U.S. FOOD & DRUG ADMINISTRATION

Equivalence Criteria for In Vitro BE Tests for Locally Acting Drug Products: The Earth Mover's Distance Approach

Challenging Statistical Issues with In Vitro and In Vivo Bioequivalence Studies

Session II: In Vitro BE Statistical Issues

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Disclaimer

- The opinions expressed in this presentation are those of the speaker and may not reflect the position of the U. S. Food and Drug Administration

Earth

Outline

- Background
- Method
- Case study
- Conclusion
- Frequent Q&A

Background

- In vitro bioequivalence (BE) assessment is an important part of BE evaluation.

- By mechanism of drug action, the locally acting drug product frequently needs to utilize in vitro BE study for BE evaluation.

- In this presentation, we report an application of in vitro BE study based on particle size distribution (PSD).

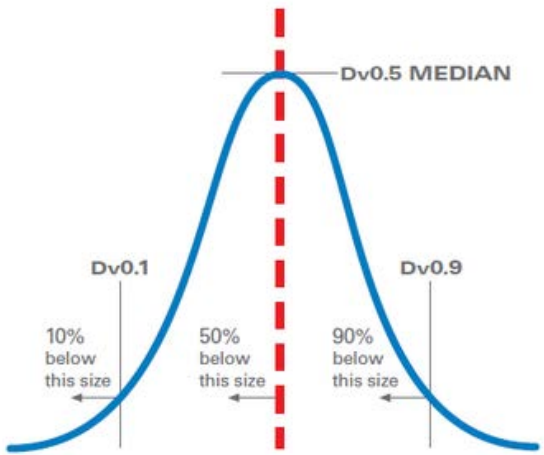
Background

- Considering that PSD is a valuable indicator for characterizing physical and chemical properties of a material, the PSD comparisons can be a useful tool for BE assessment.

- The FDA has recommended the population bioequivalence (PBE) statistical approach on D50 and SPAN values to compare PSD of generic and reference listed drug (RLD) products when appropriate.

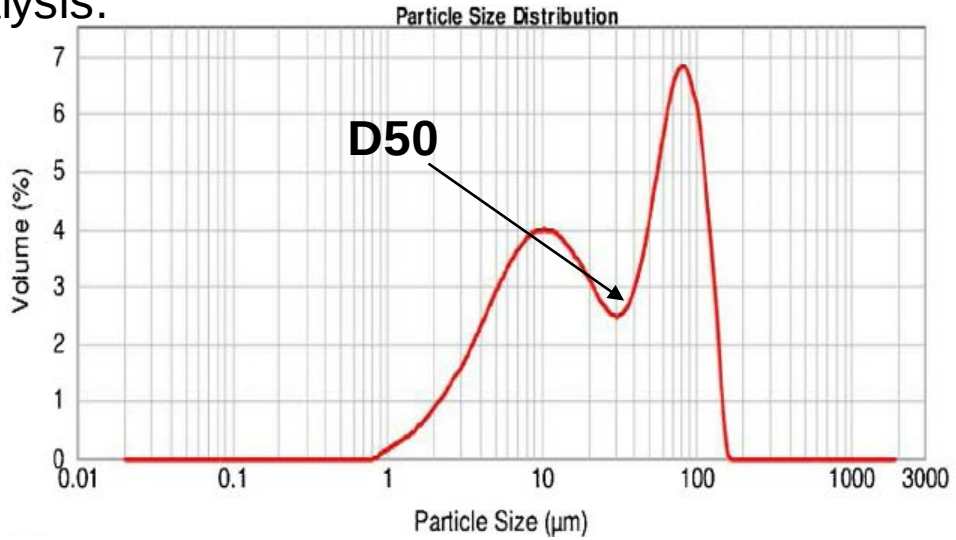
Why EMD rather than D50/SPAN?

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



Mono-modal (single-peak) assumption is applied.

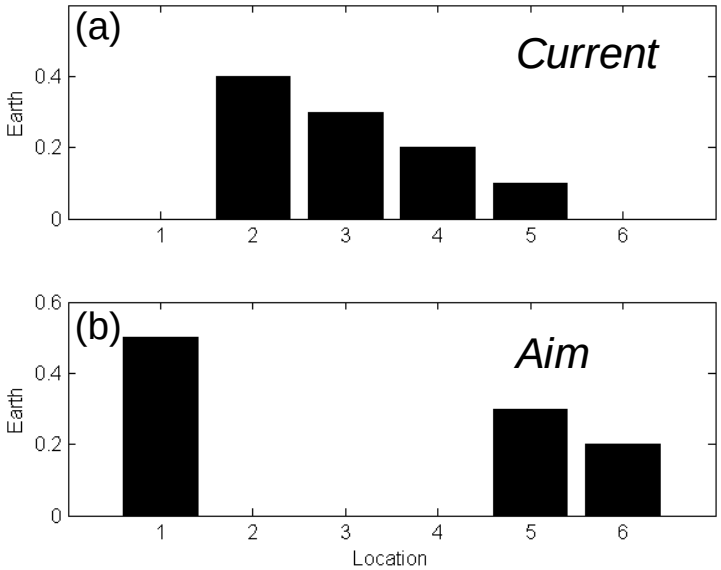
For a complex (e.g., multimodal) PSD profile, D50 and SPAN may not be appropriate metrics for the profile analysis.



