Dissolution Testing for Generic Drug Products - Present and Future Considerations

Banu S. Zolnik, Ph.D.
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality
CDER, US-FDA

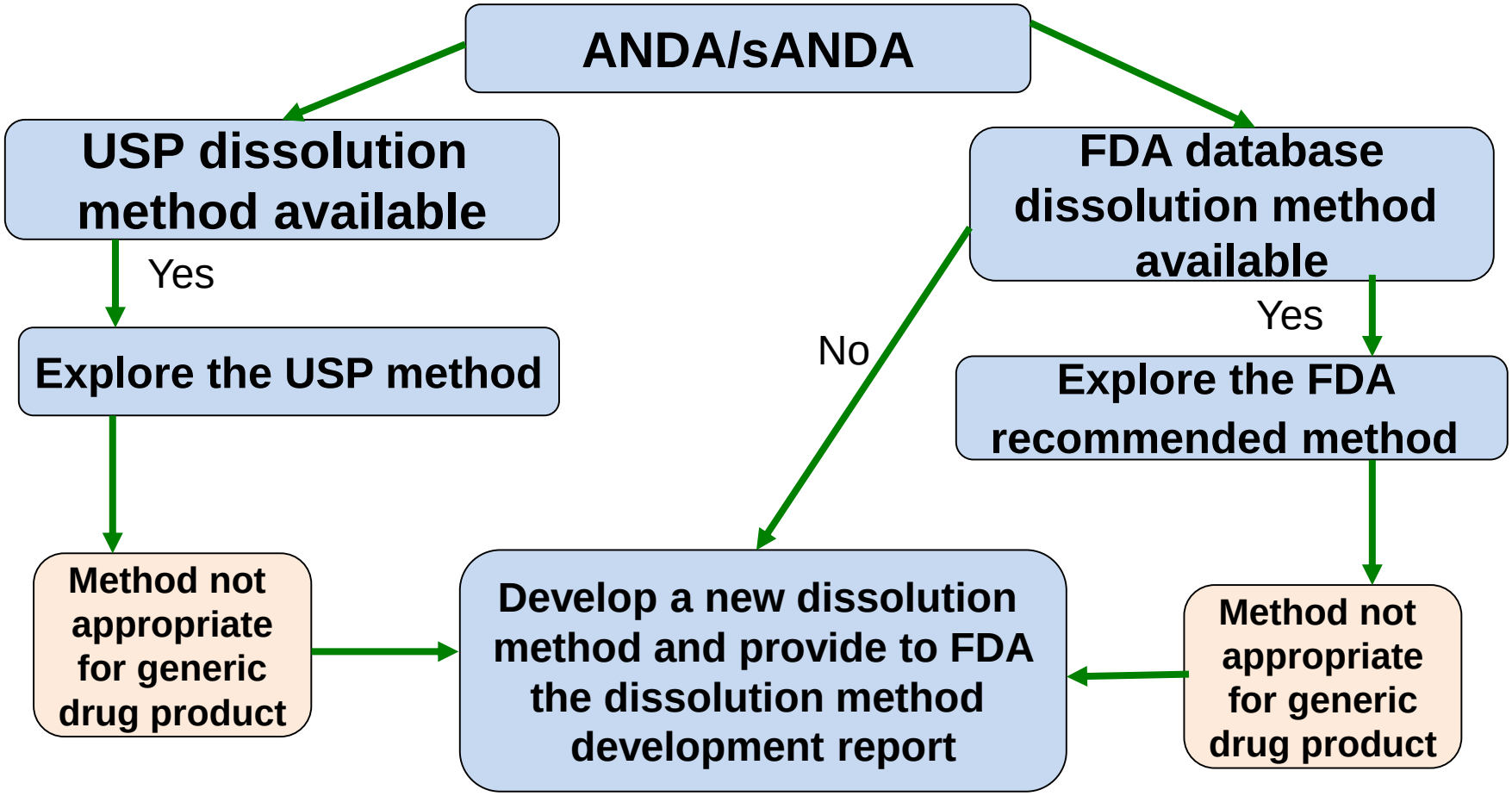
This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

SBIA REdI Generic Drug Forum 2017, Silver Spring , MD

Outline

- Current approaches for dissolution testing for generic drug products
- Present to future considerations
- Product specific dissolution method
- Setting of dissolution acceptance criteria
- Common deficiencies identified in ANDAs
- Conclusions

Current Approach: Dissolution Testing



FDA Dissolution Method: http://www.accessdata.fda.gov/scripts/cder/dissolution/

Moving Forward

Present to Future Considerations:

- Product specific dissolution methods
  - Development
  - Validation
  - Implementation
- Product specific acceptance criteria/criterion
  - Setting based on proposed drug product dissolution data
- Communications between FDA and Applicants
  - Teleconferences
  - Interactive communications
  - Advice correspondences

Product Specific Method Development

Three Critical Components:

1. Evaluation of the method
2. Discriminating ability
3. Selection of acceptance criteria

1. Evaluation of the Method

- Solubility profile
- Selection of the apparatus
- In vitro dissolution/drug release media
- Rotation/Agitation speed
- Sink conditions
- Data supporting selection of surfactant

