# Bootstrap approach for dissolution similarity testing, performance and limitations

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Pfizer WORLDWIDE RESEARCH, DEVELOPMENT AND MEDICAL

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# Introduction

## Outline:

- Use of the f2 for dissolution profile similarity testing and the issue with large within batch (unit-to-unit) variability

- Introduction to bootstrapping as a statistical technique

- Applications of bootstrapping for dissolution profile similarity testing

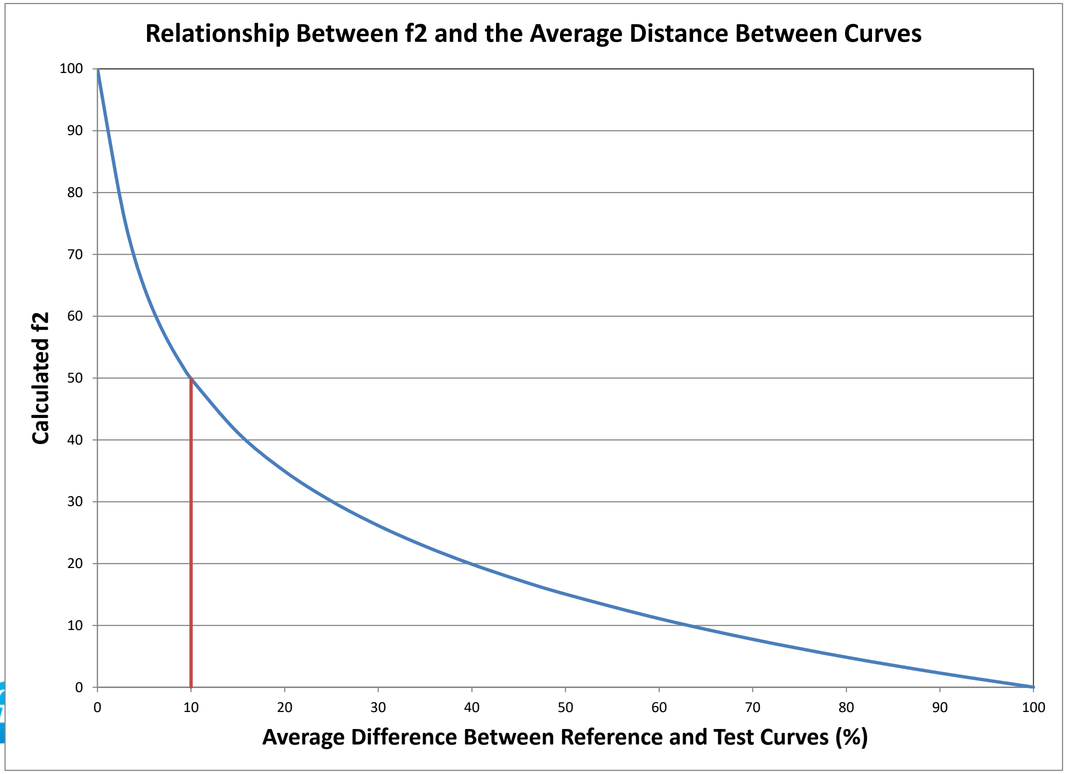
- Summary of Pros/Cons of using bootstrapping

# Dissolution Profile Similarity Comparison

## Most Commonly Used Test – $f_2$

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

**Moore, J. W. and H. H. Flanner, 1996, "*Mathematical Comparison of Dissolution Profiles*", *Pharmaceutical Technology*, 20 (6):64-74.**

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# Dissolution Profile Similarity Comparison

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

**Shortly after Moore and Flanner published their article, it was suggested that the $f_2$ statistic might be problematic when the within batch variability was high due to there being too much uncertainty in the estimates of the means.**