Here is the place where the **EMD** comes into play for whole profile comparison.

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 histogram, the EMD can be used to assess the difference between histograms.

Procedure of EMD

1. Generate location table (*f*)

Location Table (*f*)

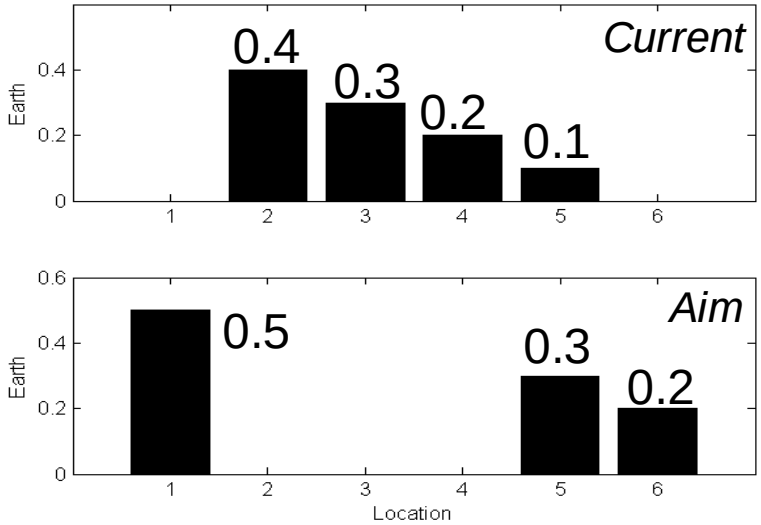
Locations of 'Aim' pile

	1	5	6
2	1	3	4
3	2	2	3
4	3	1	2
5	4	0	1

Locations of 'Current' pile

a) Prior knowledge can be used to define specific distances between locations.

b) Usage of location table enables the comparison between distributions in different spaces.



2. Find working-flow (*x*) to **minimize total cost (SUM(*x***f*))**

3. **EMD = SUM(*x***f*)/SUM(x)**

Working-flow table (*x*)

Locations of 'Aim' pile

	1	5	6
2	0.4000	0	0
3	0.1000	0.1184	0.0816
4	0	0.1210	0.0790
5	0	0.0606	0.0394

Locations of 'Current' pile

Note:

(1) EMD offers the optimal cost considering both the amount (*x*) and distance (*f*) of earth needed to move.

(2) If considering the pile as the histogram, the cost refers to the **TRUE distance** 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.

Population Bioequivalence (PBE)

