Never Ending Role of Dissolution in Drug Development

Vinod P. Shah, Ph.D., FAAPS, FFIP.

(Formerly with US FDA) Pharmaceutical Consultant,

North Potomac, MD., USA

Disso India 2023

12th Annual International conference on Dissolution Science and Applications

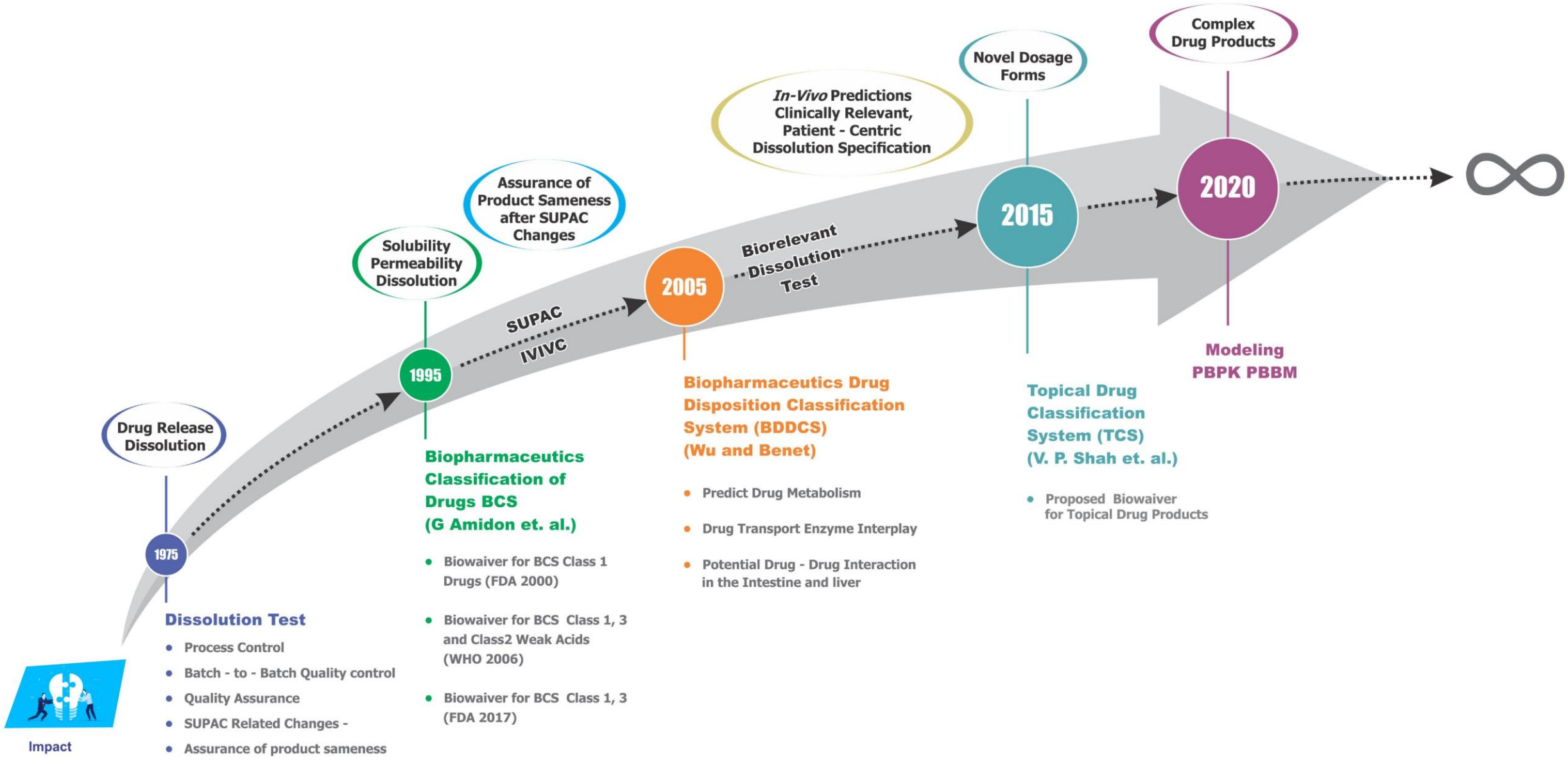
"Importance of Dissolution Science and Technology in Drug Development and Drug Quality Assurance"

