Rational Statistical Analysis Practice In Dissolution Profile Comparison: FDA Perspective

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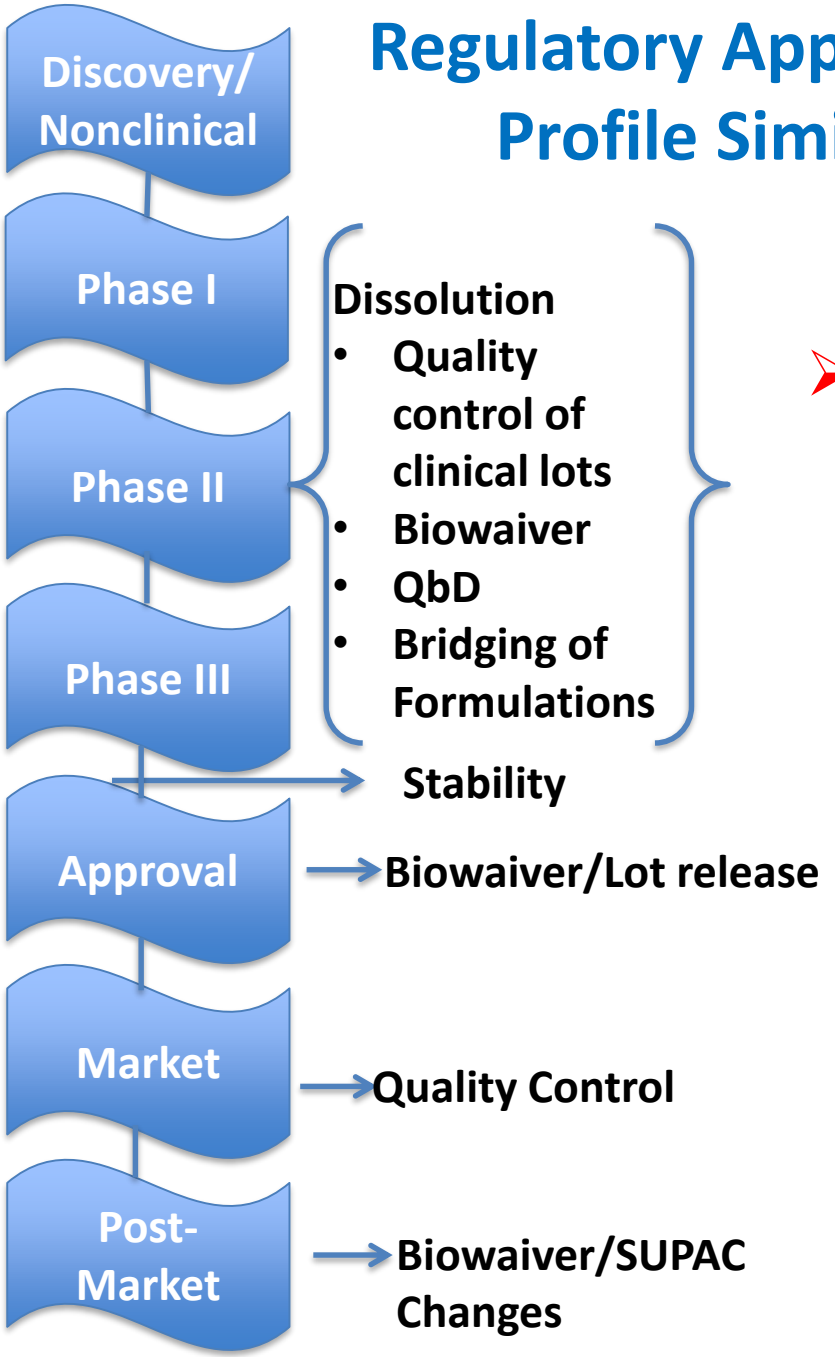
Outline

- Background
- Regulatory Application of f_2 Metric
- Case Studies/Current Practices
- Thought Process in Dissolution Similarity Testing
- Challenges

Regulatory Application of Dissolution Profile Similarity Assessment



- In vitro dissolution profile comparison is used to demonstrate similarity between a test and a reference product for
  - Biowaiver for lower/higher strengths
  - Bridging between formulations
  - Minor/moderate variations described in SUPAC guidance

