

**BIOEQUIVALENCE SUMMARY TABLES FOR DRUG PARTICLE SIZE DISTRIBUTION (PSD) BY MORPHOLOGICALLY DIRECTED RAMAN SPECTROSCOPY (MDRS)**

**Table 1. Product Batch Information**

	TEST					REFERENCE		
<b>Product Name</b>								
<b>Dosage Form</b>								
<b>Strength</b>								
<b>Manufacturer</b>								
<b>To-be-Marketed Production Batch Size</b>								
Study	Batch/ Lot No.	Potency*	Batch/ Lot Size		Manufacture Date	Batch/ Lot No.	Potency*	Expiration Date
			Theoretical (units) -if applicable	Actual (units)				
Morphologically Directed Raman Spectroscopy (MDRS)								

\*Data obtained from Certificate of Analysis

Please add row(s) as needed to list other in vitro/ in vivo bioequivalence study(ies) and include corresponding batch/ lot numbers from each test.

**Table 2. Study Information**

<b>Study No.</b>				
<b>Study Title</b>				
<b>Study Report Location and Link</b>				
<b>Study Site Name and Address</b>				
<b>Principal Investigator</b>				
<b>Analyst(s)</b>				
<b>Study Dates</b>				
SOP(s)	No.	Title	Effective Date (Revision Date - if any)	Location and Link
Please add row(s) as needed.				

**Table 3. Method Development**

**Table 3.1. Instrument Details**

<b>Type/ Model</b>	
<b>Manufacturer</b>	
<b>Last Performance Qualification (PQ) Date</b>	
<b>Optical Size Range (µm)</b>	
<b>Spectral Range (cm<sup>-1</sup>)</b>	
<b>Spectral Resolution (cm<sup>-1</sup>)</b>	
<b>Size of Scan Area (unit<sup>2</sup>)</b>	
<b>Laser Specification</b>	
<b>a. Wavelength (nm)</b>	

<b>b. Power Output (mW)</b>	
<b>c. Laser Spot Size (μm)</b>	
<b>Minimum Measurable Particle Size (μm)</b>	

**Table 3.2. Sample Preparation**

<b>Method</b>	<input type="checkbox"/> Wet measurement (If “Wet”, fill Table 3.2.a) <input type="checkbox"/> Dry measurement (If “Dry”, fill Table 3.2.b) <input type="checkbox"/> Other (please specify and provide relevant information under Table 3.2)
<b>Sample Substrate (plate details with dimensions)</b>	
<b>Sample Preparation Steps</b> [for nasal and orally inhaled drug products please also specify the spray#(s) and life stage(s), if applicable].	
<b>Temperature of the Laboratory</b>	
<b>Data Location</b> (link for representative images of prepared sample on plate/slide)	

**Table 3.2.a. Wet Sample Preparation**

<b>Is any pressure applied to the cover slip?</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Is any sealant used?</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No (If “Yes”, describe sealant.)
<b>Is the sample modified (e.g., diluent, surfactant, contrasting agent) from its native state? *</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No (If “Yes”, please provide location and link of supporting experimental data)
<b>Has the sample undergone ultrasonication, evaporation or freezing?*</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No (If “Yes”, please provide location and link of supporting experimental data)
<b>Volume of sample used (unit)</b>	
<b>Is the volume of sample optimized? *</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No (If “Yes”, please provide location and link of supporting experimental data)
<b>Settling time (unit)</b>	
<b>Is the settling time optimized? *</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No (If “Yes”, location and link of experimental data)

\* Please provide supporting experimental data in the study report and relevant location and link in Table 3.2.a.

**Table 3.2.b. Dry Sample Preparation**

<b>Dispersion Method</b>	
<b>Solid Dispersion Unit (SDU) Settings (if applicable)</b>	Injection Pressure (bar)
	Injection Time (ms)
	Settling Time (sec)
	Powder volume

**Table 3.3. Particle Imaging and Morphology Analysis**

<b>Number of Particles Imaged</b>	
<b>List of Distinct Morphological Groups</b> (e.g., primary particle, spherical, rodlike, oval, needle shape, rough surface, smooth surface, agglomerate, touching particle etc)*	
<b>Percentage (%) of touching particles? *</b>	

(Please provide detailed information)	
<b>Percentage (%) of aggregates of particles? *</b> (Please provide detailed information)	
<b>Data Location</b> (link for individual particle images)	

\* Please provide supporting experimental data and images of individual particles in the study report and relevant link and location in Table 3.3.

