Evaluation of Dissolution Profile Similarity for Bioequivalence Assessment

2022 FDA-CRCG workshop:

Best Practices for Utilizing Modeling Approaches to Support Generic Product Development

Session 4: *Development of Quantitative Comparative Approaches to Support Complex Generic Drug Development*

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Regulatory Application of Dissolution Similarity Assessment

Comparison of in vitro dissolution profiles is used to demonstrate similarity between reference and test product in different regulatory applications, for example:

- Quality control of drug product
- Biowaiver of other strengths
- Bridging between formulations
- Stability
- SUPAC changes

Dissolution Similarity Assessment Methods

Model-Independent Approaches

- Similarity factor-f2
- Multivariate Confidence Region Procedure
- F2-bootstrapping

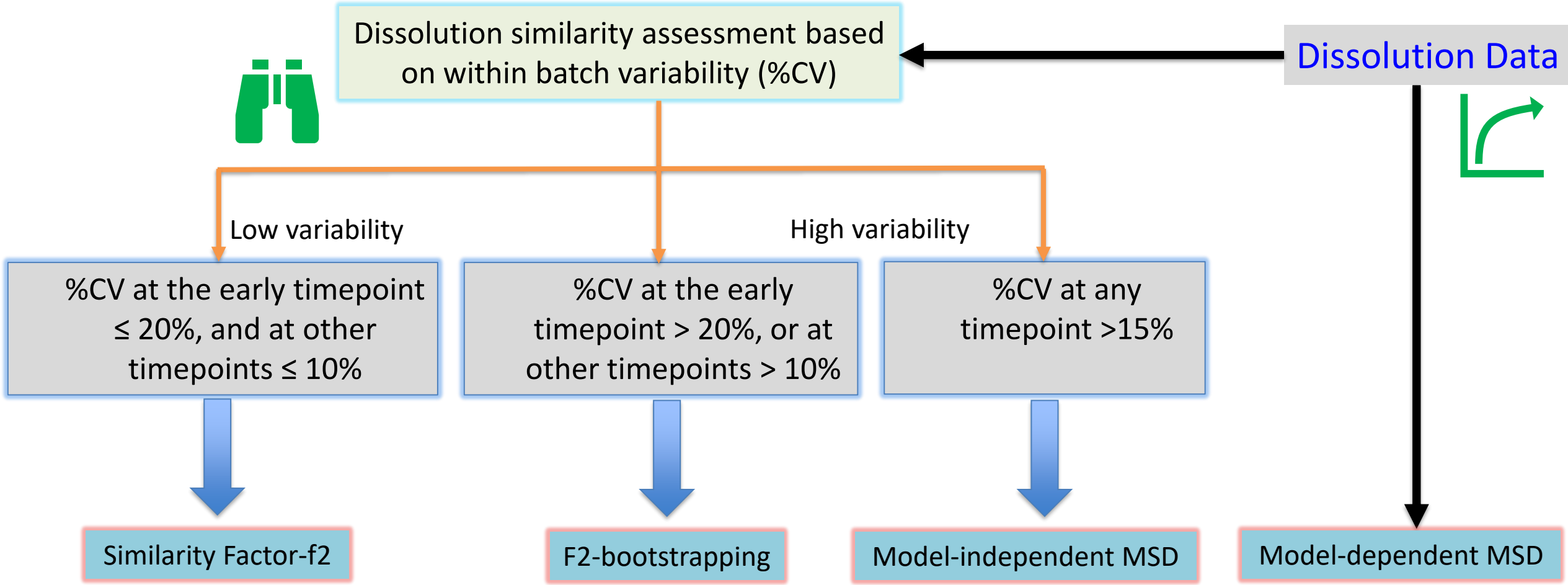
(not listed in the guidance)

Model-Dependent Approaches

- Linear
- Quadratic
- Logistic
- Weibull
- Probit

FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, August 1997, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dissolution-testing-immediate-release-solid-oral-dosage-forms

Dissolution Similarity Assessment



MSD: multivariate statistical distance

FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, August 1997, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dissolution-testing-immediate-release-solid-oral-dosage-forms

Similarity Factor-f2

1. 12 units from each reference and test with same timepoints (minimum of 3 timepoints)
2. Only one measurement should be considered after 85% dissolution
3. %CV at earlier timepoint should be ≤ 20%, and at other timepoints should be ≤ 10%
4. Dissolution conditions should be the same and using recently manufactured batches
5. Dissolution similarity is determined when f2 ≥ 50

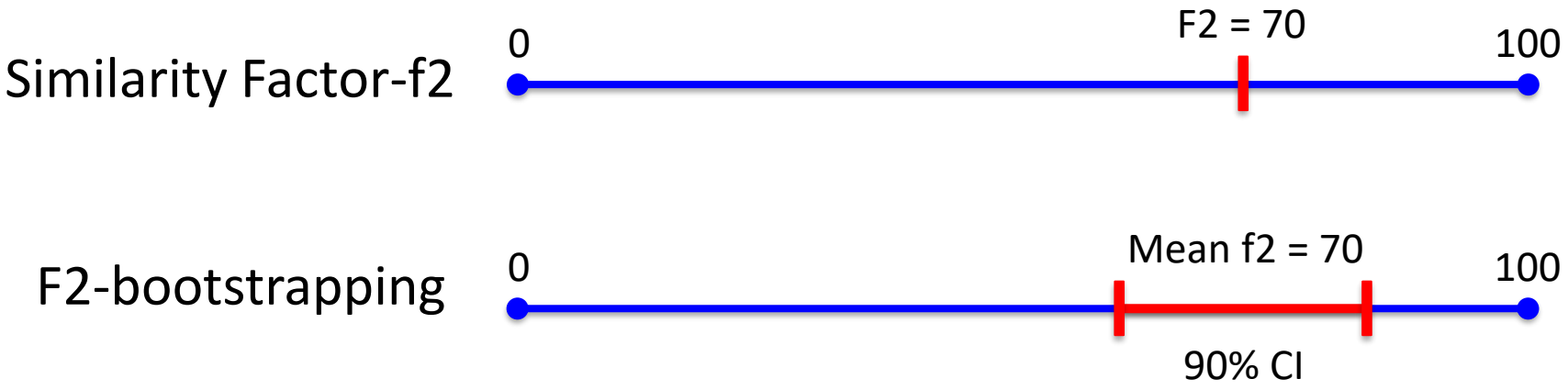
$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

where n is the number of time points, Rt is the dissolution value of the reference (prechange) batch at time t, and Tt is the dissolution value of the test (postchange) batch at time t.

FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, August 1997, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dissolution-testing-immediate-release-solid-oral-dosage-forms

F2-Bootstrapping

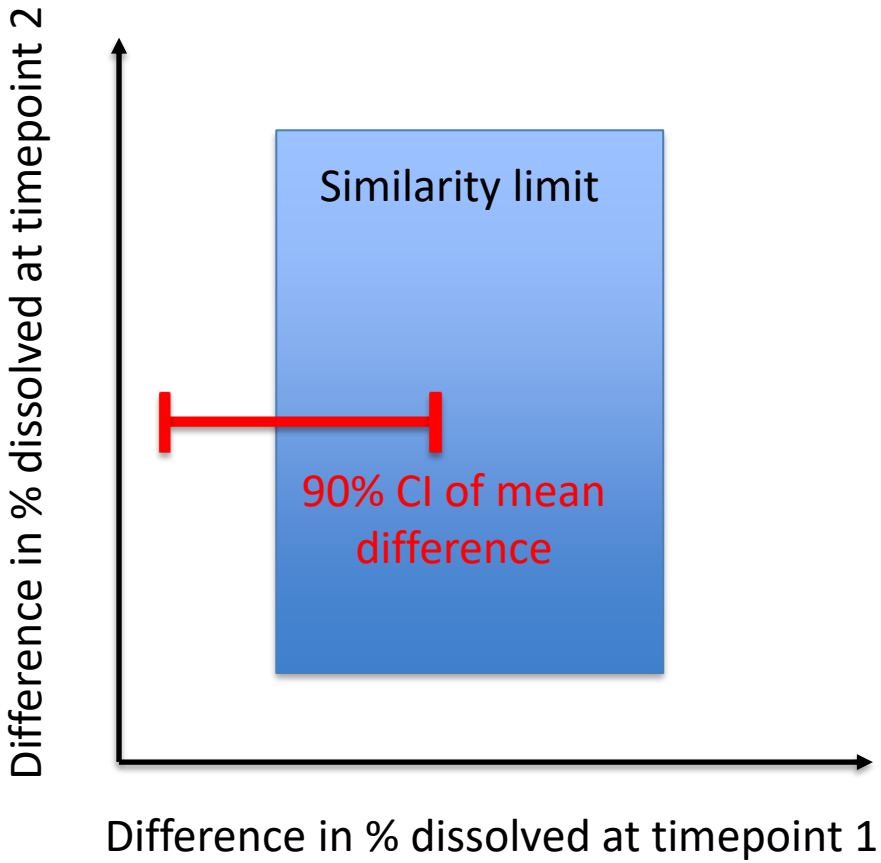
- Sample with replacement from the original reference and test product profiles separately[1]
- Similarity factor-f2 is computed for each bootstrap sample
- Similarity is determined based on f2-bootstrap mean and 5th percentile of computed f2



The Annals of Statistics, 7, 1-26, 1979

Model-Independent MSD

The MSD procedure relies on the calculation of the Mahalanobis Distance (D_M)



$$D_M = \sqrt{(\boldsymbol{R}_t - \boldsymbol{T}_t)^T (S_{pooled})^{-1} (\boldsymbol{R}_t - \boldsymbol{T}_t)}$$

Vector of the mean dissolution of the test product

Vector of the mean dissolution of the reference product

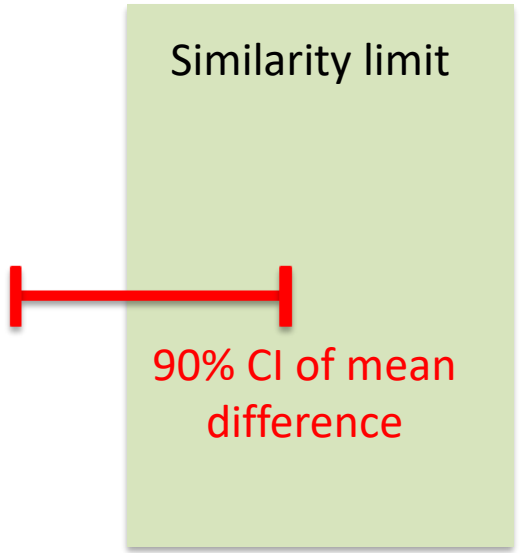
Variance-covariance matrix pooled across both profiles

Dissolution similarity is obtained when the upper limit of the 90% CI is ≤ similarity limit

Drug Information Journal 30, 1105-1112.

Model-Dependent MSD

- Fitting a model with no more than three parameters (e.g., Weibull model) to dissolution data
- A similarity region is set based on variation of parameters of the fitted model
- Calculate the MSD in model parameters between test and reference batches.
- Dissolution similarity is obtained when the upper limit of the 90% CI is ≤ similarity limit



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Comparison Between Dissolution Assessment Methods

- Currently, both f2 bootstrapping and Model-independent MSD are frequently used for dissolution profile comparisons when dissolution data have high variability.[1,2]

  → However, the results between these two methods may not be consistent[2]

- F2 bootstrapping test and its 90% CI are more restrictive compared to Model-independent MSD[1,2]

  ↑ %CV enlarges CI to a point where it is difficult to conclude for similarity between actual similar dissolution profiles[2]

1. M-CERSI Workshop, In Vitro Dissolution Profiles Similarity Assessment in Support of Drug Product Quality: What, How, and When, May 21-22, 2019
2. Eur J Pharm Biopharm. 2017 Mar;112:67-74

Objectives

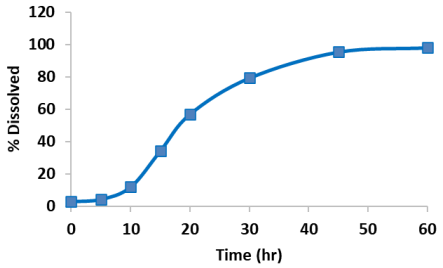
To compare and identify the appropriate method to evaluate similarity between highly variable dissolution profiles by using in silico generated dissolution data

Specific Aims/Steps

1. Selecting reference in vitro dissolution data from products with different release behavior
   - Drug 1: Immediate release (IR) tablet formulation
   - Drug 2: Delayed-release (DR) tablet formulation
   - Drug 3: Extended-release (ER) tablet formulation
2. Simulating test dissolution profile at pre-specified theoretical f2 values compared to the reference profile
3. Simulation of reference and test dissolution profiles
4. Dissolution similarity assessment and comparison between different methods

