A Statistical Bioequivalence Approach Based on Earth Mover's Distance for Equivalence Testing of Particle Size Distribution

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PURPOSE

Particle size distribution (PSD) manifests important properties of particulate materials, including particulates in drug products. In the evaluation of generic drug products formulated as suspensions, emulsions, and liposomes, size distribution comparisons of particles or globules to the branded product can provide useful information regarding in vitro and in vivo performance. For some drug products, the FDA has recommended the population bioequivalence (PBE) statistical approach on D50 and SPAN values to compare PSD of test and reference products when appropriate. However, when a PSD exhibits a complex (e.g., multimodal) pattern, D50 and SPAN may not be appropriate metrics for PSD profile analysis. To address this concern, the earth mover's distance (EMD) [1] which does not make underlying assumptions on the mode of distribution is proposed as a new metric for establishing equivalence based on PSD profile comparison.

METHOD(S)

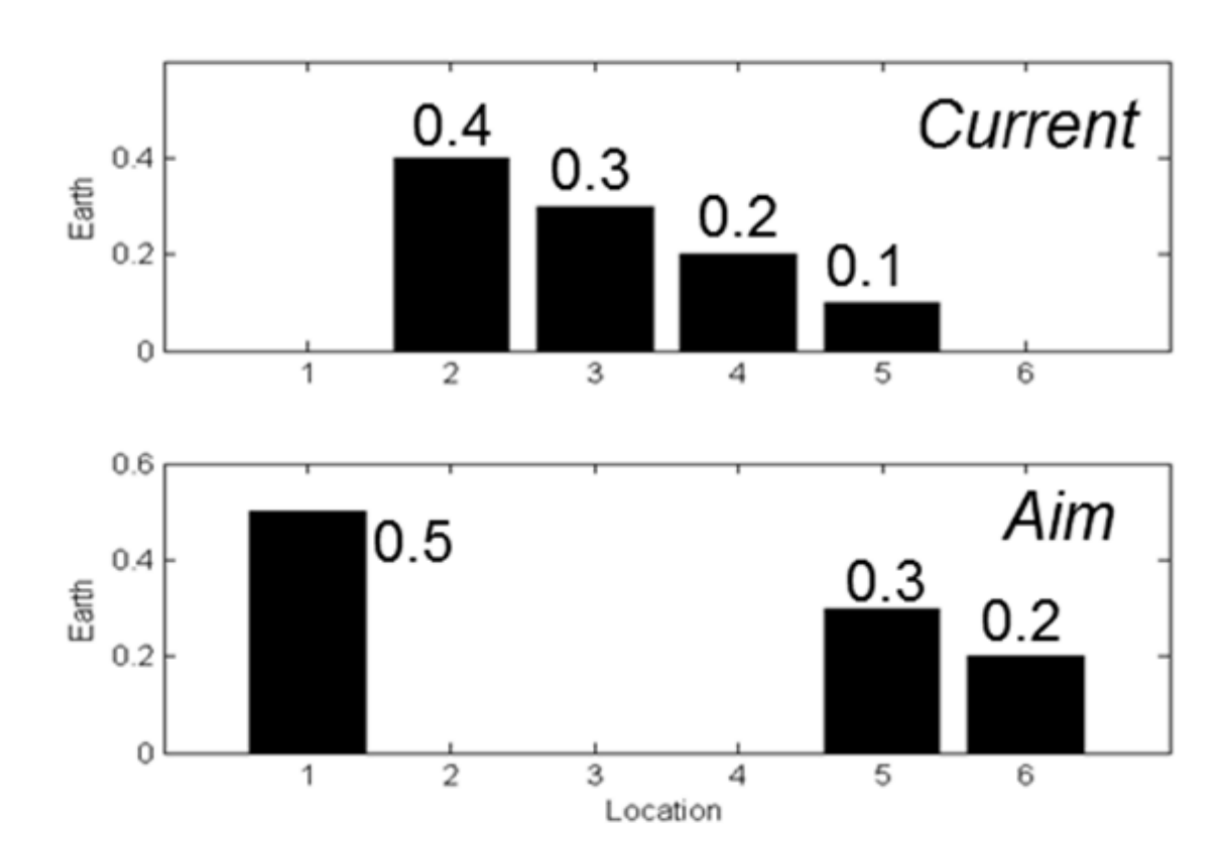### D50 / SPAN is not suitable for complex profile analysis