**Table 3.4. Raman Spectrum (Molecular Fingerprinting) and Spectral Classification of API and Excipients**

<b>API used for Raman Spectral Library</b>	
<b>Source and Purity of API</b>	
<b>Polymorph of API (if any)</b>	
<b>API Exposure Time (seconds)</b>	
<b>Raman Spectral Region for API (x cm<sup>-1</sup> to y cm<sup>-1</sup>)</b>	
<b>Signature Peaks for API (cm<sup>-1</sup>)</b>	
<b>Excipient(s) Used for Raman Spectral Library</b>	
<b>Excipient(s) Exposure Time (seconds)</b>	
<b>Raman Spectral Region for Excipients (x cm<sup>-1</sup> to y cm<sup>-1</sup>)</b>	
<b>Is there any overlapping peak(s) in signature peak region?</b>	<input type="checkbox"/> No <input type="checkbox"/> Yes (if yes, provide detailed information)
<b>Sample Stage/ Substrate (background spectrum)</b>	
<b>Location and Link for Representative Spectrum of API and Excipients (Intensity vs Raman Shift, cm<sup>-1</sup>)</b>	
<b>Cut-off for Raman Spectral Correlation</b>	

**Table 3.5.a. Morphology Filter Selection for T Product**

Filter Selection for T Product*					
API	No Filter	Filter(s) combination	Filter(s) combination	Filter(s) combination	Add Columns as needed
<b>API Particle Count</b>					
<b>Excipient Particle Count</b>					
<b>Total Particle Count</b>					
<b>% API Particles</b>					
<b># API Particles Removed</b>					
<b># Excipient Particles Removed</b>					
<b>% API Particles Retained</b>					
<b>% Excipient Particles Removed</b>					
<b>Morphology Filter(s) Combination that Adequately Fit for T Product</b>					
<b>Data Location</b> (link for normalized distribution curves for API and excipients including plots of normalized particles count vs morphology filter)					

\*e.g., Circular equivalent (CE) diameter, aspect ratio/ elongation, circularity, convexity, intensity mean, solidity, etc.

**Table 3.5.b. Morphology Filter Selection for R Product**

Filter Selection for R Product*					
API	No Filter	Filter(s) combination	Filter(s) combination	Filter(s) combination	Add Columns as needed
<b>API Particle Count</b>					
<b>Excipient Particle Count</b>					
<b>Total Particle Count</b>					
<b>% API Particles</b>					
<b># API Particles Removed</b>					
<b># Excipient Particles Removed</b>					
<b>% API Particles Retained</b>					
<b>% Excipient Particles Removed</b>					

<b>Morphology Filter(s) Combination that Adequately Fit for R Product</b>	
<b>Data Location</b> (link for normalized distribution curves for API and excipients including plots of normalized particles count vs morphology filter)	
<b>Final Morphology Filter(s) Combinations Selected that Adequately Fit for both T and R Products</b>	

\*e.g., Circular equivalent (CE) diameter, aspect ratio/ elongation, circularity, convexity, intensity mean, solidity, etc.

**Table 3.6. Determination of Minimum Number of Particles to be Measured**

<b>Was API Particle Size Distribution Measured with Different Particles Count?</b>				<input type="checkbox"/> No <input type="checkbox"/> Yes (if yes, provide following information)		
<b>Program/ Software Used</b>						
<b>Particle Count</b>	<b>N</b>	<b>D10(μm)</b>	<b>D50(μm)</b>	<b>D90(μm)</b>	<b>Dmean(μm)</b>	<b>SPAN</b>
		Mean ± %RSD	Mean ± %RSD	Mean ± %RSD	Mean ± %RSD	Mean ± %RSD
		Mean ± %RSD	Mean ± %RSD	Mean ± %RSD	Mean ± %RSD	Mean ± %RSD
		Mean ± %RSD	Mean ± %RSD	Mean ± %RSD	Mean ± %RSD	Mean ± %RSD
		Mean ± %RSD	Mean ± %RSD	Mean ± %RSD	Mean ± %RSD	Mean ± %RSD
		Mean ± %RSD	Mean ± %RSD	Mean ± %RSD	Mean ± %RSD	Mean ± %RSD
Please add additional row(s) as needed						
<b>Optimized Particles Count Selected for Final Method</b>						

