Decrease *RTR, IR, and CR Regulatory Actions Due to Dissolution Deficiencies, and Increase Approval During First Review Cycle*: *A Biopharmaceutics Perspective*

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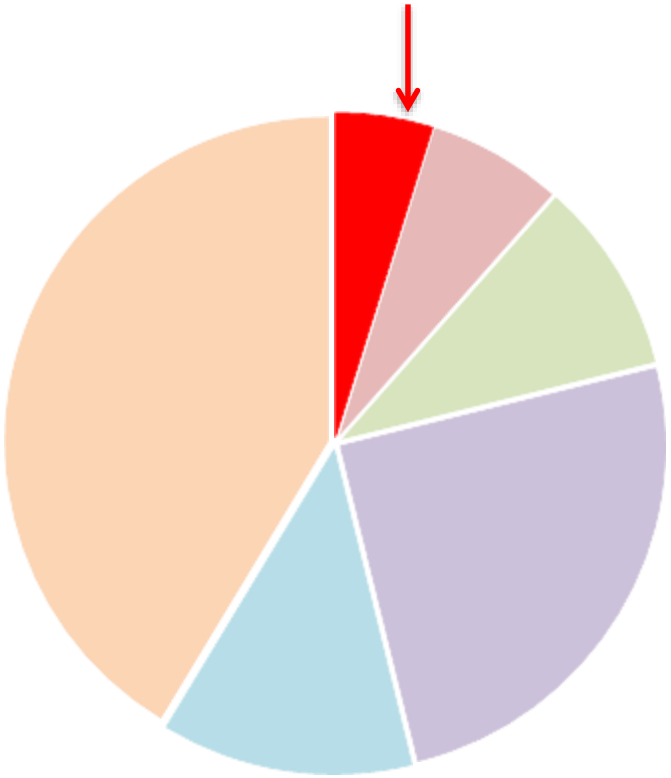
RTR: Refuse to Receive, IR: Information Request, CR: Complete Response

Outline

- **ANDAs and RTR Regulatory Action**
  - **Dissolution deficiencies**
- **Considerations for selection of dissolution method & criteria/criterion**
  - **Historical perspective**
  - **Current perspective**
- **Common dissolution deficiencies**
- **Moving forward and future directions**
- **Conclusions**

Frequent Dissolution Deficiencies Leading to RTR for Filing ANDA Submissions

5% due to dissolution related issues (FY 2018)



Complete data NOT provided (N<12 units)

Data for all the strengths NOT provided

Data for split tablets (*functional scored tablets*), NOT provided

Multi-pH dissolution media data for ER products, NOT provided

Data on alcohol dose dumping NOT provided or incomplete data provided

Ref: 2019 GDF, by Phuong (Aiden) Nguyen and Varun Vasudeva

Biopharmaceutics Advice to Applicants that Would Help to Avoid RTRs Due to Dissolution Deficiencies

- **Select an appropriate product specific dissolution method for Quality Control (QC). Submit Dissolution method information**
- **Provide justification for selection of the dissolution method**
- **Submit complete dissolution profiles [comparative in vitro dissolution data (12-unit individual data test vs. reference listed drug (RLD)] for all strengths**
- **MR dosage forms:**
  - **Multimedia [pH 1.2, 4.5, 6.8] testing data (if applicable)**
  - **Alcohol dose dumping dissolution data (if applicable)**
- **Functional scored tablets: Split tablet dissolution profiles**

Biopharmaceutics Advice to Applicants that Would Help to Avoid RTR Due to Dissolution Deficiencies Cont..