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

Where,

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

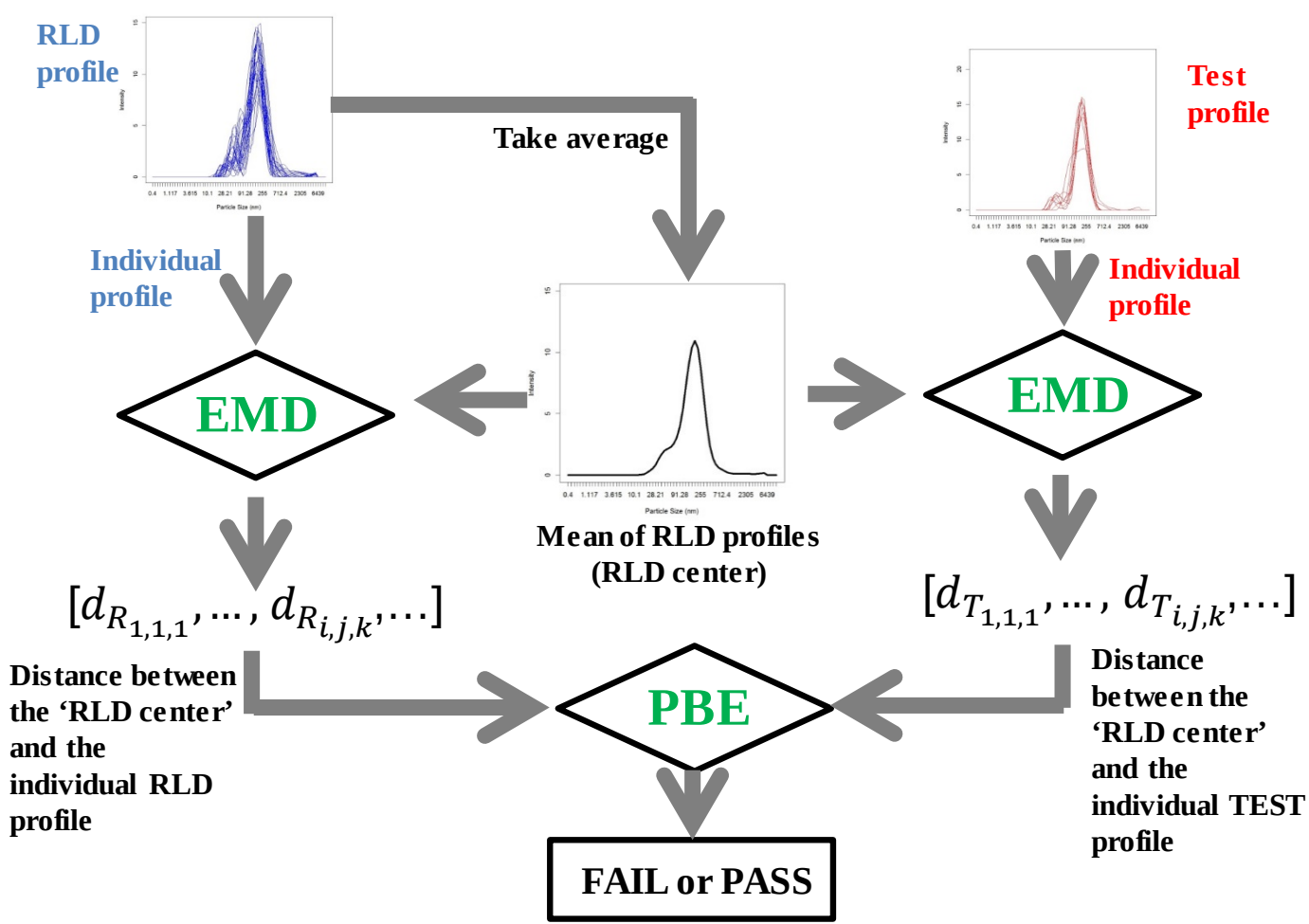
σ_T^2, σ_R^2: Total variance of T and R products

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

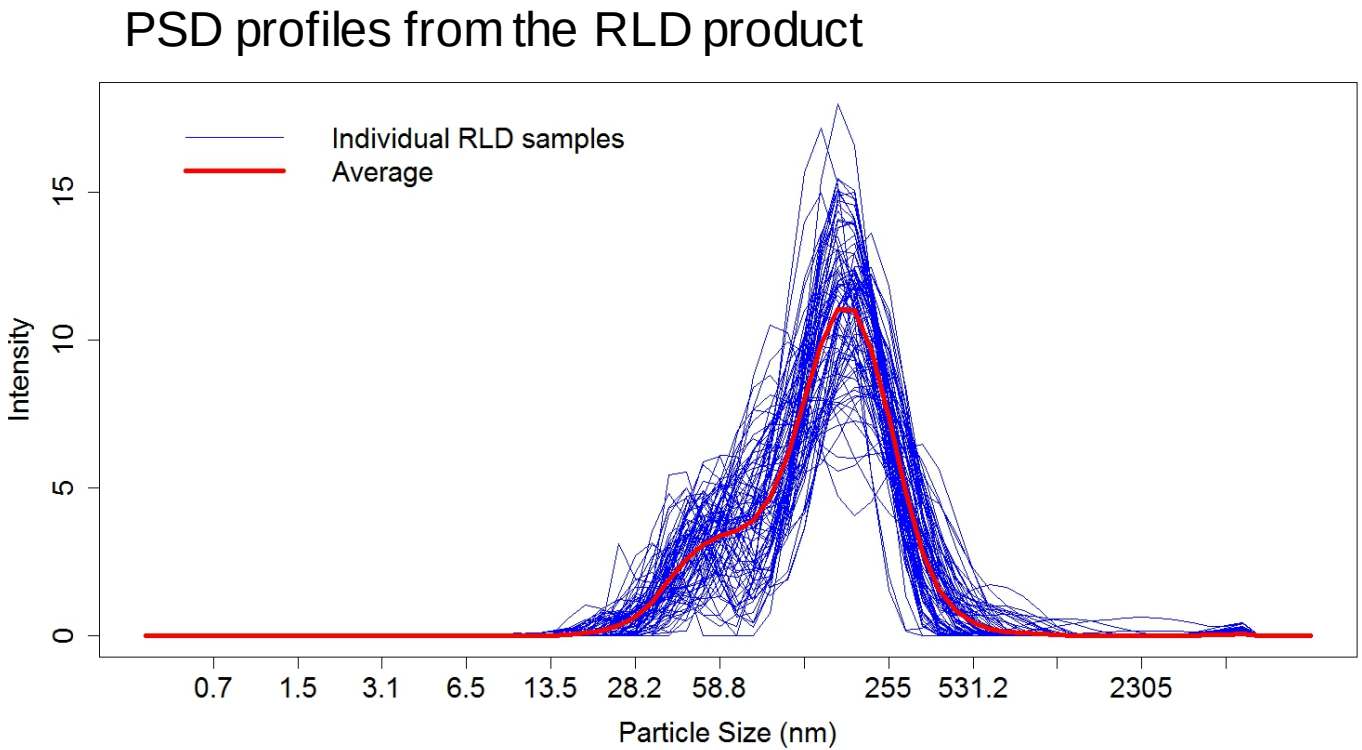
θ_p: Regulatory constant (θ_p= 2.0891) calculated as following:

