Quantitative Methods for Determining Equivalence of Particle Size Distributions

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 2: Advanced Analytical and Statistical Methods for Assessing Particle Size Distributions

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Background

- Considering that particle size distribution (PSD) is a valuable indicator for characterizing physicochemical properties of a material, the PSD comparisons can be a useful tool for bioequivalence (BE) assessment.

- The FDA has recommended equivalence approaches to compare PSD of generic and reference listed drug (RLD) products when appropriate.

Learning Objectives

- This presentation aims to provide:
  - An overview of the recommended quantitative approaches for determining equivalence of PSD
  - Hypothetical case examples of equivalence assessment of complex PSD (e.g., multimodal)

General Framework

Monomodal

Complex (e.g., multimodal)

Mean/Width (e.g., D50/SPAN)

Profile comparison (e.g., Earth mover's distance)

Population Bioequivalence (PBE)

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$$\frac{(\mu_T-\mu_R)^2+(\sigma_T{}^2-\sigma_R{}^2)}{\sigma_R{}^2}\le\theta \quad \textbf{or} \quad \frac{(\mu_T-\mu_R)^2+(\sigma_T{}^2-\sigma_R{}^2)}{\sigma_{T0}{}^2}\le\theta$$

Where,

$\mu_T-\mu_R$: Mean difference of T (log scale) and R (log scale) products

$\sigma_T{}^2, \sigma_R{}^2$: Total variance of T and R products

σ_{TO} : Regulatory constant (σ_{TO}= 0.1)

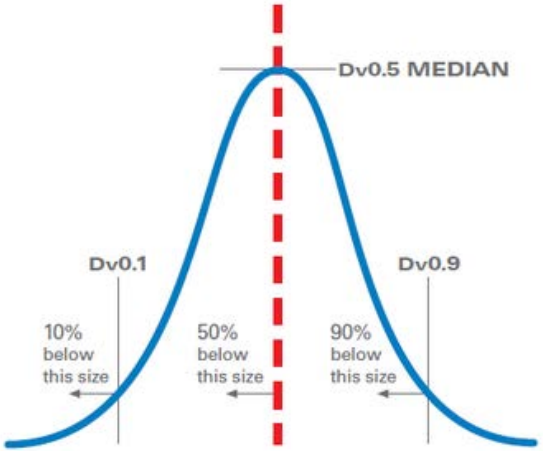
θ_p: Regulatory constant (θ_p= 2.0891) calculated as following:

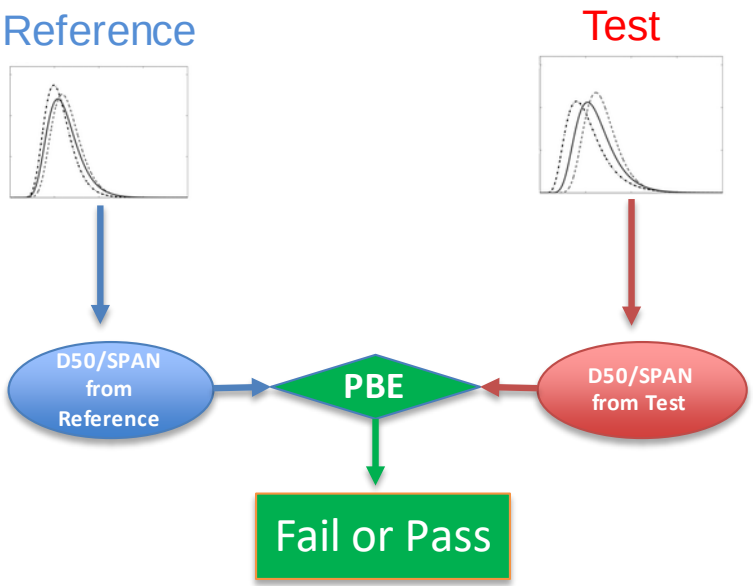
$$\frac{[\ln(1.11)]^2+0.01}{0.1^2}=2.089$$

Note: the BE criterion (θ_p) is determined from the log-transformation of the data.

