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# Decision Tree for Dissolution Profile Comparison in Product Quality Assessment of Similarity

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# Disclosure

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# Outline

- The $f_2$ factor and regulatory Application – Bioequivalence (BE) and Similarity (Quality Control)
- Model independent statistical methods
- Simulation studies
- Decision tree and real case studies
- R Shiny tool

# $f_2$ Similarity Factor

- $f_2$ factor:

$$f_2 = 50 \times log_{10}\left[\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{p}(R_t - T_t)^2}{p}}}\right]$$

where $p$ is the number of time points, $R_t$ and $T_t$ are the mean dissolution values at time point $t$ for reference batch and test batch, respectively.

- $f_2$ = 100 would mean the mean difference at each time point is 0.
- If $f_2 \geq 50$ the two profiles are considered "bioequivalent" or "similar."
- Average mean difference equal to 10 results in $f_2$ around 50.

# $f_2$ Rules (FDA 1997 Guidance)

- N=12 of (i) Reference (or prechange) and (ii) Test (or postchange) products
- Use the Mean values only for calculation
- Model Independent Method - most suitable for dissolution profile comparison when three to four or more dissolution time points are available
  - Same time points (minimally 3 times points)
  - Only one measurement should be considered after 85% dissolution of both the products
  - %RSD – NMT 20% at early points (e.g. 10 minutes); NMT 10% for all other points

# Regulatory Applications – Focused on "*Efficacy*" and "*Quality*"

- **Bioequivalence Assessment**: Establishes procedure for granting biowaivers
  - New Drug and generic drug application
  - Higher strengths
  - Lower strengths

- **Quality Assessment**: Assures product "*Sameness*" under FDA, WHO, Japanese and European guidance, e.g. Scale-Up and Post-Approval Changes (SUPAC)

# When and Where Similarity Factor ($f_2$) is Required

- Comparing dissolution profiles
  - Evaluate relative in vitro performance resulting from changes in raw materials, formulation and/or manufacturing for both development and commercial products
- Prior to regulatory filing
  - Support study for impact assessment concerning formulation and process variables during product development, scale-up and optimization
    - Formulation & process design, assessment of critical material attributes (CMAs), critical process parameters (CPPs), design space, risks, and development of control strategy, etc
- Post-approval
  - Justify certain levels of product and manufacturing process changes
    - Raw materials, source, formulation, process, scale, equipment and manufacturing site, etc.

# What if $f_2$ assumptions are not satisfied?

- It is critical to identify a right tool/method in order to make meaningful assessment for product quality
  - ➢ Model independent statistical methods
    - $f_2$ bootstrap (Shah, et al. 1998)
    - Tsong's MSD method (Tsong, et al. 1996)
    - SK method (Saranadasa and Krishnamoorthy 2005)
    - Saranadasa's Hotelling's $T^2$ based method (Saranadasa 2001)
    - Intersection union test (Berger and Hsu 1996)

- Simulation studies were performed to evaluate the power and type I error of different approaches.

- Around 80 real cases data were used for assessment.

# Model Independent Statistical Methods

Methods are based on some function of the distance between the profiles at each time point

- $f_2$ – Euclidean distance (pythagorean theorem) based on equal weights (1/p)
- Tsong's MSD and Hotelling's $T^2$– Euclidean distance weighted by standard deviations and correlations
- SK – common distance weighted by complex function of standard deviations and correlations
- Intersection Union Test – maximum distance weighted by standard deviations

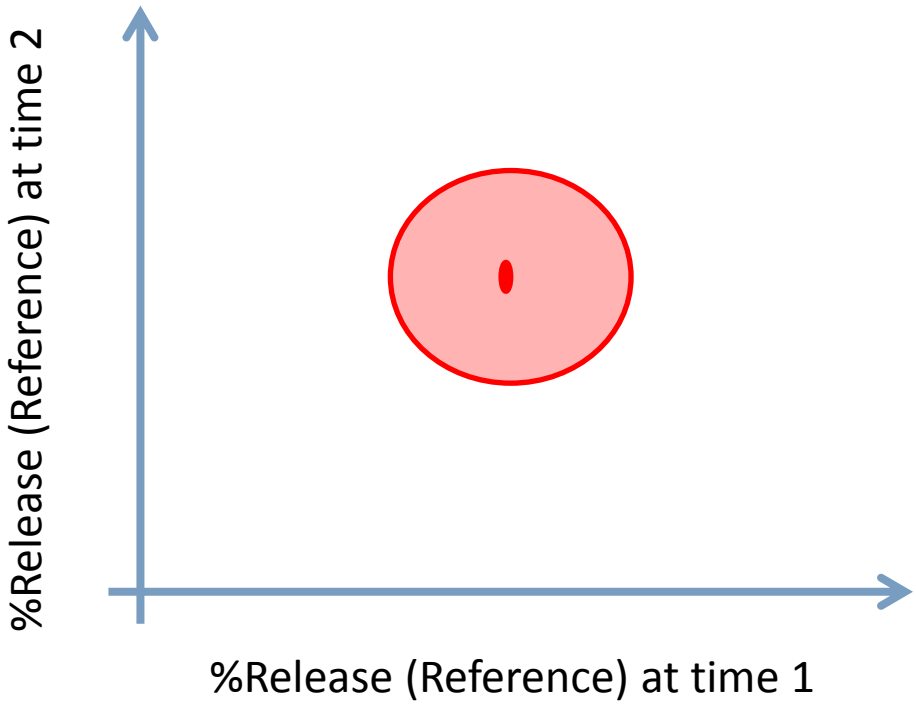
# $f_2$ Similarity Factor

Using 2 time points as an example

Circle of radius ~ $10\sqrt{2}$ centered at average of the reference at the two dissolution time points

If the distance between the averages for the reference and test is inside the circle then the profiles are similar