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

Mono-modal assumption

Complex (Multi-modal) profile
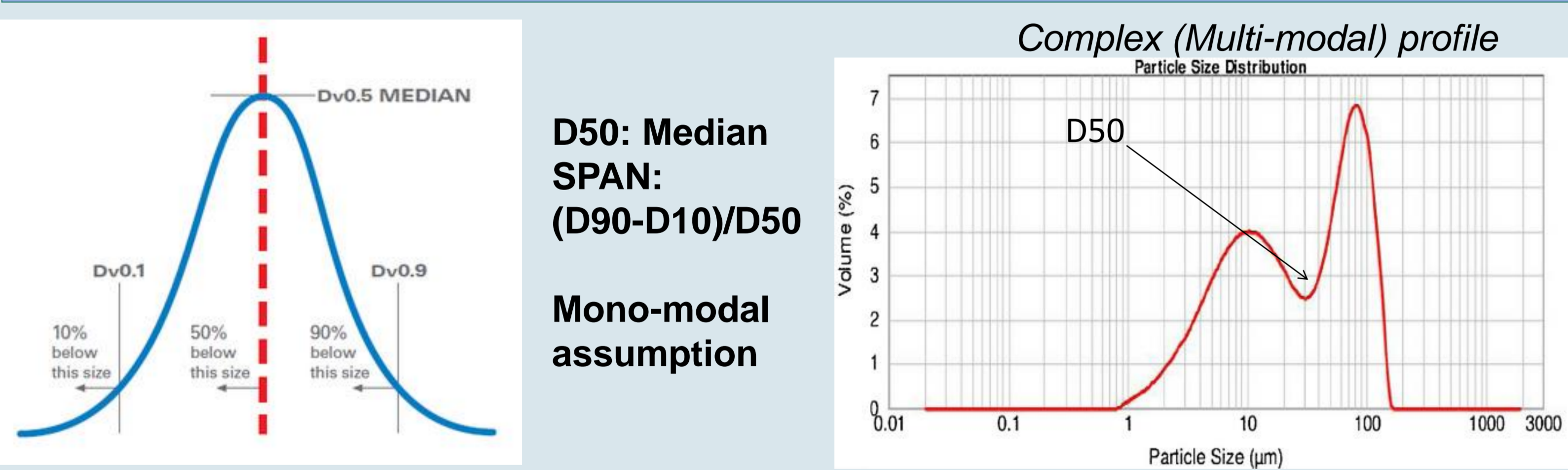
Earth Mover's Distance (EMD) for whole profile analysis

Procedure of EMD

1. Generate location table (*f*)

Location Table (*f*)

	Locations of 'Aim' pile		
	1	**5**	**6**
Locations of 'Current' pile			
2	1	3	4
3	2	2	3
4	3	1	2
5	4	0	1

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

Working-flow table (*x*)

	Locations of 'Aim' pile		
	1	**5**	**6**
Locations of 'Current' pile			
2	0.4000	0	0
3	0.1000	0.1184	0.0816
4	0	0.1210	0.0790
5	0	0.0606	0.0394

3. EMD = SUM(*x*∗*f*)/ SUM(*x*)

EMD is essentially a '*cross-bin*' measure that accounts for both the amount and distance of earth moving, suitable for assessing the dissimilarity between two distributions or histograms.