# $f_2$ Guidance for Immediate Release Products

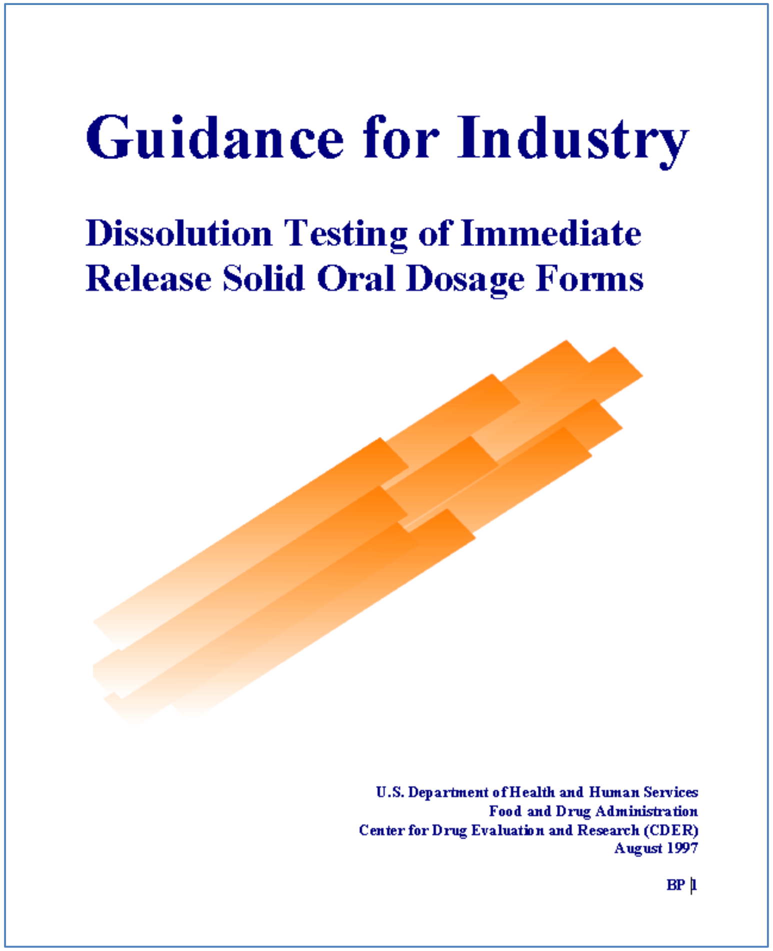
## Varies by Country

| Criteria | USA | EMA | Brazil | Canada |
|---|---|---|---|---|
| # of time points | Minimum of 3 | Minimum of 3 (excluding 0) | Minimum of 5 (excluding 0) | Adequate sampling until 90% of drug is dissolved or an asymptote is reached. |
| Last time point | When both Reference and Test batches have reached 85% released | When either the Reference or the Test batch reaches 85% released | When both Reference and Test batches have reached 85% released | When both Reference and Test batches have reached 85% released |
| **Limits on variability** | RSD < 20% at early time points and < 10% at all other time points | RSD < 20% at first time point and < 10% at all other time points | RSD < 20% at early time points (first 40%) and < 10% at all others | RSD < 20% at early time points and < 10% at all other time points |

# Alternatives to $f_2$ when variability criteria not met

**Bootstrapping as an alternative does not appear in any of the regulatory guidances.**

- Shah, V.P., Y. Tsong, P. Sathe and J.P. Liu, 1998, “In Vitro Dissolution Profile Comparison – Statistics and Analysis of the Similarity Factor, $f_2$”, Pharmaceutical Research, Vol. 15, No. 6, pp 889-896.