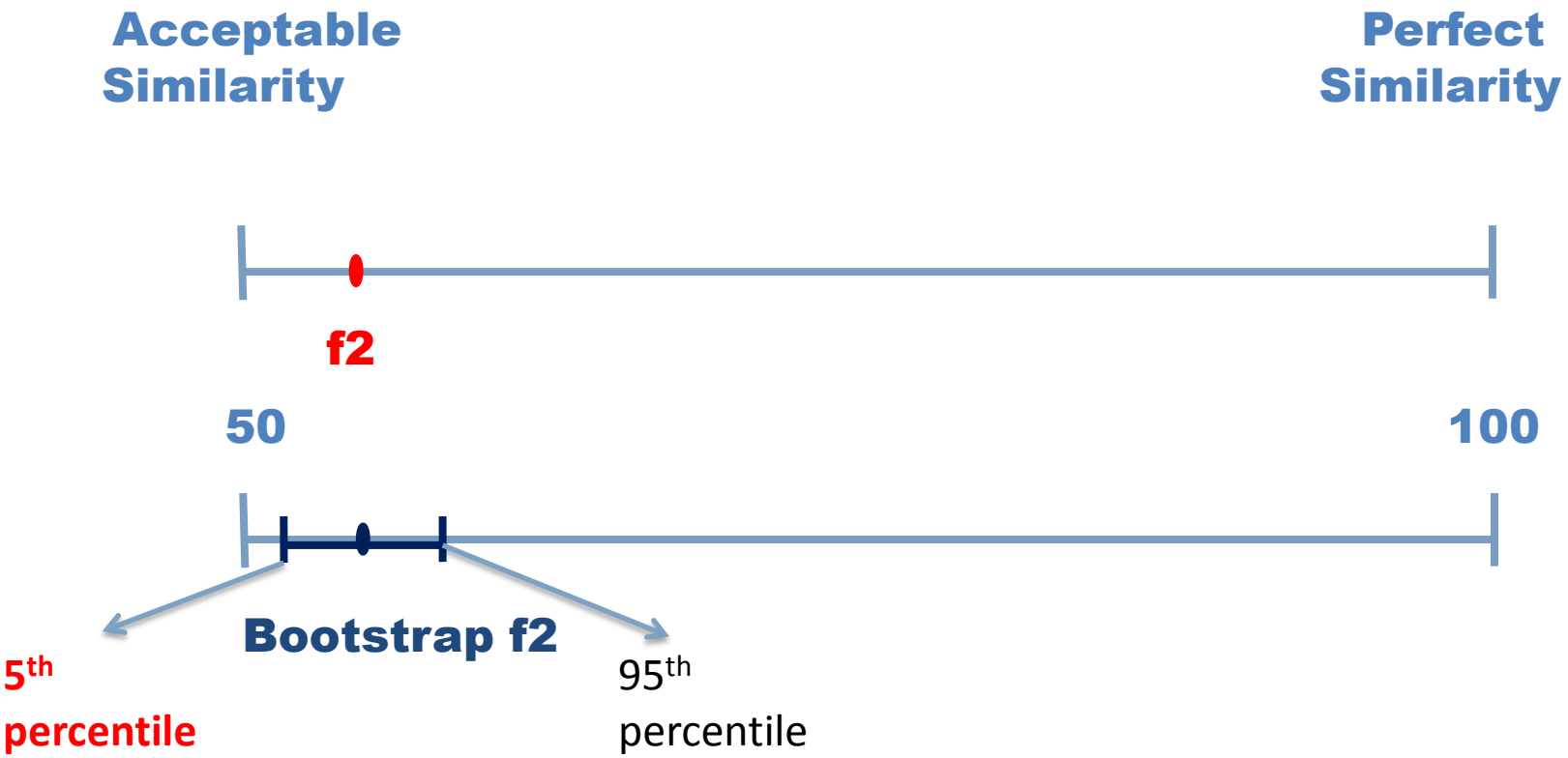
Does not include standard deviation or correlation in the statistic




David J LeBlond, John J Peterson, Stan Altan, "The Posterior Probability of Dissolution Equivalence", MBSW, May 25, 2011

# $f_2$ Similarity Factor and $f_2$ Bootstrap

- $f_2$ transforms a multidimensional region to a single number
- Bootstrap confidence interval includes variation

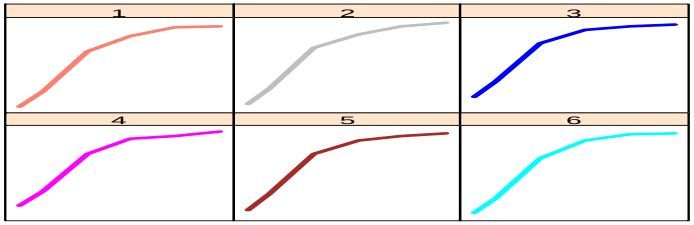



Shah, V. P., Tsong, Y., Sathe, P., and Liu, J. (1998) In Vitro Dissolution Profile Comparison – Statistics and Analysis of the Similarity Factor, f2. Pharmaceutical Research 15(6), 889-886

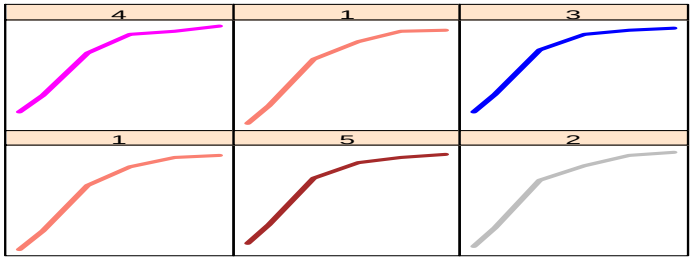
# $f_2$ Bootstrap

Sample with replacement from the original test and reference product profiles separately. Compute $f_2$ for each bootstrap sample. Determine the 5$^{th}$ percentile of the computed $f_2$ values. Similarity is claimed if the 5$^{th}$ percentile of the computed $f_2$ values ≥ 50.