Mumbai, India. June 26 & 27, 2023

Never Ending Role of Dissolution …

- Understanding the science of drug dissolution is very essential – it is a must.
- It is pivotal in determining product performance - drug efficacy, safety and quality of a dosage form.
- It is a key attribute for determining bioavailability of a drug.
- It is a vital parameter to assure batch-to-batch consistency.
- Dissolution testing plays a major role in the decision-making process.
- Dissolution test is prescribed in all applicable pharmacopeial monographs.
- Regulatory Acceptance: Drug approval, Bioequivalence, Biowaiver, SUPAC.
- Challenge: Simulating dynamic in-vivo environment in an in-vitro test condition - developing IVIVC.
- Challenge: Development of technologies for dissolution of Complex drug products.

Progressive Application of Dissolution and Related Concepts



Dissolution Test

- It plays an important role in BCS-based biowaiver
  → **Reducing Regulatory Burden**
- It functions as a signal of **Bio*in*equivalence.**
- **Today dissolution testing is recognized as a gold standard for performance testing.**

Dosage form Tests - Quality Tests and Performance Test

- Dosage form 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 (identification, assay, content uniformity and impurity), 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.

Dosage Form Taxonomy (USP)

Route of Administration	Intended site of release	Dosage Form Examples	Dosage Form Quality Tests	Dosage Form Performance Tests*
Parenteral	Body tissues and fluids	Injectables, Liposomes, micro and nano particles, implants, stents	<1>	<1001>**
Oral	Gastro intestinal tract	Tablets and capsules, liquids	<2>	<701>, <711>
Topical / Transdermal	Skin	Semisolids, TDS	<3>	<724>, <1724>
Mucosal (Local or Systemic)	Mouth, eye, ear, rectum, vagina, intra-uterine	Films, tablets, liquids, suspensions, suppositories	<4>	<1004>**
Inhalation	Nasal cavity, lung	Liquids, aerosols, powders	<5>	<601>, <602>, <603>, <604>, <1601>

Dissolution Test

- Dissolution / Drug release test is the drug product performance test. It is a specific quality attribute of the dosage form that links to BA and BE. Therefore, the dissolution method should be meaningful, able to characterize the quality of the drug product and capable of distinguishing significant changes in the formulation or manufacturing process that might affect the in vivo performance, and should be sensitive to any changes in product integrity during its shelf life.

Dissolution Related FDA Guidances

- IR Dissolution Guidance
- ER (IVIVC) Dissolution Guidance
- SUPAC Guidances (IR, MR, SS)
- BCS (Waiver) Guidance
- General BA/BE Guidance
- IR / HS drug substance / Dissolution Guidance
- Product Specific (draft) guidances

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

Dissolution Related General Chapters in USP

<701> Disintegration

<711> Dissolution

<724> Drug Release

<1711> Oral Dosage Forms-Performance Tests

<1087> Apparent Intrinsic Dissolution – Dissolution test procedures for rotating disk and stationary disks

<1088> In vitro and in vivo evaluation of the dosage forms

<1090> Assessment of solid oral drug product performance and interchangeability , BA, BE and dissolution

<1092> The Dissolution Procedure: Development and Validation

<1094> Capsules – Dissolution Testing Related quality Attributes

<1724> Semisolid Drug products – Performance Tests

Dissolution Guidance

- Provides recommendations on the development of dissolution test methodology, approaches for setting specifications and the regulatory applications.