Guidance for Industry

Dissolution Testing of Immediate Release Solid Oral Dosage Forms

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 1997

BP 1

# Bootstrapping

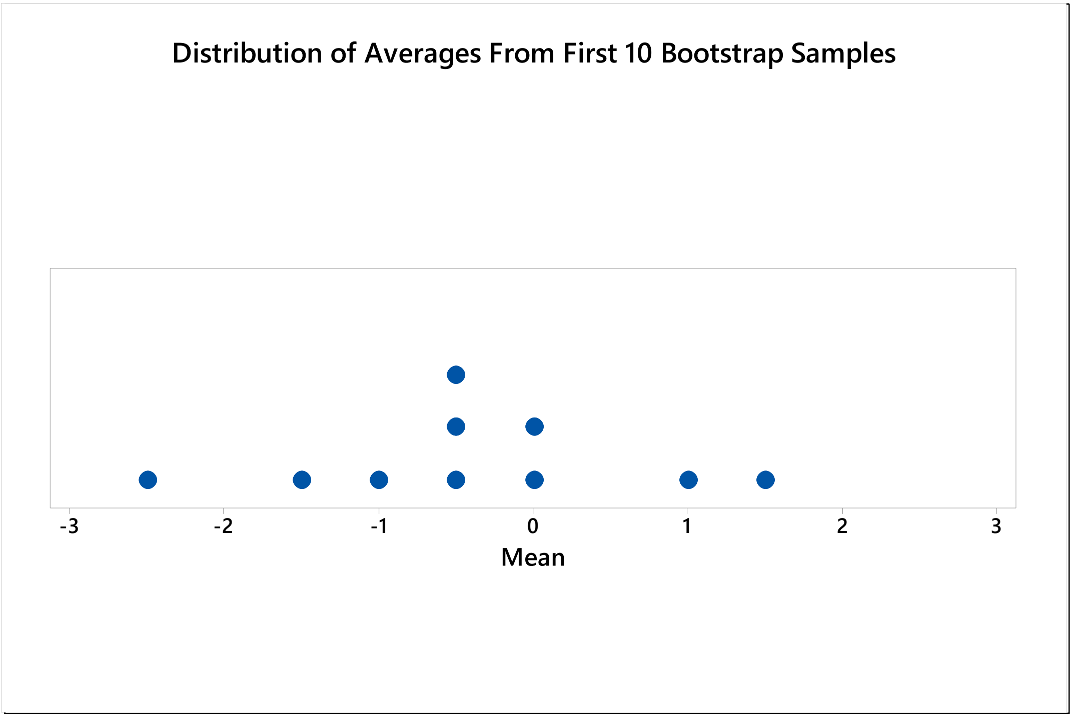
- Bootstrapping is a statistical technique for generating an estimate of the sampling distribution of a statistic that was introduced by Bradley Efron in 1979 *("Bootstrap Methods: Another Look at the Jacknife"*; The Annals of Statistics, Vol. 7, No. 1, pp 1-26.)

- Technique based on using available data to resample from the data with replacement to generate the sampling distribution of a statistic where the theoretical distribution is complex or unknown

**Bootstrapped $f_2$** – generate distribution of $f_2$ values based on observed data; if lower 5th percentile is greater than 50 – declare similarity

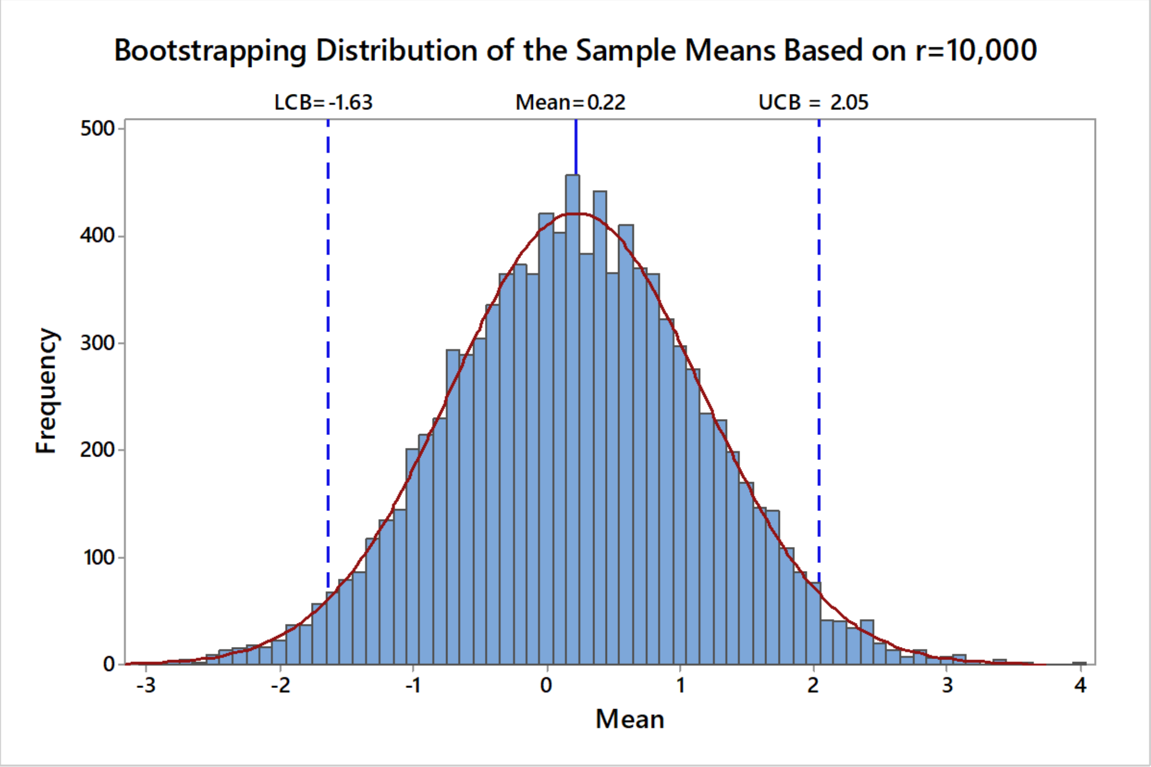
# Bootstrap Example – Confidence Interval for Sample Mean