**Table 4: Final MDRS Method Parameters**

<b>Sample Carrier</b>	
<b>Illumination</b>	
<b>Cal Intensity</b>	
<b>Optics (Magnification)</b>	
<b>Type of Focus</b>	
<b>Threshold</b>	
<b>Trash Size (pixels)</b>	
<b>Scan Area</b>	
<b>Hole Filling</b>	
<b>Morphology Filters</b>	<b>Circular equivalent (CE) Diameter:</b> <b>Aspect ratio/ Elongation:</b> <b>Circularity:</b> <b>Intensity Mean:</b> <b>Convexity:</b> <b>Solidity:</b>
<b>Particle Number</b>	
<b>Exposure Time</b>	
<b>Number of Co-adds</b>	
<b>Low Laser Power</b>	
<b>Chemical Library</b>	
<b>Chemical Analysis</b>	
<b>Pre-processing</b>	
<b>Raman Correlation Score</b>	

Note: If you used any orthogonal method(s) for PSD measurement of active ingredient particles that are not suitable for evaluation by MDRS, please provide detailed study report and relevant BE summary tables for the orthogonal method separately. The orthogonal method(s) for PSD measurement should be validated appropriately and the validation report should be submitted.

**Table 5: Method Validation**

**Table 5.1. Accuracy\***

Size (known) of Standard Particles (unit)	X1 (unit)	X2 (unit)	X3 (unit)	X4 (unit)	Add columns as needed
<b>Measurements</b>	<b>CE Diameter (unit)</b>				
1					
2					
3					
<b>Mean</b>					
<b>SD</b>					
<b>%RSD</b>					
<b>Location and link of performance qualification (PQ) data</b>					

\* Please provide performance qualification (PQ) data less than a year old at the time of study along with the study report and provide location and link in Table 5.1.

**Table 5.2. Precision**

<b>RLD/RS Product Batch/ Lot (with expiration date) # Used for Method Validation</b>	
For nasal and orally inhaled drug products please also specify the spray#(s) and life stage(s), if applicable.	

Replicates	CE Diameter (unit)			SPAN
	Dv10	Dv50	Dv90	
1				
2				
3				
4				
5				
6				
<b>Mean (N=)</b>				
<b>SD</b>				
<b>%RSD</b>				
<b>Range</b>				

**Table 5.2.a. Intermediate Precision (By Date)**

Day 1				
Replicates	CE Diameter (unit)			SPAN
	Dv10	Dv50	Dv90	
1				
2				
3				
4				
5				
6				
<b>Mean (N=)</b>				
<b>SD</b>				
<b>%RSD</b>				
<b>Range</b>				
Day 2				
Replicates	CE Diameter (unit)			SPAN
	Dv10	Dv50	Dv90	
1				
2				

3				
4				
5				
6				
Mean (N=)				
SD				
%RSD				
Range				
% Difference between Means of Day 1 and Day 2				
Inter-day %RSD				

Table 5.2.b. Intermediate Precision (By Analyst)

Analyst 1				
Replicates	CE Diameter (unit)			SPAN
	Dv10	Dv50	Dv90	
1				
2				
3				
4				
5				
6				
Mean (N=)				
SD				
%RSD				
Range				
Analyst 2				
Replicates	CE Diameter (unit)			SPAN
	Dv10	Dv50	Dv90	
1				
2				
3				
4				
5				
6				
Mean (N=)				
SD				
%RSD				
Range				
% Difference between Means by Analyst 1 and Analyst 2				
Inter Analyst %RSD				

Table 5.3. Specificity

Placebo*				
Replicates	CE Diameter (unit)			SPAN
	Dv10	Dv50	Dv90	
1				
2				
3				
4				
5				
6				
Mean (N=)				
SD				

<b>%RSD</b>				
<b>Range</b>				
<b>Placebo Spiked with API</b>				
<b>Replicates</b>	<b>CE Diameter (unit)</b>			
	<b>Dv10</b>	<b>Dv50</b>	<b>Dv90</b>	<b>SPAN</b>
<b>1</b>				
<b>2</b>				
<b>3</b>				
<b>4</b>				
<b>5</b>				
<b>6</b>				
<b>Mean (N=)</b>				
<b>SD</b>				
<b>%RSD</b>				
<b>Range</b>				

\* Please provide composition and manufacturing details of placebo and Raman spectrum (overlay) of background, placebo and placebo spiked with API in the report. Please identify the characteristic peak(s) for placebo and API and submit relevant particle images in the study report. Please provide relevant location and link of images in Table 5.3.

