Have we Reached the Limits of using Dissolution Tests in Pharmaceutical Industry?

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Outline

- Importance of Dissolution
- Biowaiver – dose proportionality, IVIVC, BCS
- SUPAC – IR, MR, SS
- Progressive application of dissolution :
  Dissolution – BCS – BDDCS
- Biorelevant dissolution test
- Reducing regulatory burden:
  Increasing importance of dissolution
- Novel dosage form
- Product quality and product performance test

Dissolution Test

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

Policy Related Dissolution BA/BE Guidances

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

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
  - <1094> Capsules – Dissolution Testing and Related quality Attributes
  - <1724> Semisolid Drug products – Performance Tests

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 Test

- Mild enough to detect manufacturing and process variables that may affect in vivo performance of the product
- Should not be overly discriminative
- Basket (100 rpm) or Paddle (50-75 rpm) in 500-1000 mL of aqueous medium
- Use of surfactant with justification

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

Dissolution Specifications

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 comparison for granting biowaivers**
  - **For accepting product “sameness” under scale-up and post-approval changes**

Dissolution – Gelatin Capsules

- Capsules – Pellicle formation due to cross linking
- Use and selection of enzyme (2^{nd} tier) based on pH of the dissolution medium (dm)
- Dissolution medium with pH equal or below 4.0 Enzyme pepsin – activity of NMT 750,000 U/L of the dm.
- Dissolution medium with pH above 4.0 and below 6.8. Enzyme papain – activity of NMT 550,000 U/L of the dm or bromelain – activity of NMT 30 GDU/L of dm.
- Dissolution medium with pH equal or above 6.8. Enzyme: pancreatin – activity of NMT 2000 U/L of the dm.
- Pre-soaking with enzyme – if surfactant is in the dm.

Extended Release Drug Products

- **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)