Relevant Guidances

- Dissolution Testing of Immediate Release Solid Oral Dosage Forms
- Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Guidance for Industry
- Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations
- Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation
- SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation Bioavailability and Bioequivalence Studies for Orally Administered Drug Products, General Considerations
- FDA Guidances for specific generic drug products

Prerequisites for the Application of Dissolution Profile Comparisons

- Discriminatory dissolution method
- Thorough understanding of sources of dissolution variability
- In the case of additional strength biowaivers, compositional proportionality, linear PK and in vivo clinical studies on the highest strength/Bio strength
- Post approval changes, as defined in the SUPAC guidances

Dissolution Profile Comparison Approaches

1. Model Independent

- f_2
- Multivariate confidence region procedure

2. Model dependent

- Weibull
- Linear
- Quadratic
- Logistic
- Probit

f_2 Similarity Factor

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

Where n is the number of time points, R_t is the dissolution value of the reference (prechange) batch at time t, and T_t is the dissolution value of the test (postchange) batch at time t

- 12 units
- 3- 4 or more dissolution points
- Time points should be the same (e.g. 15, 30, 45 and 60 minutes)
- Reference batch should be most recently manufactured prechange product
- Only one measurement should be considered after 85% dissolution of both products
- The %CV at the earlier time points (e.g., 15 minutes) is not more than 20% and at other time points is not more than 10%
- Dissolution measurements should be made under same conditions and the dissolution profiles should have the same time points

Current Regulatory Practice: Highly Variable Dissolution Data

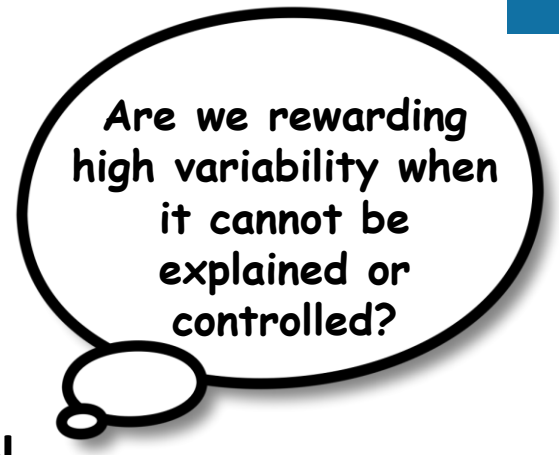
- For highly variable dissolution data when the CV is more than 20% at early time points or more than 10% at later time point, f_2 does not apply[1]

- Multivariate analysis (MVA), calculate 90% confidence region of the Mahalanobis distance for the difference in the amount dissolved at different sampling times

- f_2 bootstrapping method to calculate 90% confidence interval of the f_2 similarity factor

1. Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. August 1997. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070237.pdf.

Variability

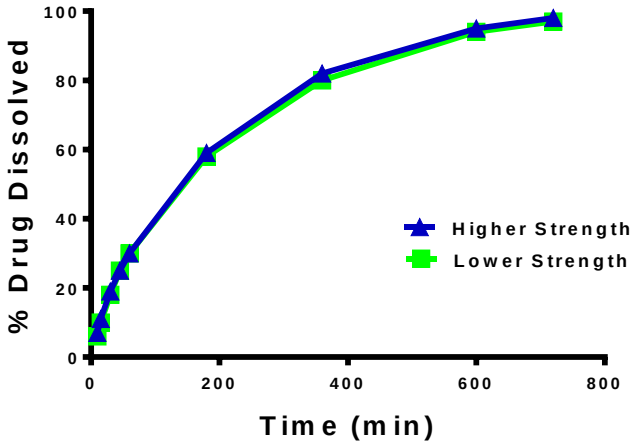


- Dissolution Method related
- Analytical Method related
- Manufacturing Process Related
- Drug substance related
- Drug product related
- Other unexplained sources