- Provides methods for dissolution profile comparison and indications as to when dissolution is sufficient for biowaivers.

Similarity factor f_2

New and Generic Medicines

- **New Medicines (NDA)**
  - Based on the experience gained during the drug development process and in vivo performance of appropriate test batches
  - Based on acceptable clinical, pivotal bioavailability and/or bioequivalent batches
- **Generic Medicines (ANDA)**
  - Based on the acceptable bioequivalent batch of the drug product
  - Generally the same as first entry (pioneer) drug product

Dissolution Based Biowaivers

- **Conventional Release Products**
  - Lower strengths, proportional formulations, dissolution profile comparison, f_2
  - Drug products with highly soluble drug substances **(BCS class 1 and 3)**

- **Extended Release Products**
  - Lower strengths, proportional formulations and same release mechanism
  - Beads in a capsule - Profile comparison in one medium
  - Tablets - Profile comparison, pH 1.2, 4.5, 6.8

BCS

Biopharmaceutics Classification System

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

Biopharmaceutical Classification System

	High Solubility	Low Solubility
High Permeability	**Class 1** High Solubility High Permeability Rapid Dissolution	**Class 2** Low Solubility High Permeability
Low Permeability	**Class 3** High Solubility Low Permeability	**Class 4** Low Solubility Low Permeability

Amidon et al., Pharm Res 12: 413-420, 1995

Major Routes of Drug Elimination

	High Solubility	Low Solubility
High Permeability	**Class 1** Metabolism	**Class 2** Metabolism
Low Permeability	**Class 3** Renal & Biliary Elimination of Unchanged Drug	**Class 4** Renal & Biliary Elimination of Unchanged Drug

From Les Benet

BCS Related FDA 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 → Revised December 2017.**

- **Dissolution Guidance:** Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products High Solubility Drug Substances
  - **August 2018** (for BCS Class 1 & 3 drugs).
- **ICH M9**

Global BCS Guidances

WHO

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

  WHO Technical Report Series, No. 937, 2006 : Annex 7, p 347-390 → 2015 → WHO Technical Report Series, No. 1003, 2017: Annex 6, p 181-236.

EMEA

- European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP), guidance on the investigation of bioequivalence, 2010.