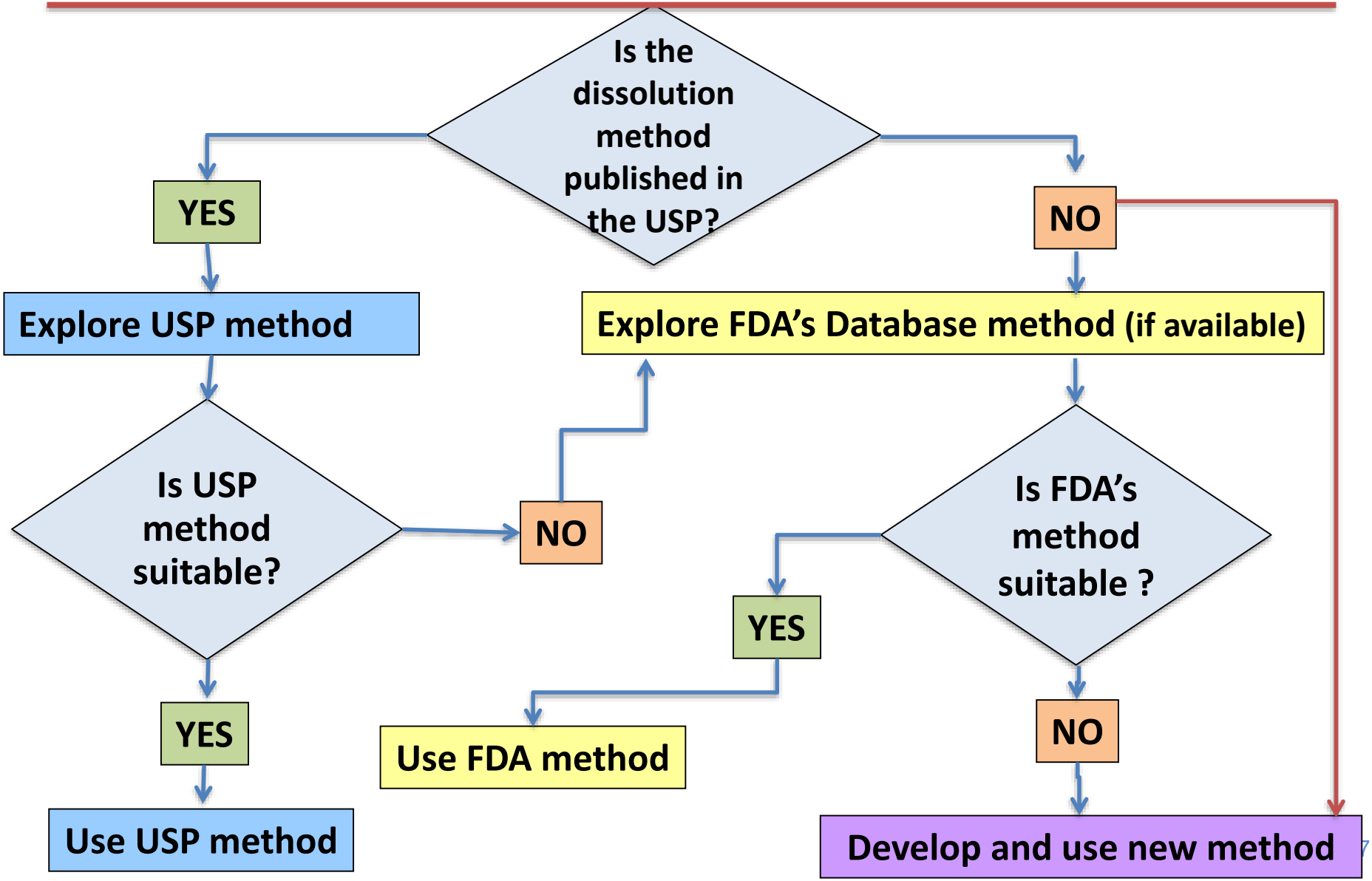
- **Follow recommendations provided in the Product-Specific Guidances for Generic Drug Development:**

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081327.htm

- **If you have any question related to dissolution testing: submit a Controlled Correspondence via email to** GenericDrugs@fda.hhs.gov