Simulation and Analysis Approach

Reference profile from RLD/bio-batch

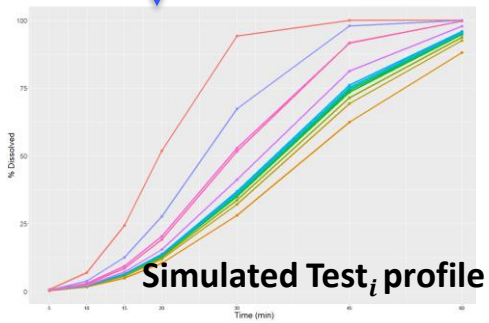


+ %CV

1000 simulations of reference profile

Sim. 1

Sim. 1000



Simulated Test$_i$ profile

Unit	t_1	t_2	....	t_{13}
U1	%			
U2				
....				
U12				

Each Simulation

Each single simulation has 12 units

+ %CV

1000 simulations of test$_i$ profile

Sim. 1

Sim. 1000

F2-bootstrapping (frequency: 10000)

Model-independent MSD (acceptable difference = 10%)

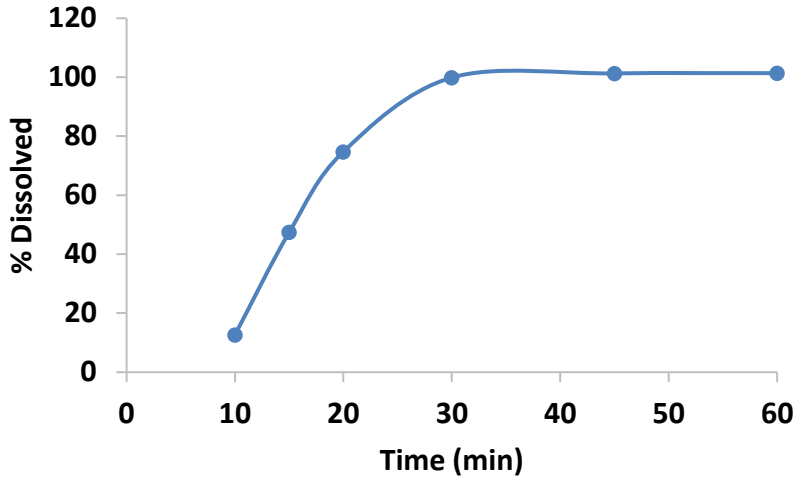
Model-dependent MSD

Calculate passing rate

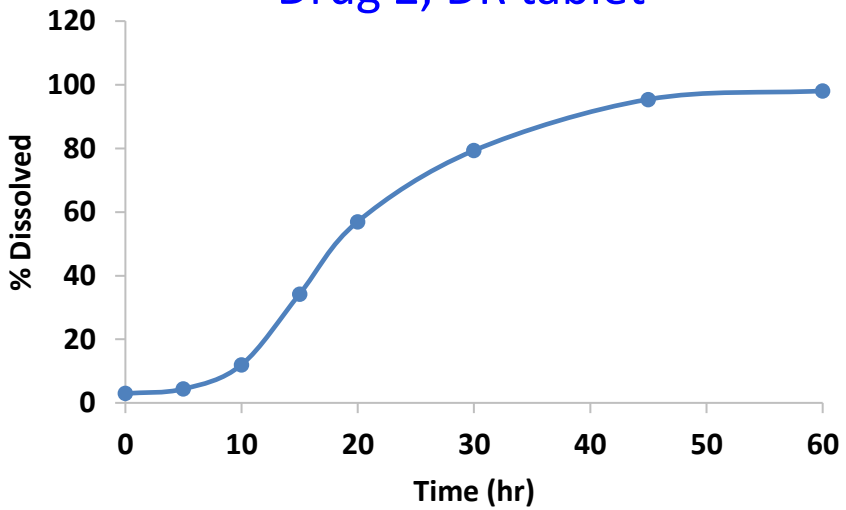
RLD: reference listed drug

Selecting Reference in Vitro Dissolution Profiles

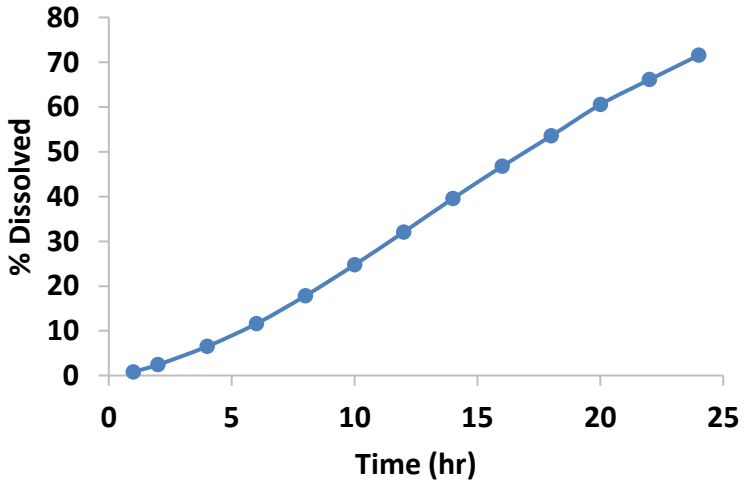
Drug 1, IR tablet