Case study 1-Biowaiver for a Lower Strength

ER Formulation

Dissolution Medium	Sampling times (minutes) (Higher Strength)									f_2
	10	15	30	45	60	180	360	600	720	
pH 6.8	7 (6.5)	11 (4.3)	19 (2.5)	25 (2.3)	30 (1.8)	59 (0.7)	82 (0.5)	95 (0.8)	98 (0.8)	NA
pH 4.5	7 (5.8)	11 (4.8)	19 (3.6)	25 (2.8)	30 (2.4)	59 (1.7)	83 (1.5)	96 (1.1)	98 (0.7)	NA
0.1 N HCL	7 (8.4)	11 (7.1)	18 (3.2)	25 (1.7)	30 (2.3)	57 (1.6)	81 (1.5)	95 (1.4)	98 (1.5)	NA
(Lower Strength)										
pH 6.8	6 (6.8)	10 (5.1)	18 (3.3)	25 (2.8)	30 (2.3)	58 (1.3)	80 (1.1)	94 (0.7)	97 (0.8)	91.8
pH 4.5	7 (2.6)	10 (1.9)	19 (1.5)	25 (1.1)	30 (0.9)	58 (1)	81 (0.6)	95 (0.3)	98 (0.6)	93.2
0.1 N HCL	7 (3.8)	11 (2.5)	19 (1.9)	25 (1.5)	31 (1.4)	59 (0.9)	82 (0.6)	96 (0.8)	99 (0.7)	92.5

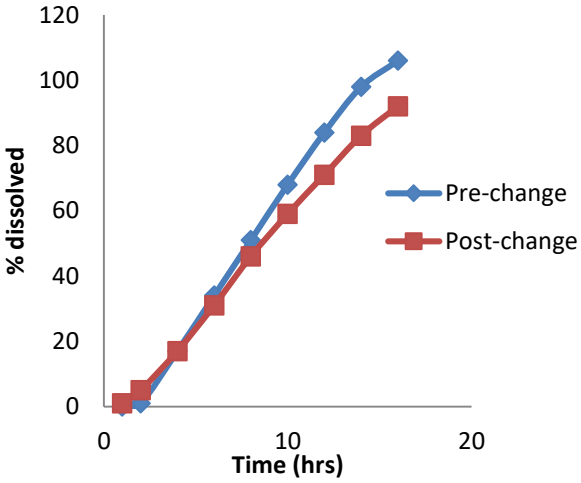


- Variability within guidance limits
- Multi pH dissolution profiles
- Linear PK
- One point after 85%
- f_2 limits met
- Biowaiver granted based on dissolution comparison

Case study 2-f_2 not Applicable

ER Formulation

Ref	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs	14 hrs	16 hrs
Mean	0	1	17	34	51	65	82	95	102
%RSD	44.6	17. 8	19.3	14.1	10.8	9.2	7.9	5.8	1.6
Test	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs	14 hrs	16 hrs
Mean	1	5	17	31	45	58	73	81	93
%RSD	42.1	11.4	17.4	11.2	8.3	5.4	4.2	4.8	5.3



- f_2 not applicable due to high variability

  -The within-batch variability of drug release at early time points is high (more than 20 % CV),

- Multivariate Statistical Distance (MSD) was used to conduct the analysis with the assumption that the dissolution data are normally distributed

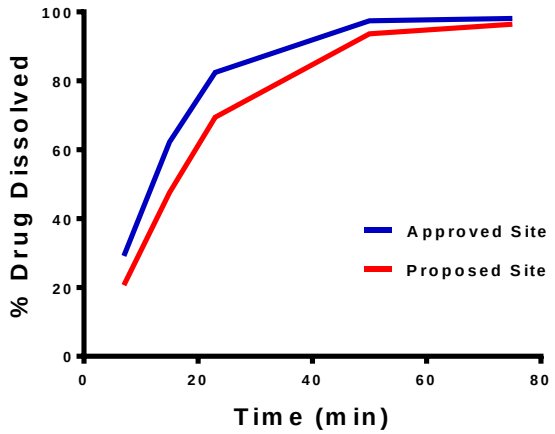
Case Study 2: Results and Conclusion

Dissolution Media	10 mg strength
pH 1.2 buffer	PASS (MSD: 24.5 90% CI: 1.3-9.5)
pH 4.5, Acetate buffer	PASS (MSD: 55.5 90% CI: 3.5-10.2)
pH 6.8, phosphate buffer (QC medium)	PASS (MSD: 45.9 90% CI 2.7-7.1)
pH 7.5 phosphate buffer	PASS (MSD:63.4 90% CI: 2.0-5.20)