Monomodal PSD

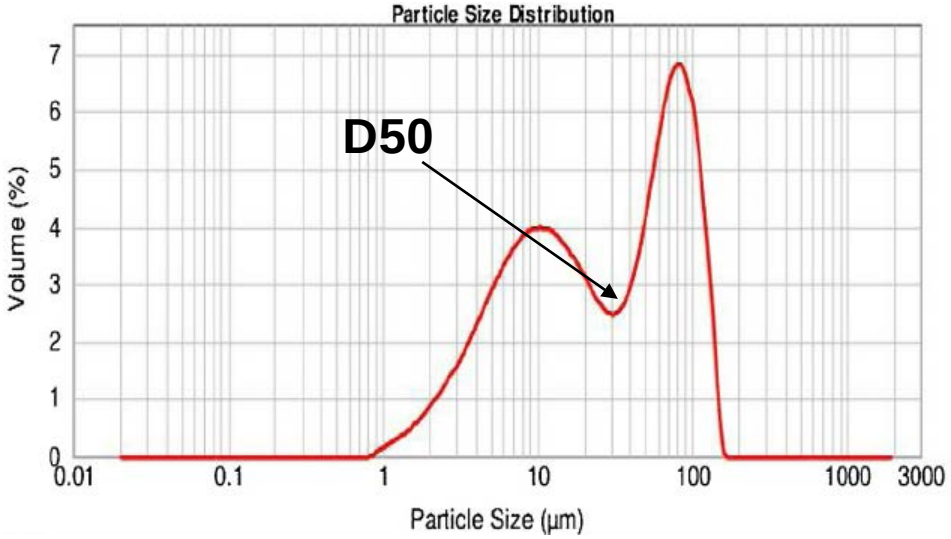
D50: Median
SPAN: (D90-D10)/D50





Complex PSD

For a complex (e.g., multimodal) PSD profile, D50 and SPAN may not carry most important information.

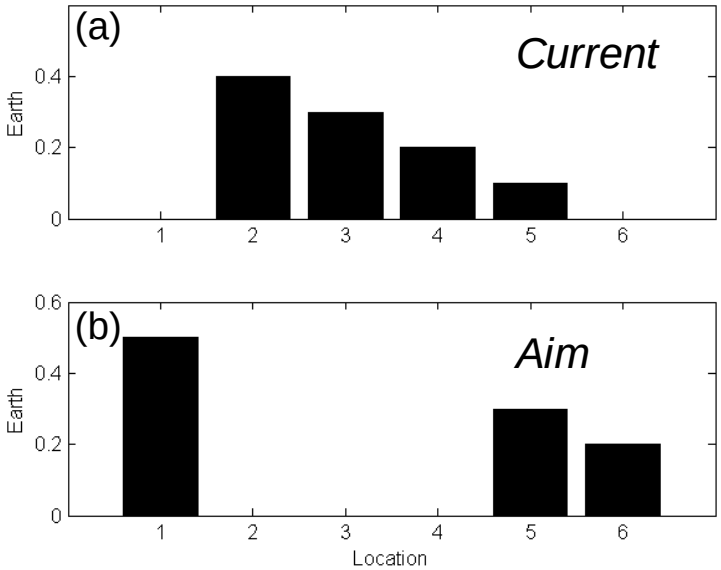


For this type of PSD, whole profile comparison may be needed. One algorithm recommended in guidance* is the earth mover's distance (**EMD**) for profile comparison.

*Draft Guidance on Cyclosporine Emulsion: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine_ophthalmic%20emulsion_RLD%20050790_RV09-16.pdf

What is EMD?

EMD was derived from a transportation question:



What is the minimum cost of moving earth from the '*Current*' pile to the '*Aim*' pile?

