Equivalence testing of complex particle size distribution profiles based on earth mover's distance

Complex Generic Drug Product Development Workshop

Session 3: Complex Formulations/Dosage Forms

September 12, 2018

Meng Hu, PhD.

Division of Quantitative Methods and Modeling,

Office of Research and Standards

OGD | CDER | US FDA

Earth

Outline

- Background
- Method
- Case study
- Conclusion

Background

- The particle size distribution (PSD) comparisons can be a useful tool to assess equivalence between a generic product and the reference listed drug (RLD) product.

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

Background

Recently, a new method, namely earth mover's distance (EMD), is recommended in the product-specific guidances (PSGs) for PSD analysis.

Contains Nonbinding Recommendations

Draft Guidance on Cyclosporine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient:	Cyclosporine
Dosage Form; Route:	Emulsion; ophthalmic
Strength:	0.05%
Recommended Study:	Two options: in vitro or in vi

I. In vitro option:

To qualify for the in vitro option for this drug product al
met:

i. The test and reference listed drug (RLD) formulatio
quantitatively (Q2)[2] the same[3].

ii. Acceptable comparative physicochemical characteri
formulations. The comparative study should be perf

Contains Nonbinding Recommendations

Draft Guidance on Barium Sulfate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient:	Barium sulfate
Dosage Form; Route:	For suspension; oral
Strength:	98% (334 g / bottle)
Recommended Studies:	In vitro study

Additional Comments:

- The proposed test drug product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).
- Test and reference drug products should have comparable physicochemical properties, including but not limited to, viscosity across a range of shear rates (e.g., low, medium, and high), and pH.
- The comparative analyses should be performed on at least three lots of the test drug product

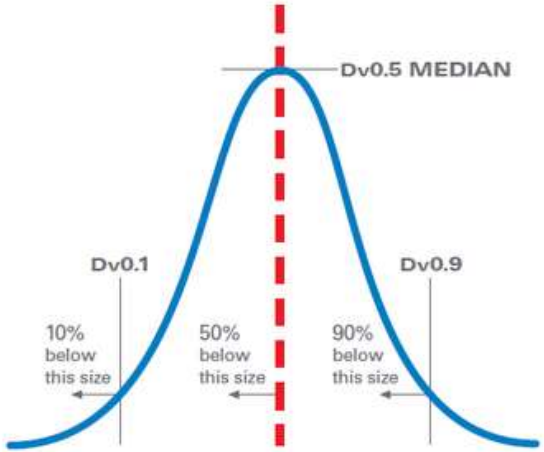
The EMD-based approach described in the PSG for cyclosporine ophthalmic emulsion

Bioequivalence based on (95% upper confidence bound): Considering the fact that the shape of the globule size distribution of this product may not be mono-modal, the conventional population BE based on D50 and SPAN may not be sufficient to demonstrate bioequivalence.

Instead, the equivalence between the test and RLD formulations in the shape of the globule size distribution (such as the presence of multiple peaks) should be demonstrated by a method proposed by the sponsor. A statistical metric is preferred to assess the difference (e.g., in terms of distance) between the shapes of distribution profiles. One suggested approach is the earth mover's distance (EMD)[5] method, which computes the minimal cost needed to transform one distribution into the other using an optimization algorithm. An average profile of all RLD samples (i.e., RLD center) is calculated and served as the reference profile to compute the distance between a RLD or a test sample to the RLD center. After obtaining the profile distances between each RLD sample and the RLD average ('RLD' – 'RLD center' distance), and the profile distances between each test sample and the RLD average ('TEST' – 'RLD center' distance), a statistical metric should be employed to quantify the difference between the two categories of distances. One suggested method is the population BE test[6,7]. In order to properly account for variability of the reference product and to achieve adequate power, a sufficient number of samples and replicates should be used.

