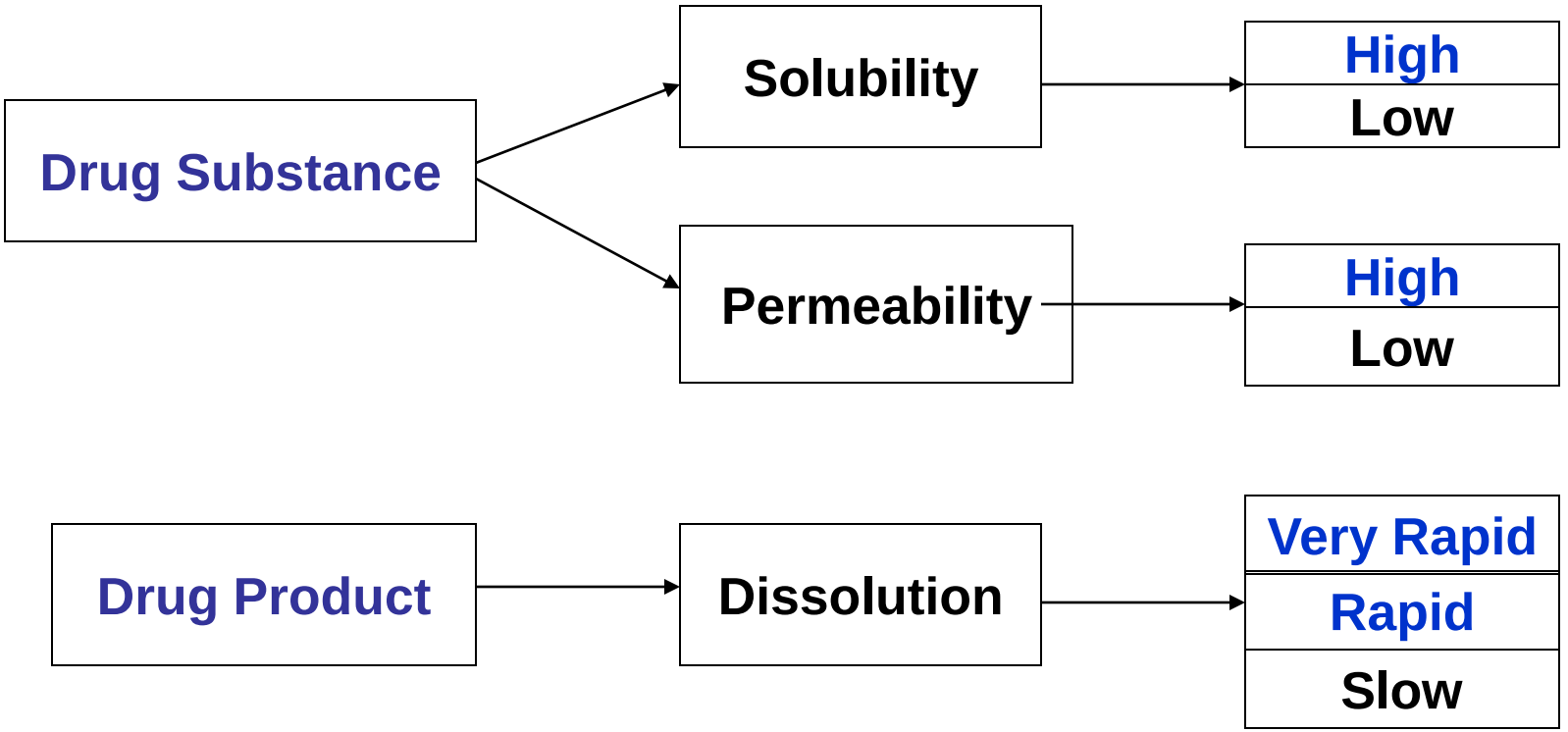
August 2000

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**

FDA Guidance - Waiver for Class 1 Drugs

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)

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

(Bio)-Equivalence Test

Equivalence test is a test that determines the equivalence between the multisource (test) product and the comparator (reference) product using *in vivo* and/or *in vitro* approaches.