- A random sample of 24 observations are taken from a Normal distribution with mean 0 and a standard deviation of 5.
- Want to construct a 95% confidence interval about the mean
- To construct a bootstrapped confidence interval for the mean.
  - Sample 24 observations with replacement from the original data set.
  - Calculate the average for each random sample
  - Do many times



# Bootstrapping Example

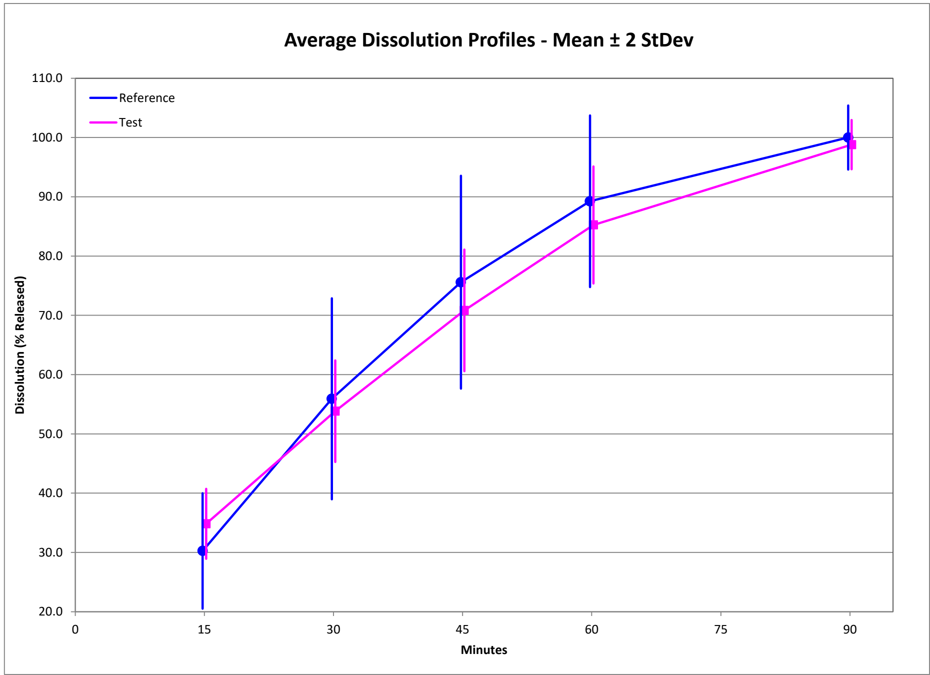
- Repeat the process a large number of times (say, 10,000). The resulting distribution of the sample means appears below.
- For this example, the bootstrapped 95% confidence interval is determined by identifying the points corresponding to the $2.5^{th}$ and $97.5^{th}$ percentiles (dashed lines below at -1.63, 2.05)