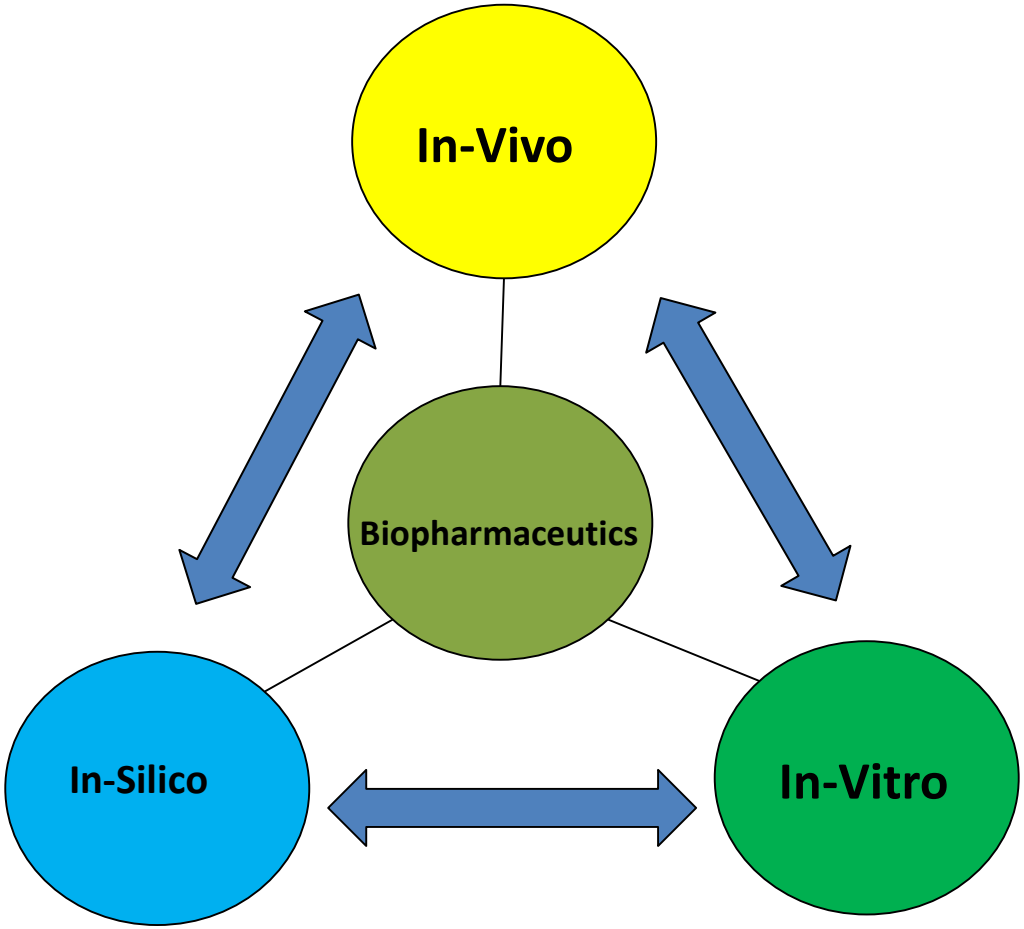
Biopharmaceutics Considerations for Selection of Dissolution Method and Acceptance Criteria/Criterion for Generic Drug Products

Selection of Dissolution Method for Generic Drug Products: HISTORICAL PERSPECTIVE