ICH

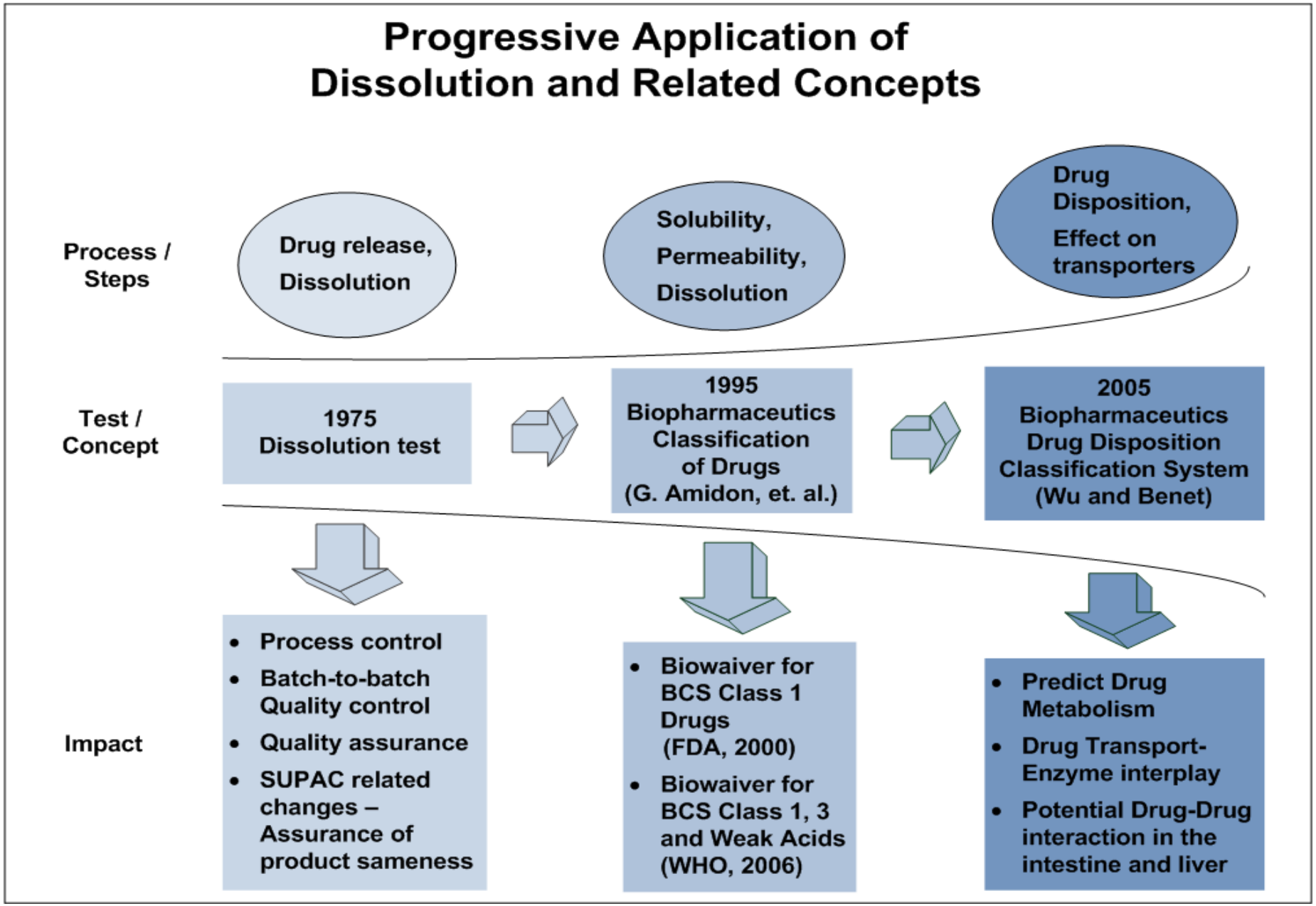
- Biopharmaceutics Classification System-Based Biowaivers (M9), 2019.

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.



Ref: VP Shah, J Pharm Sci. 102: 2895-7, 2013.

Complex Generics

Complex Generics

- A simple generic is a copy of a small molecule reference drug and is chemically identical to its branded counterpart.
- A ***Complex Generic*** is a generic that could have a complex active ingredient, complex formulation, complex route of delivery, or a complex drug device combinations.
- Complex generics are those that are inherently difficult to duplicate.
- Complex Generics present unique drug development and regulatory challenges for demonstrating **sameness of active ingredient and/or formulation and/or BE.**

Complex Generics

- Complex **drug substances** - peptides, polymers, iron colloids,
- Complex **formulations** - liposomes, emulsions, suspensions and polymeric materials, iron colloids,
- Complex **route of delivery** - locally acting drugs, topical dermatological drugs, ophthalmic drugs.
- Complex **drug-device combination** – inhalation products, auto-injectors, Transdermal systems.

Complex Products

Complex	Example	Product
API	Peptides, Complex mixtures, natural source products	Glatiramer Acetate
Formulations, Dosage Forms	Liposomes, Emulsions, Transdermal, Long Acting Injectables	Liposomal formulations, PLGA formulations
Routes of Delivery	Locally acting drugs such as dermatological and complex ophthalmological drugs	Acyclovir Cream, Cyclosporine emulsion
Drug-Device combinations	Dry powder inhalers, Nasal sprays, Transdermals	Mometasone nasal spray; Autoinjector
Other products	Complexity or Uncertainty about approval pathway	Abuse deterrent opioid formulation

Examples of In Vitro Release test used in Complex Generics

Dissolution – In Vito Release

- Dissolution is the quality attribute that best represents the drug product performance.
- General principles of dissolution test should be applicable to in vitro release of Complex Generic dosage forms.
- An in vitro release rate reflects the combined effect of several physical and chemical properties of both the drug substance and the drug product.
- Manufacturing methods and processes may change formulation attributes, thereby affecting the rate of drug release and drug’s bioavailability.