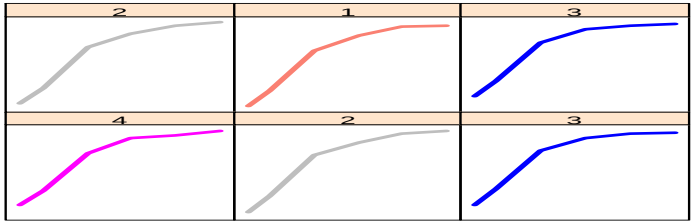
Original data for six tablets




1$^{st}$ Bootstrap Sample




2$^{nd}$ Bootstrap Sample




**Recommended when $f_2$ usage requirements on variation are exceeded (Paixão, et al. 2017, Mangas-Sanjuan, et al. 2016, Wu 2014).**

# Multivariate Statistical Distance Method: Tsong et al. (1996)

Multivariate Statistical Distance (MSD)

$$D_M = \sqrt{(R-T)'\Sigma^{-1}(R-T)}$$

Vector of averages for Test
at each dissolution time point

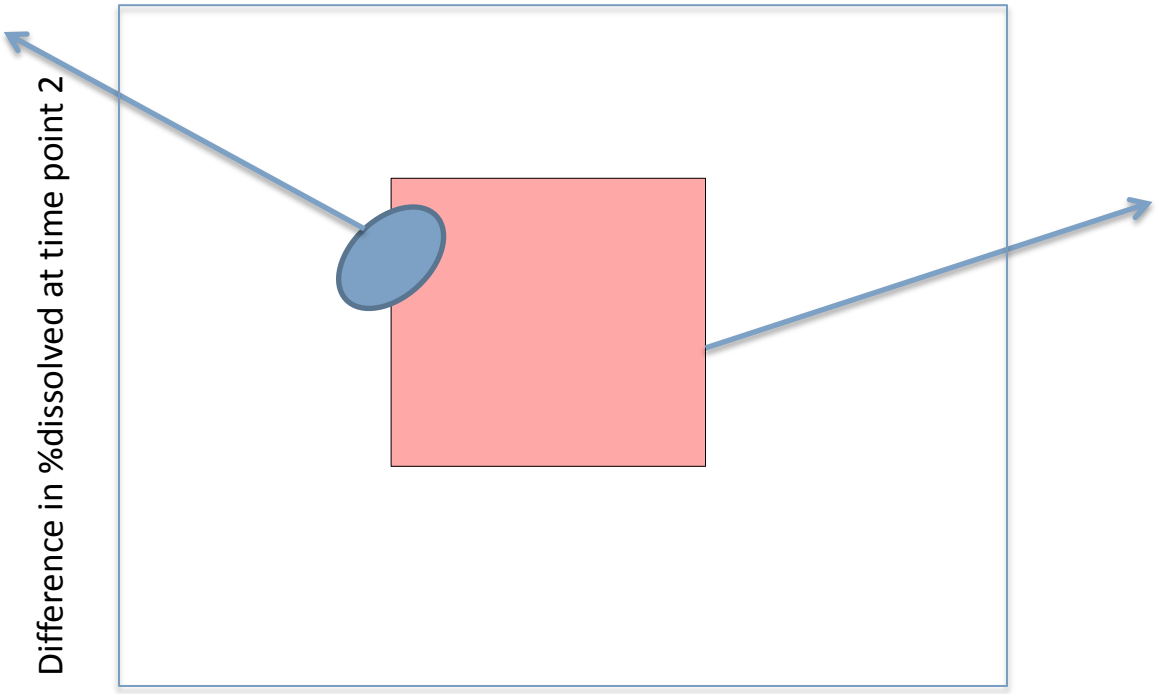
Vector of averages for Reference
at each dissolution time point

Covariance Matrix

Covariance matrix is unit diagonal for $f_2$
Covariance matrix is unstructured for Tsong's MSD method