2. Discriminating Dissolution Method

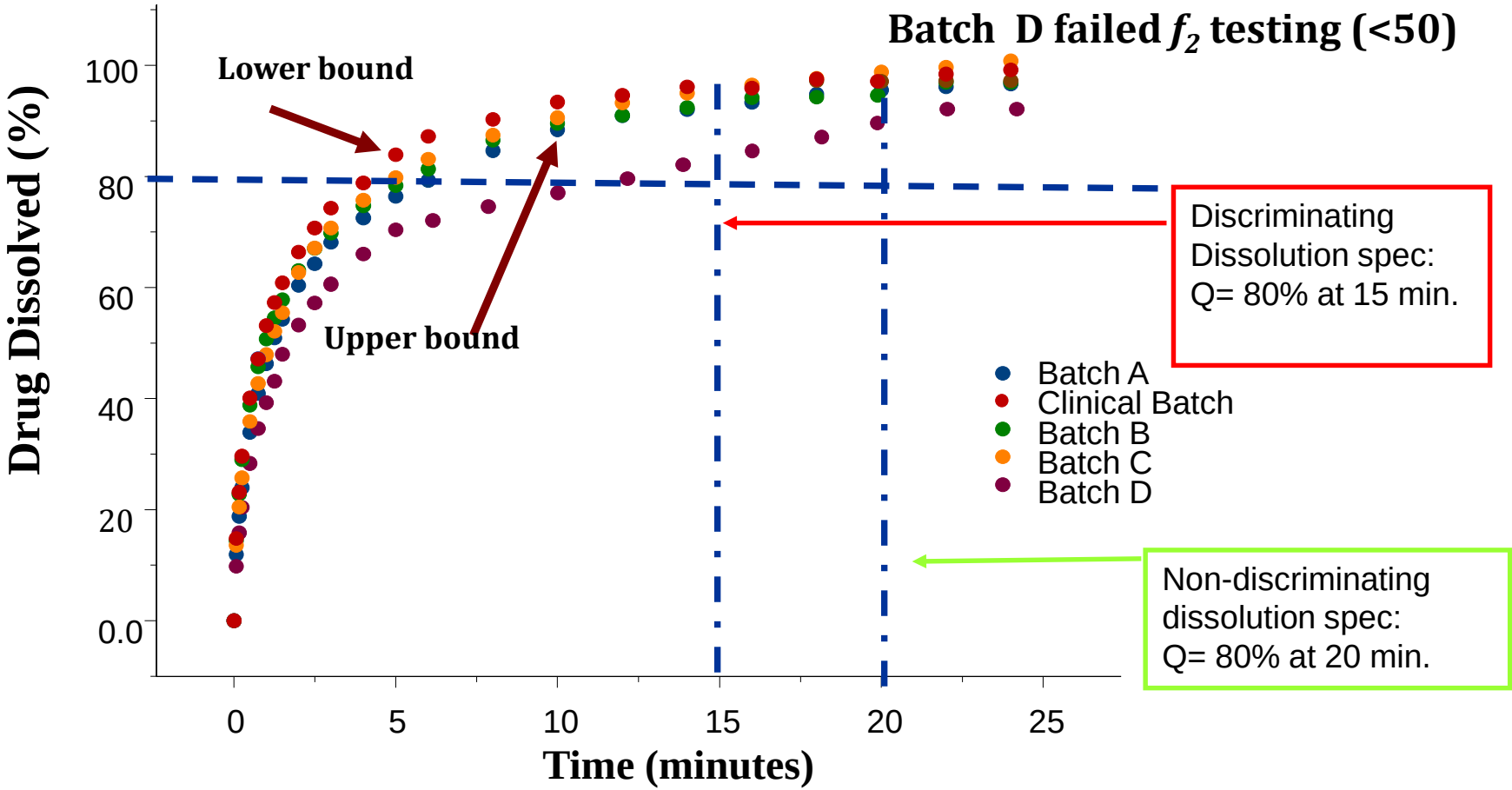
- Differentiates drug product batches manufactured under target conditions for which bioequivalence has been demonstrated, from those batches manufactured with intentional/non-intentional variations which are not bioequivalent.

3. Acceptance Criteria/on

IR Products

- Setting based on overall data (BE & stability 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 that one spec value may be needed.

Different Particle Size Ranges



Ref: 2012 AAPS presentation by Dr. Sandra Suarez Sharp

3. Acceptance Criteria

ER products:

- Setting based on overall data (BE & stability 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 Acceptance Criteria Based on BE