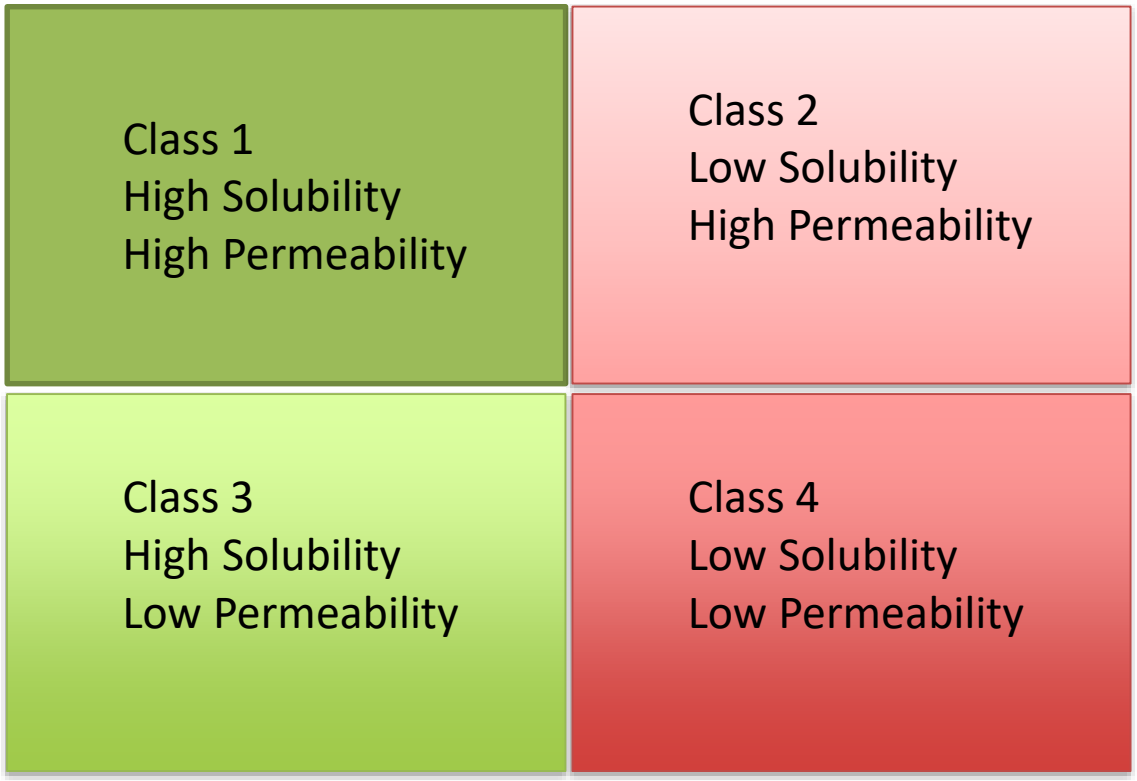
Selection of Dissolution Method

CURRENT PERSPECTIVE-Biopharmaceutics Approach



Dissolution method is product specific

BCS Provides a Framework for Risk Evaluation of IR Drug Products



2017 GUIDANCE: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

*IR Drug Products Containing Highly Soluble Drug Substance

For solid orally-administered IR drug products with highly soluble drug substance/ rapidly dissolving

- **No absorption from the Oral cavity [ODT and sublingual]**
- **NOT the narrow therapeutic index (NTI) drug products**
- **No rapid onset of action is required**
- **No excipient that can impact the drug absorption**
- **No stability concerns**

Dissolution Testing Conditions provided in Guidance* can be used

***2018 GUIDANCE:** Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

*Oral Solid IR-Drug Products with High Soluble API/Rapidly Dissolving**

Guidance – Recommended Dissolution Testing Conditions:

A: Basket Method (USP apparatus 1)

500 mL of 0.1N HCl in aqueous medium

37±0.5°C/100 RPM

No surfactant in medium

or

B: Paddle Method (USP apparatus 2)

500 mL of 0.1N HCl in aqueous medium

37±0.5°C/50 RPM

No surfactant in medium

Guidance – Recommended Acceptance Criterion

Q=80% in 30 minutes.

***2018 GUIDANCE:** Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

Selection of Dissolution Method for Generic Drug Products

- IR products: In general, either the USP or FDA method could serve as the starting point for the development of an optimal dissolution method for the proposed generic drug product.
  - Applicants should demonstrate that the USP or FDA database method is appropriate for their proposed drug product. If the method is not adequate, Applicants should develop and validate a new method for their drug product.

- Modified Release Drug Products: In general, new dissolution methods are developed (case-by-case basis).
  - Applicants should submit the dissolution method development and validation report containing complete information/data demonstrating suitability of the selected method.