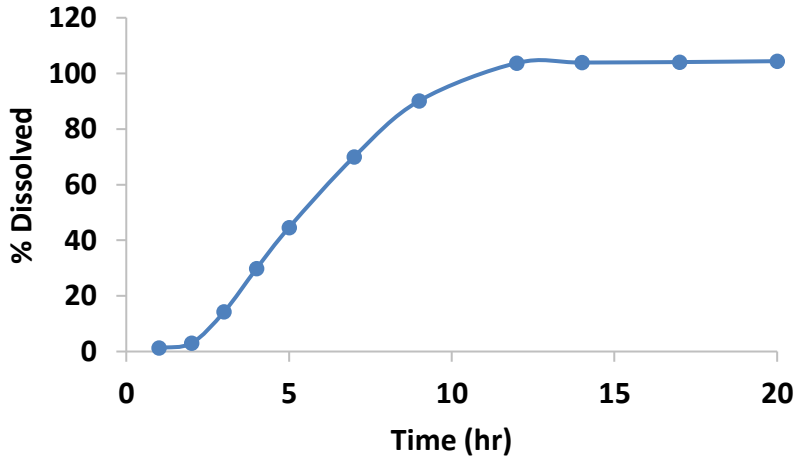
Drug 2, DR tablet



Drug 3, ER tablet, pH 4.5



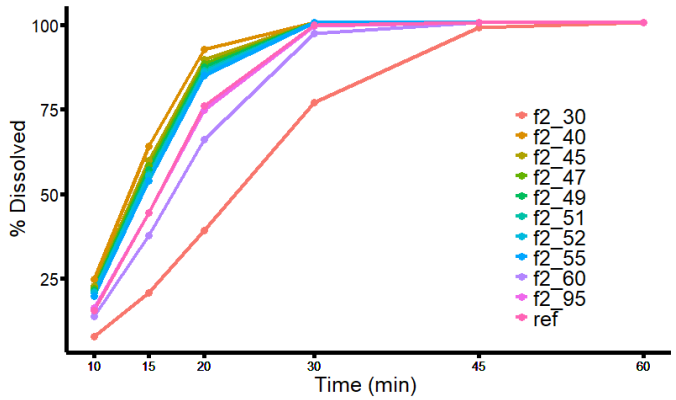
Drug 3, ER tablet, pH 6.8



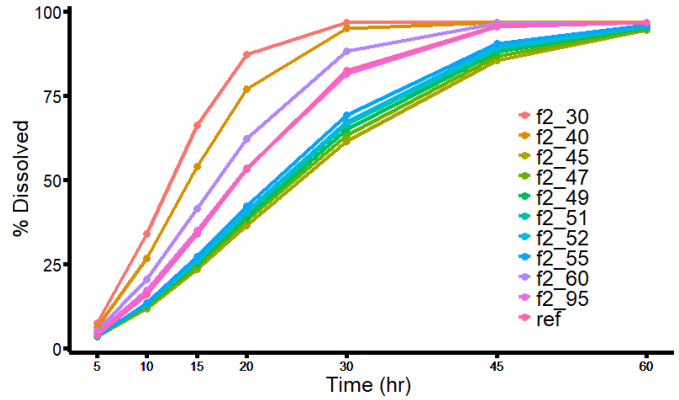
Generation of Test Dissolution Profiles

Test dissolution profiles were generated from the reference profile at pre-specified theoretical f2-values for each formulation

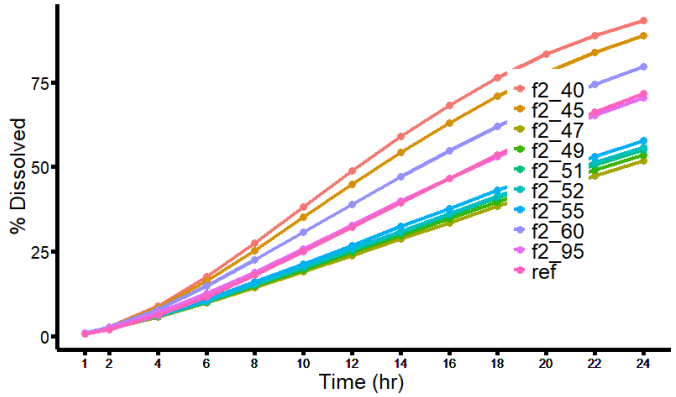
Drug 1



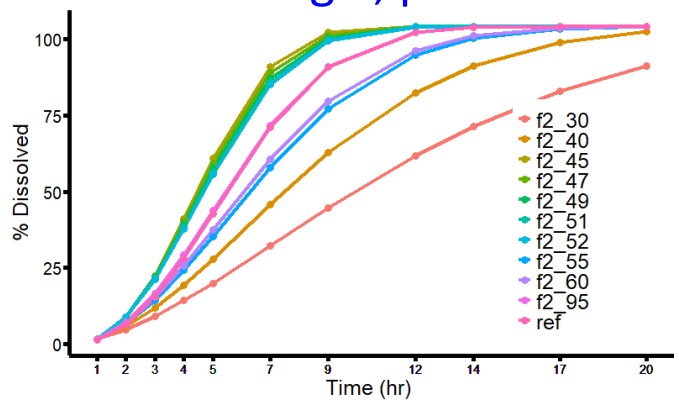
Drug 2



Drug 3, pH 4.5



Drug 3, pH 6.8



Simulation of Dissolution Profiles

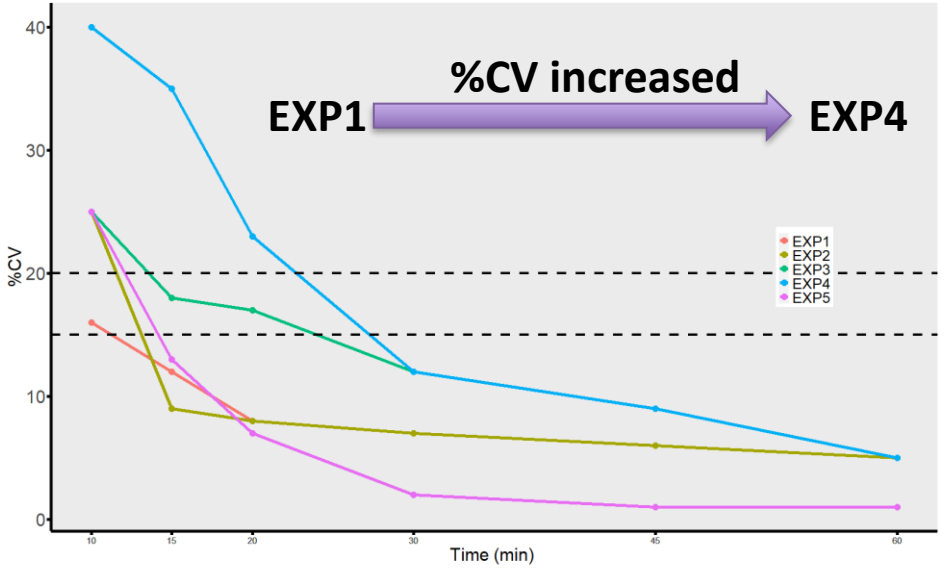
- Different levels of within batch variability (%CV) were introduced at each timepoint during simulation for both reference and test dissolution profiles