Progressive Application of Dissolution

Dissolution

Quality Control

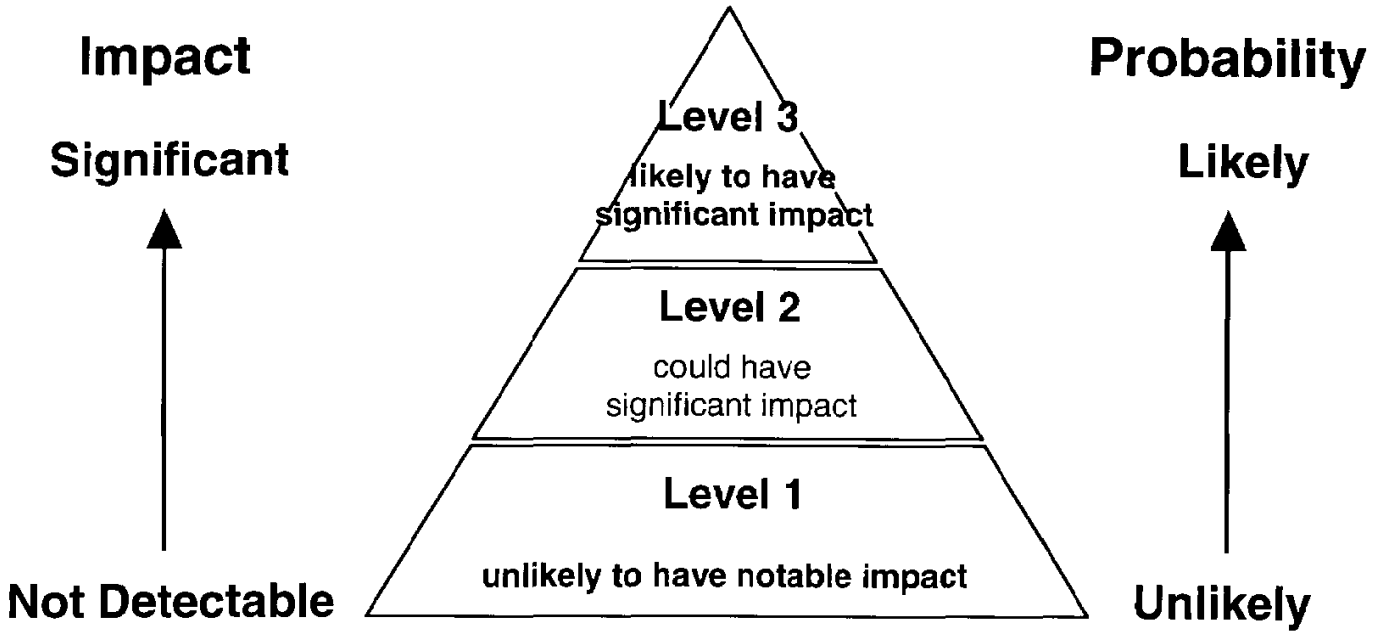
SUPAC

Biowaiver

BCS

SUPAC Initiatives

Quality and Performance



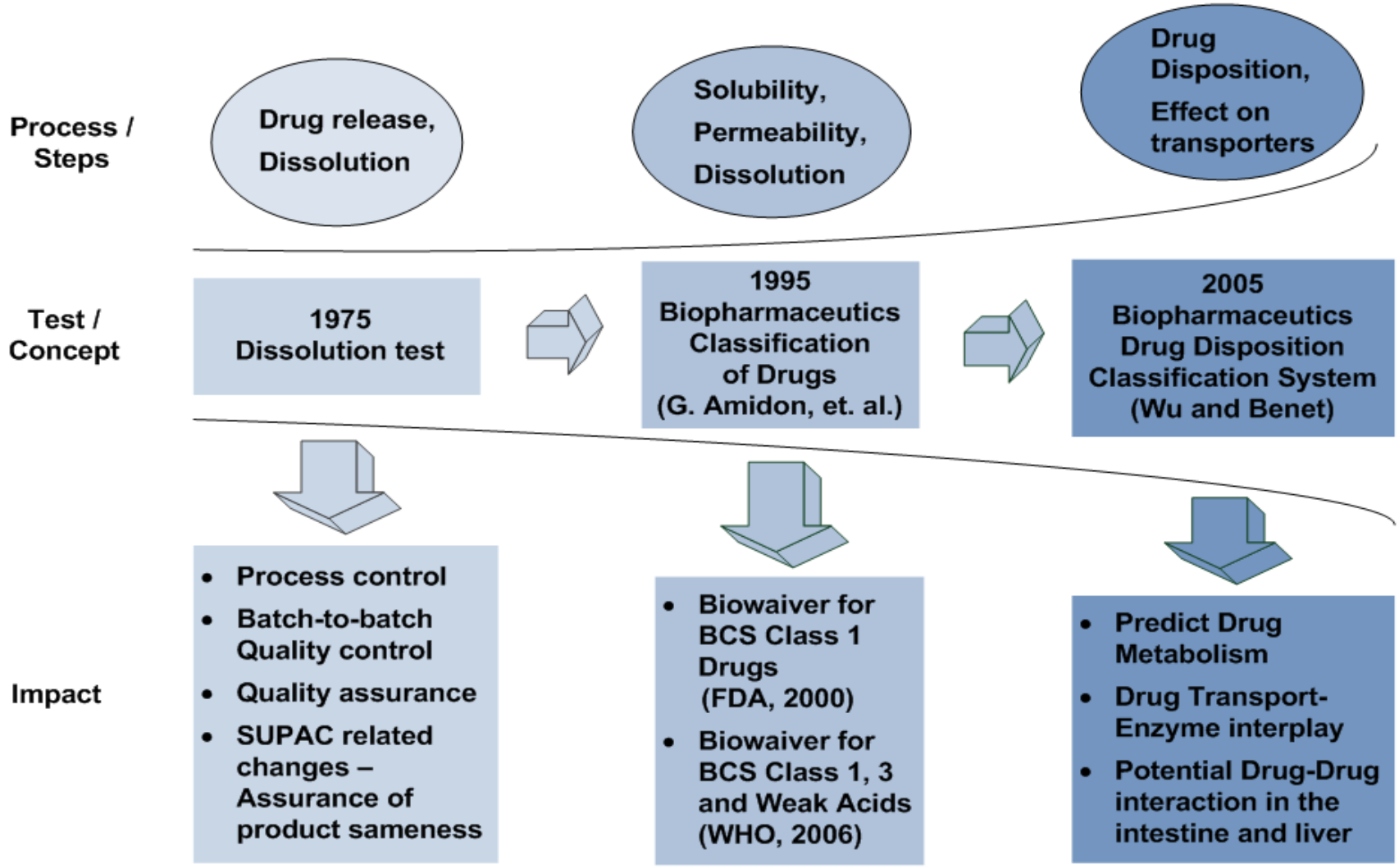
Product Sameness

An attribute of products indicating that they will perform in a similar manner in terms of physicochemical properties and is presumed to allow a link back to the batches tested for safety, efficacy or bioequivalence.

Product Sameness = Requalifying (approved) Product after 'change'

Immediate Release Products:	***In Vitro* Dissolution Tests**
Modified Release Products:	***In Vitro* Dissolution Tests**
Semi-solid Dosage Forms:	***In Vitro* Release Test**
Transdermal Dosage Forms:	***In Vitro* Release Test**

Progressive Application of Dissolution and Related Concepts



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

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**

Dissolution Based Biowaivers

- **Conventional Release Products**
  - Lower strengths, proportional formulations, dissolution profile comparison, 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, pH 1.2, 4.5, 6.8

Dosage Form Tests

- **Product Quality Test**

  Intended to assess attributes such as assay, content uniformity, pH, minimum fill, microbial limits

- **Product Performance Test**