Product Specific Method Development - Optimization

Three Critical Components:

1. Evaluation of the selected method
2. Demonstration of discriminating ability
3. Selection of acceptance criteria

1. Evaluation of the Selected Method

- Solubility and stability in various pH media
- Sink conditions
- Selection of in vitro dissolution/drug release media
- Selection of the testing apparatus
- Selection of rotation/agitation speed
- Data supporting selection of surfactant [*type and amount of surfactant*]
- Method validation data (*dissolution testing conditions and analytical method*)

2. Discriminating Dissolution Method

A discriminating dissolution method should able to:

- Reject batches manufactured with intentional meaningful variations in the critical material attributes (CMA) and critical process parameters (CPP) (i.e., aberrant formulations with ± 10-20% changes outside the specification limits).
- Detect the change(s) in the drug product occurring during the accelerated and stress conditions.
- Differentiates drug product batches manufactured under target conditions for which bioequivalence has been demonstrated, from those batches which are not bioequivalent.

3. Setting Acceptance Criteria

IR Products

- Setting based on overall data (BE & exhibit batches).
- Collection of complete dissolution profile data (n=12).
- The selection of spec-time point should be where NLT 80% (Q) of drug is dissolved.
- For slow dissolving products, more than one time-point value may be needed.

3. Setting Acceptance Criteria cont…

ER Products:

- Setting based on overall data (BE & exhibit batches).
- Collection of complete dissolution profile data (n=12).
- At least three spec time-points covering the initial, middle, and final phases of the dissolution profile.
- Dissolution acceptance criteria range for the initial and middle time points is based on mean target value ±10%.
- NLT 80% of label amount as a limit for the last time-point.

Selection of Dissolution Acceptance Criteria Based on BE

Available data for drug products used in failed and acceptable BE studies

↓

Use all available CMC, in vitro dissolution and in vivo PK data for development/validation/selection of optimal dissolution method with adequate discriminating ability

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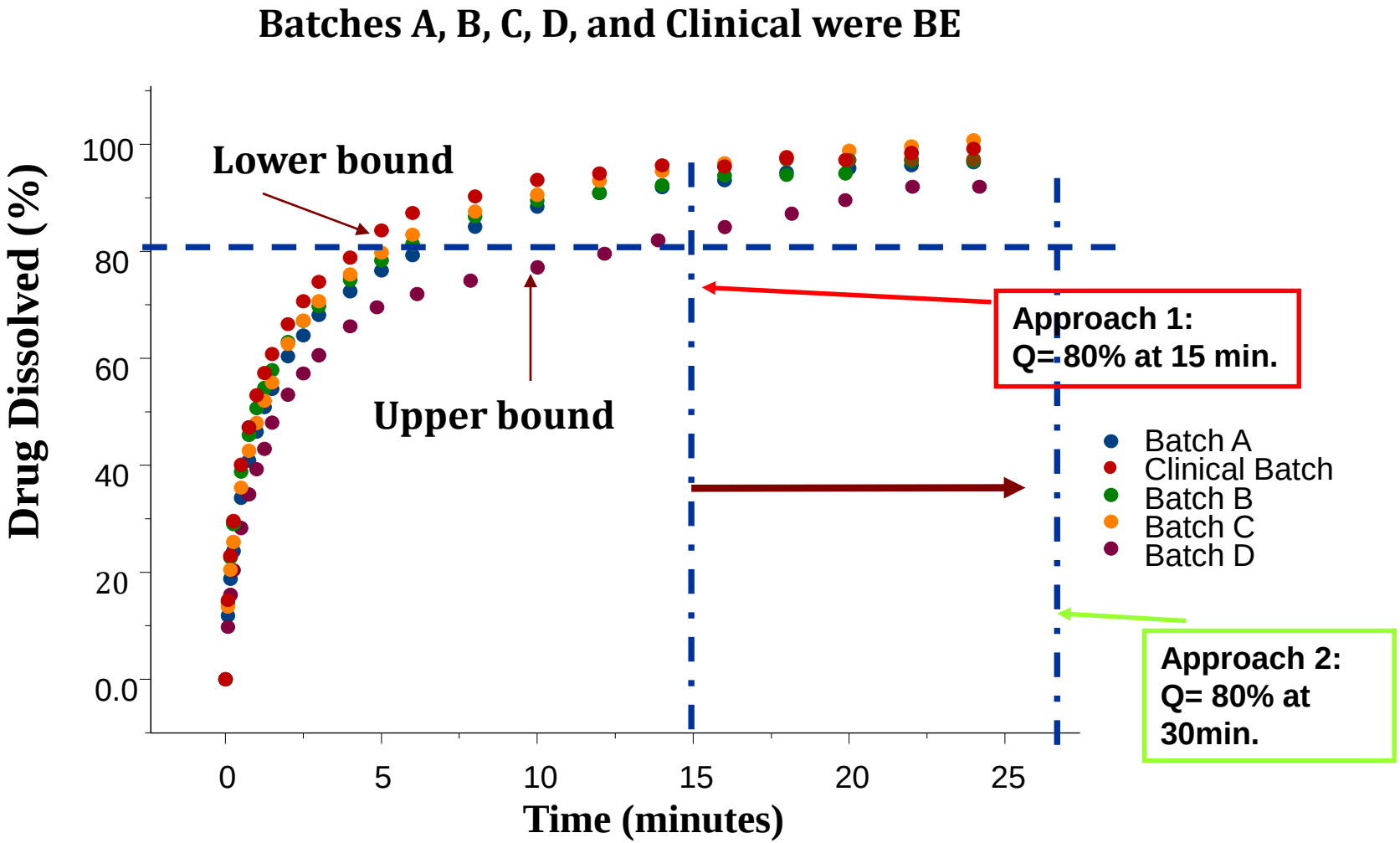
Based on in vitro (dissolution) and in vivo BE results set dissolution acceptance criteria/ion to ensure similar (BE) product performance