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

The BE criterion (θ_p) is determined from the log-transformation of the data


RLD profile
Take average
Test profile
Individual profile
Individual profile
EMD
EMD
Mean of RLD profiles (RLD center)
$[d_{R_{1,1,1}}, \ldots, d_{R_{i,j,k}}, \ldots]$
$[d_{T_{1,1,1}}, \ldots, d_{T_{i,j,k}}, \ldots]$
Distance between the 'RLD center' and the individual RLD profile
PBE
Distance between the 'RLD center' and the individual TEST profile
FAIL or PASS

Case Study – PSD profile analysis



Hypothetical Case Study – PSD profile analysis

- Method validations
  - RLD vs. RLD
  - RLD vs. Negative control
  - Simulations

- Applications to equivalence assessments
  - RLD vs. Test sample X
  - RLD vs. Test sample Y

Data for Hypothetical Study

- Reference listed drug (RLD) – 8 lots
- Negative control - 3 lots
- Test sample X – 3 lots
- Test sample Y – 3 lots

Case Study – PSD profile analysis

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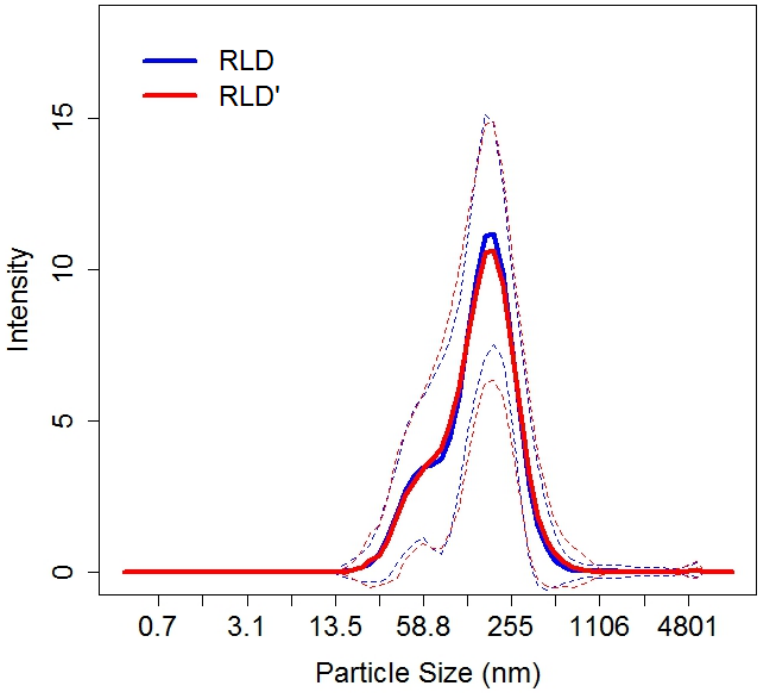
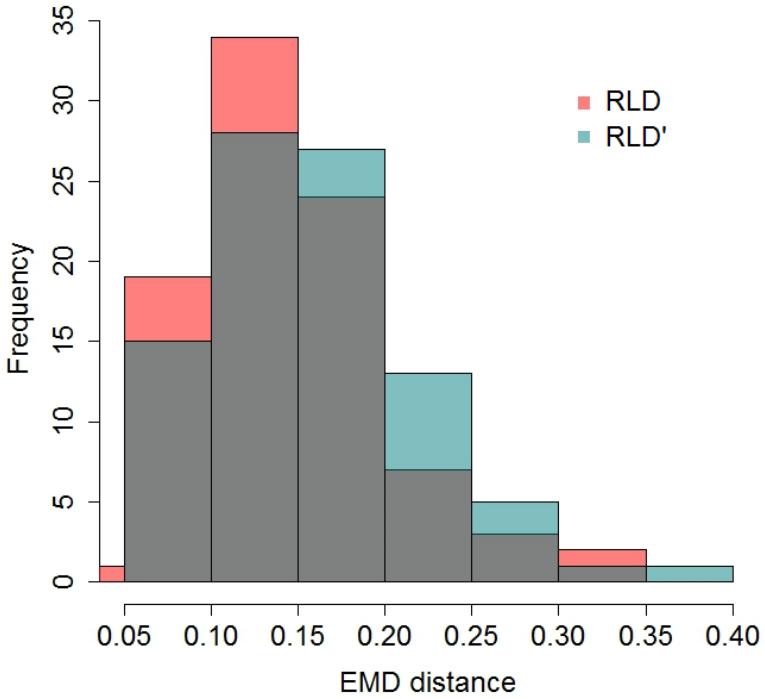
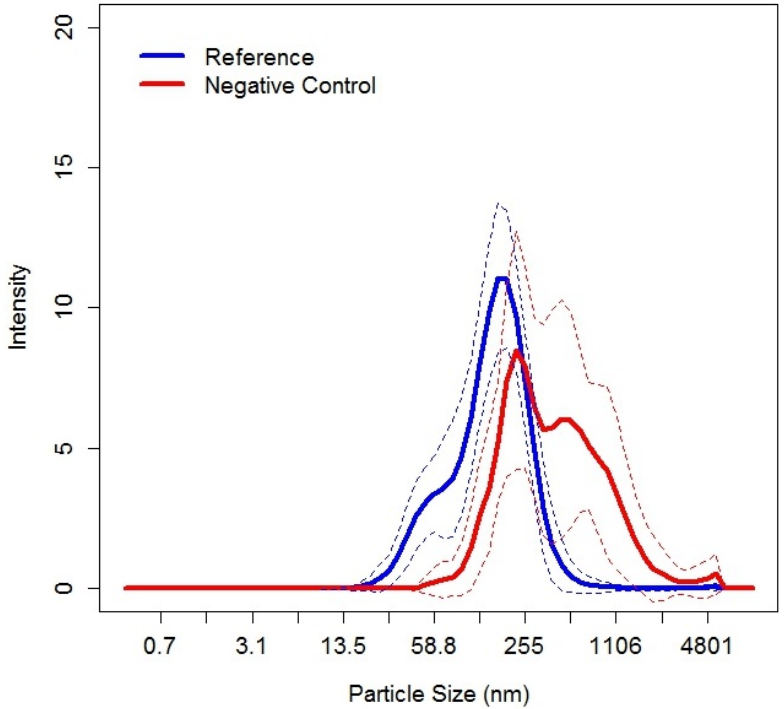
RLD vs. RLD

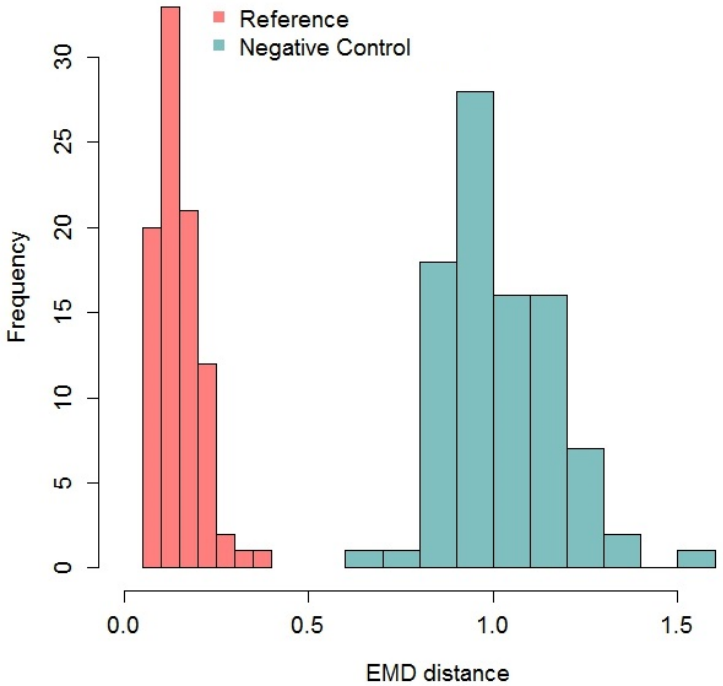




The PBE is applied to the EMD distances from two groups, concluding equivalence.