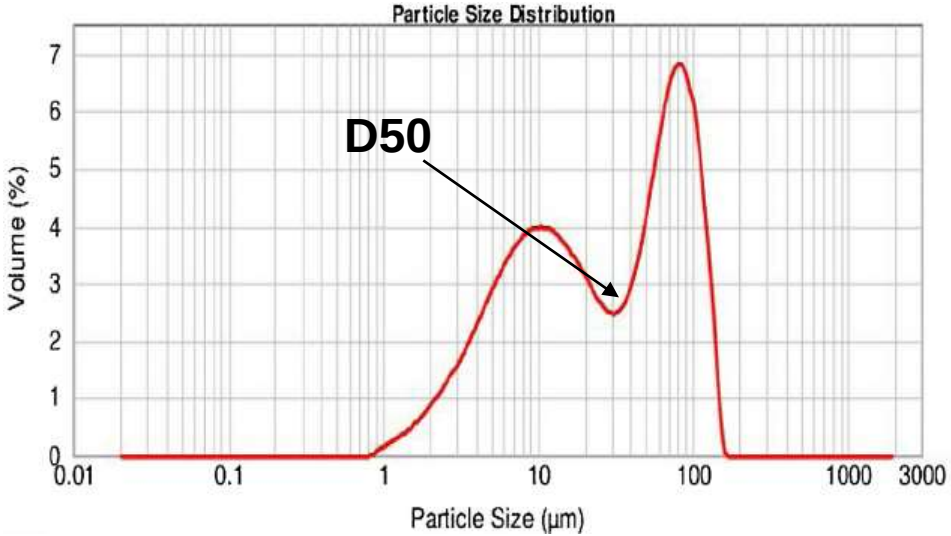
Why EMD rather than D50/SPAN?

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



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

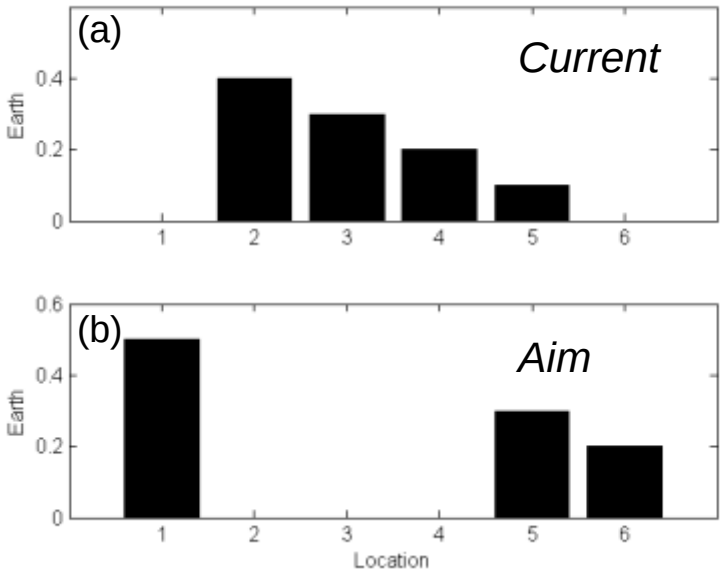
For a complex (e.g., multimodal) PSD profile, D50 and SPAN may not be appropriate metrics for the profile analysis.



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.