  Designed to assess product performance and in many cases relates to drug release from the dosage form.

Pharmaceutical Dosage Forms

- **Traditional solid oral dosage forms → dissolution test** e.g., tablets, capsules, suspensions
- **Novel dosage forms → In vitro release test** e.g., transdermal patches, semisolids, liposomes, stents, implants

Pharmaceutical Dosage Forms

- Oral – Dissolution test
  - Tablets, capsules, suspension
- **Topical – Drug release test**
  - **Semisolids: cream, ointment, gel**
- Parenteral – Drug release test
  - Liposomes, microspheres, emulsion
- Mucosal – Drug release test
  - Suppositories, medicated gum
- Inhalation – Particle size distribution and dissolution (!)

Topical Drug Classification System - TCS

Q1, Q2 Same Q3 Same	TCS class 1
Q1, Q2 Same Q3 Different	TCS class 2
Q1, Q2 Different Q3 Same	TCS class 3
Q1, Q2 Different Q3 Different	TCS class 4

Ref.: Shah, V.P., et al, Int J Pharm. 491: 21-25, 2015

Novel / Special Dosage Forms - Report

FIP/AAPS Joint Workshop Report: Dissolution / In vitro Release Testing of Novel / Special Dosage Forms:

CK Brown, HD Friedel, AR Barker, LF Buhse, S Keitel, TL Cecil, J Kraemer, JM Morris, C Reppas, MP Sticklemeyer, C Yomota, VP Shah.

- *AAPS PharmSciTech:* Vol 12, Issue 2, 782-794, 2011
- *Dissolution Technologies:* Vol 18 (4), 51-64, 2011.
- *Die Pharmazeutische Industrie:*
- *Indian J of Pharm Sci: 73(3), 338-353, 2011.*