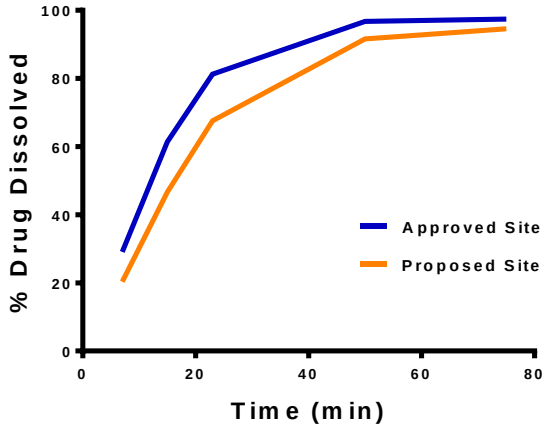
- The upper 90% Confidence Interval of MSD was smaller than the Max MSD between Test and Reference batches, indicating similarity between them
- Same in process controls
- Same control strategy
- Level 3 site change was supported

Case Study 3-Inconclusive Results

Active 1



Active 2

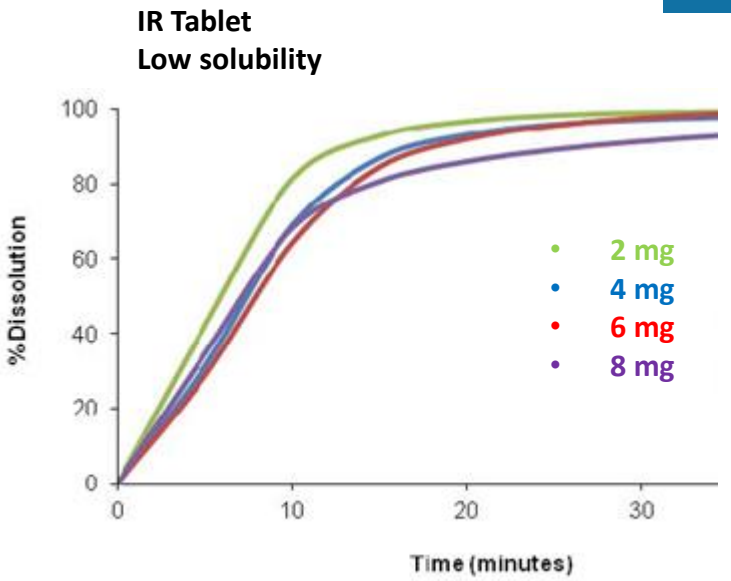


- IR formulation, low solubility actives
- High within batch variability at early time points
- MSD indicated similarity and Bootstrap indicated dissimilarity
- Additional data requested for 3 more batches
- 5 out of 9 pairwise comparisons were not similar
- In addition high variability of lower strength could not be explained
- Applicant's analysis was with 5 points and included an extra time point after 85% release
- Applicant predefined similarity limit as 15%
- Proposed manufacturing site change for lower strength was not supported

CV (%)	7	15	23	50	75
Lower strength for active 1 at approved site	22.02	16.88	14.8	2.21	1.53
Lower strength for active 2 at proposed site	36.52	27.11	19.48	7.64	4.21
Lower strength for active 2 at approved site	21.52	15.97	14.44	2.25	1.42
Lower strength for active 2 at proposed site	36.34	27.31	20.29	7.69	4.17

Case Study 4-Strength Dependent Dissolution

- Waivers were requested for lower strengths
- Discriminatory Dissolution Method
- Compositionally Proportional formulations
- Linearity demonstrated across the dose range
- 4 mg and 6 mg were eligible for waivers based on f_2>50 along with above stated information
- f_2 for 2 mg <50
- Differences in sink conditions were explored by testing 4 x2 mg compared to the 8 mg strength at the same volume.
- f_2 >50
- Wavier was supported for all the three lower strengths.



Strength	f_2 as compared to 8 mg strength
2 mg	36
4 x 2 mg	62

Dissolution Profiles Comparisons with Different Statistical Methods: Internal Analysis

- Currently, both f2 bootstrapping and MDT are frequently used for dissolution profile comparisons when dissolution data have high variability. However, the results between these two methods may not be consistent

- This study compared the Mahalanobis distance test (MDT) and bootstrapping f_2 methods for their regulatory application

Methods

- Dissolution Data with high variability (NDA's) were used for analysis

- Data were selected with the following criteria
  1. %CV >20% at earlier time points (e.g., 5, 10 and 15 minutes) or >10% at later time points
  2. Presence of more than three sampling times

- Each dataset was analyzed for dissolution similarity using both MDT and f_2 bootstrapping methods

Methods, cont.