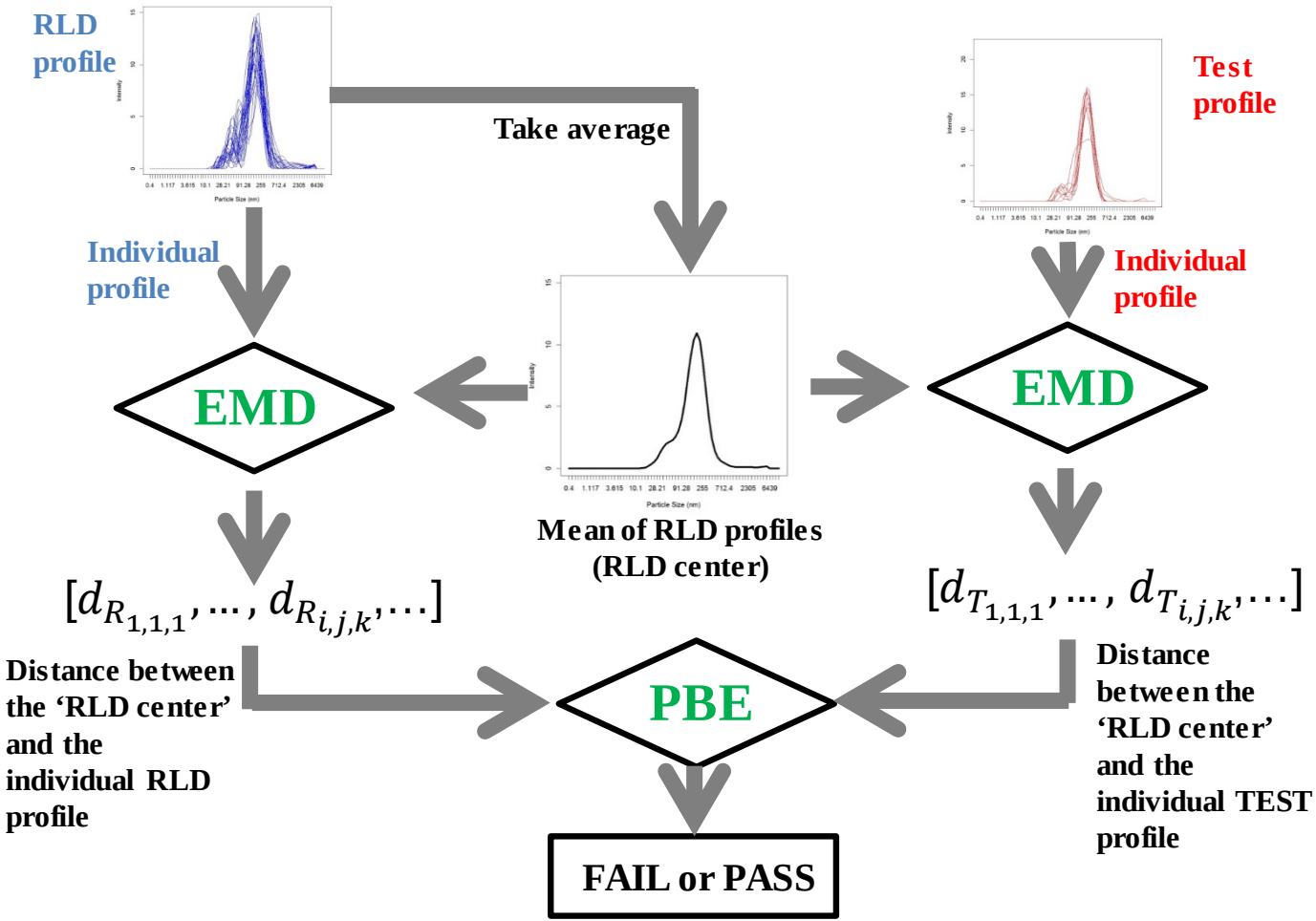
Note:

1. The cost includes 'amount of earth moved' and 'moving distance.'
2. If the earth pile is considered as a histogram, the EMD can be used to assess the difference between histograms.

