M-CERSI WORKSHOP

In Vitro Dissolution Profiles Similarity Assessment in Support of Drug Product Quality: What, How, and When

May 21-22, 2019

School of Pharmacy, Baltimore, MD

BREAKOUT SESSION B DAY 1:

Best practices for performing dissolution similarity for regulatory applications

GROUP G2: Pharmacy Hall N310

GROUP G1: Pharmacy Hall N306

Moderators: Krista Witkowski (Merck); Elena Rantou (FDA)

Scribes: Poonam Delvadia (FDA), Karin Rosenblatt (Abbvie)

Session Background: Topic Summary

Discussion on:

a) Number of time points
b) Number of batches/replicates
c) Definition on high variability and early time points
d) Variability (%RSD vs SD)
e) Inconsistent results across different method of dissolution similarity assessment
f) Estimation of data for missing time points for dissolution similarity assessment
g) Exclusion of time points for dissolution similarity assessment
h) Rules/Criteria for application of all methods
i) Application of similarity assessment vs acceptance criterion(a)
j) Rules or guidance for rounding dissolution results

Session Background: Perspectives

Perspectives may be different depending on the “hat” you are wearing –
What role you take within an organization, team, or project…

Roles / Disciplines / Stakeholders may include:

- Analytical Scientist
- Statistician, Mathematician, or Quantitative Scientist
- Regulatory Scientist
- Biopharmaceutics Scientist
- Clinical Pharmacology Scientist
- Quality / Process / Product Subject Matter Expert (SME)
- Patient
- Others?

BO Session B, Day 1, Question 1
Part 1 (G2)
Time: 2:15 to 3:15 pm

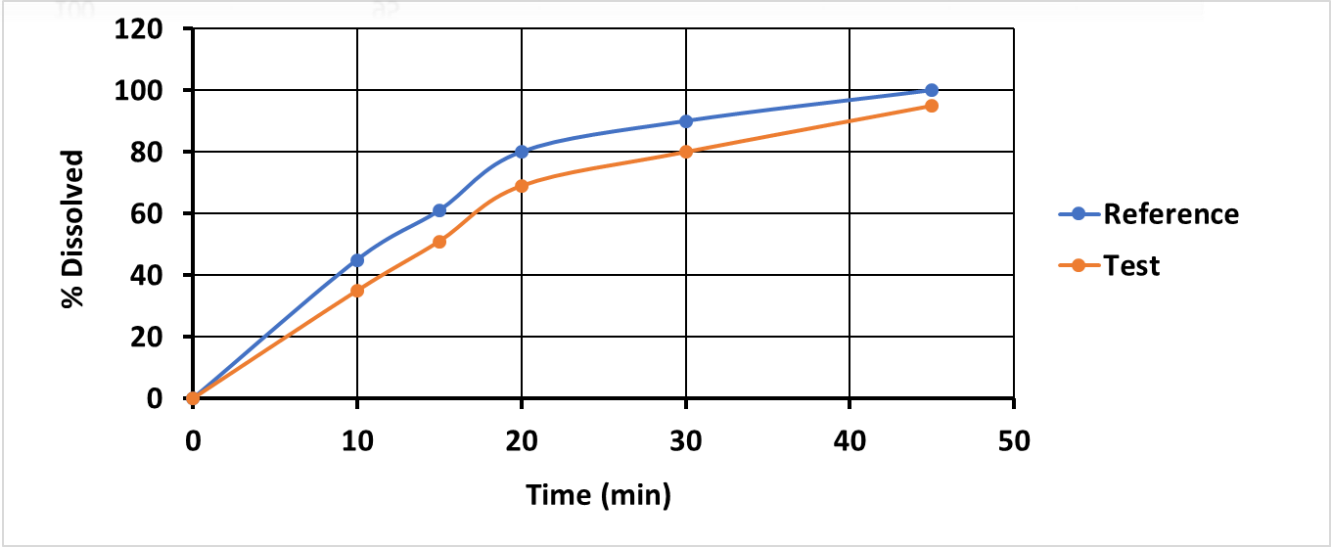
When reference and test reaches ≥85% dissolution at different time points, what time points should be considered for dissolution similarity test based on f2? For example, if reference reaches >85% dissolution at 30 min and test reaches >85% dissolution at 45 min, should data up to 30 min or 45 min be considered for f2 test?