Note:
(1) EMD offers the optimal cost considering both the amount (*x*) and distance (*f*) of earth needed to move.
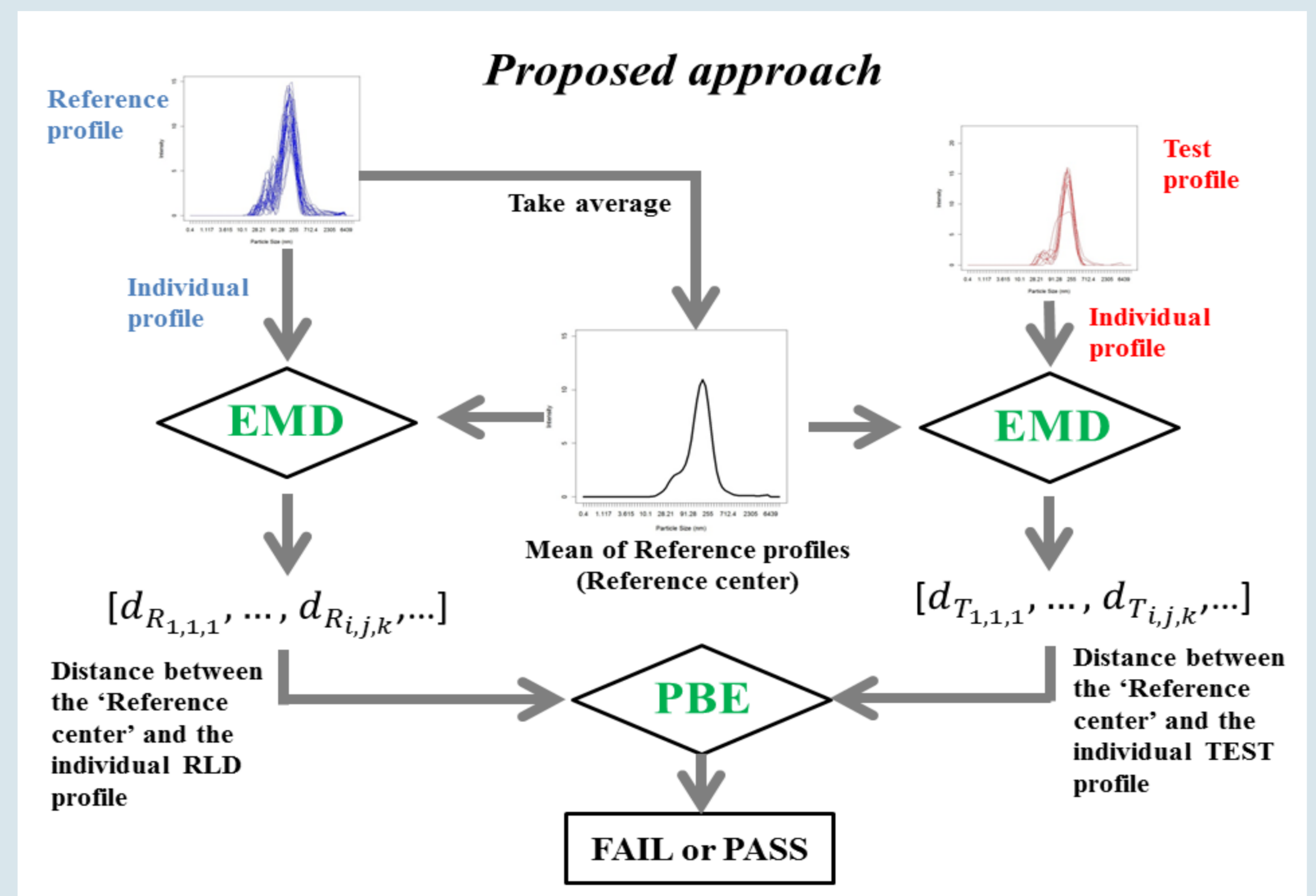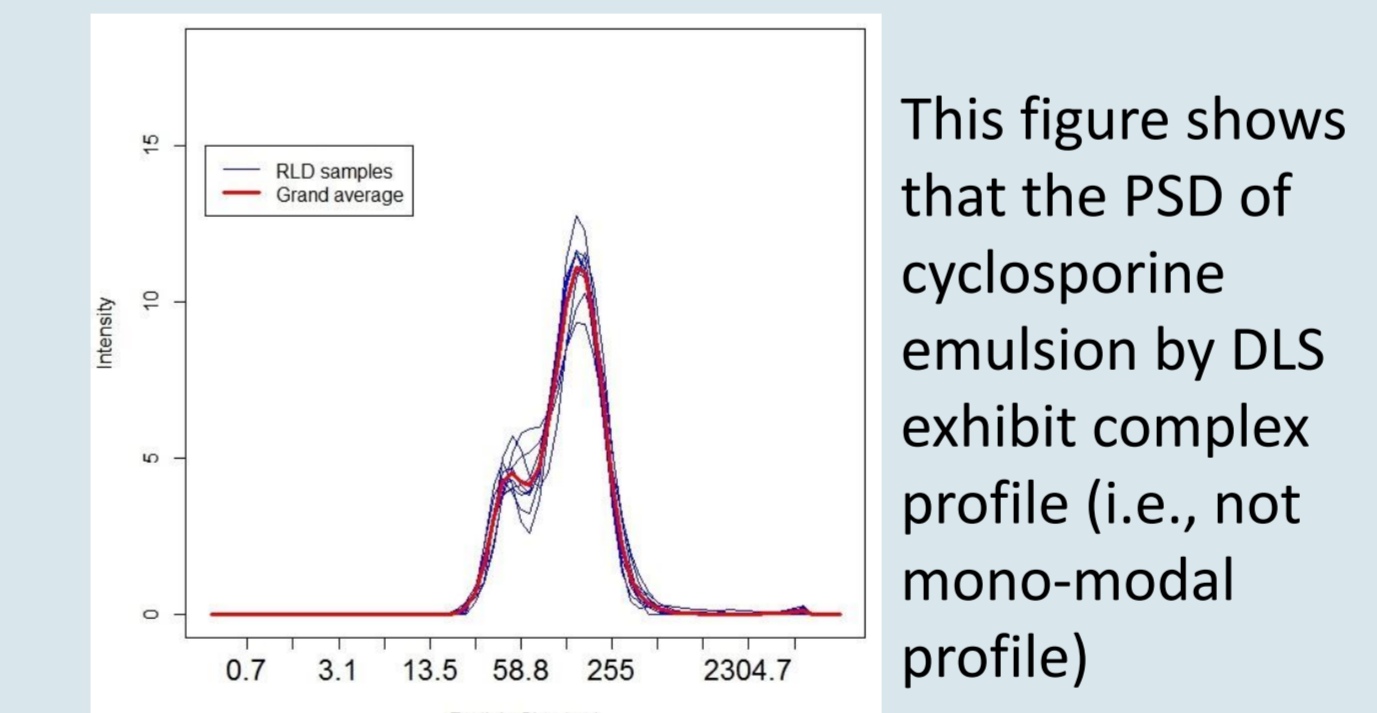(2) If