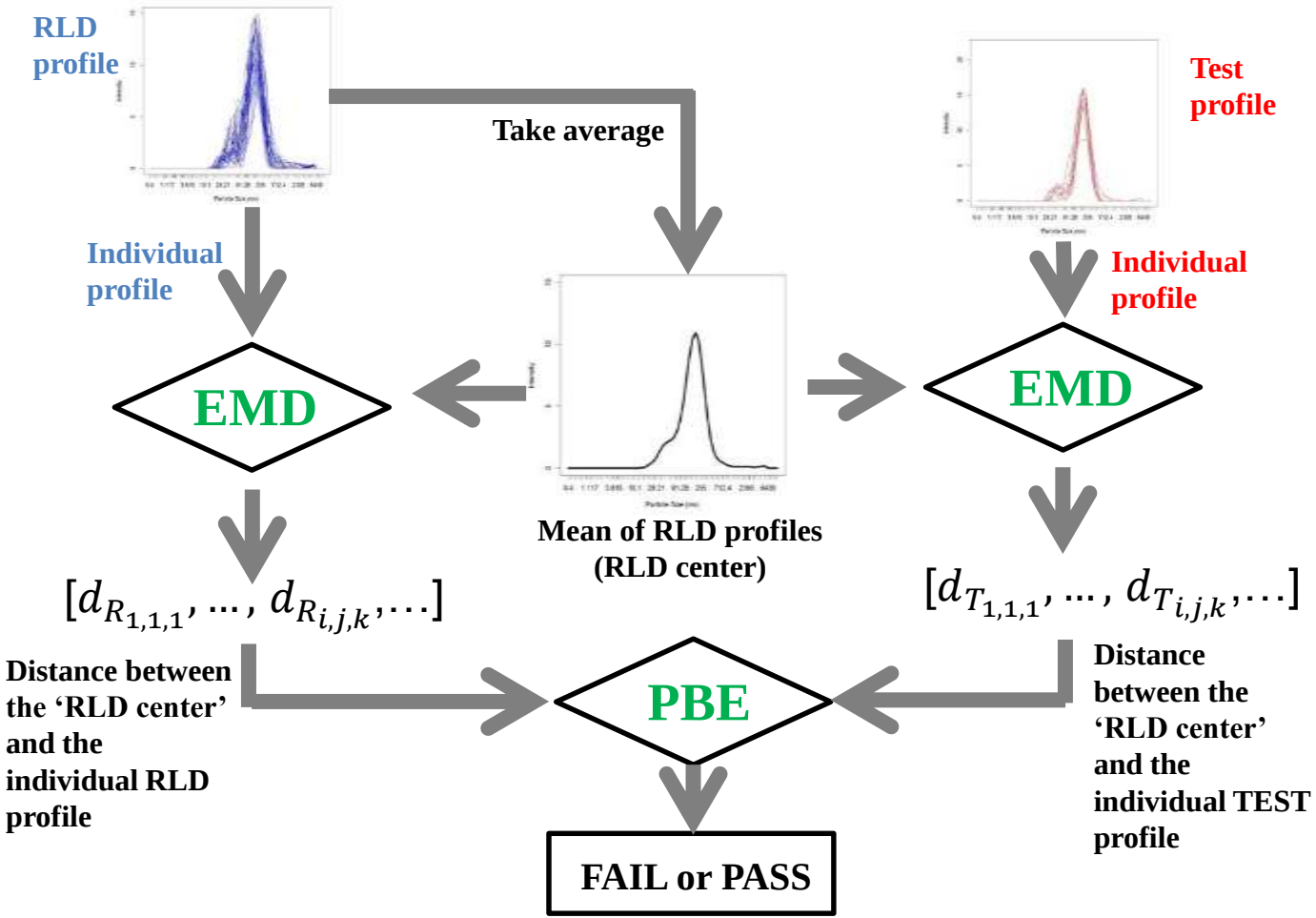
EMD for profile comparison

- 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.

