Dissolution Method Development for Generic Drug Products

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This presentation reflects the views of the presenter and should not be construed to represent FDA’s views of policies.
Outline

• Role of dissolution method development
• Current approaches for dissolution method development for generic drugs
• Product specific dissolution method
• Common deficiencies identified in the applications
• Summary
Dissolution testing as a tool...

• A quality control
  • Batch-to-batch consistency
  • Provide quality assurance

• Important for formulation development

• Biowaiver purposes

• In vitro BE studies

• Alcohol-induced dose dumping

• Post-approval manufacturing changes
Role of Dissolution Method Development

- Process Parameters
- Material Attributes
- Formulation variables

Dissolution

Formulation variables

Material Attributes

Dissolution

Process Parameters
Current Approaches for Dissolution Method Development

- **USP method available**
  - Yes: Follow USP method
  - No: FDA recommended method available

- **FDA recommended method available**
  - Yes: Follow FDA recommended method
  - No: New dissolution method development report

**FDA Dissolution Method**
http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm?PrintAll=1
Product Specific Method Development

Three Components:

1. Evaluation of the method
2. Discriminating ability
3. The acceptance criterion
1. Evaluation of the method

• Solubility profile
• Selection of the apparatus
• In vitro dissolution/release media
• Rotation/Agitation speed
• Sink conditions
• Data to support selection of surfactant
2. Discriminating Dissolution Method

- Differentiates drug products manufactured under target conditions vs. formulations with meaningful variations for the most relevant manufacturing variables
Different Particle Size Ranges

Batch D failed $f_2$ testing (<50)

Discriminating Dissolution spec: $Q = 80\%$ at 15 min.

Non-discriminating dissolution spec: $Q = 80\%$ at 20 min.

Ref: 2012 AAPS presentation by Dr. Sandra Suarez Sharp
Based on bioequivalence batches

Manufacture product variants with different release characteristics

Select optimal dissolution method with adequate discriminating power

Determine bioavailability for product variants

Determine dissolution rates resulting in similar in vivo performance

Dissolution specifications chosen to ensure similar (BE) product performance
Illustration of the dissolution profiles based on BE batches

Batches A, B, C, D, and Clinical were BE

Lower bound

Upper bound

Approach 1:
Q= 80% at 15 min.

Approach 2:
Q= 80% at 20 min.

Ref: 2012 AAPS presentation by Dr. Sandra Suarez Sharp
3. Acceptance Criterion

• Bioequivalence batches

• At least 85% of the drug is dissolved
  or

• Where plateau of drug dissolved is reached

• The selection of time point should be where \( Q = 80\% \) of drug dissolved.
Applications: Common deficiencies

- Dissolution method development is not included in the application
- Fails to demonstrate that dissolution method is discriminating
  - No information on critical material attributes and process parameters
- Data do not support the proposed acceptance criterion
- There is no dissolution data for lower strength waivers, alcohol dose dumping studies, multi-media testing for MR products.
Applications: Common deficiencies

- There is no method transfer report when method validation is conducted at a different site
- Dissolution data collected on aged lots
- Individual dissolution data is not submitted.

Summary

• Dissolution method is product specific

• Three Components
  1. Evaluation of the method
  2. Discriminating ability
  3. The acceptance criterion
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Questions?

Evaluation: surveymonkey.com/s/GDF-D2S8