In Vitro Equivalence Test

In vitro equivalence test is a dissolution test that includes dissolution profiles comparison between the multisource product and the comparator product in three media: pH 1.2, 4.5 and 6.8.

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

BCS Class 1- HS/HP - Biowaiver

- **Rapid dissolution**
  - 85% or greater in 30 minutes or less in pH 1.2, 4.5 and 6.8 (profile comparison with reference, similarity factor $f_2 \geq 50$)

- **Very rapid dissolution**
  - 85 % or greater in 15 minutes or less in pH 1.2, 4.5 and 6.8 (no need for profile comparison)

BCS Class 2 – LS/HP - Biowaiver * (For weak acids)

- Rapid dissolution – 85% or greater in 30 minutes or less in pH 6.8 and

- The test product exhibits similar dissolution profiles to the reference product in pH 1.2, 4.5 and 6.8

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

BCS Class 3 – HS/LP – Biowaiver *

- Test and reference products are very rapidly dissolving – 85% dissolution in 15 minutes or less in pH 1.2, 4.5 and 6.8

- The dosage form do not contain any inactive ingredients that are known to alter GI motility and permeability

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

Biopharmaceutics Classification System

A Tool For Risk Management

- BCS is a framework for identifying low-risk products based on solubility, intestinal permeability (absorption) and dissolution.
- Minimize the risks associated for decisions on biowaivers
- Assessment of Risk
  - Risk of bioinequivalence
  - Likelihood of bioinequivalence occurrence and severity of consequences
- Risk Factors
  - Failure to emulate in vivo dissolution process
  - Excipient modify GI motility/gastric emptying

Emerging Trends in BCS …

Emerging Trends in BCS & Biowaivers

- Workshops - scientific discussion to suggest changes
- Solubility - pH range: 1.2 to 6.8
- High Permeability / Absorption: 85%
- Review of BCS data base at FDA
- Research - Excipient effect on class 3 drugs:
  - PQRI research
  - FDA research

BCS Data Base at FDA

BCS-based Applications at FDA

- Fifty five (55) drug products evaluated.
- 35/55 (64%) classified as BCS Class 1.
- 28/55 were from the New Drugs side.
  - 15/28 (54%) got class 1 determination.
- 27/55 from the OGD side.
- 21/27 (78%) classified as BCS Class 1.

Courtesy M Mehta, FDA. Information as of ~2012

BCS-based Applications at FDA

- New Drug Applications: 28 cases
  - 13/28 at the IND stage
    - 6 class 1 determination and agreement on biowaivers
    - 2 insufficient information
    - 5 turned down
  - 15/28 were at the NDA review stage
    - 9 class 1 determination and related regulatory relief
    - 2 turned down
    - 4 insufficient information

Courtesy M Mehta, FDA Information as of ~2012

BCS-based Research Projects

BCS Class 3 Drugs

- High Solubility/Low Permeability drugs
- Permeability is a major rate controlling step
- Absorption is controlled by physiological and biopharmaceutical factors rather than formulation factors
- Excipients play an important role

Effect of Excipient

- Excipients should not modulate/alter permeability of BCS Class 3 drugs
- Excipients should not influence intestinal residence time
- Excipients should not alter GI motility and permeability
- Excipients should not alter PK absorption profile

Impact of Excipient

- **Impact of Excipient on Drug Absorption**

  (What happens? Why is this a concern?)