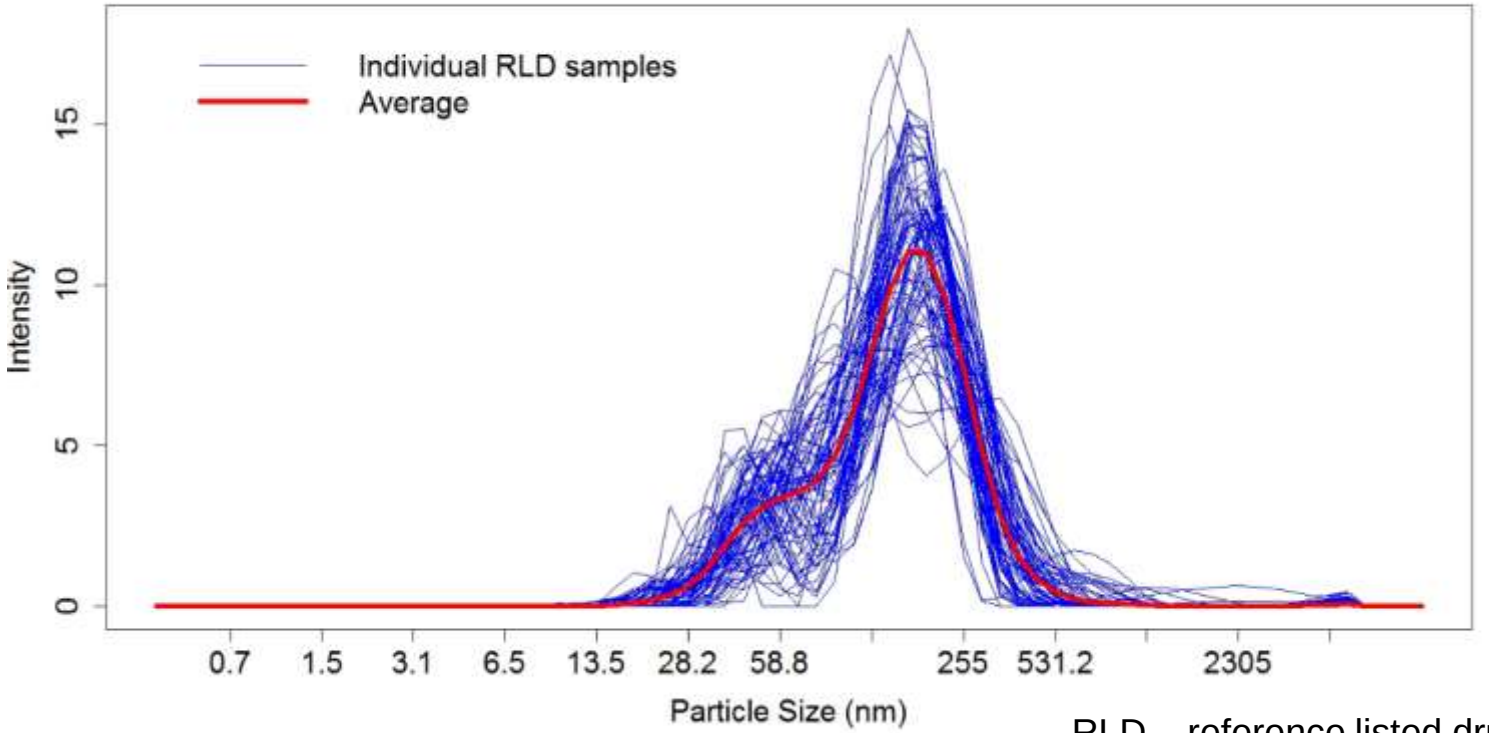
- The EMD can be used to compare the PSD profiles for equivalence test.

Equivalence approach based on EMD



Case Study - cyclosporine ophthalmic emulsion

PSD profiles from cyclosporine ophthalmic emulsion (RLD)



RLD – reference listed drug

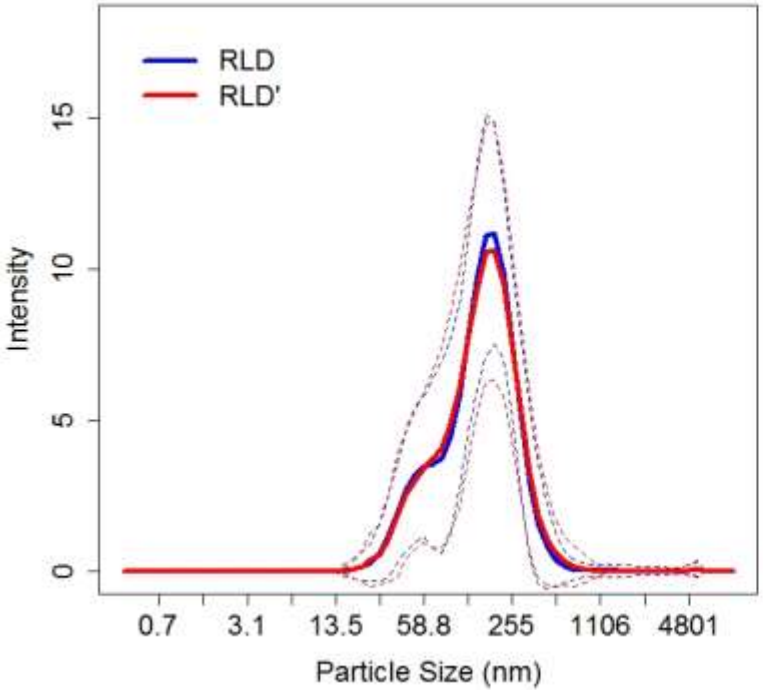
Case Study – PSD profile analysis for cyclosporine ophthalmic emulsion