# MSD: Tsong et al. (1996)

Confidence region of mean difference



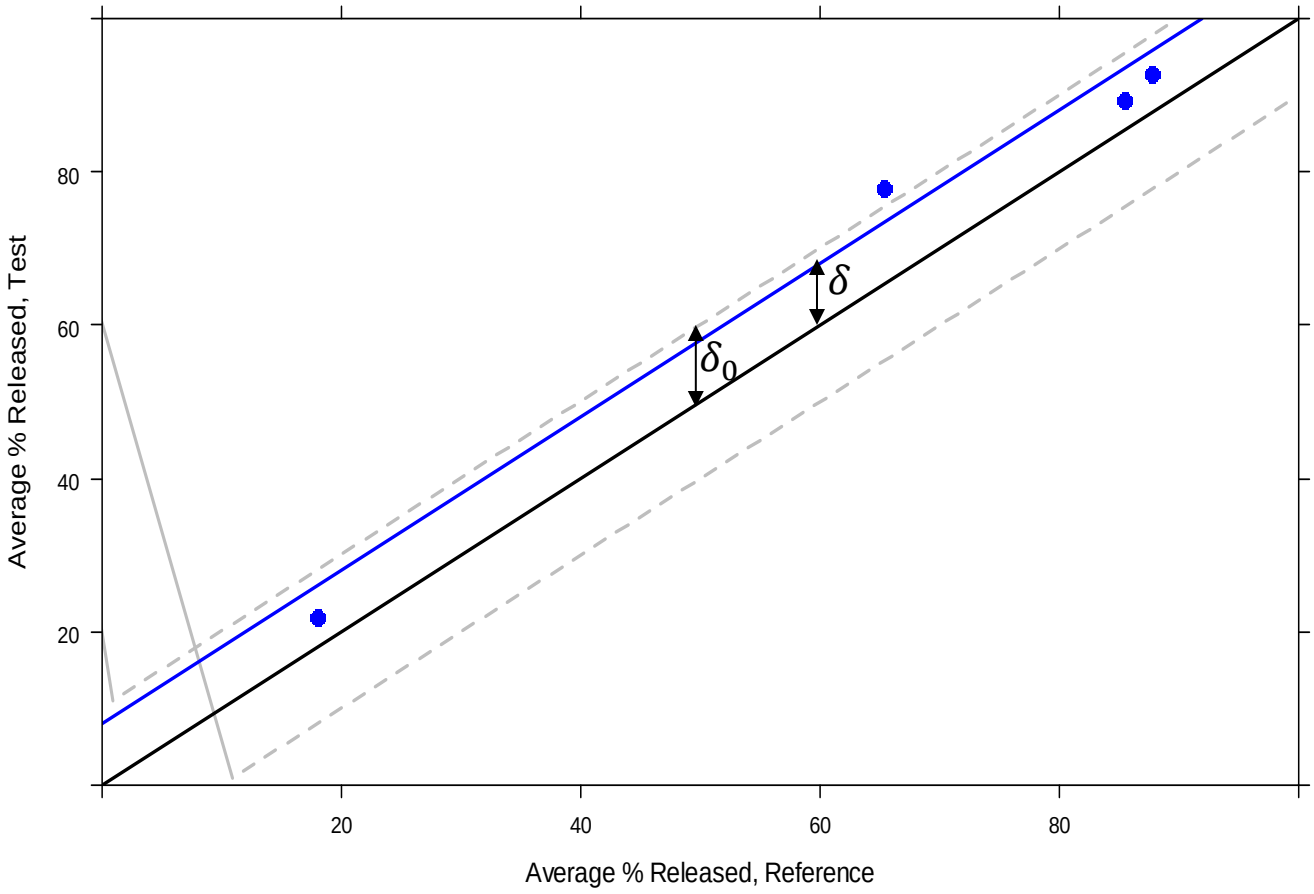

Similarity Region

If the confidence region falls within the similarity region, then similarity.

Tsong Y, Sathe PM, and Shah VP (2003) In vitro dissoltuion profile comparison, pp 456-462, in Encyclopedia of Biopharmaceutical statistics, Marcel Dekker

# Saranadasa and Krishnamoorthy (SK) Method

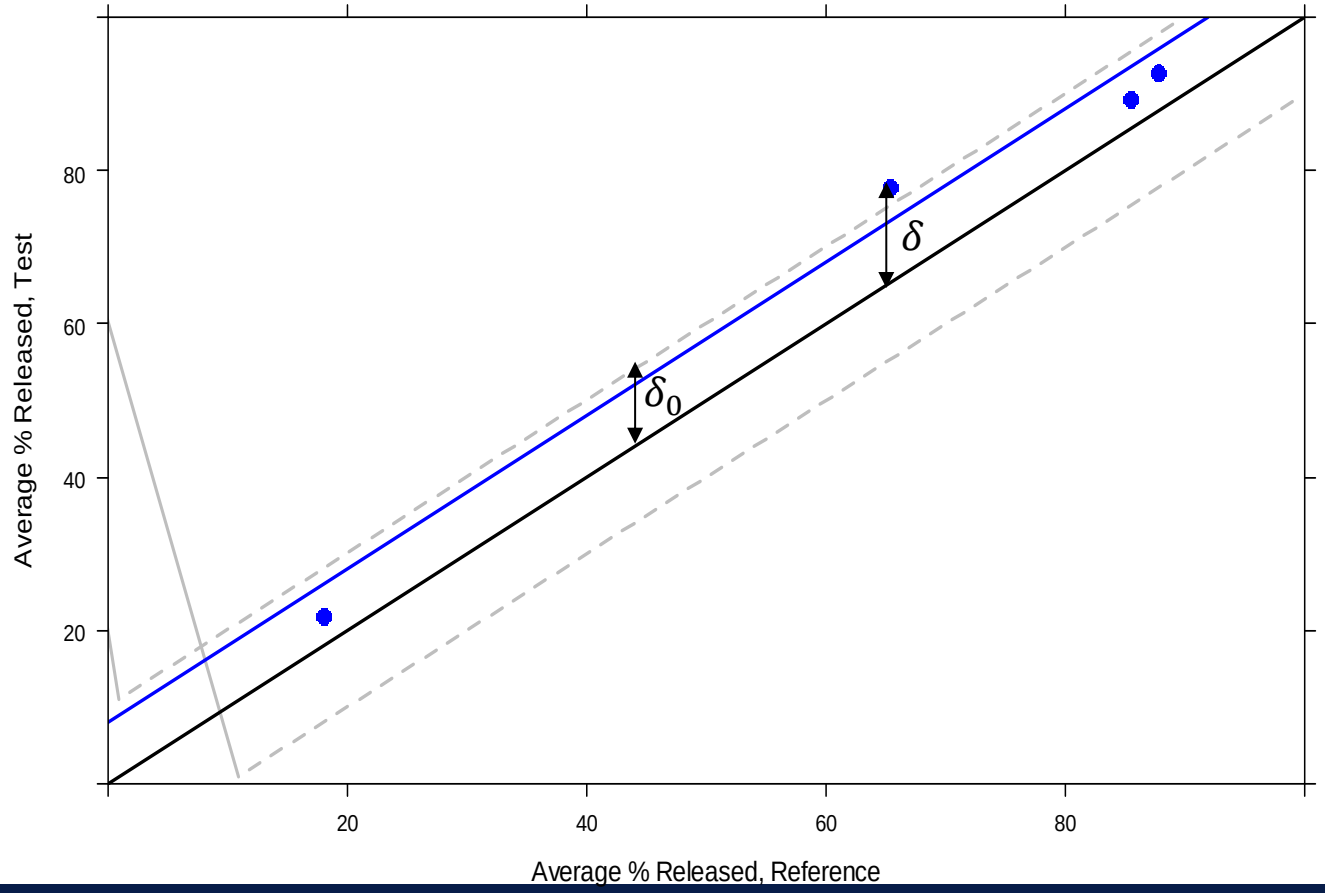
SK Method - Is the distance of the best fitting line, parallel to the 45 degree line, more than 10% away?