considering the pile as the histogram, the cost refers to the **TRUE distance** between histograms.
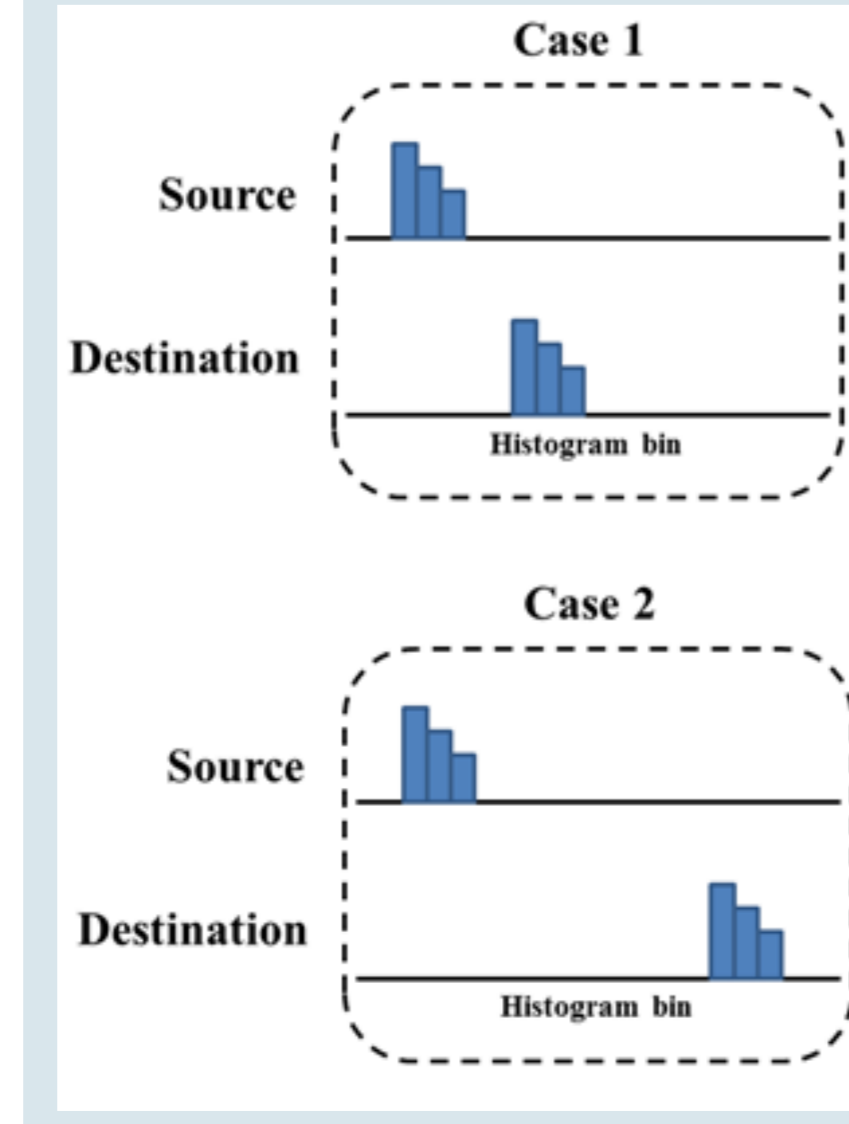
EMD-based Equivalence Testing approach for Complex PSD