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

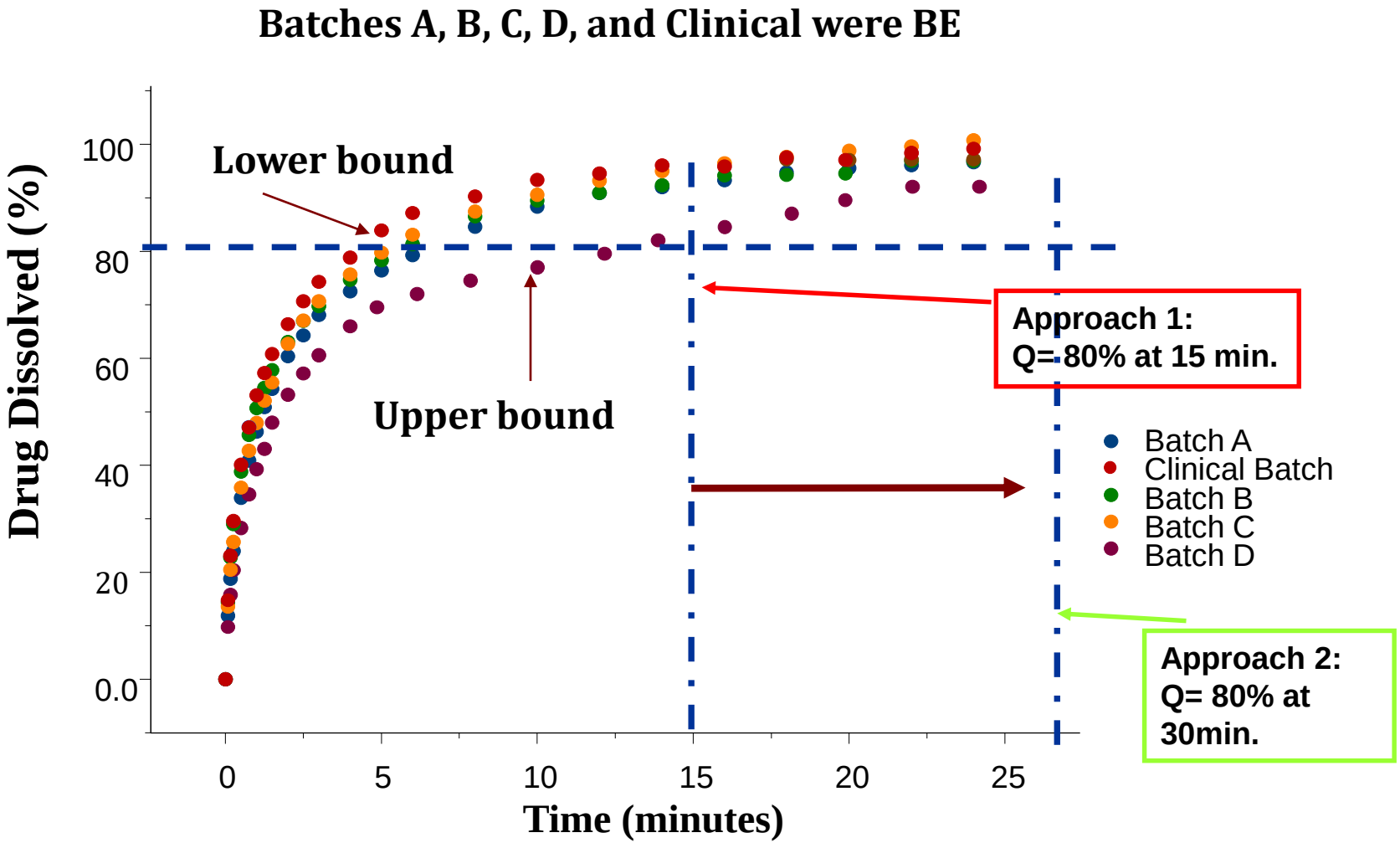
↓

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

↓

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 ANDA submissions

New Dissolution Method is Needed

- If USP and FDA's data-base dissolution methods are not available, or the available methods are not appropriate for the proposed generic drug product, **a new, product specific dissolution method should be developed.**

Note: *Once the new dissolution method is approved by FDA, please petition the USP to add the new dissolution method to the USP monograph for the drug product.*

Common Deficiencies in ANDAs 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 for assay of dissolution samples (i.e., linearity, accuracy, precision, etc.).

Common Deficiencies in ANDAs cont.

Functional Scoring

- No dissolution data are submitted to support scoring of tablets.

Recommendation:

Complete dissolution profile data for whole and split tablets using an optimal dissolution method.

Guidance: Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation

Common Deficiencies in ANDAs

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 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, dissolution profile data should include more than 3 time points.*

Common Deficiencies in ANDAs

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

Conclusions

- Dissolution method is product specific.
- Setting of the dissolution acceptance criteria/criterion should be based on the data of the proposed product.
- Interactive open communications between FDA and ANDA Applicants is important.
- ANDA submissions should include complete data in order to optimize review efficiency/approvals and decrease the number of information request deficiencies.

Acknowledgements

- *Paul Seo, Ph.D.*
- *Angelica Dorantes, Ph.D.*
- *Elsbeth Chikhale, Ph.D.*
- *Sandra Suarez-Sharp, Ph.D.*
- *Okpo Eradiri, Ph.D.*
- *Jing Li, Ph.D.*
- *Gerlie Gieser, Ph.D.*
- *Om Anand, Ph.D.*

Thank you for your Attention!

Please complete the session survey:

surveymonkey.com/r/GDF-D1S12


FDA
U.S. FOOD & DRUG
ADMINISTRATION