Setting Dissolution Criteria Based on BE Batches



Ref: 2012 AAPS presentation by Dr. Sandra Suarez Sharp

Common Deficiencies in ANDAs related to Dissolution Testing

Common Deficiencies in ANDAs: Pre-Approval

Product's proposed dissolution acceptance criteria/criterion not appropriate

- Dissolution acceptance criteria/criterion for proposed drug product, are not supported by dissolution data or data support tighter limit(s).

Recommendation:

Propose dissolution acceptance criteria/criterion based on the proposed drug product's own dissolution data.

IRs: BCS class 1 and 3: Q=80% in 30 minutes
BCS class 2 and 4: Time point when Q = 80%

MR: Mean +/-10% range and 80% for the last time point

DR: Biphasic: Acid stage and Buffer stage [based on the product design and the dissolution data]

Common Deficiencies in ANDAs: Pre-Approval cont..

Dissolution Method Validation Data

- Submission does not include the method validation report and/or method transfer report when method validation is conducted at a different site.

Recommendation:

Include the validations of discriminating ability, testing methodology (i.e., robustness, etc.), and analytical method used to assay dissolution samples (i.e., linearity, accuracy, precision, etc.).

Common Deficiencies in ANDAs: Pre-Approval cont..

Functionally Scored Tablets

- Submission does not include dissolution data/ complete profiles supporting scoring of tablets.

Recommendation:

Dissolution Testing Data from N=6 tablets split non-mechanically (for a total of n=12 halves or n=18 for trisects, etc.) and N=6 tablets split mechanically. Each individual segment should be tested in its own vessel in proposed QC dissolution medium using the approved dissolution method. The dissolution profile from each segment and total vs. the whole tablet should be compared.

Common Deficiencies in ANDAs: Pre-Approval cont..

High Variability Observed in Dissolution Data

- Dissolution data indicate high variability, which is not justified with supporting information/data.

Recommendation:

Provide the root cause for the observed high variability of the dissolution profile data and include the measures that will be implemented to resolve it.

Explain the impact that the variability will have on the in vivo performance of the drug product.

Common Deficiencies in ANDAs: Pre-Approval cont..

Incomplete Stability-Dissolution Data

- Stability-dissolution data are only provided for the proposed sampling time point.

Recommendation:

- Complete dissolution profile data at all the time-points of the stability program should be included in the ANDA submission.

Common Deficiencies in ANDAs: Post-Approval cont..

SUPAC Changes for IR & MR supplemental ANDAs

- Dissolution data collected on aged (expired) lots
- Pre-change vs. post- change dissolution data are incomplete

Recommendations:

- Complete pre-change and post-change dissolution profile data should be included in the sANDA.
- For MR drug products, provide complete dissolution profile data (more than 3 time points).

