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

MAY 21, 2019

Day 1

Breakout Session A

2:15 – 4:15 PM

GROUP G1: Pharmacy Hall N310: 2:15-3:15 PM

GROUP G2: Pharmacy Hall N306: 3:15-4:15 PM

Breakout Sessions A1, Day 1

- Definition/discussion of similarity terminology - How should “similarity” be most usefully defined?

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Question 1

- **How do you define the dissolution profile similarity?**
  a) Do you define "profile similarity" via the **average difference**, via the maximum difference, via a **multivariate similarity region**, or maybe in a **completely different way**?
  b) Should the definition **depend on the product/application**?
  c) Should regulatory guidance **emphasize the importance of defining similarity**?
  d) Should similarity limits apply to **observed % dissolution data** or to **hypothetical/expected values**?
  e) What is the appropriate statistical hypothesis for similarity testing? i.e.,
     a) A **significance** test (assume equality unless contradicted by data)
     b) An **equivalence** test (assume non-similarity unless contradicted by data).
  f) Related to 1e. above, what confidence/significance levels are appropriate?

Question 2

Is it meaningful to **switch similarity definitions/statistical hypotheses** as part of a "similarity decision tree" (e.g., switching from f2 to Mahalanobis distance when variability is high)?

Question 3

Assume that data from several batches per reference (REF) and test (TEST) group is available. **How do you define "profile similarity" in case of several batches per REF and/or TEST group?**

- Do we want to make inference about **batches** or **processes**?
- The more batches are available the higher is the **representativeness** of the REF/TEST sample for making inferences about the processes/future batches. Are there applications in which it makes sense to **pairwise compare each REF batch to each TEST batch**? What does the pairwise batch-to-batch comparison approach mean for the **power** of the evaluation?
- What does it mean, if the **comparison of the REF group to itself** via pairwise batch-to-batch comparisons procedure would **fail**?
- What are the concerns from a scientific perspective?

Question 4

Should we also test for **equivalence/similarity of variances** or should we **focus on the shift in location**?

Question 5

How do we **control for drift** in our similarity comparisons **over the product life-cycle**?

- For instance if A is similar to B and B is similar to C, how do we assure that C is similar to A?
- Would it not be more consistent to compare new formulations to some **fixed standard of performance**?
- Would this not result in **greater experimental resources** being available for testing the TEST formulation?
- What are the concerns from a **scientific perspective**?

Question 6

For the purpose of dissolution similarity testing, should the **dissolution results** for both reference product and generic product be **obtained at the same time**?

In other words, would it be acceptable to use the **historical REFERENCE DATA** without re-performing the dissolution testing on the reference product? Or is it necessary to **always perform the in vitro dissolution test for both the TEST and the reference in parallel**?

Action BO A1, Day 1, Q1

Key points discussed (related to the Question)	Consensus or Agreement reached	Possible scenarios or options (if no consensus is reached)	Action items and responsible person(s)

Action BO A1, Day 1, Q2

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Action BO A1, Day 1, Q3

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Action BO A1, Day 1, Q4

Key points discussed (related to the Question)	Consensus or Agreement reached	Possible scenarios or options (if no consensus is reached)	Action items and responsible person(s)

Action BO A1, Day 1, Q5

Key points discussed (related to the Question)	Consensus or Agreement reached	Possible scenarios or options (if no consensus is reached)	Action items and responsible person(s)

Action BO A1, Day 1, Q6

Key points discussed (related to the Question)	Consensus or Agreement reached	Possible scenarios or options (if no consensus is reached)	Action items and responsible person(s)

Action BO A2, Day 1, Q1

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Action BO A2, Day 1, Q2

Key points discussed (related to the Question)	Consensus or Agreement reached	Possible scenarios or options (if no consensus is reached)	Action items and responsible person(s)

Action BO A2, Day 1, Q3

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Action BO A2, Day 1, Q4

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Action BO A2, Day 1, Q5

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Action BO A2, Day 1, Q6

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