In Vitro Release Test – Complex Generics

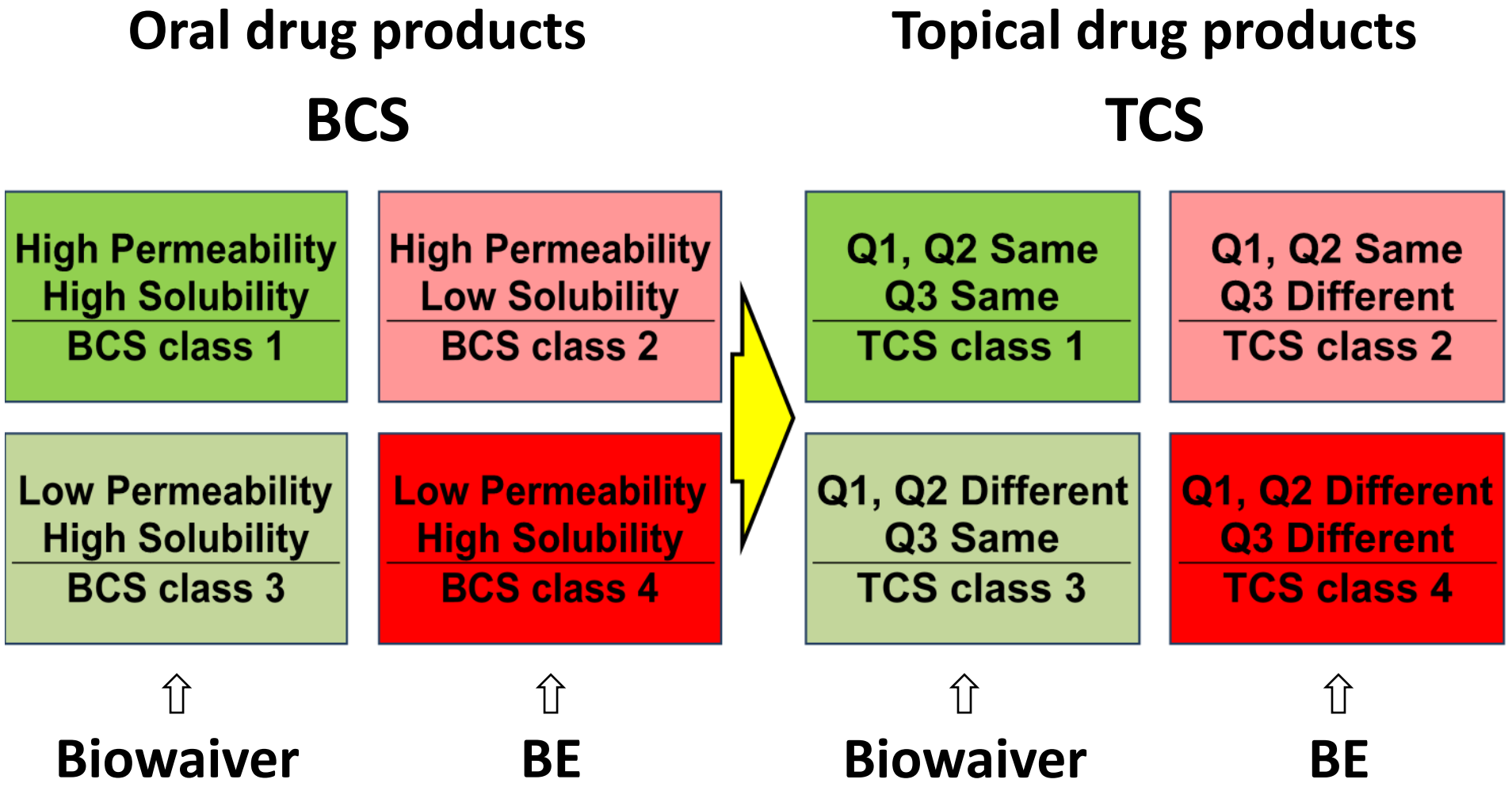
- **Implants, Microparticles, Liposomes**
  - Sample and separate, Dialysis, Apparatus 2, 4 (flow through) and 7.
- **Ophthalmic Drug Product**
  - Microdialysis, Vertical diffusion cell, Apparatus 4
- **Transdermal Drug Products**
  - Apparatus 5 (paddle over disc assembly), Apparatus 6 and 7
- **Semisolid (creams, ointments and gel) drug products**
  - Vertical diffusion cell, Enhancer cell, Apparatus 4 with semisolid adopter.
- **Inhalation Drug Products**
  - PSD – Dose collection – Dissolution
  - Dissolution – Apparatus 4, 5, Vertical diffusion cell.