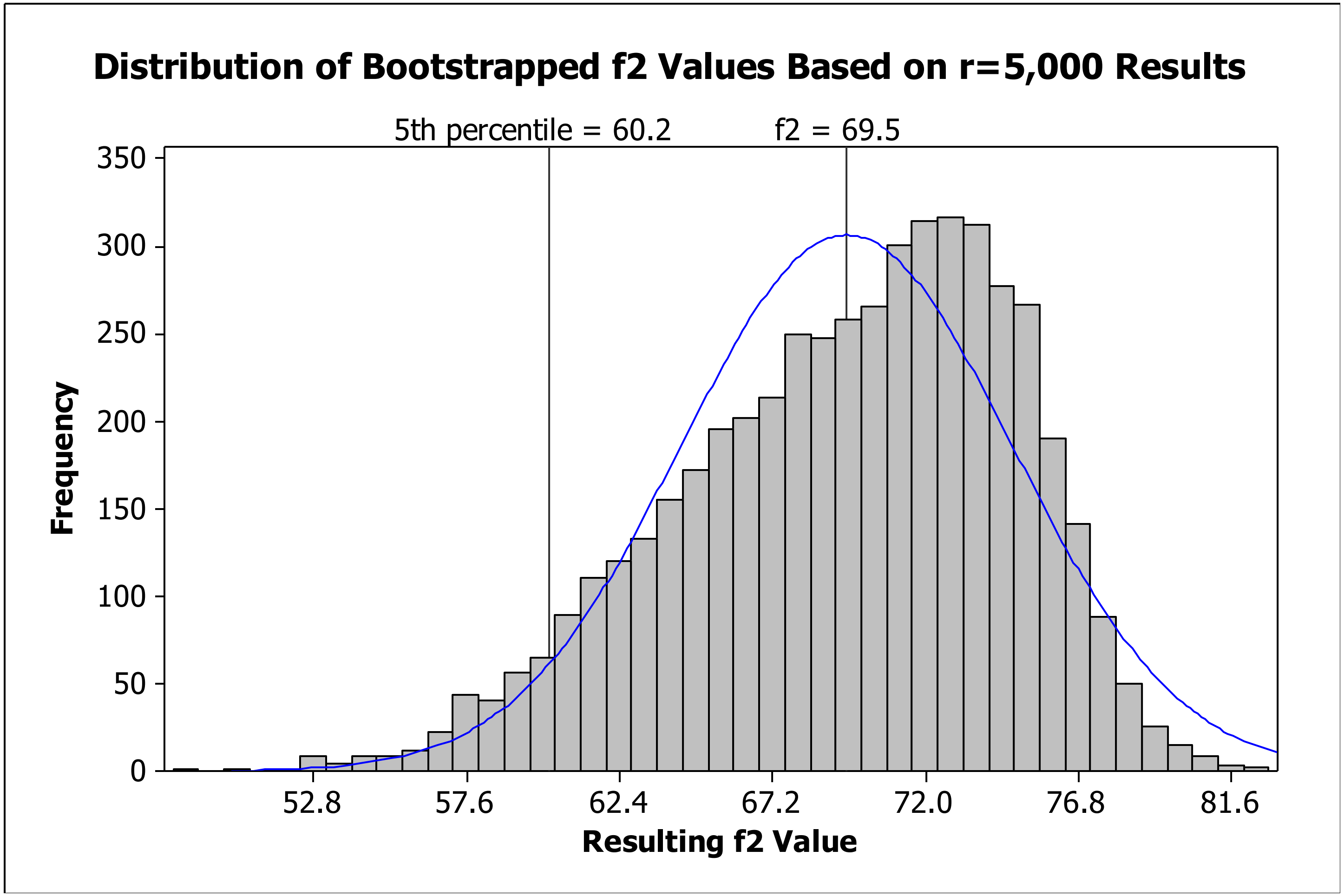
# Bootstrapped $f_2$ analysis from product transfer

| Dissolution Time Points (min) | Reference Sample | | Test Sample | |
|---|---|---|---|---|
| | Mean | RSD | Mean | RSD |
| 15 | 30.3 | 16.1 | 34.8 | 8.5 |
| 30 | 55.9 | **15.2** | 53.8 | 8.0 |
| 45 | 75.6 | **11.9** | 70.8 | 7.2 |
| 60 | 89.3 | 8.1 | 85.3 | 5.8 |
| 90 | 100 | 2.7 | 98.8 | 2.1 |

**Variability of reference sample at 30 and 45 minute dissolution time points is greater than that recommended by most regulatory agencies**