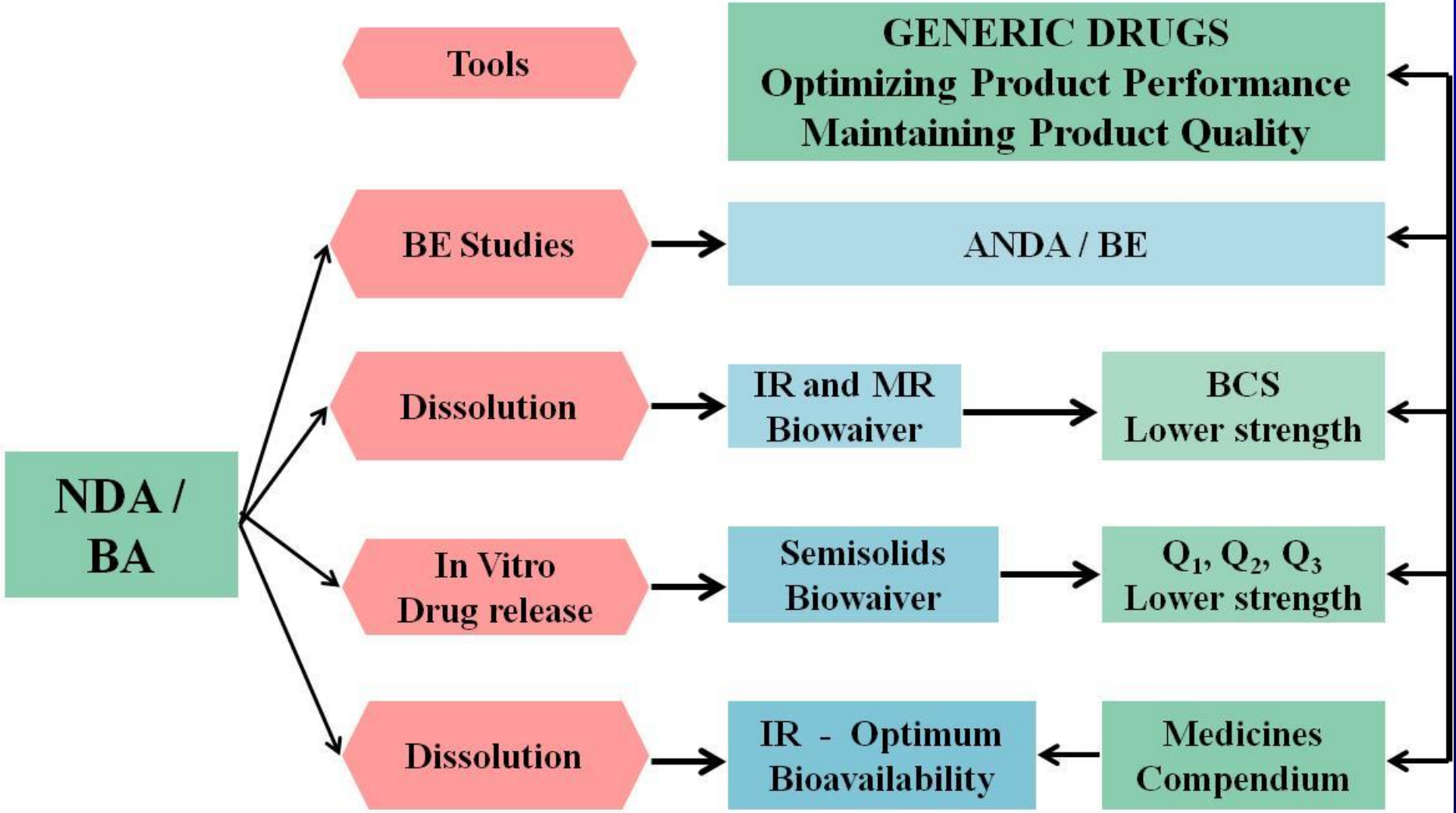
FIP/RPSGB Workshop in London – October 20-21, 2008

AAPS/FIP Workshop in Los Angeles – November 7-8, 2009

Progressively Reducing Regulatory Burden

Increasing Importance of Dissolution

Progressively Reducing Regulatory Burden



Ref: VP Shah et.al., The AAPS Journal. 16: 621-624, 2014

Importance and Role of Dissolution Testing

- Increasingly in vitro dissolution testing is relied on to assure product performance
- An appropriate dissolution test procedure is a simple 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.