Topical Drug Classification System (TCS)* (*proposed)

- **TCS** is a framework for classifying topical drug products based on
  - qualitative (Q1) and quantitative (Q2) composition,
    (the role of inactive ingredients, if not Q1)
  - microstructure arrangements of matter (Q3) and
  - *in vitro* release (IVR) similarity.
- **TCS** is a classification system of topical drug products, which when applied will help in approval of generic topical drug products, without conducting *in vivo* studies, but assuring product efficacy and safety.

Ref: VP Shah et.al., Int J Pharmaceutics: 491 (2015) 21-25

BCS and TCS



Ref: VP Shah et.al., Int J Pharmaceutics. 509 : 35-40 (2016).

Dissolution

- Dissolution testing remains one of the pharmaceutical industry's most straight forward, least expensive QC tools to assure product performance.
- Dissolution test distills all the information that is known about the performance of a pharmaceutical product in a laboratory setting.
- Dissolution is used as a surrogate of BE.
- Dissolution serves as an important quality step in the tech transfer process.
- Research is now focused on ways to extend and improve IVIVC and make real-time release testing reality.
- **Research in computer simulation, PBPK modeling, predictive in vivo dissolution, defining 'safe space' for product Quality attributes such as dissolution, is all on the rise.**

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 used as a surrogate in vitro bioequivalence test
- Biowaiver criteria set based on dissolution profile comparison.