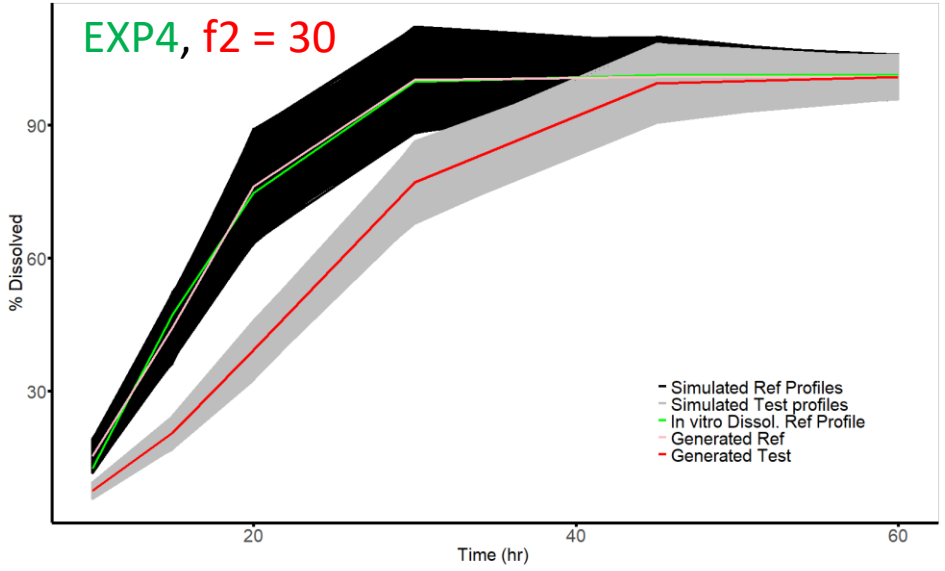
- All simulated dissolution profiles have high %CV; therefore, similarity limit (conventional f2) is not applicable