SK method assumes two parallel curves.

# Intersection Union Test (IUT) Method

Using a constant threshold of 10%, is the maximum distance from the 45 degree line more than 10% away? Allowable distance threshold can vary by time point

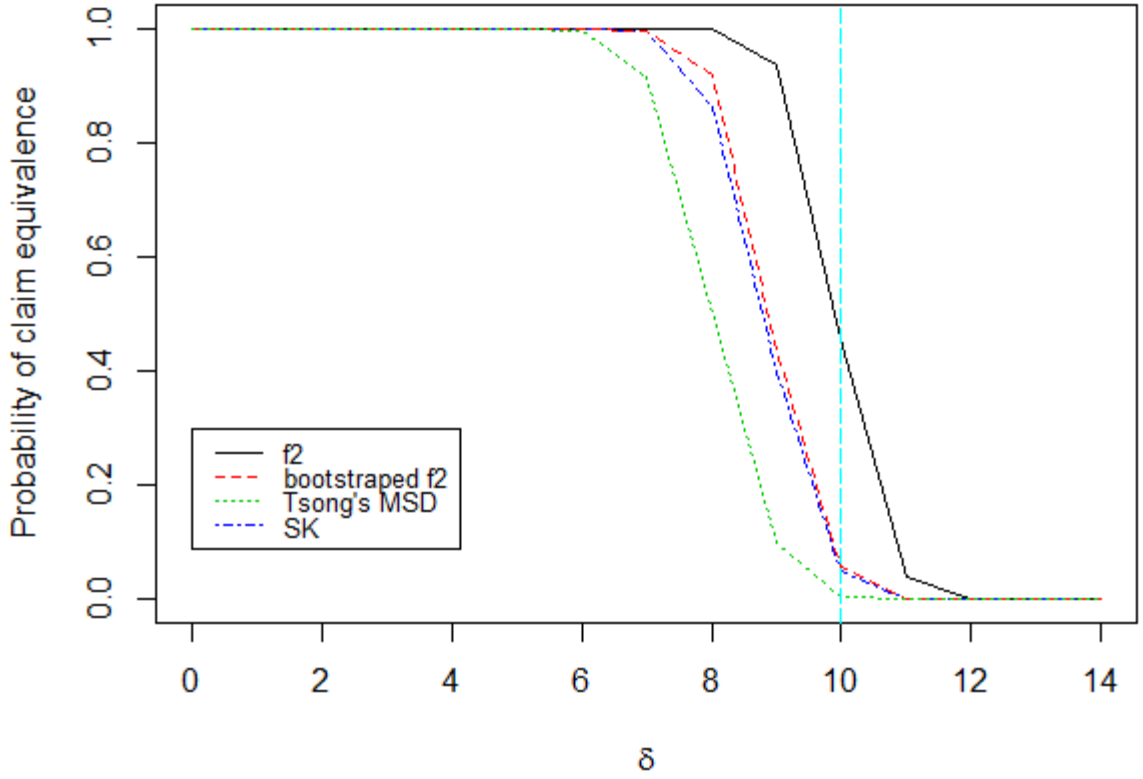



Based on Two One-Sided Test (TOST) for each time point

**IUT is very conservative and has very low power to claim similarity.**

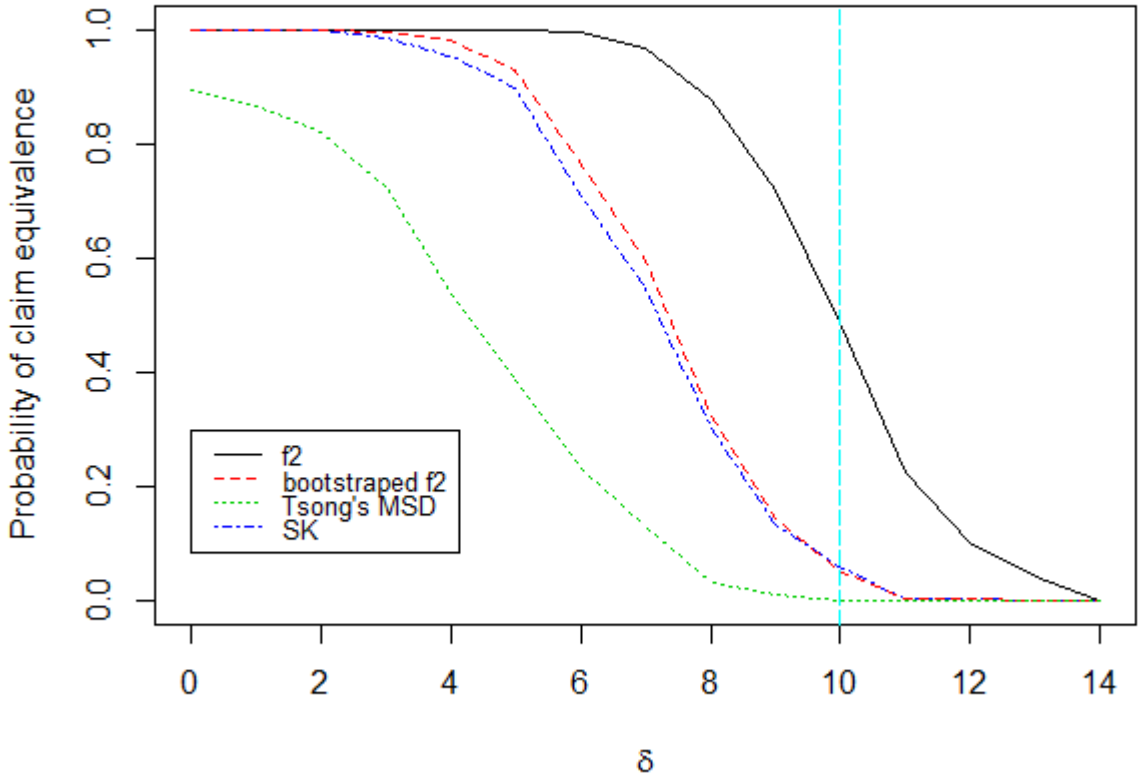
# Simulation Study

- Mean for test profile =(35, 45, 70, 85) and compound symmetry covariance structure with correlation=0.5. Assume equal covariance matrices.