Proposed approach

$[d_{R_{1,1,1}}, \ldots, d_{R_{i,j,k}}, \ldots]$

Distance between the 'Reference center' and the individual RLD profile

Mean of Reference profiles (Reference center)

$[d_{T_{1,1,1}}, \ldots, d_{T_{i,j,k}}, \ldots]$

Distance between the 'Reference center' and the individual TEST profile

PBE → FAIL or PASS

RESULT(S)

Study Case

Product	Cyclosporine Emulsion
Sample	8 Reference lots and 1 negative control [2]
PSD method	Dynamic light scattering (DLS)

This figure shows that the PSD of cyclosporine emulsion by DLS exhibit complex profile (i.e., not mono-modal profile)

Simulations

Simulation I – Performance of EMD
- A bi-modal profile (black) is shifted to its right side (red).
- EMD is used to assess the difference between the 'Original PSD' and 'Shifted PSD'.

Simulation II – Performance of EMD-based equivalence testing approach
- Test profiles (red) are generated by varying the Reference (blue) profiles.
- The proposed approach is applied to perform equivalence testing.

Equivalence testing within Reference samples

Bold solid line: *mean*
Thin dashed line: *standard deviation*

The right figure shows that the calculated EMD distances from the Reference and Test are in the same range.

The PBE test shows that the two groups of EMD distances are equivalent (i.e., the linearized criteria is less than zero [3])
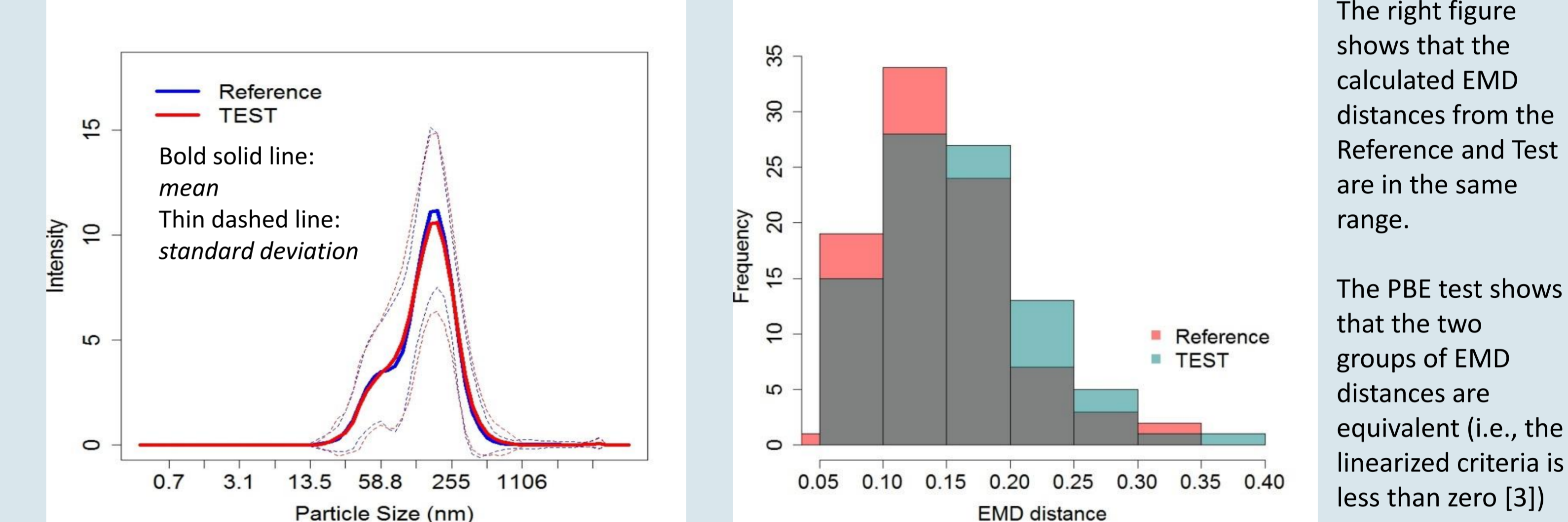
3 RLD lots were randomly chosen from all 8 RLD lots as 'Reference', while another 3 RLD lots were randomly chosen from the left 5 RLD lots as 'Test'. The proposed approach was applied to perform equivalence testing between 'Reference' and 'Test'. Above procedure was repeated 1000 times to calculate the passing rate (100%). Above figures show the PSD profiles of 'Reference' and 'Test' (left) and calculated EMD distances (right) from a random selection.

