Breakout Session
Day 1, Session D

What are the advantages and disadvantages of currently available “statistical” approaches for dissolution?

Moderators: Xiaoyu Cai (FDA), Kim E Vukovinsky (Pfizer)

Scribe: Amy Zhang (Huizi Zhang) (GSK), Zachary Bergeron (Agios)

Method	Summary
f2	$f_2 = 50 \times log_{10}\left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{n}(R_t - T_t)^2}{n}}}\right]$ • Minimum of 3 – 5 timepoints <85% dissolved • Restriction on variability (e.g. RSD < 20% at early time points and < 10% at all other time points) • Some variability globally on these requirements • Calculated value must be >50
Bootstrap f2	• Sample 24 observations with replacement from the original data set (pre- and post- change). • Calculate the f2. • Repeat the process a large number of times (say, 10,000), forming a distribution. • f2 at 5th percentile must be >50

Multivariate Statistical Distance (MSD)	• Mahalanobis distance-based approaches: multivariate standardized difference between the expected values of test and reference products is less than the similarity limit. (FYI: f2 is based on non-standardized diff.)
	  ○ Approximate Confidence Limit for Mahalanobis Distance approach (Tsong et al., 1996)
	  ○ Bootstrapped Mahalanobis Distance
	  ○ T2EQ approach (T^2 test + margin of Tsong et al., 1996 + EMA 2010 guidance margin restriction)
	• Confidence interval approaches on aggregated criteria: map the multivariate profile down to a univariate measure (e.g. assuming constant mean difference at all time points), and compare it with the similarity limit
	• Confidence region approaches on disaggregated criteria: compare the estimated multivariate confidence region with pre-defined similarity region (can be rectangular or ellipsoid)

Disso Safe Space	Establish the Dissolution Safe Space based on (clinical) batches used to establish an In Vitro-In Vivo Correlation (IVIVC).Alternatively, a safe space can be developed in-silico (i.e., PBBM). The test batch is acceptable if its dissolution profile falls within the established safe space

Method	Summary
Weibull	A general empirical equation when adapted to the dissolution/release profile expresses the accumulation of fraction of drug in solution.
Bayesian	Inferences about the values of uncertain parameters are obtained by combining information from data with prior knowledge to obtain a multivariate posterior distribution of model parameters.
Intersection Union Test	A test procedure that uses an equivalence test at each of the dissolution time points to demonstrate that the mean difference at each time point is within the interval of ±10%.

Day 1 BO Session D

Part 1 - Time: 2:15 to 3:15 pm in Room N211

1. This morning, f2, bootstrap f2, MSD, Weibull, and Bayesian methods for dissolution profile comparison were discussed. Are there other approaches (e.g. Disso Safe Space, IUT) than the ones discussed in the morning session? Please add to the list.	G3/G4
2. On the table there is a summary of the pros/cons of each method discussed, do you agree with the pros/cons? Are there any additional? Please add to the list. Please note of you disagree with any of the pros/cons.	G3/G4
3. What could be considered as an alternative approach to the f2 testing when one product has rapid dissolution and the other has very rapid dissolution?	G3/G4

	f2	Bootstrap f2	Multivariate Statistical Distance (MSD)
Pros	• Regulation	• well understood; in use a long time • Easy to conceptualize method/answer • does not require any distributional assumptions • Software (DDSolver) available	Mahalanobis distance-based approaches: • use standardized difference, consider the variance and covariance of the measurements from each time points Confidence interval approaches on aggregated criteria: • The multivariate question is simplified with less parameters Confidence region approaches on disaggregated criteria: • The multivariate question is simplified by only considering marginal behavior (rectangular region)
Cons	• Can only be used when assumptions on variability and # time points hold • Comparative data must be collected at same time points	• does not address the issues of biorelevance that apply to the f_2 • not clear what rules should apply to time point selection • while software is available, some can be complex for non-statisticians • known bias with bootstrapping	General: difficulty to determine what equivalence margin to use Mahalanobis distance-based approaches: • strong influence of correlation / hard to understand for non-statisticians Confidence interval approaches on aggregated criteria: • the constant mean difference assumption may not valid Confidence region approaches on disaggregated criteria: • no clear guidance on the shape of the similarity region • it can be conservative if the number of sampling time point becomes large

	Disso Safe Space	Bayesian
Pros	• directly answers the question on whether formulation or process change affects human PK (which is a surrogate for efficacy and safety). • Reduces the misclassification rate for batches that are bioequivalent to the Biobatch (or pivotal clinical batches) despite having “dissimilar” (i.e. F2<50) dissolution profiles.	• Probability metric (PPS) supports risk assessment • Single coherent approach • Based on simple counting exercise (MCMC) • Leverages prior information as appropriate • Equivalence format rewards good experimental design & high data information content • Widely available software
Cons	• Up-front investment in IVIVC development (IVIVC may not be achieved in all cases). • The global regulatory acceptance is unknown.	• Software novel/unfamiliar • Forces difficult (but critical) communication • Coverage properties require calibration studies • Uncertain regulatory landscape

	Weibull	Intersection Union Test
Pros	• Hierarchal model representing known sources of variability • Permits estimation of non-observed time points • Parameters related to rate and extent of dissolution in a first order process • Permits a concise comparison in relation to parameters of the model which have natural interpretation	• Uses well established equivalence test procedure which guarantees the α level of the test • Know what the parameters being tested are • Can be used when the variances do not meet variability assumptions required for f2 • Can be used when the variances between the test and reference samples are unequal • Can be generalized to multiple test or reference batches
Cons	• Complex modeling which may require advanced statistical tools and predictive calculations • No single parameter representing the intrinsic dissolution rate • Early portion of the profile not well characterized	• Deviates from the general principle espoused by the f2 of testing for some general average difference across the time points • Simulations have showed it to be very conservative due to the point above • Is ± 10% the right equivalence region

	Other	Other
Pros		
Cons		

Day 1 BO Session D Part 2 - Time: 3:15 to 4:15 pm in Room N314	
1. When should/could each of the methods be used? Please comment on the relevant paper provided at your table.	G3/G4
2. Are there specific times when you would not use a method?	G3/G4
3. What challenges do users and regulators have in implementing each?	G3/G4

Method	When to Use	When to not use
f2	When data satisfies regulatory assumptions	When variability or time point requirements are violated
Bootstrap f2	When variability conditions of f2 are violated	
Multivariate Statistical Distance (MSD)	When the within batch variation is high	General: when the measurements are not taken at the same sampling timepoints for reference and test products Mahalanobis distance-based approaches: • when high correlation among timepoints, may have singular matrix Confidence interval approaches on aggregated criteria: • when the assumption of constant mean difference is violated Confidence region approaches on disaggregated criteria: • when the sampling time point is large

Method	When to Use	When to not use
Disso Safe Space	When dissolution profile data from BE batches are available	When dissolution profile data from BE batches are not available
Weibull	• Empirical approach • Can be applied almost universally	Limited in use in establishing IVIVC
Bayesian	• Inference based approach • Can be applied almost universally	Questionable acceptance without prior dialog with respective regulatory body
Intersection Union Test	• Can be used any time but suggested to use when variability conditions of f2 are violated • Can be used when multiple test/reference batches are present	• Based on how conservative it is in simulation studies, should almost never use it. • Should not be used when there are multiple test/reference batches and the batch-to-batch variability is large