# Bootstrapped $f_2$ analysis from product transfer



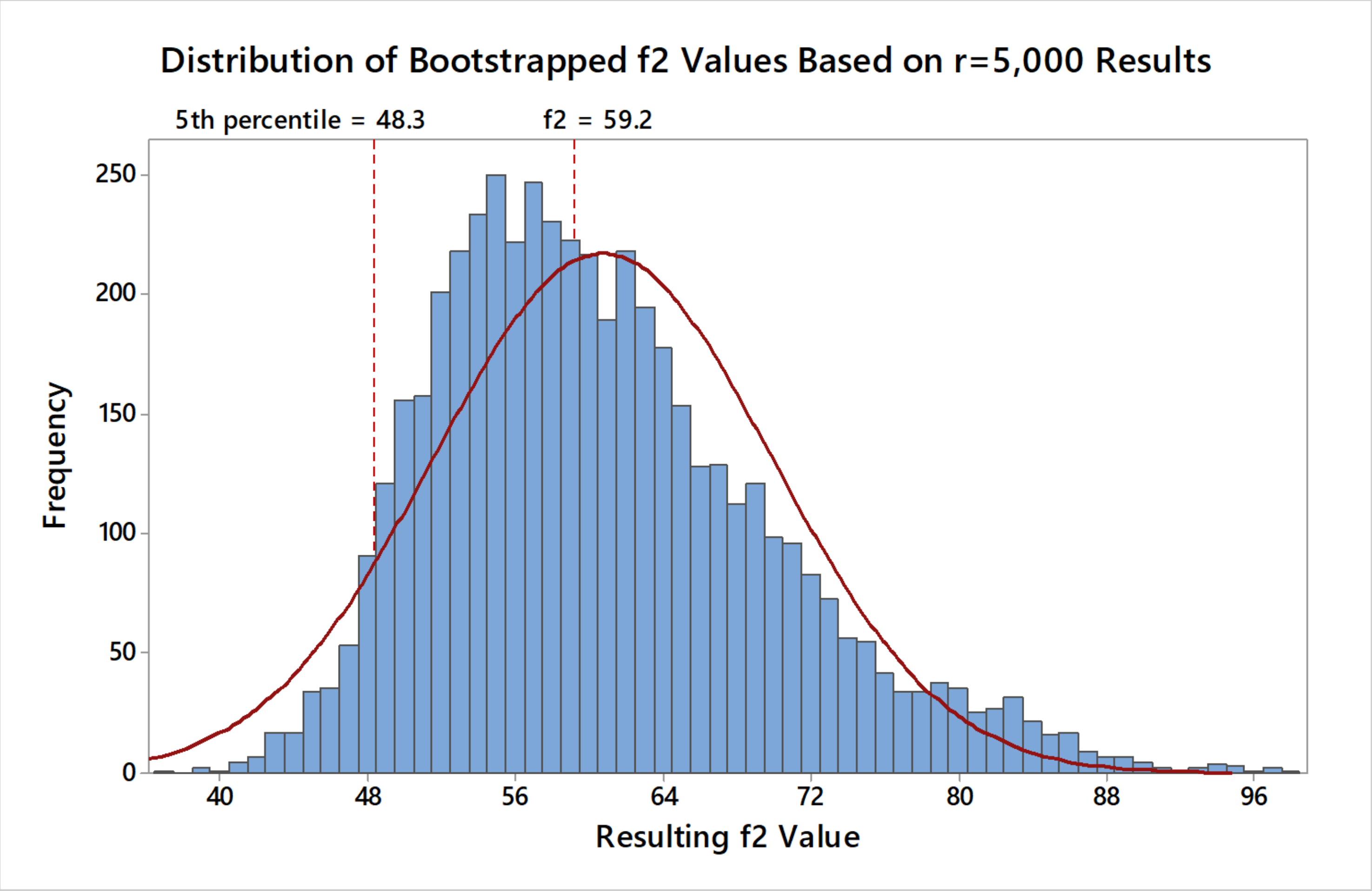

**Bootstrapped $f_2$ $5^{th}$ percentile > 50**

# Example with large variability

| Dissolution Time Points (min) | Reference Sample | | Test Sample | |
|---|---|---|---|---|
| | Mean | RSD | Mean | RSD |
| 10 | 47.2 | 13.8 | 37.3 | **28.6** |
| 15 | 60.9 | 10.0 | 52.7 | **20.0** |
| 20 | 70.0 | 8.4 | 64.0 | **13.5** |
| 30 | 80.6 | 6.1 | 77.8 | 7.2 |
| 45 | 89.5 | 3.1 | 88.5 | 3.2 |

**Variability of test sample at multiple time points is greater than that recommended by most regulatory agencies**

# Example with large variability




**Bootstrapped $f_2$ 5$^{th}$ percentile < 50**

# Summary – Bootstrapped $f_2$ analysis

**Bootstrapped $f_2$ – is a statistically acceptable and valuable approach for comparing dissolution profiles**

**Pros:**

- well understood technique which has been around for a long time
- provides a simple answer which most people can conceptualize
- does not require any distributional assumptions
- software is available for doing the simulations (DDSolver)

# Summary – Bootstrapped $f_2$ analysis

**Bootstrapped $f_2$** – is a statistically acceptable and valuable approach for comparing dissolution profiles

**Cons**:

- does not address 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
- may be conservative???

# Conclusion

***Thank you!***

**Any Questions?**