Within batch variability

Simulated profiles

Drug 1



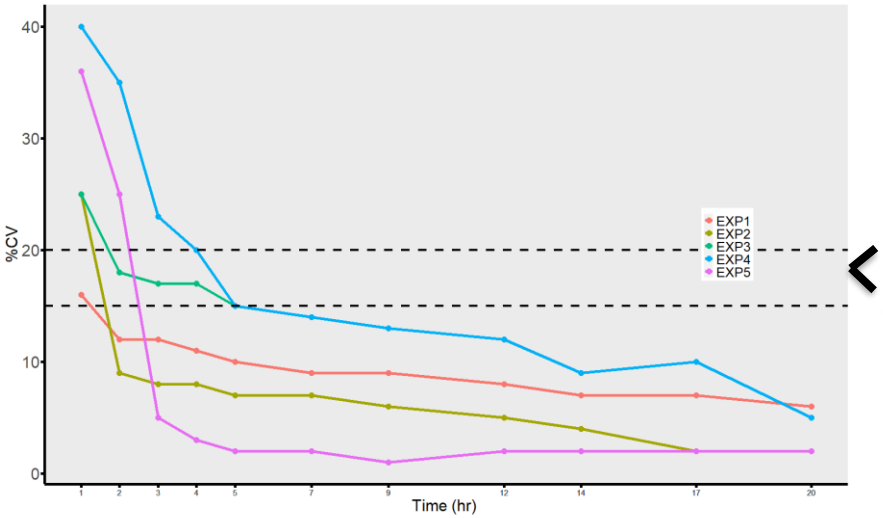


EXP5: %CV from in vitro dissolution data of reference product

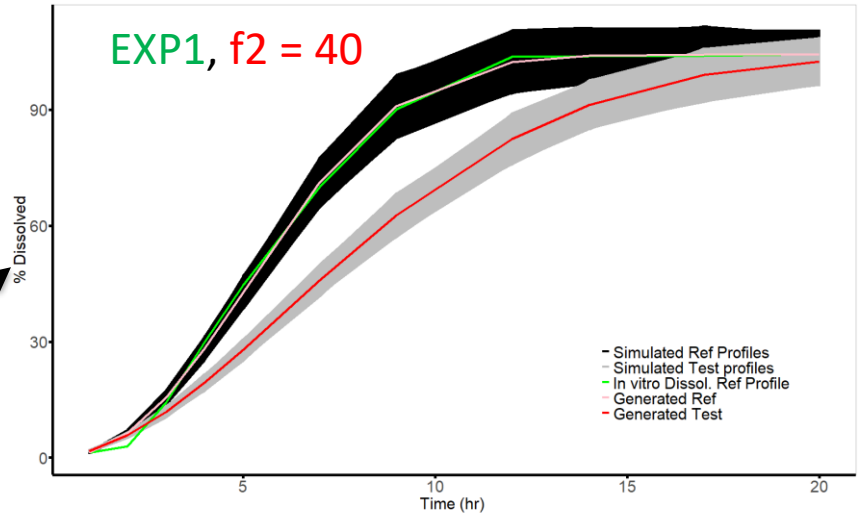
Simulation of Dissolution Profiles

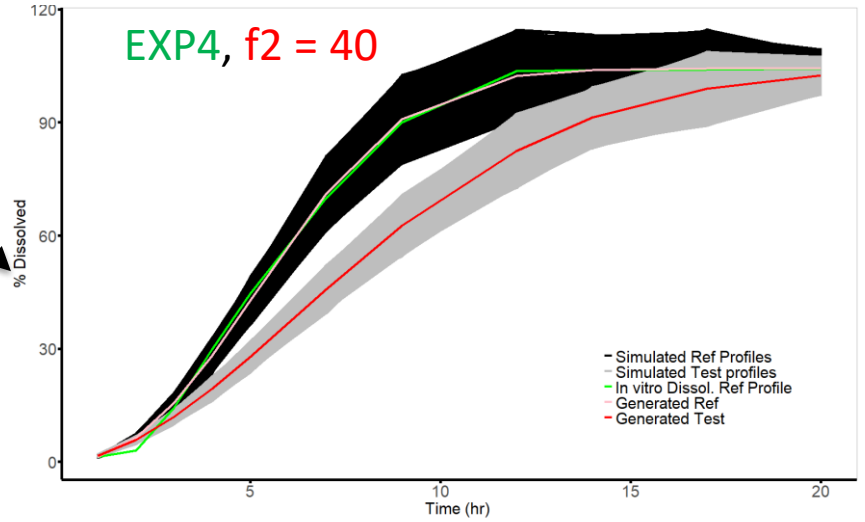
Drug 3, pH 6.8

Within batch variability



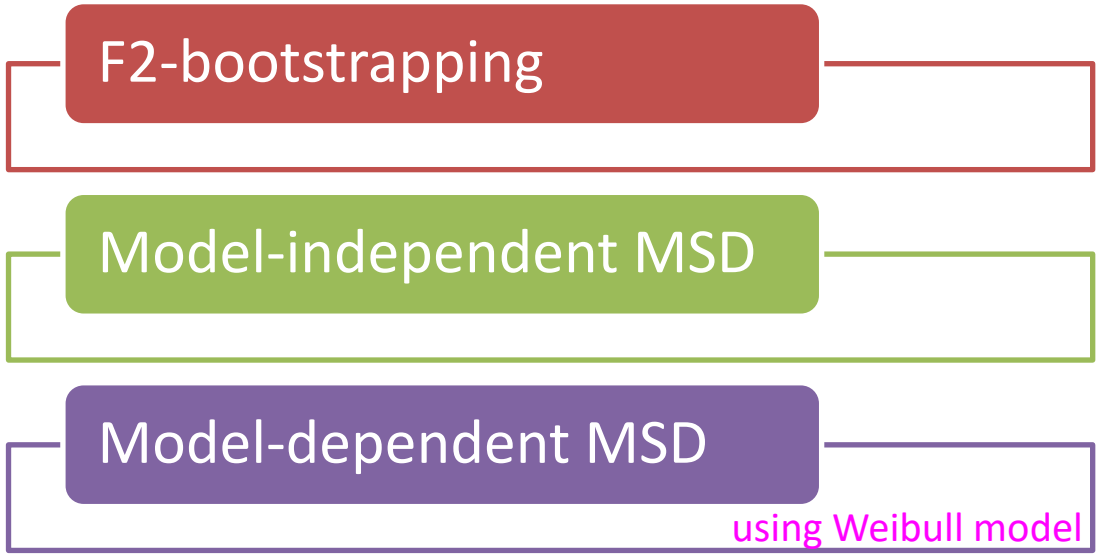
Simulation





Dissolution Similarity Assessment

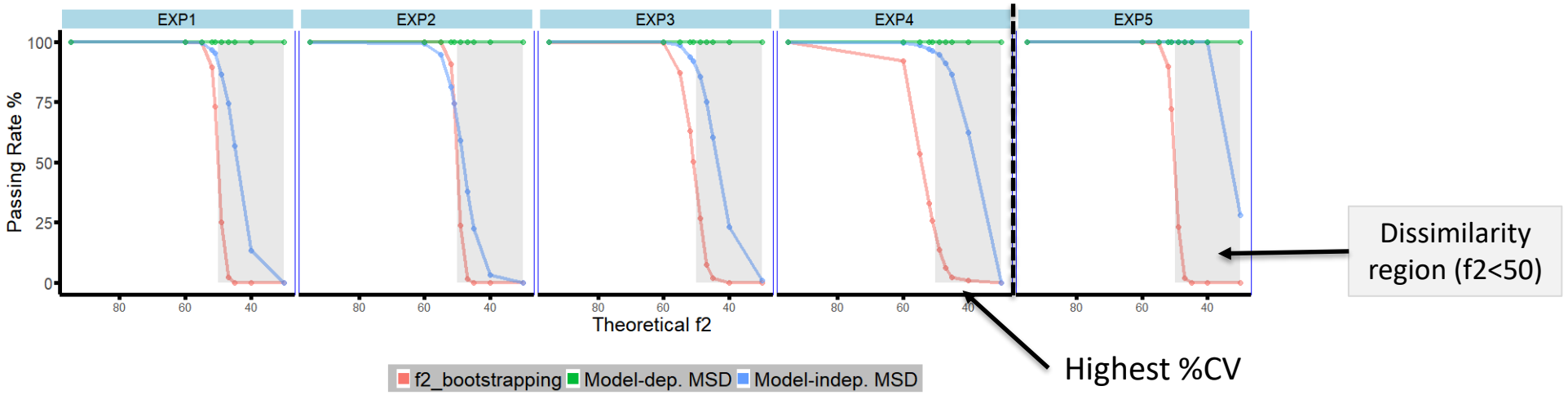
- Three methods were used to assess dissolution similarity between simulated test and reference profiles:



- The passing rate (i.e., showing dissolution similarity) at each theoretical f2 value was compared between the three methods

Comparison Between Dissolution Similarity Assessment Methods

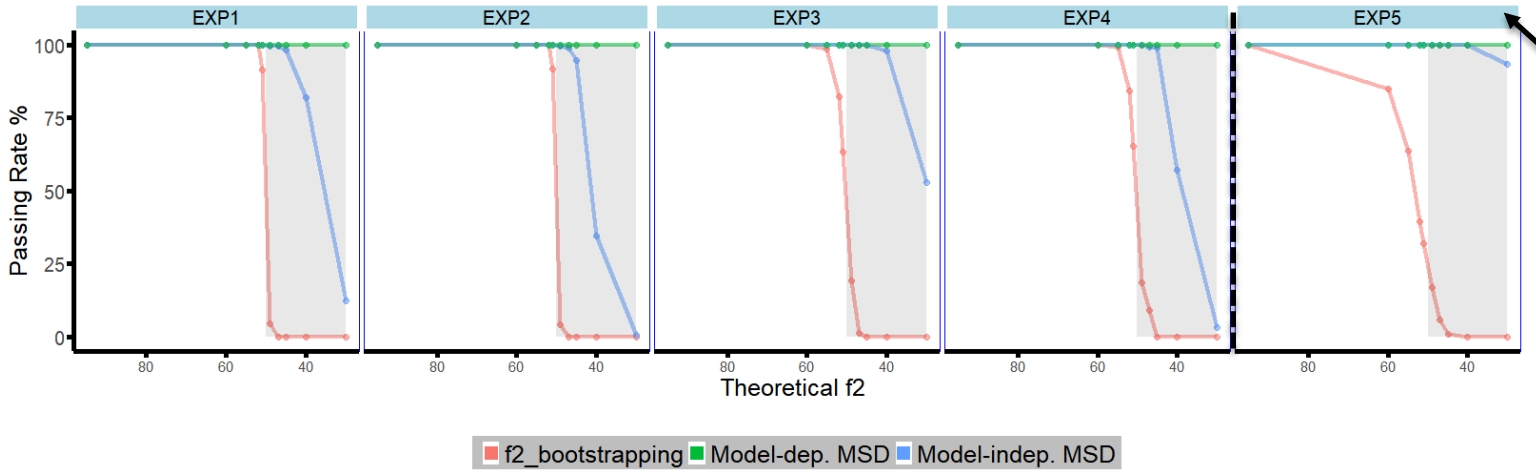
Drug 1



- F2-bootstrap successfully identified dissimilar dissolution profiles in EXP1-5
- F2 bootstrap is more conservative compared to model-dependent and model-independent MSD approaches
- With increased %CV (EXP4), f2-bootstrap partially (25-54%) identified similar dissolution profiles (at f2=51-55)