EMD for profile comparison

- The EMD is a widely used tool in pattern recognition, machine learning, computer vision, etc., especially for discriminant analysis of the histogram-type data.
- PSD (intensity) is the typical histogram data.
- The EMD can be used to compare the PSD profiles for equivalence test.

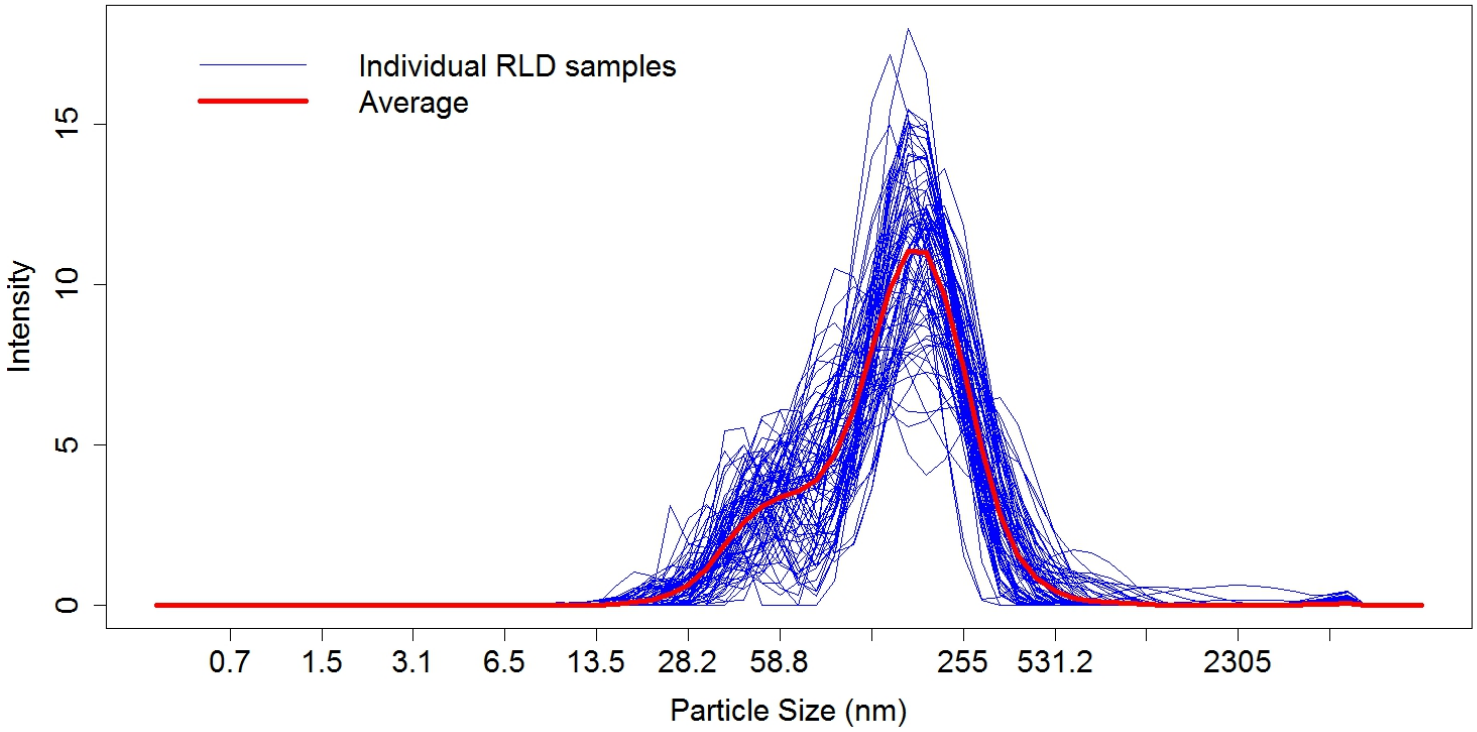
Equivalence approach based on EMD



A Hypothetical Study for the Equivalence Testing of Complex PSD

- Data
  - RLD
  - Negative control
  - Test sample X
  - Test sample Y
- Equivalence tests
  - RLD vs. RLD
  - RLD vs. Negative control
  - RLD vs. Test sample X
  - RLD vs. Test sample Y