Common Deficiencies in ANDAs: Post-Approval cont..

IVRT Data for Semi-Solid Dosage Forms

- The IVRT information/data is not included to support post approval changes for semi solid drug products.

Recommendation:

- The IVRT development report with complete information/ data supporting the selection of the components of the method and its validation should be submitted in the sANDA.

Refer to the SUPAC–SS guidance for conducting the IVRT study

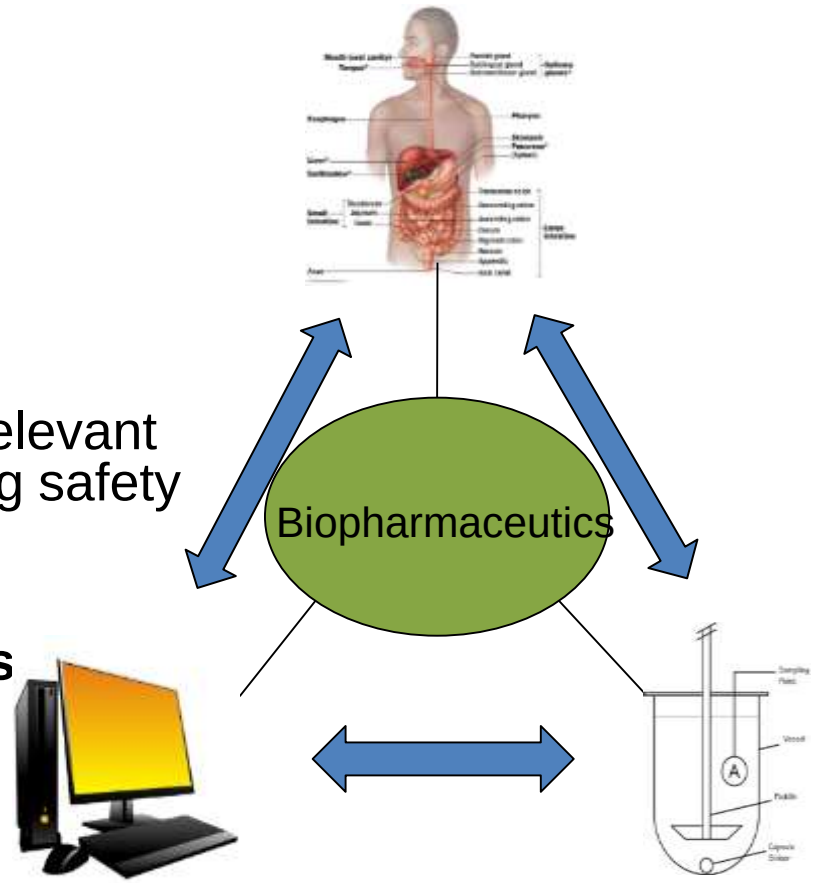
Moving Forward

Future Considerations:

- **Clinical Relevance**
  - Biorelevant dissolution
  - IVIVC/R
  - In silico modeling

- **Risk Assessment** based on clinically relevant product attributes, which impact the drug safety and efficacy

- **Product specific dissolution methods**
  - Development
  - Validation
  - Implementation



- **Product specific acceptance criteria/criterion**
  - Setting based on proposed drug product dissolution data

Conclusions

- **Refuse to Receive, filing IRs, dissolution deficiencies can be avoided by submitting complete information/data.**
- **Major Biopharmaceutics deficiencies leading to a CR regulatory action for an ANDA submission are rare.**
- **Considerations for increase First Cycle Approvals**
  - Dissolution method is product specific and has the following characteristics (i) Discriminating, (ii) Robust/Rugged, (iii) Complete dissolution profile, (iv) Correlate to In Vivo, (v) Transferrable, and (vi) Variability is controlled
  - Setting of the dissolution acceptance criteria/criterion should be based on the data of the proposed product.
  - Submission of complete information/data in order to optimize review efficiency and decrease the number of information request deficiencies.

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