Comparison Between Dissolution Similarity Assessment Methods

Drug 2

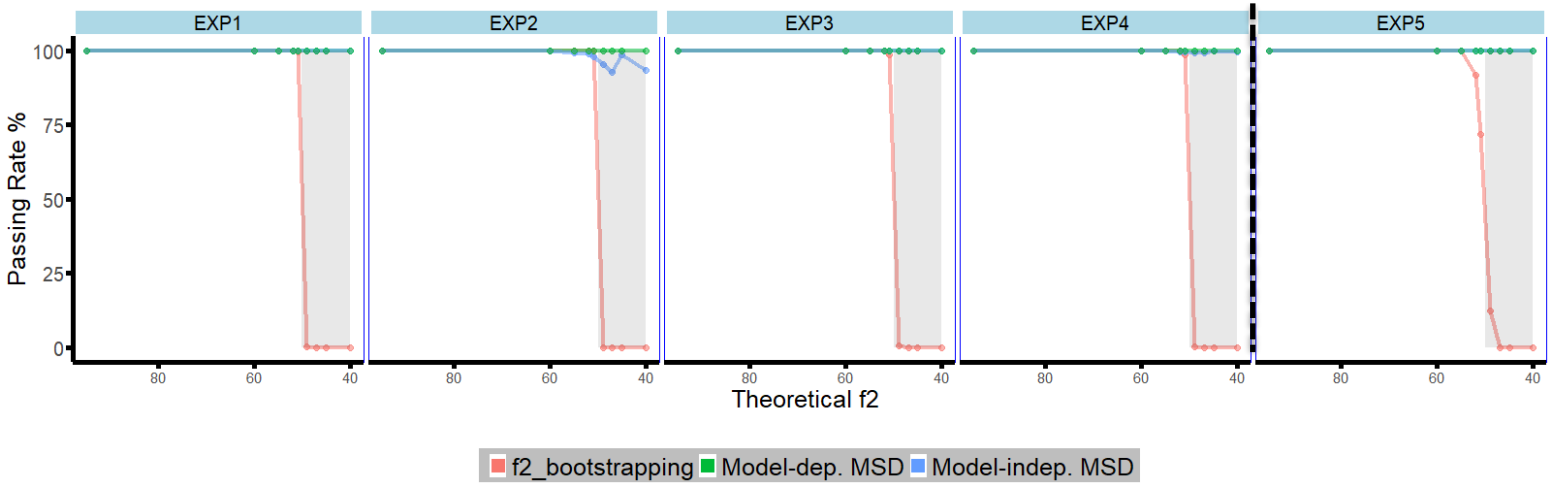


Highest %CV

- F2-bootstrapping successfully identified dissimilar dissolution profiles in EXP1-5
- F2 bootstrap is more conservative compared to model-dependent and model-independent MSD approaches
- With increased %CV (EXP5), f2-bootstrap partially (32-64%) identified similar dissolution profiles (at f2=51-55)
- Model-independent MSD approach showed inconsistent conclusion

Comparison Between Dissolution Similarity Assessment Methods

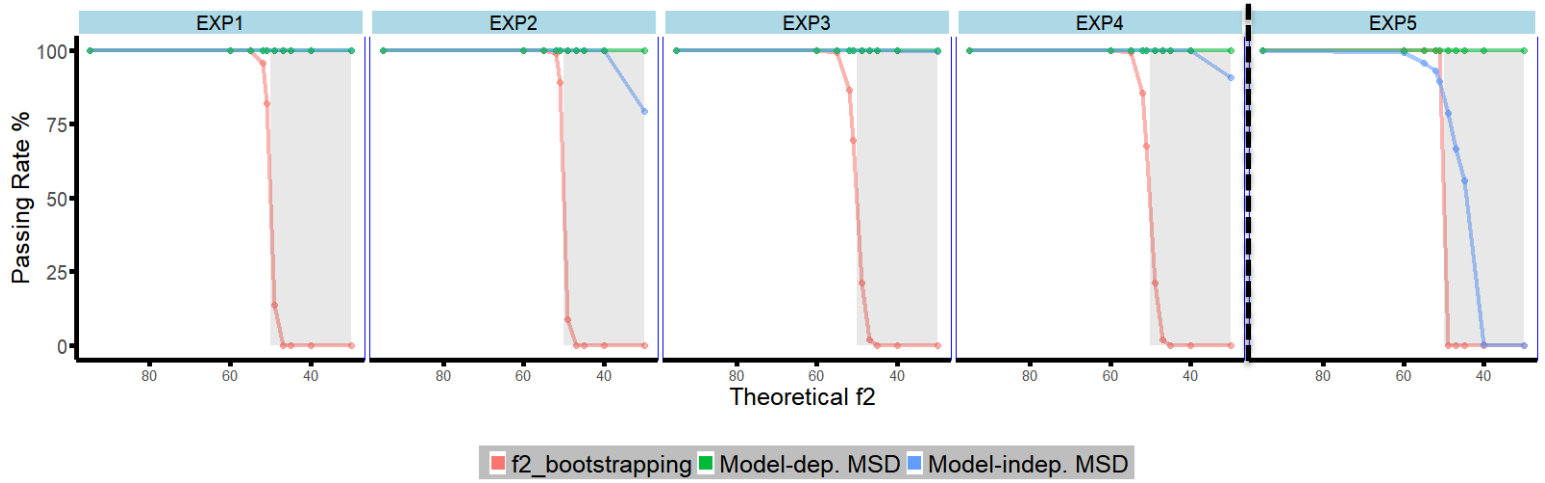
Drug 3, pH 4.5



- F2 bootstrap is more conservative compared to model-dependent and model-independent MSD approaches