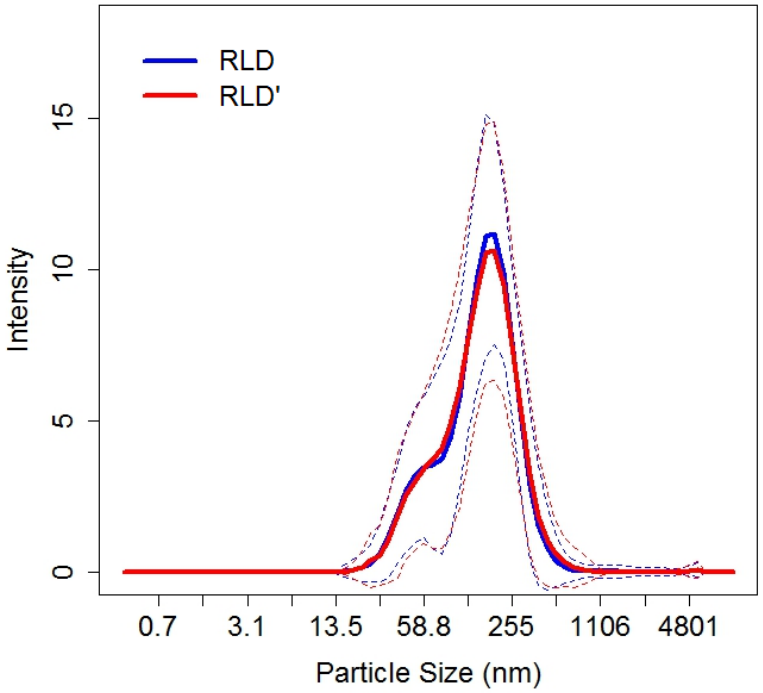
PSD profiles from a RLD product

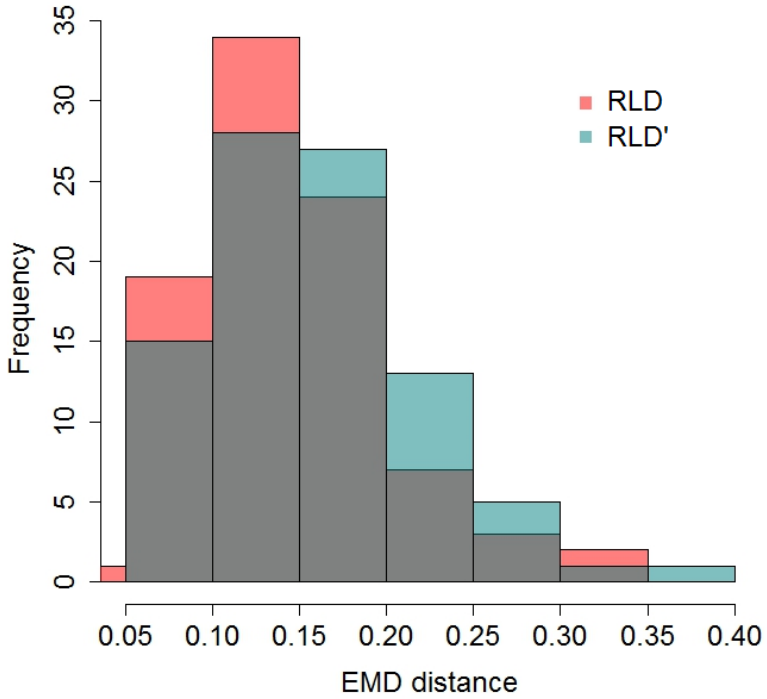


Data for Hypothetical Study

- RLD – 8 lots
- Negative control – 3 lots
- Test sample X – 3 lots
- Test sample Y – 3 lots