RLD vs. Negative Control





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

Simulations – performance test

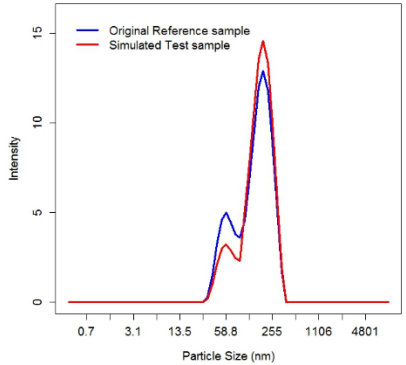
Based on real PSD profiles

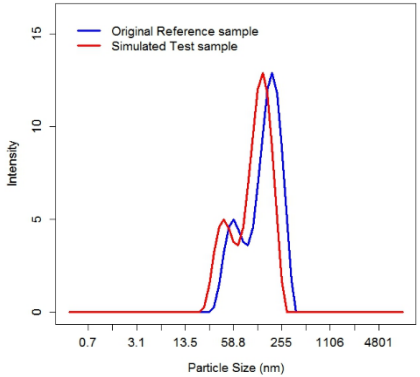
Systematically changing profile

Systematically shifting Profile

Compare EMD with other distance methods

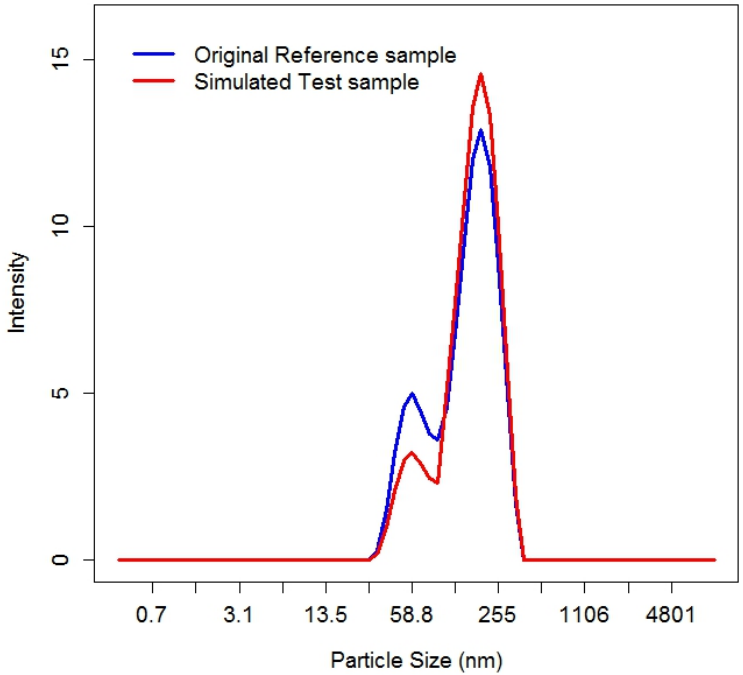
- Euclidean distance
- Kolmogorov–Smirnov (K-S) distance