Testing between Reference and Negative Control samples

Bold solid line: *mean*
Thin dashed line: *standard deviation*

The right figure shows that the calculated EMD distances of Negative Control are far away from the calculated EMD distances of Reference.

The PBE test shows that the two groups of EMD distances are not equivalent (i.e., the linearized criteria is greater than zero [3])
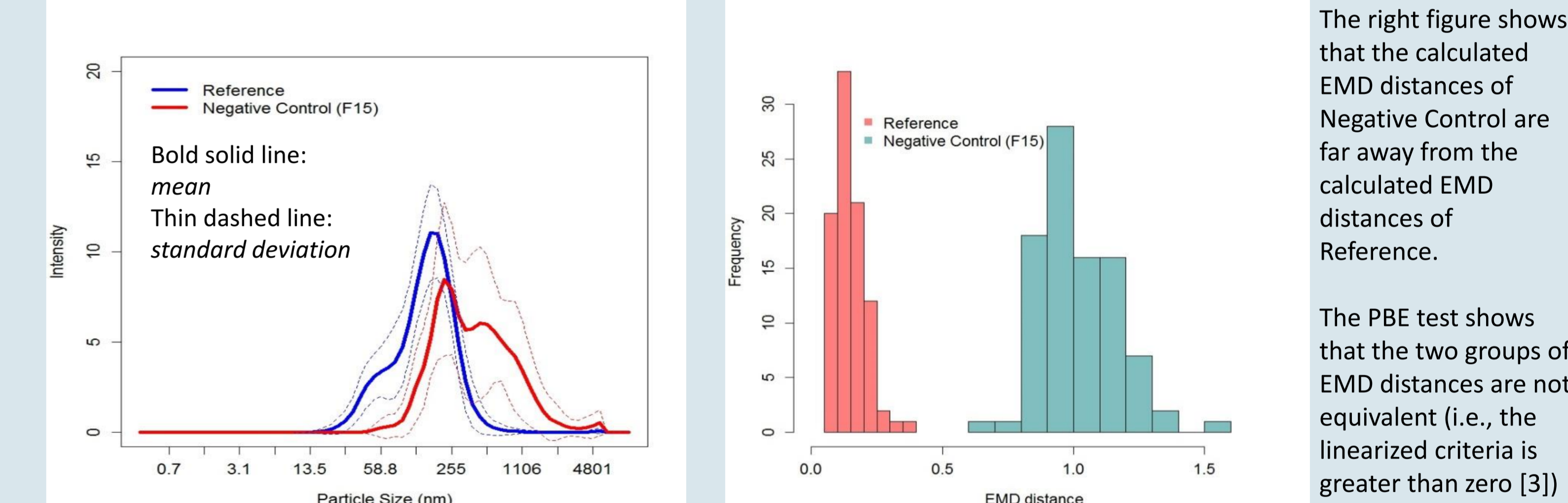
3 RLD lots were randomly chosen from all 8 RLD lots as 'Reference', while the negative control samples were used as 'Test'. The proposed approach was applied to perform equivalence testing between 'Reference' and 'Test'. Above procedure was repeated 1000 times to calculate the passing rate (0%). Above figures show the PSD profiles of 'Reference' and 'Test' (left) and calculated EMD distances (right) from a random selection.

CONCLUSION

The proposed EMD-based approach can be used as a new metric in determining PSD equivalence between test and reference products that possess a complex (e.g., multimodal) particle size distribution.

REFERENCE

1) Rubner Y, et al. (2000) Int J Comput Vis 40, 99–121.
2) Rahman, et al. Mol. Pharmaceutics 2014, 11, 787–799
3) https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf

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