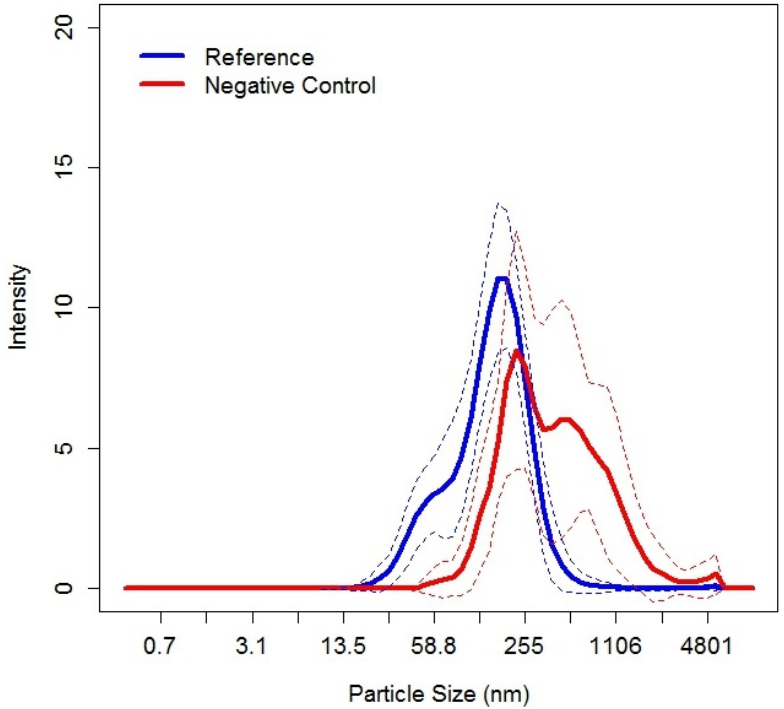
RLD vs. RLD

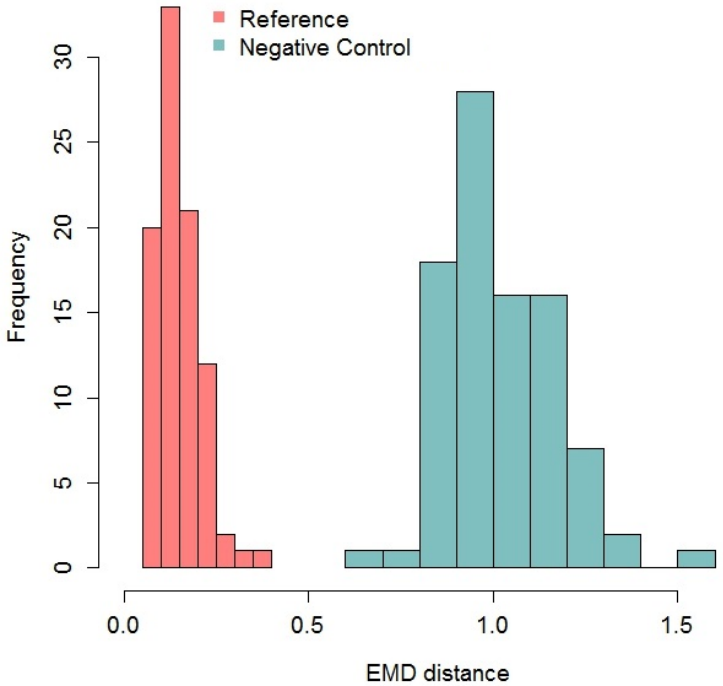




The PBE is applied to the EMD distances from two groups, concluding equivalence.