Comparison Between Dissolution Similarity Assessment Methods

Drug 3, pH 6.8



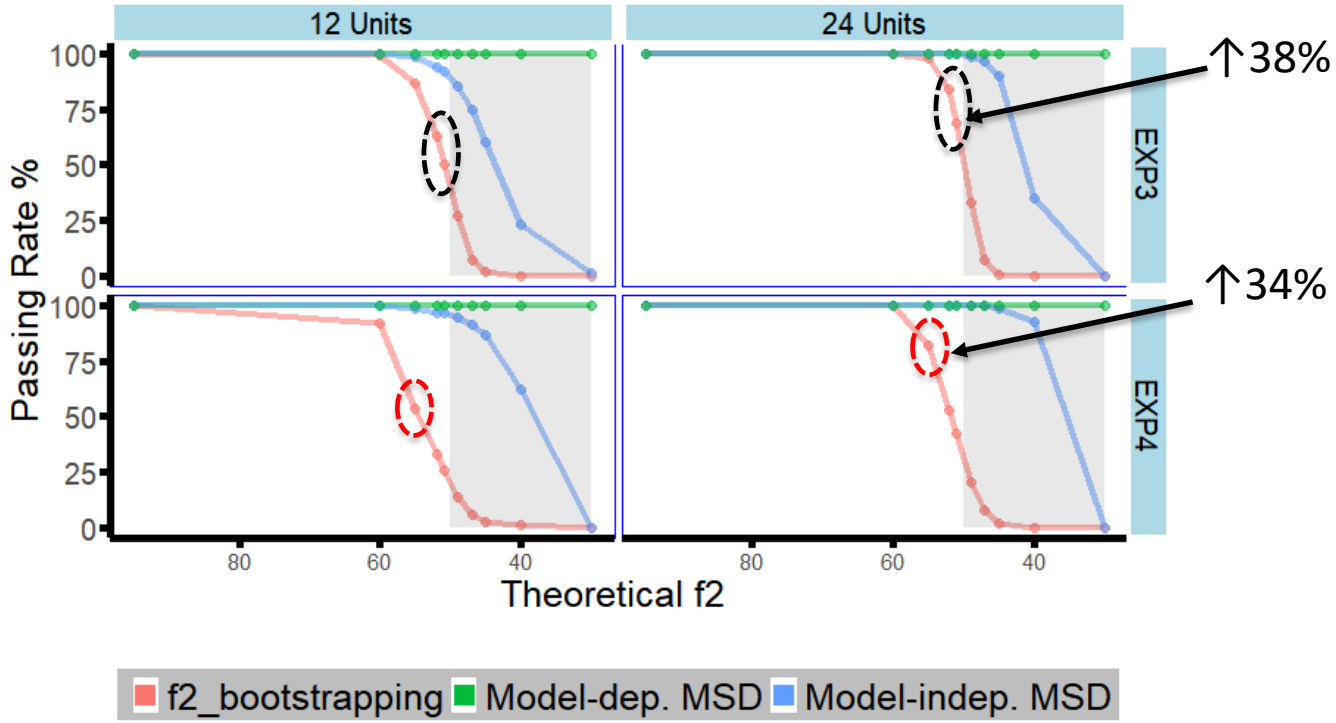
- F2 bootstrap is more conservative compared to model-dependent and model-independent MSD approaches
- Model-independent MSD approach showed inconsistent conclusion

Increasing the Number of Simulated Units May Change The Sensitivity of Assessment Methods

- Exploratory assessment showed that increasing the number of units from 12 to 24 increased the sensitivity of f2-bootstrapping method to identify similar dissolution profiles

- Inconsistent finding observed with model-independent MSD approach

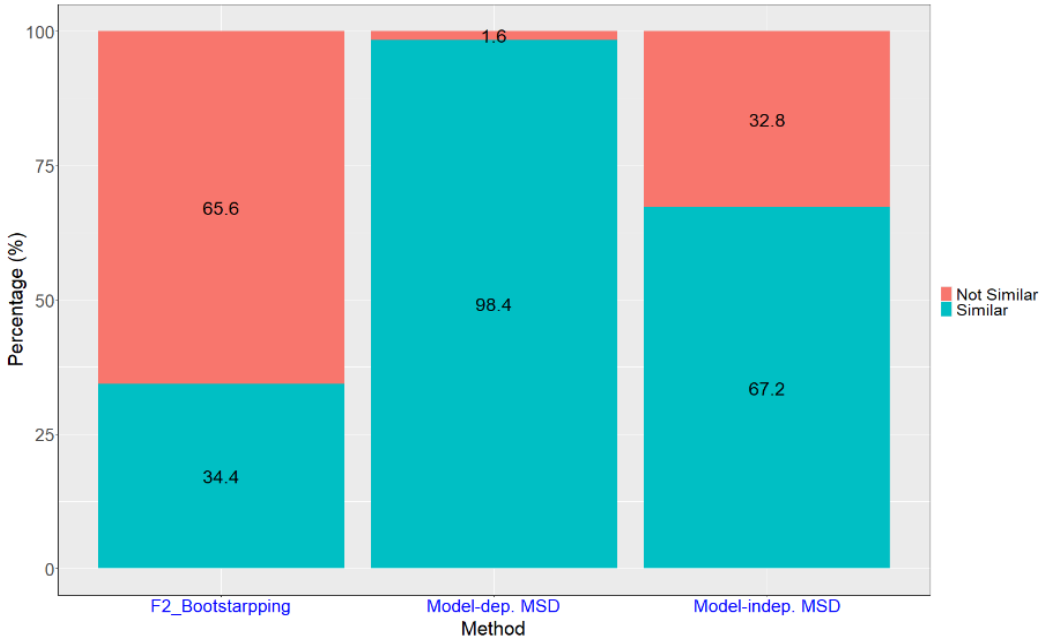
Drug 1



Analysis of Dissolution Data from ANDA Applications

- Dissolution profiles (128 dataset, each 12 units) were collected from multiple ANDA applications for ER, DR, and IR tablets; IR capsule; and oral powder

- %CV > 20% at earlier sampling timepoint and/or >10% at later sampling timepoints



F2-bootstrapping method is more conservative compared to model-dependent and model-independent MSD procedures

✓ Dissimilar concluded by f2-bootstrapping analysis and similar concluded by model-independent MSD = 48 (37.5%) datasets

✓ Dissimilar concluded by model-independent MSD and similar concluded by f2-bootstrapping analysis = 6 (4.1%) datasets

Summary

- In comparison to MSD approaches, the f2-bootstrapping analysis method is more conservative for dissolution profile comparison for highly variable dissolution profiles based on the example cases provided

- Conclusion on the conservativity and restrictiveness of f2-bootstrapping is consistent with previously reported findings[1,2]

- Physiological based pharmacokinetics (PBPK) modeling and/or in vivo in vitro correlation (IVIVC) can be used to assess the risk of dissolution deviation on in vivo performance

1. M-CERSI Workshop, In Vitro Dissolution Profiles Similarity Assessment in Support of Drug Product Quality: What, How, and When, May 21-22, 2019
2. Eur J Pharm Biopharm. 2017 Mar;112:67-74

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Thank you