Q1 Graphic

	% Dissolved	
Time (min)	Reference	Test
0	0	0
10	45	35
15	61	51
20	80	69
30	90	80
45	100	95

Upto 45 min: f2 is 51.12

Upto 30 min: f2 is 49.34



BO Session B, Day 1, Question 2
Part 1 (G2)
Time: 2:15 to 3:15 pm

Consider the following from the perspective of *feasibility and planning for* selection, sampling and employing batches for a similarity study (i.e., put statistical similarity method definition aside, which will be considered in another session.)

- When multiple batches of test and reference are employed, under what conditions (e.g., formulation/process/batch/study) should a single “pooled” comparison vs. multiple comparisons of all combination of individual batches, be made?
- Also: Solicit feedback on the following new approach: To account for better representation of profiles (in light of batch-to-batch variability, etc.) and a more meaningful comparison, consider an ongoing monitoring approach where dissolution profiles are measured for every "nth" batch. Rather than comparing 1 batch to 1 batch (or 1 to 3, etc.), use some measure of multiple profiles for a group of "representative" batches across dates of manufacture or development.

BO Session B, Day 1, Question 3
Part 1 (G2)
Time: 2:15 to 3:15 pm

What additional information or data would be needed for the decision making when similarity outcomes are inconsistent across different methods?

Consider also: if decision tree approach is used for comparison method selection, suppose multiple subsets of same submission (such as multimedia, hardness, coating subsets) are addressed independently, such that different comparison methods may be prescribed within the same data submission. Should there be some "preference" to use a common method within a submission?

BO Session B, Day 1, Question 4
Part 1 (G2)
Time: 2:15 to 3:15 pm

Early timepoints with a lower release (e.g., 25%) usually have variability (%RSD) higher than 20% (already due to the method variability).

- Is it possible to use such data for f2 test?
- The use of %RSD artificially inflates the significance of the variability at lower release values (eg.: up to 20-30% released) for early timepoints (5-10 min). As result the acceptability of variability based on %RSD at lower release values becomes more stringent than for higher values where SD and %RSD become comparable. Since the true variability is reflected in the SD (as it is expressed in actual % of claim) should variability not better be expressed as SD instead of %RSD?
- Are there suggestions for different limits on the %RSD for early time points (depending on mean dissolution and/or time point and/or how many time points available i.e., related to the importance of this early timepoint release)?

BO Session B, Day 1, Question 5
Part 1 (G2)
Time: 2:15 to 3:15 pm

What is the appropriate number of batches (test and reference drug) to determine dissolution similarity?

Also: How many replicates within each batch should be tested?

n=6, 12, 24?

BO Session B, Day 1, Question 1
Part 2 (G1)
Time: 3:15 to 4:15 pm

During drug product development, often time points of dissolution profile (generated using same method) do not match across development batches and pivotal clinical batches.

In such scenario, what are the best practices for dissolution similarity assessment?

Can % dissolved be estimated for missing time point to perform dissolution similarity test? If yes (OK to estimate missing points), how % dissolved for missing time points should be estimated?

BO Session B, Day 1, Question 2
Part 2 (G1)
Time: 3:15 to 4:15 pm

When implementing MVA analysis and f2 bootstrapping, should the same principles as conventional f2 calculation (e.g., total number of time points, number of time points after 85% dissolution) be followed?

BO Session B, Day 1, Question 3
Part 2 (G1)
Time: 3:15 to 4:15 pm

Is it appropriate to exclude certain time point(s) from dissolution similarity calculation?

If so, can we determine a rule for the exclusion of points in the dissolution profile comparison?

BO Session B, Day 1, Question 4
Part 2 (G1)
Time: 3:15 to 4:15 pm

Which CV criterion do you use to define "highly variable" profiles? Do you use

a. The "20%- 10%-criterion"

b. The "within-batch CV < 15%-criterion"

In case of (a.) what is an early time point?

i. The first time point (EMA)

ii. The first 40% of all time points (ANVISA)

iii. Other definition?

BO Session B, Day 1, Question 5
Part 2 (G1)
Time: 3:15 to 4:15 pm

Why do we use profile similarity evaluations rather than evaluations against specifications or what are advantages of using the profile similarity over specifications?

BO Session B, Day 1, Question 6
Part 2 (G1)
Time: 3:15 to 4:15 pm

What are the rules or guidance for rounding the dissolution measurements and/or results when conducting a dissolution similarity test?

Overall Conclusions