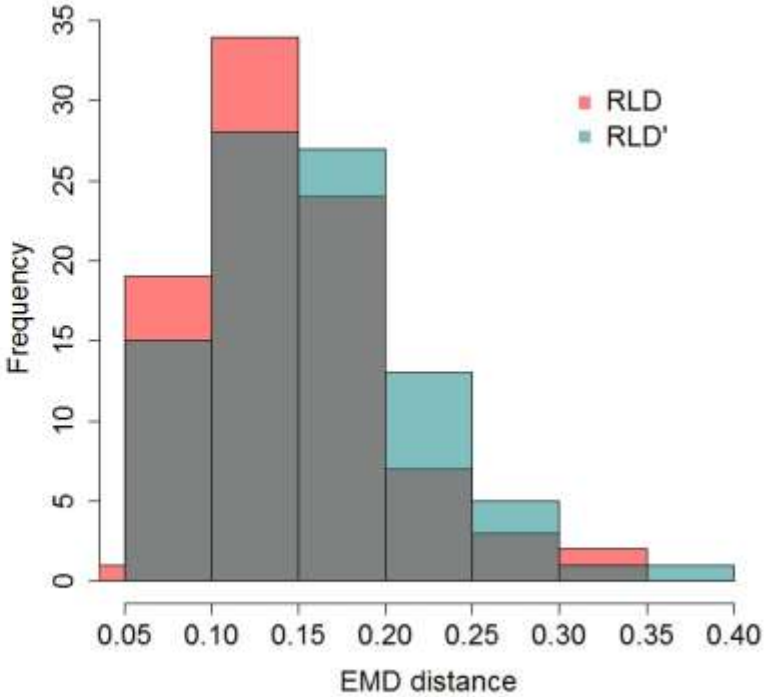
- Demonstrate the usefulness of developed approach
  - RLD vs. RLD
  - RLD vs. Negative control
  - Simulations