- RSD%=(5.7, 4.4, 2.9, 2.4)% for test profile
- Assume parallelism between reference and test dissolution profiles (δ: constant difference over time points between two profiles)



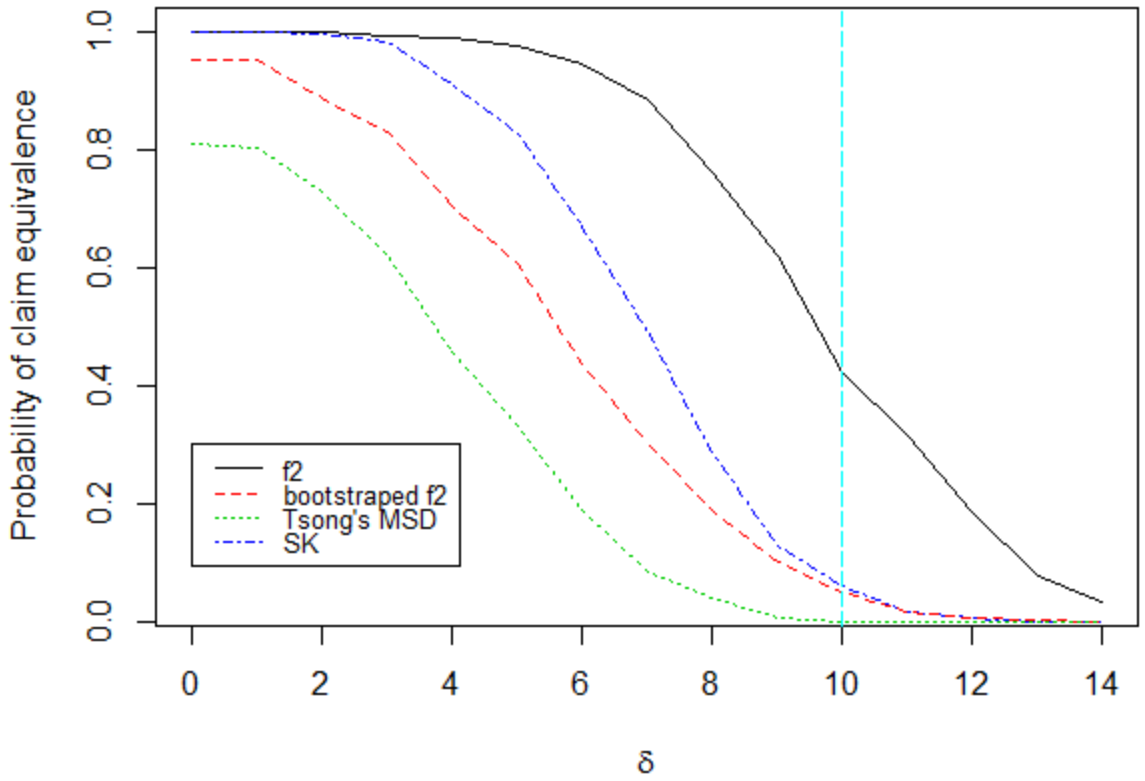
# Simulation Study

- Assume equal covariance matrices and RSD% = (14.3, 11.1, 7.1, 5.8)% for test profile



# Simulation Study

- Assume equal covariance matrices and RSD% = (28.6, 22.2, 7.1, 5.8)% for test profile



# Simulation Study

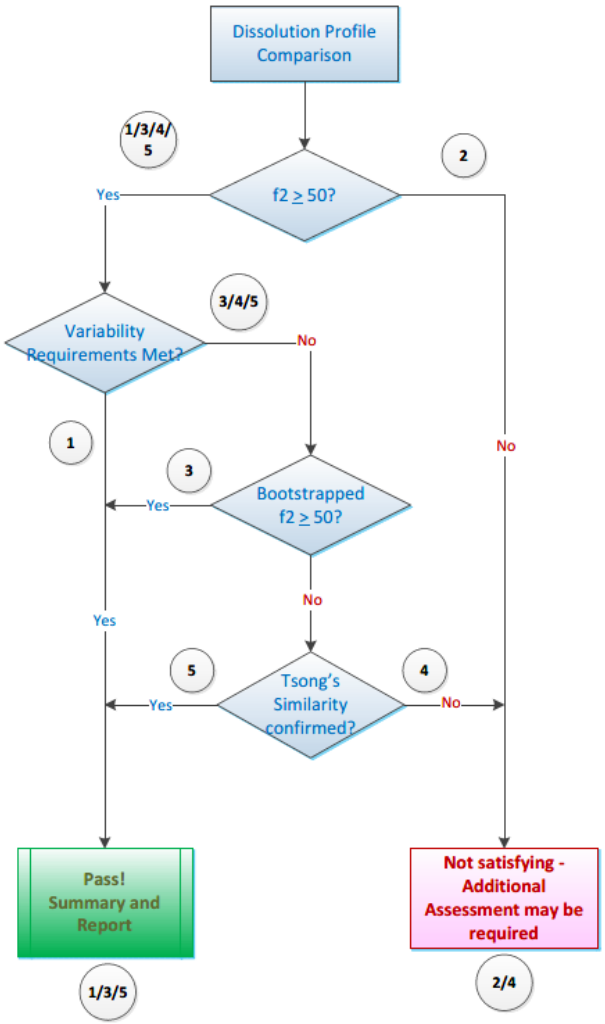
- Assume equal covariance matrices and RSD% = (28.6, 22.2, 7.1, 5.8)% for test profile