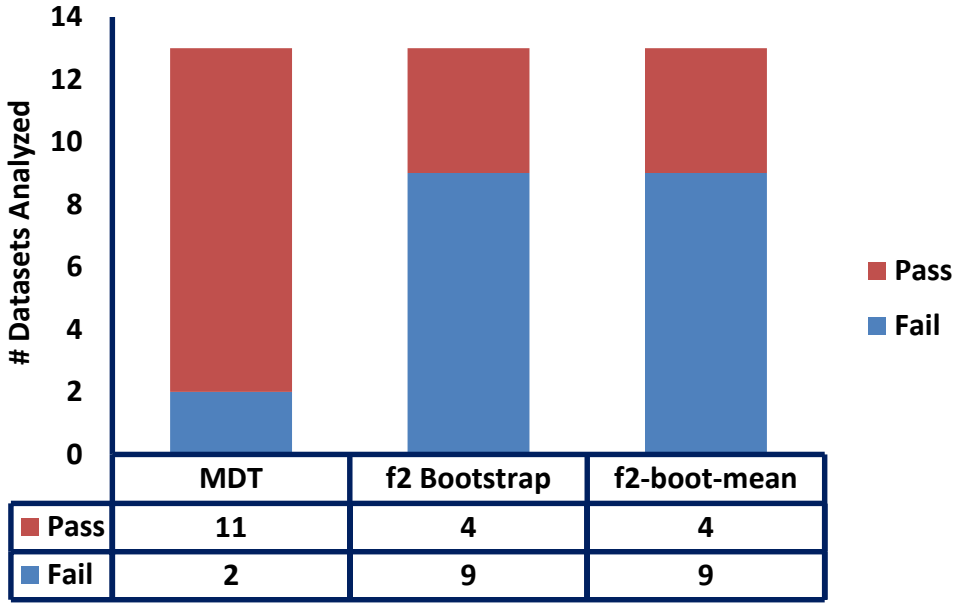
1. Mahalanobis Distance Test (MDT)

- The M-Distance between the mean of test batch X1 and the mean of reference batch X2
- Similarity region MR was calculated as (Dg was set at 10%)
- Two dissolution profiles were considered similar if CR⊂MR.

2. f_2 Bootstrap

- The dissolution data was resampled with replacement (10, 000 times)
- Multiple estimates of f_2 factor were obtained
- Confidence interval was derived using Bias-Corrected and Accelerated (BCA) method

Internal Analysis: Results and Conclusion



	MDT	f2 Bootstrap	f2-boot-mean
Pass	11	4	4
Fail	2	9	9

- f_2 bootstrap test seemed more restrictive compared to MDT
- Further studies are needed to confirm these results

Points for Consideration

- **Knowing the cause of high variability**
  - If source of variability comes from the dissolution method

—Establish adequate dissolution method (maintain discriminating capability and avoid variability from dissolution operation)

