

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 A DAY 2

The Value of Similarity Testing Considering Clinically Relevant Specifications and Safe Space

GROUP G1: Pharmacy Hall N306; Time: 1:30-2:30 pm

GROUP G3: Pharmacy Hall N211; Time 2:30-3:30 pm

Moderators: Sandra Suarez (FDA), Gregory Rullo (AZ)

Scribe: Elisabeth Kovacs, Andreas Abend (Merck)

Session Background

- Product quality “sameness” can be demonstrated by showing dissolution similarity using the f_2 equation or other statistical approaches. Currently, it is the common approach for:
 - Bridging minor to moderate changes throughout drug product life-cycle
 - Additional strength biowaiver
 - Supporting demonstration of BE for when in vivo BE is not feasible
- Similarity testing is implemented under the assumption that the dissolution method is discriminating
 - However, in the absence of in vitro in vivo link, dissolution methods can be “over” or “under” discriminating which may put patients at risk (i.e., for an under discriminating method) and may increase the burden to pharmaceutical companies (i.e., for an over discriminant method)

Session Background (cont.)

- Clinically Relevant Drug Product Specifications (**CRPDS**), which are established based on *in vitro in vivo* link are becoming an expectation in regulatory submissions
- When developed, a safe space can be defined
 - In this context, dissolution profiles generated on product variants using a clinically relevant dissolution method and that fall within the safe space are considered bioequivalent

One question raises as: when a safe space has been established, is dissolution similarity testing still applicable? Why or why not? If applicable, under which circumstances?

BO Session A, Day 2, Question 1

Part 1 (G1)

Time: 1:30-2:30 pm

- **Is there a need to challenge/compare the predictive ability of the current dissolution similarity statistical tools using in vivo data?**

BO Session A, Day 2, Question 2

Part 1 (G1)

- **What is the future of dissolution similarity testing in the context of clinically relevant specifications (e.g., based on safe space concept)?**
- a. What is the value of comparative dissolution testing using “test and reference batches” when the specifications have been demonstrated to be clinically relevant?
 - b. What is the risk of using similarity testing when the dissolution method(s) used to assess in vitro performance are not proven clinically relevant? What can be done to mitigate risk?
 - For new products (BCS 2 and 4) for which CRDPS are not being established?
 - For mature products where dissolution development and clinical data may not be available?

BO Session A, Day 2, Question 3

Part 1 (G1)

- **Bias in dissolution similarity results can occur from emphasis on early timepoints. Should the time points selected for defining the dissolution profile need justification on its in vivo relevance?**
 - a. For example, for ER products the first time point is expressed as NMT and is intended to prevent dose dumping . Is variability at this timepoint critical?

BO Session A, Day 2, Question 4

Part 1 (G1)

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- **What is the value/meaning of similarity testing when dissolution profiles are rapidly dissolving, i.e., drug products with highly soluble drug substances? Is there a need for additional control strategy elements when C_{max} and T_{max} are critical?**
- a. When f₂ test fails (e.g., post change dissolution profile is faster) for rapidly dissolving drug product containing highly soluble drug substances, is there a need for additional testing or corrective measures? Which are these?
 - b. The criterion for very rapid dissolution is silent on variability before the 15min timepoint. For BCS class 1 based biowaiver, should this be the case for when C_{max} is critical? If C_{max} is critical what additional mitigation strategies are needed?

BO Session A, Day 2, Question 5

Part 1 (G1)

- **What is the risk of implementing alternative test to f2 when the source of variability in dissolution profiles is proven to be drug product manufacturing related?**
- Should corrective measures of in process controls be taken in consideration instead as part of risk mitigation strategies?

BO Session A, Day 2, Question 6

Part 2 (G3)

Time: 2:30-3:30 pm

➤ **With respect to post-approval changes, we would like to confirm that achieving clinically relevant understanding and a safe space should be considered more powerful (i.e. in terms of regulatory flexibility) than the historical approaches of an f2 comparison/BCS-based biowaiver (as outlined in SUPAC). Is this a consistent understanding?**

- In situations where no failures of bioequivalence have been observed, but the dissolution profile comparison does not meet the similarity criterion can the variability and locations of profiles observed in pre-change commercial batches form a safe space within which post approval dissolution should fall?
- In situations where no failures of bioequivalence have been observed, but the dissolution profile comparison does not meet the similarity criterion, is it scientifically appropriate to determine a safe space for justifying manufacturing proven acceptable ranges/design spaces using modeling and simulation?

BO Session A, Day 2, Question 7

Part 2 (G3)

- **The interpretation of compendial dissolution (data) which allows for stages of acceptance where limits are considerably wider than would normally be seen when looking at actual drug release results (from the biobatch), and how these wide limits for individual values fit with the clinical consequences.**

BO Session A, Day 2, Question 8

Part 2 (G3)

- If f2 is borderline (e.g., 49.45), what additional information/data should be considered in assessing the impact of dissolution similarity failure on the in vivo performance of the drug product?

BO Session A, Day 2, Question 9

Part 2 (G3)

- **Are the current statistical tools/approaches implemented as part of dissolution similarity testing adequate for demonstration of BE? If not, what additional data are needed? Are current sampling strategies, study design, mathematical/statistical equations applicable in this case?**

Overall Conclusions