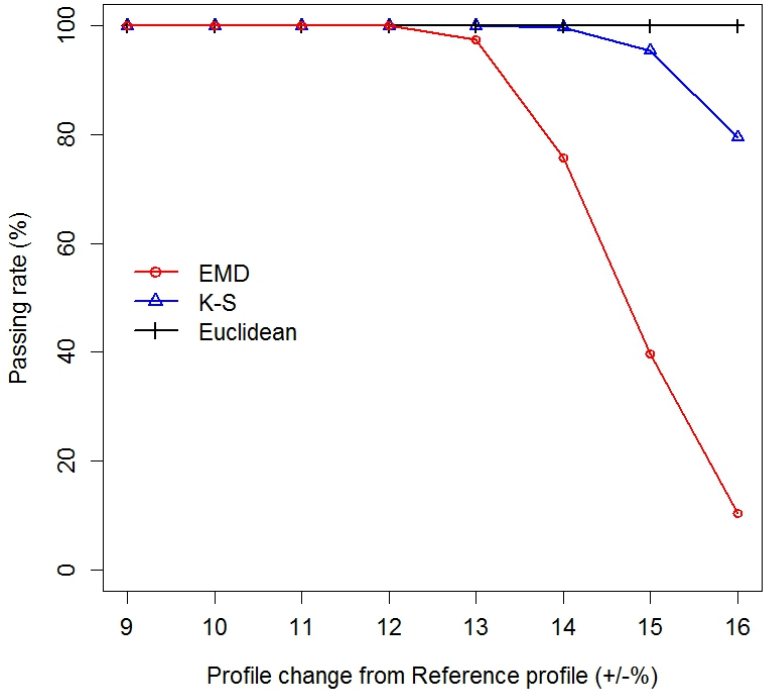




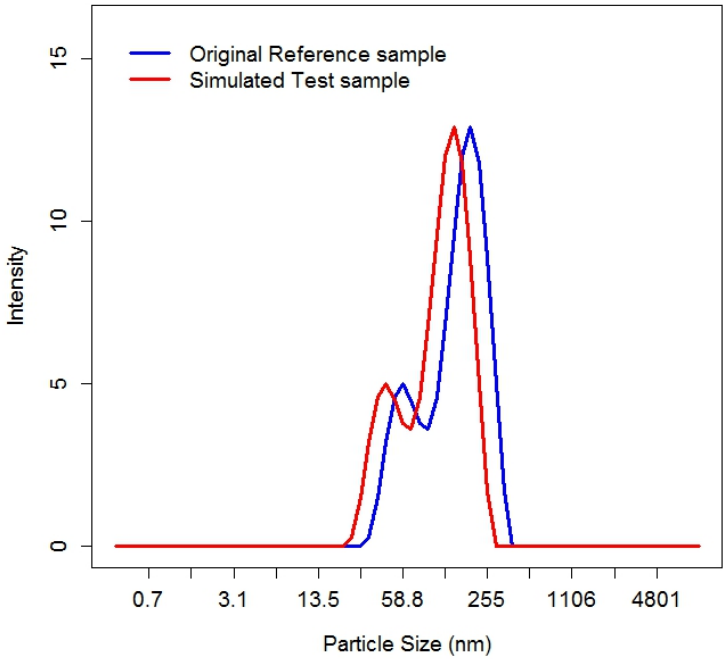
Simulations - Profile changing

EMD-based equivalence approach provides the best sensitivity to discriminate the profile difference.





Simulations - Profile shifting



Passing rates (%) of equivalence tests

Number of shifted bins	Equivalence approach based on		
	EMD	K-S	Euclidean
1	100	93	100
2	0	0	100
3	0	0	47

Overall, the EMD-based approach offers the optimal performance.

Case Study – PSD profile analysis

- Method validations
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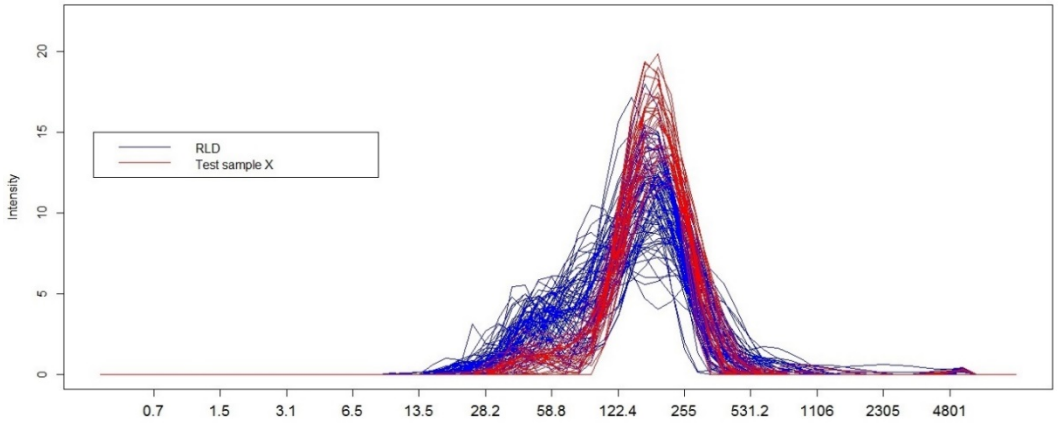
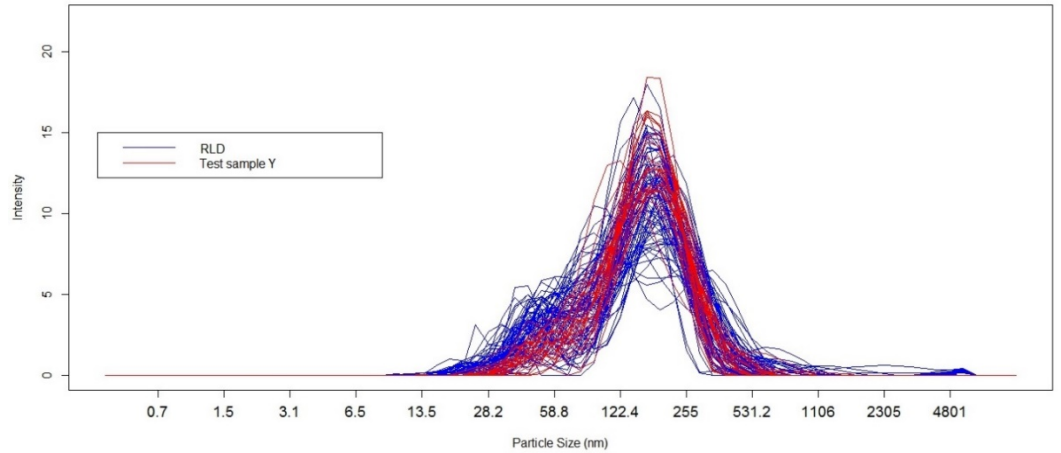
- Applications to equivalence assessments
  - RLD vs. Test sample X
  - RLD vs. Test sample Y