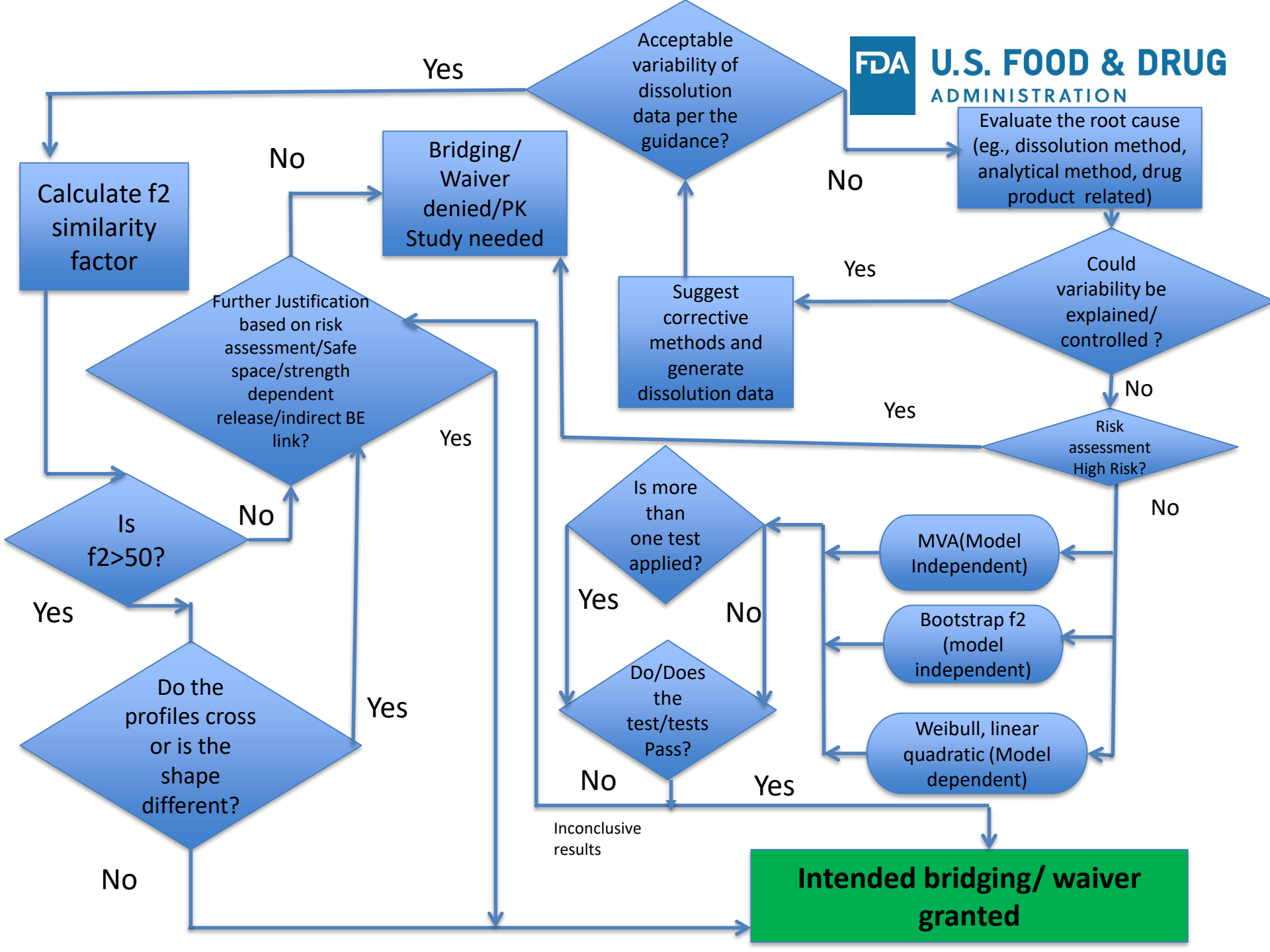
  - If source of variability (e.g. cannot be controlled) comes from drug product

—Use appropriate statistical method (s) to perform evaluate the “similarity” between formulations/batches

Challenges

- Identification of cause of variability
  - Variability based on SD vs. %RSD
  - Which acceptance criterion?
- Variability: single point vs. trend
- How early is the early time point?
- How to handle Inconclusive results
- Bias on setting of similarity limit for other tests other than f_2

Thought Process in the Application of Dissolution Similarity Testing and Beyond to Support the Approval of Minor/Moderate CMC Changes


FDA
U.S. FOOD & DRUG ADMINISTRATION
Acceptable variability of dissolution data per the guidance?
Yes
No
Calculate f2 similarity factor
Bridging/ Waiver denied/PK Study needed
Evaluate the root cause (eg., dissolution method, analytical method, drug product related)
Could variability be explained/ controlled ?
Yes
No
Suggest corrective methods and generate dissolution data
Risk assessment High Risk?
Yes
No
Further Justification based on risk assessment/Safe space/strength dependent release/indirect BE link?
Yes
No
Is f2>50?
No
Yes
Is more than one test applied?
Yes
No
MVA(Model Independent)
Bootstrap f2 (model independent)
Weibull, linear quadratic (Model dependent)
Do/Does the test/tests Pass?
No
Yes
Do the profiles cross or is the shape different?
Yes
No
Inconclusive results
Intended bridging/ waiver granted

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Thank you !


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