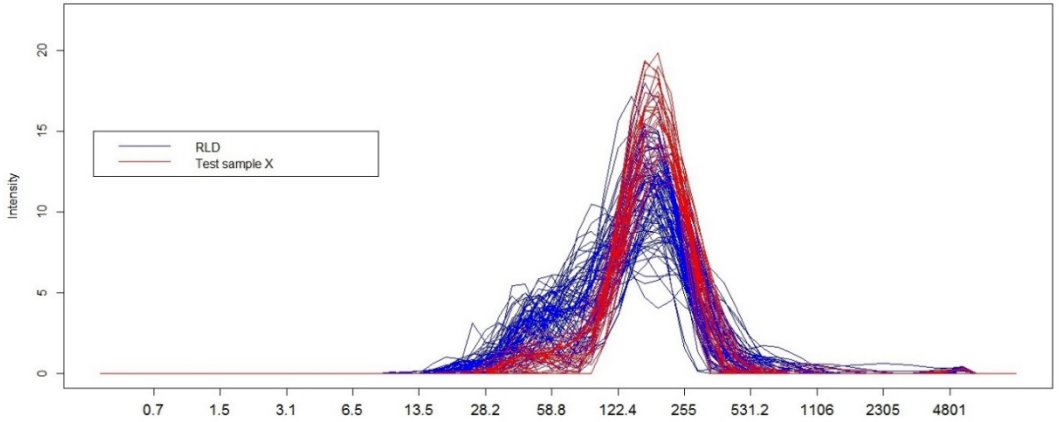
RLD vs. Negative Control



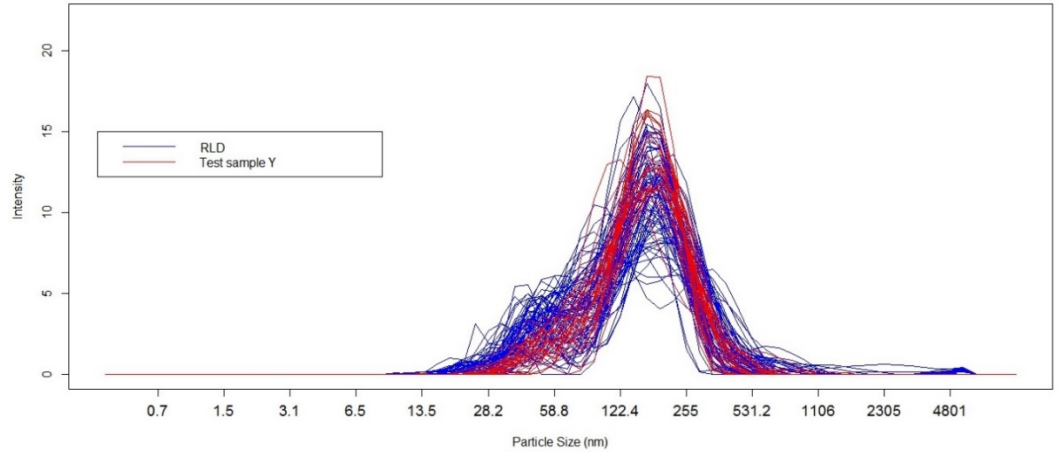


The PBE is applied to the EMD distances from two groups, concluding that equivalence can not be established.