Data for cyclosporine emulsion

- Reference listed drug (RLD) – 8 lots
- Negative control - 3 lots

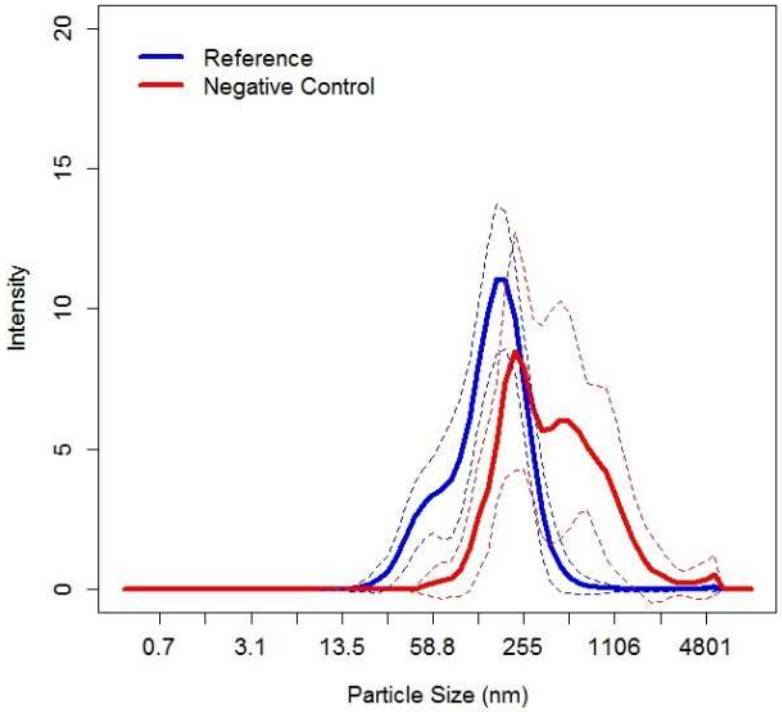
RLD vs. RLD

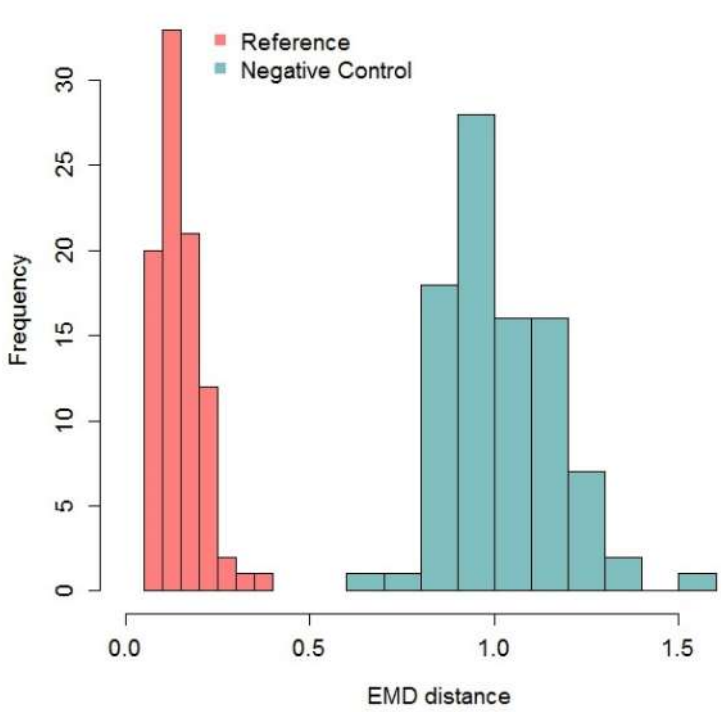




The PBE is applied to the EMD distances from two groups, concluding equivalence.