Conclusions

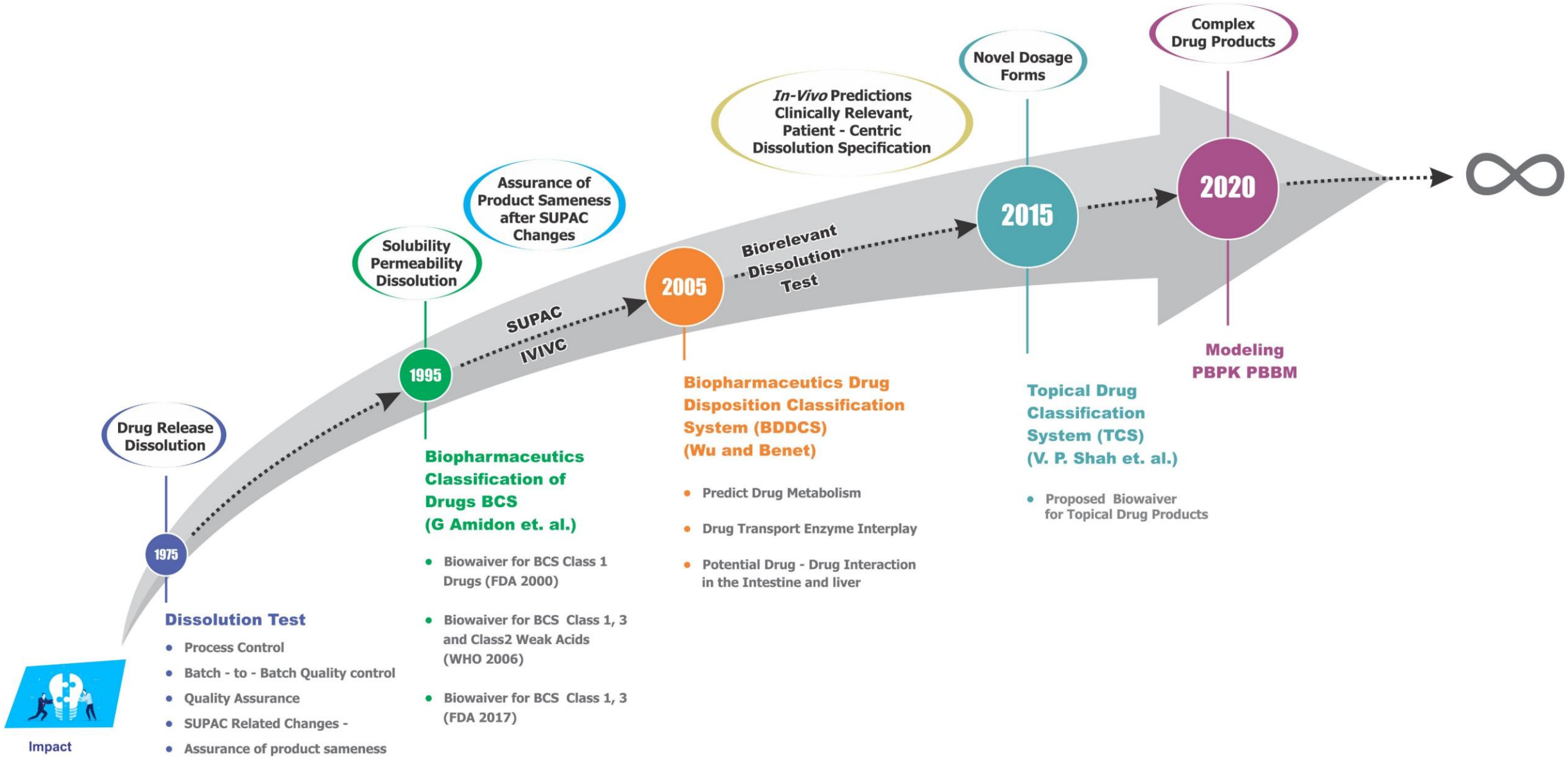
- Increasingly in vitro dissolution testing is relied on to assure product quality and performance.
- An appropriate dissolution test procedure is a simple economical method that can be utilized effectively to assure acceptable drug product quality and performance.
- Dissolution test is a biowaiver tool for reducing regulatory burden.
- Role of dissolution in Pharmaceutical drug development is continuously evolving …

Road map to bolster the pharma sector – Rajeev Raghuvanshi, DCGI.

- Union ministry of Health and Family Welfare – Deliberations on Drugs – **Quality,** Regulations and Enforcement -
- Building trust and confidence in quality of drugs, cosmetics and medical devices in the domestic and export market.
- Effective enforcement of laws at the field level to ensure quality, safety and efficacy of the drug till the last mile.
- The optimal use of Indian Pharmacopeia and adherence to its standards.
- Capacity building of state and national regulators for better and effective regulation of pharmaceuticals and medical devices.
- Creation of unified information technology platform for all regulatory activities.

Hindustan times, Banglore (India), 27-03-2023.

Progressive Application of Dissolution and Related Concepts



Thank You for Your Attention