  – Increase

  – Decrease

  – No effect

- **Experiments**

  – In vitro – provide ‘probable’ scenario (practical limitations)

  – In vivo (in human) conclusive evidence

At the intended concentration

Effect of Excipients on Caco-2 Permeability

Drugs Studied

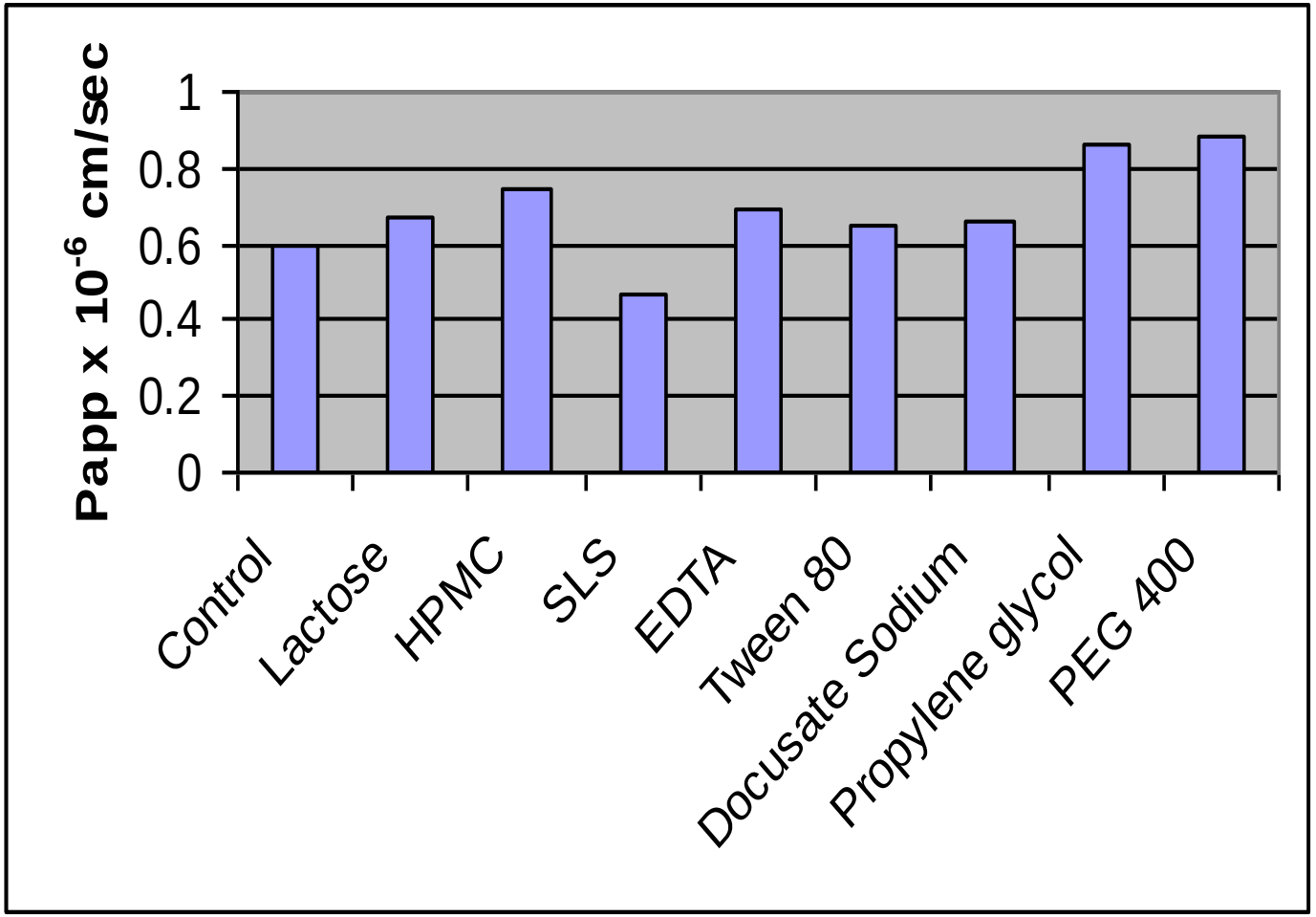
- Furosemide
- Cimetidine
- Hydrochlorothiazide
- Atenolol
- Ranitidine HCl
- Acyclovir
- Manitol

Excipients

- Sodium Lauryl Sulfate
- Tween 80
- Lactose monohydrate
- Hydroxypropyl methyl cellulose (HPMC)
- Propylene glycol
- PEG 400
- Dioctyl sodium sulfosuccinate
- Sodium EDTA
- Anhydrous cherry flavor