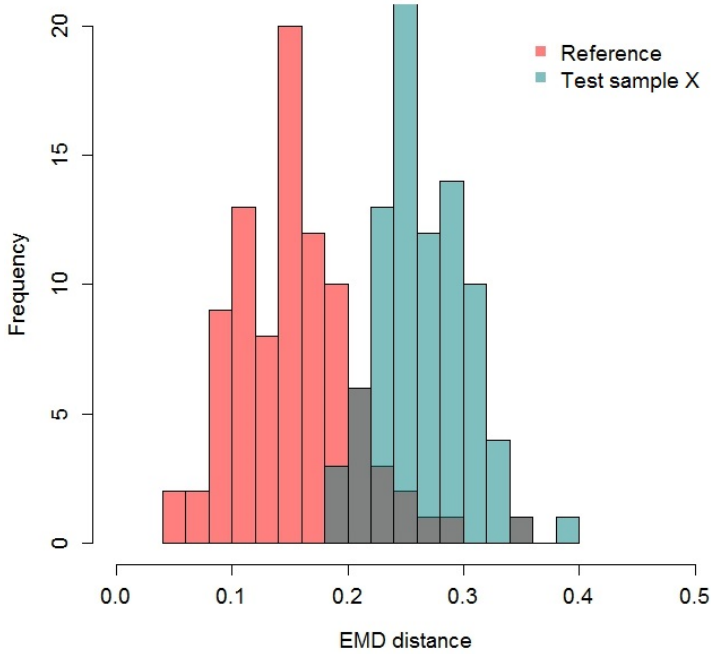
Test sample X

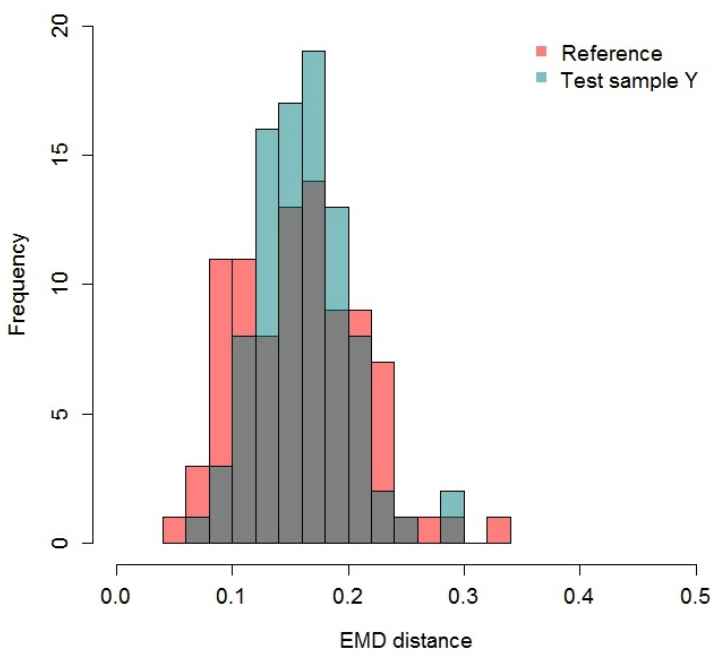


Test sample Y



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.

Conclusion

- 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).

- The developed approach can be potentially applied for other profile comparison questions for BE purpose.

Frequent Q&A

Q: What data should be provided for FDA's review for this test?

Ans: The tabulated raw data of the individual GSD profiles, including the coordinates of the %intensity and particle size for each measurement of each sample, along with the calculated EMD data, should be provided for FDA's review.

Q: Can the log-transformation step be removed from the PBE analysis?

Ans: It is not acceptable to remove the log-transformation step from the PBE analysis without proposing a new BE limit. According to the FDA guidance for the PBE analysis, the current BE limit is determined based on log-transformed data. Therefore, keeping the same BE limit while removing the step of data log-transformation for the PBE analysis is not valid.

Q: What tools can be used to implement EMD algorithm?

Ans: A free R package is currently available to implement the EMD calculation (https://cran.r-project.org/web/packages/emdist/index.html).

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