Dissolution Test Impact

- Assures product quality and performance
- Useful as a bioequivalence test
- Establishes procedures for granting biowaiver
  - New Drug and Abbreviated New Drug
  - Higher strength
  - Lower strength
- Assures product sameness under SUPAC

Conclusions

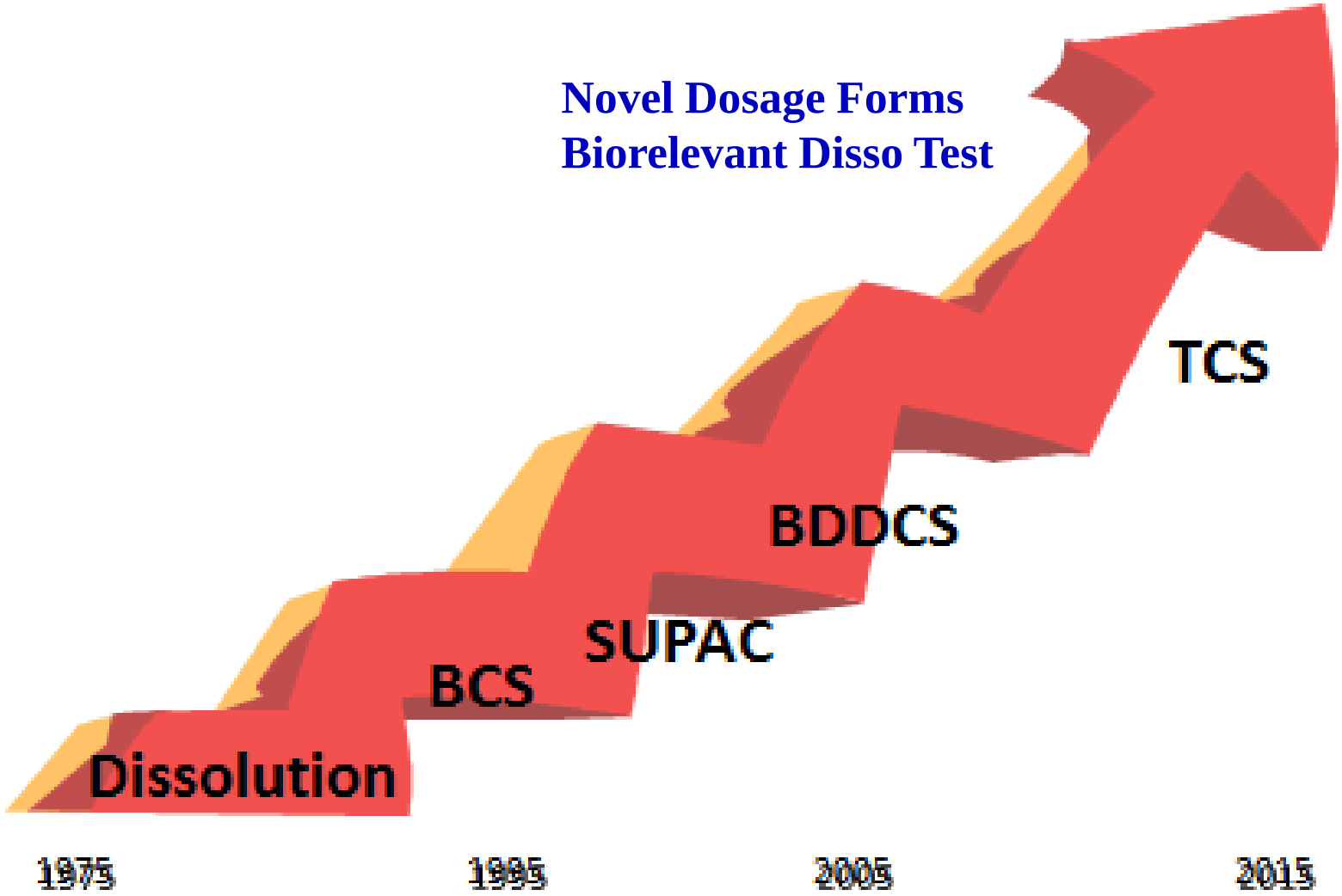
- Dissolution test has emerged as a most useful physicochemical test for assessment of drug product performance.
- Dissolution test is a biowaiver tool
- Dissolution test is a tool for reducing regulatory burden

Have we Reached the Limits of using Dissolution Tests in Pharmaceutical Industry?

Not yet, more applications

are on their way!!!

Progressive Application of Dissolution / *In Vitro* Release



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