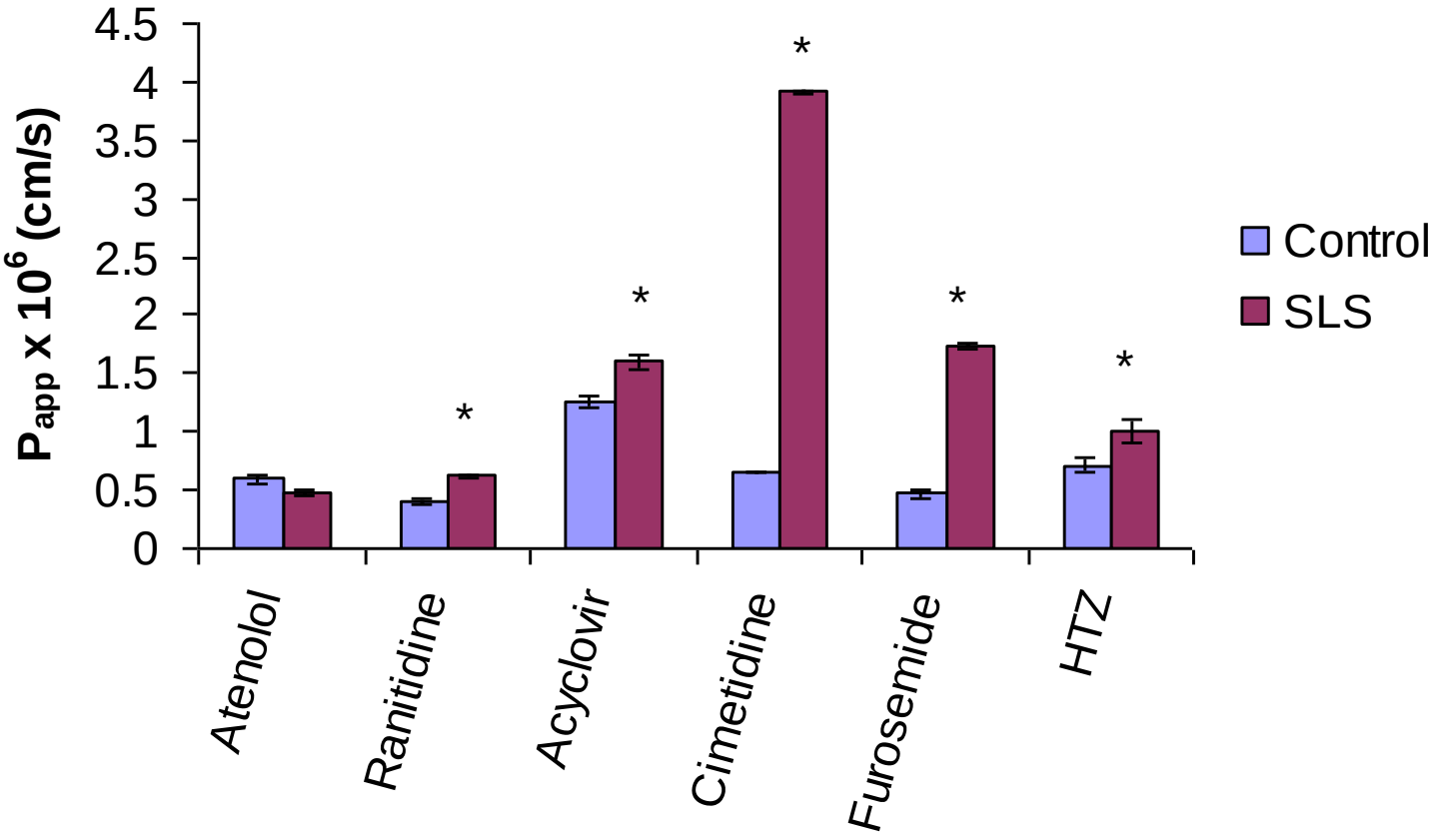
BD Rege, LX Yu, AS Hussain, JE Polli. J Pharm Sci: 90:1776-1786, 2001.