| Similarity passing rate | Mean Diff= (28, 22, 10, 5) f2=36.7 | Mean Diff= (18, 13, 8, 5) f2=45.8 | Mean Diff= (12, 10, 9, 5) f2=51.3 | Mean Diff= (10, 10, 3, 3) f2=56.4 | Mean Diff= (5, 4, 3, 3) f2=70.1 |
|---|---|---|---|---|---|
| f2 | 0.001 | 0.203 | 0.586 | 0.822 | 0.982 |
| Bootstrapped f2 | 0 | 0.014 | 0.094 | 0.257 | 0.728 |
| MSD | 0.005 | 0.054 | 0.073 | 0.373 | 0.623 |
| f2>=50 & (Bootstrapped f2 / MSD) | 0.001 | 0.041 | 0.137 | 0.445 | 0.804 |
| SK | 0.410 | 0.625 | 0.529 | 0.974 | 0.978 |
| IUT | 0 | 0 | 0.006 | 0.024 | 0.162 |

# Summary/Remarks

- IUT is very conservative and has very low power to claim similarity.
- SK method has good power to detect similarity and control of type I error when the two dissolution profiles are parallel. But when the underlying assumption of parallelism fails, SK method could be too liberal with high type I error (pass similarity when dissimilar).
- Comparing to SK, f2 bootstrap and MSD method are relatively conservative for highly variable cases.
- MSD is inconsistent in its result comparing to bootstrapped f2. MSD method is likely to be less discriminating and sensitive in some scenarios (e.g. Paixão, et al. 2017 and Mangas-Sanjuan, et al. 2016). But on the other hand, MSD method can also have higher power to detect similarity in some scenarios when the two profiles are similar.
- f2 is a conservatively biased estimator. Although f2 and MSD are testing different hypotheses, comparisons may fail bootstrap and pass MSD in part because of the conservative bias of f2.

# Decision Tree




Scenario 1: f2≥50
Pass f2

Scenario 2: f2<50;
➔Additional assessment

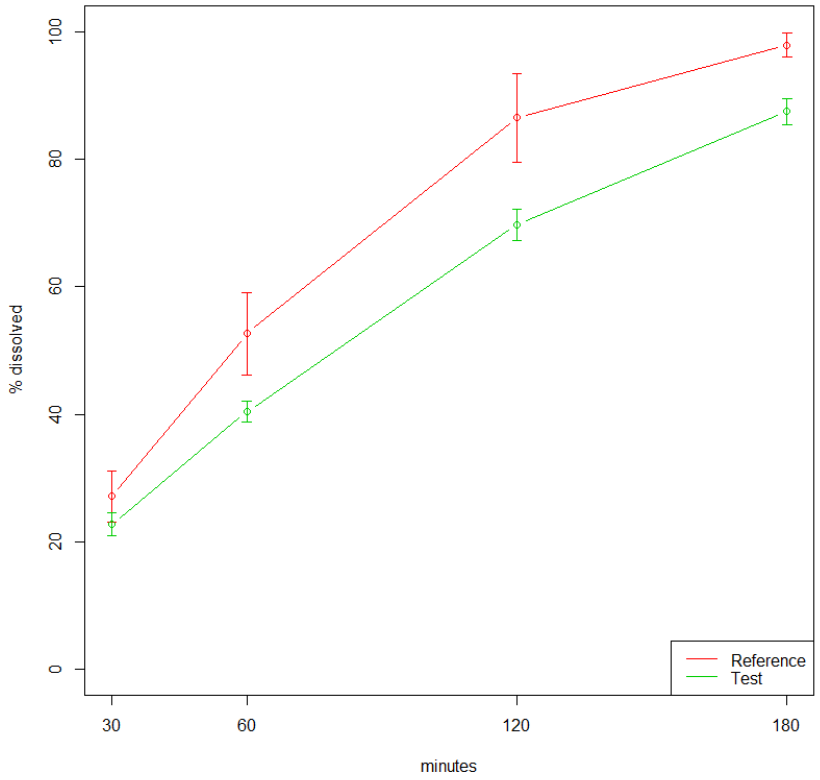
Scenario 3: f2≥50 but can't use f2;
Pass f2 Bootstrap;

Scenario 4: f2≥50 but can't use f2;
Fail f2 Bootstrap and
Tsong's MSD Method;
➔Additional assessment

Scenario 5: f2≥50 but can't use f2;
Fail f2 Bootstrap;
Pass Tsong's Method

Note: Only one measurement should be considered after 85% dissolution of both the products