RLD vs. Negative Control





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

Simulations – performance test

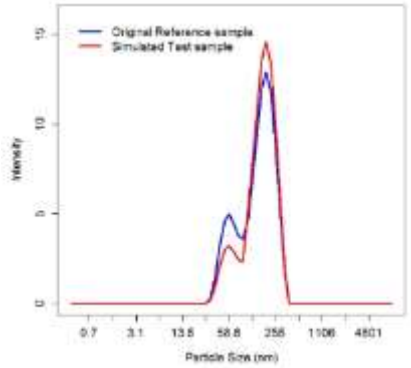
Based on real PSD profiles

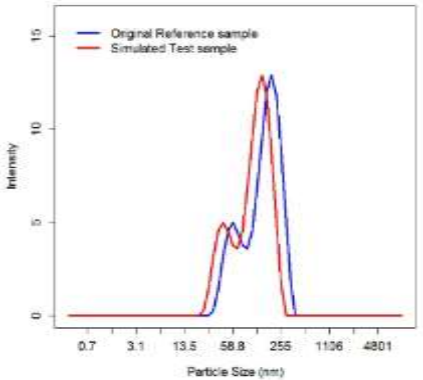
Systematically changing profile

Systematically shifting Profile

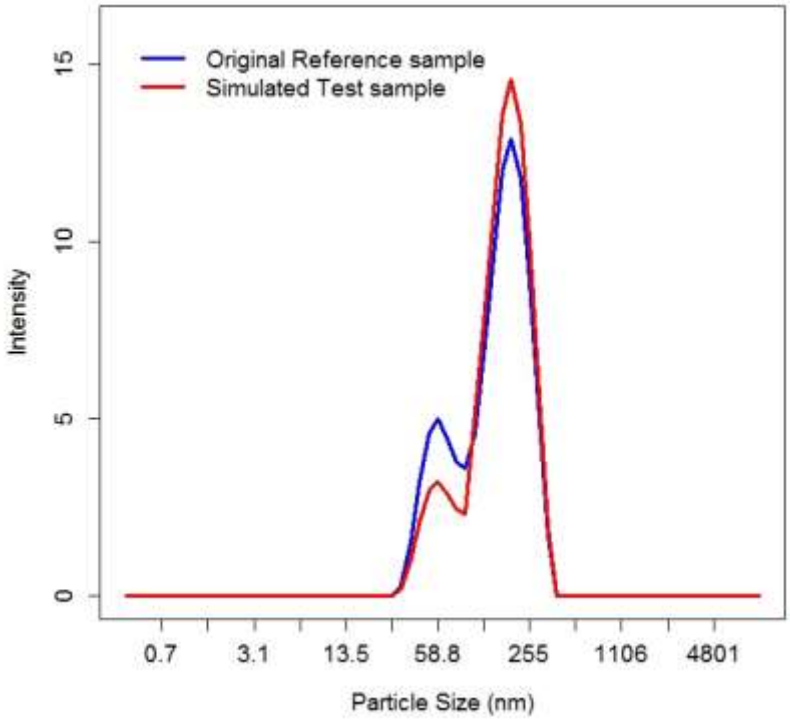
Compare EMD with other distance methods

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

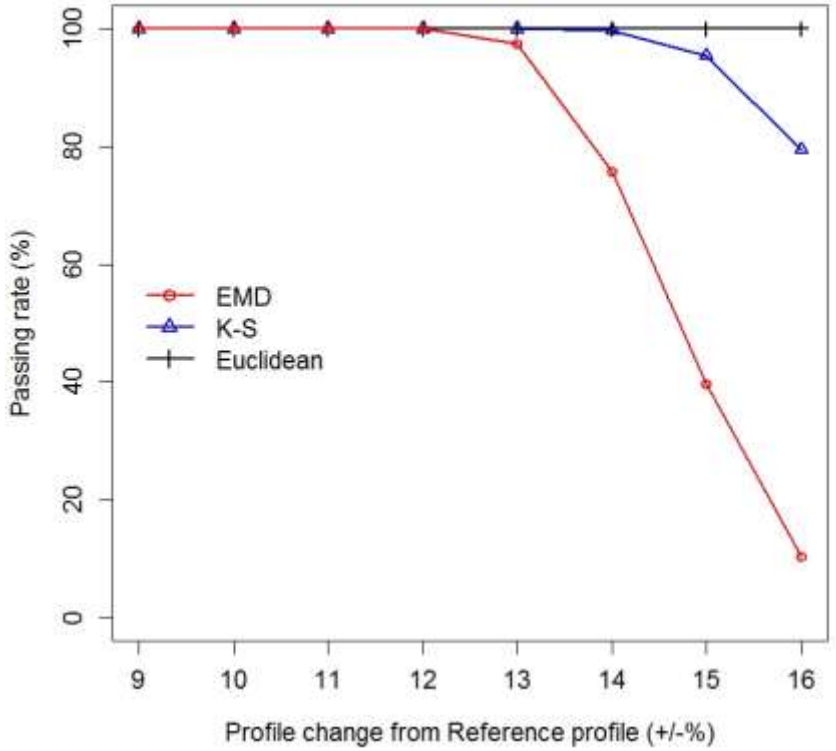




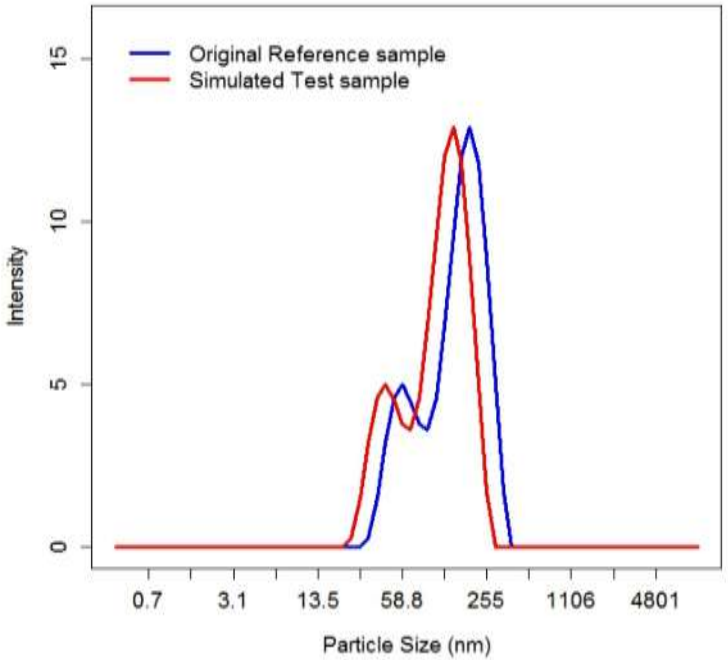
Simulations - Profile changing



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.

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).

- EMD has been recommended in our PSGs and been applied to the ANDA assessments.

Acknowledgement

OGD/ORS

Robert Lionberger
Stephanie Choi
Liang Zhao
Xiaohui Jiang
Darby Kozak
Mohammad Absar
(Now working with OCP)

OPQ/OTR/DPQR

Xiaoming Xu

OTS/OB

Yi Tsong
Meiyu Shen
Yu-Ting Weng


FDA
U.S. FOOD & DRUG
ADMINISTRATION