Excipient Effect on Permeability Atenolol



J Polli.

Sodium Lauryl Sulfate



* $p < 0.05$

J Polli.

Effect of Excipients on Caco-2 Permeability

Excipient effect was assessed by comparing absolute drug permeability in the presence / absence of excipient

- Generally most excipients had no influence on low permeability drugs
- Except SLS, no excipient affected Caco-2 monolayer integrity
- SLS moderately increased permeability of all drugs
- Tween 80 increased apical-to-basolateral permeability of furosemide, cimetidine and HCT
- Docusate sodium increased cimetidine permeability

BD Rege, LX Yu, AS Hussain, JE Polli. J Pharm Sci: 90:1776-1786, 2001.

Conclusions

- Generally most excipients had very little/no influence on absorption of low permeability of IR dosage forms (When carried out at the concentration of normal use).

- Caution should be observed and risk analysis should be carried out before considering BCS-based biowaiver.

BCS Class 3 Research Projects

- **PQRI Project**: BIOTHREE research project of National Institute of Public Health and Environment (RIVM, The Netherlands) + University of Mainz, Germany. Evaluation of commonly employed excipients in IR solid dosage forms on the intestinal permeability of several BCS Class 3 drugs to provide a basis to extend BCS biowaivers to class 3 drugs to support FDA Guidance.
- **FDA Project:** Generic Drug Research priorities: Excipient effects on permeability and absorption of BCS Class 3 drugs – University of Maryland.
- **Research Reports : Under preparation**

BCS-based Biowaiver Monographs

Biowaiver Regulations

- BCS-based Regulations differ between the regions
  - FDA – BCS Class 1
  - WHO – BCS Class 1, 2 and 3
  - EU-EMA – BCS Class 1 and 3
  - Japan – BCS ???
- Biowaiver monographs provide the best scientific judgment
- Risk associated with BCS-based biowaivers
  - consequences of bioInequivalence

The Biowaiver Project - Overview

- **Genesis of biowaiver monographs**
- Project initiated by FIP/SIG - BCS;
  Now FIP/SIG Regulatory Science/FG - BCS and Biowaiver.
- Biowaiver - In vitro assessment to waive the need for in vivo bio-studies.
- Risk assessment
- 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.

Biowaiver Monographs

- Literature review - Solubility, permeability, dissolution, bioequivalence data
  - Document summarizing all known information relevant
  - 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
- Available on FIP web page: www.fip.org
- Drug substances selected based on WHO's List of Essential Medicines + other important drugs

Biowaiver Monographs

- More than 35 biowaiver monographs, ranging from BCS class 1- 4 have been prepared and published.
- Biowaiver monographs are useful to applicants as well as to regulators as a source of information
- Reduces the cost of bringing generic product into the market
- Improves patient access to affordable medicines

Future of Biowaiver Monographs

- Continue the activity of biowaiver monographs
- Biowaiver monographs for Fixed Dose Combination products
- Consider highest dosage strength or highest single dose?
- Develop risk calculations to improve science if a biowaiver is acceptable or not