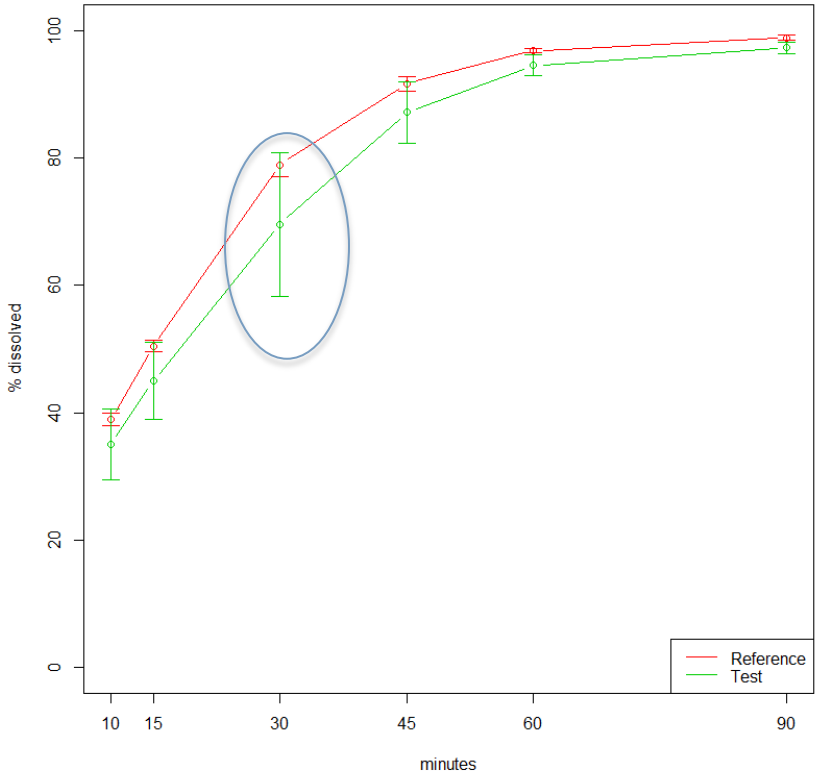
# Real example for Scenario 2




Scenario 2: f2<50;

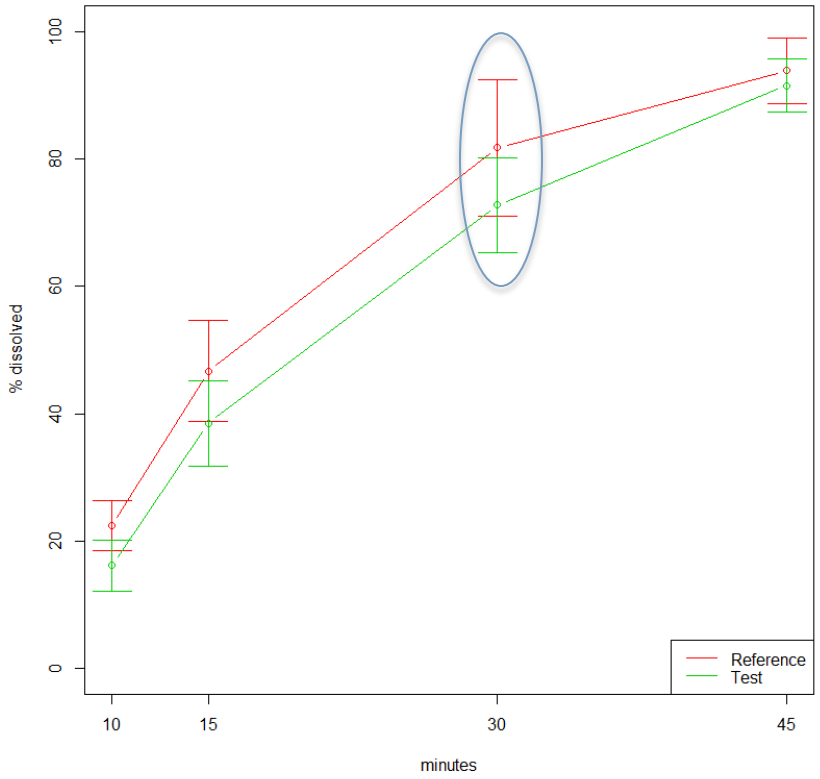
➔Additional assessment

# Real example for Scenario 3




Scenario 3: f2≥50 but can't use f2;
Pass f2 Bootstrap

# Real example for Scenario 5




Scenario 5: f2≥50 but can't use f2;
Fail f2 Bootstrap;
Pass Tsong's Method

# R Shiny App

## Dissolution Profiles Comparison

Choose Ref lot to upload

Browse... Reference.csv

Upload complete

☑ Header

Choose Test lot to upload

Browse... Test.csv

Upload complete

☑ Header

Time Unit

minutes

All time points (eg, 10,20,30)

10,15,30,45,60,90

Number of time points for comparison (>= 3)

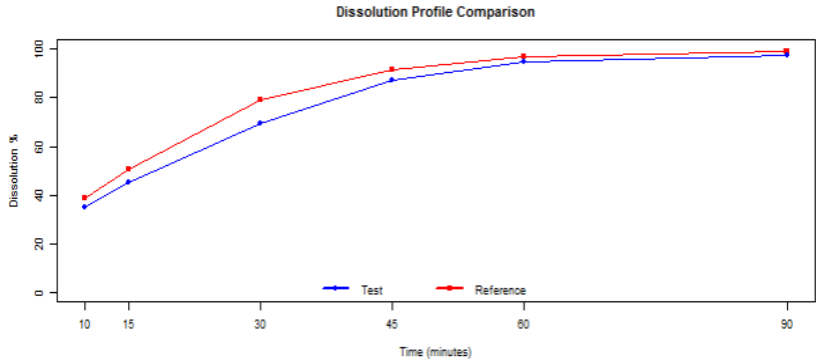
4

Plot Title

Dissolution Profile Comparison

Submit

Generate report | User Instruction




| Methods | Statistics.Value | Reference.Value | Pass.Or.Not | Recommend |
|---|---|---|---|---|
| f2 | 60.22 | >=50 | PASS | 0 |
| f2 bootstrap | 50.66 | >=50 | PASS | 1 |
| Tsong MSD | 3.43 | <= 11.55 | PASS | 0 |

The study belongs to Scenario #3. Similarity is confirmed.

Note: If similarity is confirmed, then the recommended method for similarity assessment will be highlighted yellow with value 1 in the Recommend column.

Warning: The assumptions of f2 method are not satisfied.
The CV for the later time points exceeds 10%.

# References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