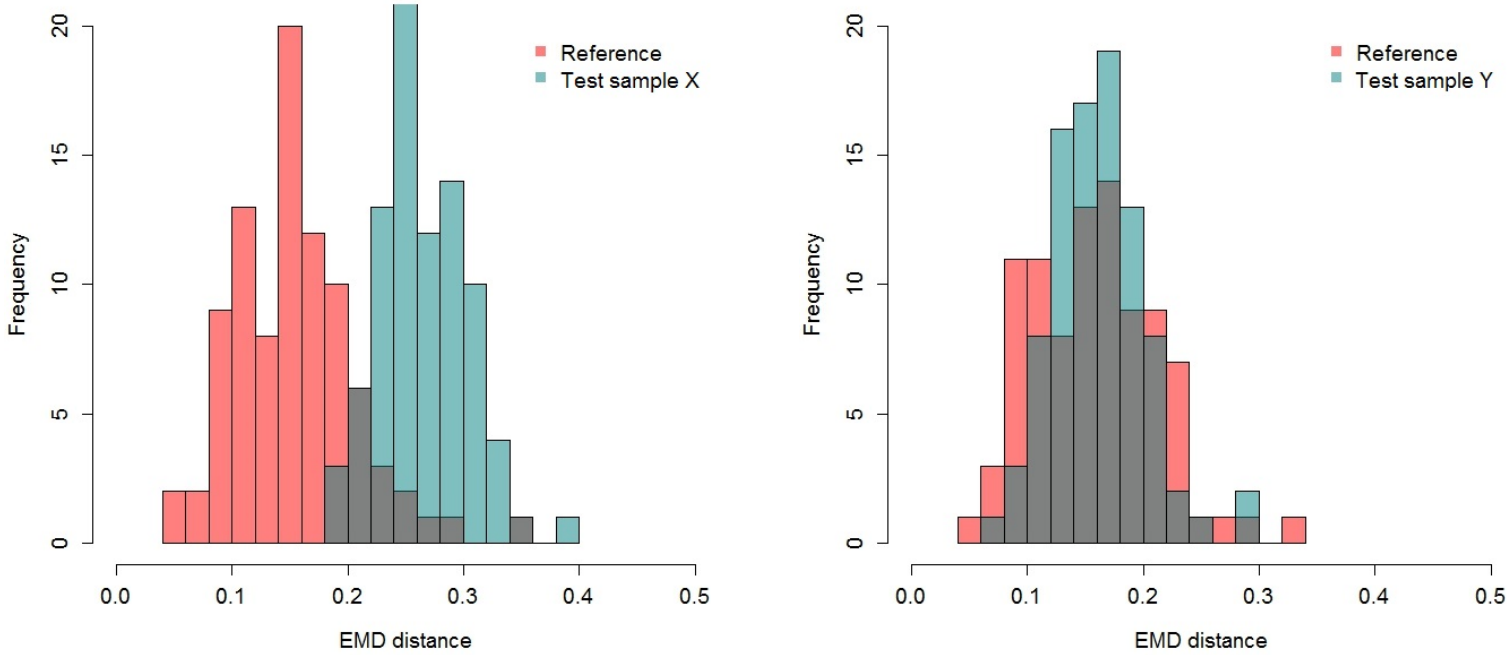
Test sample X



Test sample Y



EMD analysis for Test samples X and Y



The PBE tests show that equivalence can be established for the test sample Y, but not for the test sample X.

Conclusions

- D50/SPAN can provide critical information of a monomodal PSD for equivalence test, but may carry less-important information for the complex PSD.
- Profile comparison is considered as an effective method to assess the difference between complex PSD profiles.
  - An EMD-based equivalence approach can be used for the complex PSD profile comparison between a generic product and the RLD product.
  - The method validations show that the EMD approach is able to effectively reject the unaccepted products (e.g., negative control), and pass the accepted products (e.g., reference itself).

Challenge Question #1

D50/SPAN can be used to compare the whole profile of PSD. Is it correct?

A. Yes

B. No

Challenge Question #2

Which of the following statements is NOT true?

A. The PSD comparisons can be a useful tool for BE assessment.

B. D50/SPAN may not carry most important information for complex PSD.

C. The EMD can be used to compare the PSD profiles for equivalence assessment.

D. The PBE only considers the mean difference between test and reference.

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