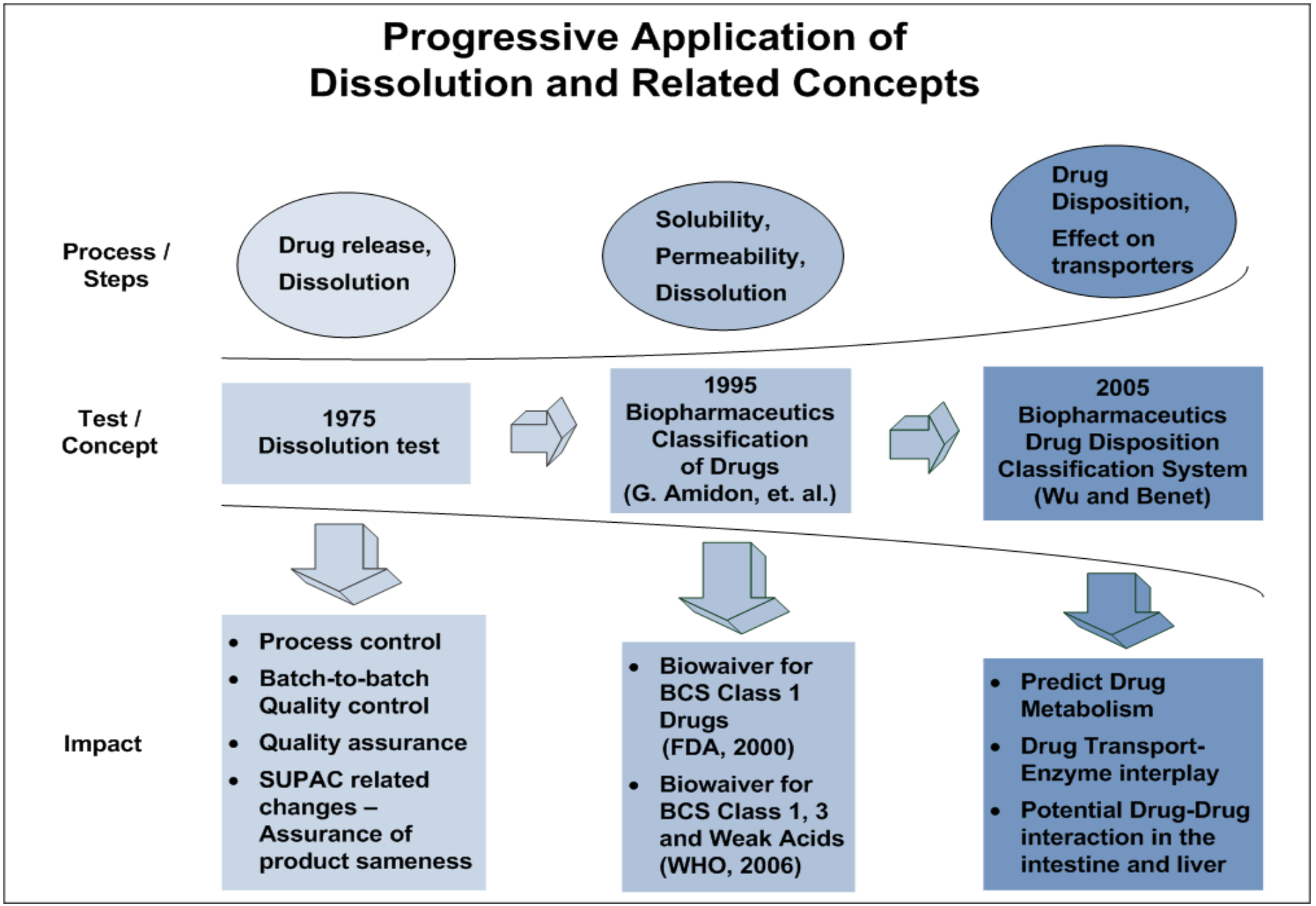
Impact of Biowaiver Monographs

- Impact on approval of multisource (generic) drug products
- Multisource drug products approved via BCS biowaiver procedure and manufactured under GMP can be assured to have same safety, efficacy and quality as the brand name product
- Lowers regulatory burden (IND/NDA/ANDA) without sacrificing the quality of the product
- Reduces the cost of bringing generic product into the market
- Improves patient access to affordable medicines

- Workshop reports
  - (1) JE Polli et.al.,
    J Pharm Sci. 93, 1375-1381, 2004
  - (2) JE Polli et.al.,
    The AAPS Journal. 10(2): 372-379, 2008.
  - More Workshops for scientific discussions ?

- Future Expectations –
- Expected revised FDA Guidance - 2014?
- Biowaiver for BCS Class 3 Drugs - ?

Progressive Application of Dissolution and Related Concepts



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

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

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

Thank You for Your Attention