**Table 5.4. Robustness**

**Table 5.4.a. Altered Sample Amount/ Volume (if applicable)**

<b>Altered Conditions</b>	<b>CE Diameter (unit)</b>			
	<b>Dv10</b>	<b>Dv50</b>	<b>Dv90</b>	<b>SPAN</b>
<b>Sample Amount/ Volume-1 (N=6)</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>
<b>Sample Amount/ Volume-2 (N=6)</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>
<b>Sample Amount/ Volume-3 (N=6)</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>
<b>Mean (N=)</b>				
<b>SD</b>				
<b>%RSD</b>				
<b>Range</b>				

**Table 5.4.b. Altered Scan Area (if applicable)**

<b>Altered Conditions</b>	<b>CE Diameter (unit)</b>			
	<b>Dv10</b>	<b>Dv50</b>	<b>Dv90</b>	<b>SPAN</b>
<b>Scan Area-1 (N=6)</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>
<b>Scan Area-2 (N=6)</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>
<b>Scan Area-3 (N=6)</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>
<b>Mean (N=)</b>				
<b>SD</b>				
<b>%RSD</b>				
<b>Range</b>				

**Table 5.4.c. Altered Settling Time (if applicable)**

<b>Altered Conditions</b>	<b>CE Diameter (unit)</b>			
	<b>Dv10</b>	<b>Dv50</b>	<b>Dv90</b>	<b>SPAN</b>
<b>Settling Time-1 (n=6)</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>
<b>Settling Time-2 (n=6)</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>
<b>Settling Time-3 (n=6)</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>
<b>Mean (N=)</b>				
<b>SD</b>				
<b>%RSD</b>				
<b>Range</b>				

**Table 5.4.d. Altered Threshold Selection (if applicable)**

Altered Conditions	CE Diameter (unit)			SPAN
	Dv10	Dv50	Dv90	
Threshold-1 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Threshold-2 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Threshold-3 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Mean (N=)				
SD				
%RSD				
Range				

Table 5.4.e. Altered Percent Overlap (if applicable)

Altered Conditions	CE Diameter (unit)			SPAN
	Dv10	Dv50	Dv90	
Percent Overlap-1 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Percent Overlap-2 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Percent Overlap-3 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Mean (N=)				
SD				
%RSD				
Range				

Table 5.4.f. Altered Particle Count (if applicable)

Altered Conditions	CE Diameter (unit)			SPAN
	Dv10	Dv50	Dv90	
Particle Count-1 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Particle Count-2 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Particle Count-3 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Mean (N=)				
SD				
%RSD				
Range				

Table 5.4.g. Altered Morphology Filters Combinations (if applicable)

Altered Conditions	CE Diameter (unit)			SPAN
	Dv10	Dv50	Dv90	
Combination-1 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Combination-2 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Combination-3 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Combination-4 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Combination-5 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Combination-6 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Mean (N=)				
SD				
%RSD				
Range				

Table 5.4.h. Altered Correlation Score (if applicable)

Altered Conditions	CE Diameter (unit)			SPAN
	Dv10	Dv50	Dv90	
Correlation Score-1 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Correlation Score-2 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Correlation Score-3 (n=6)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Mean (N=)				
SD				
%RSD				
Range				



**Table 5.4.i. Acceptance Criteria defined by SOP**

Validation Parameters	Acceptance Criteria
Accuracy	
Precision	
Intermediate Precision by Date	
Intermediate Precision by Analyst	
Specificity	
Robustness	

**Table 6. Pivotal Particle Size Distribution by MDRS**

D <sub>50</sub> Summary										
		Mean		Variability (%CV)				Mean Ratio (T/R)		
		Arith	Geo	Within Lot (n=10)			Between Lot (n=30)	Total (n=30)	Arith (n=30)	Geo (n=30)
				Lot 1	Lot 2	Lot 3				
BEG *	Test									
END*										
BEG*	Ref									
END*										

SPAN Summary										
		Mean		Variability (%CV)				Mean Ratio (T/R)		
		Arith	Geo	Within Lot (n=10)			Between Lot (n=30)	Total (n=30)	Arith (n=30)	Geo (n=30)
				Lot 1	Lot 2	Lot 3				
BEG *	Test									
END*										
BEG*	Ref									
END*										

\*Please include individual life stage data as applicable.

**Table 7: Summary of Population Bioequivalence Results**

Variable	Mean (log Scale)		Mean Difference (log Scale)	Standard Deviation		Sigma T/ Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
Dv50						
Scaled	Linearized Point Estimate		95% Upper Confidence Bound	Pass or Fail PBE		
Reference scaled						
Constant-scaled						

Variable	Mean (log Scale)		Mean Difference (log Scale)	Standard Deviation		Sigma T/ Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
SPAN						
Scaled	Linearized Point Estimate		95% Upper Confidence Bound	Pass or Fail PBE		
Reference scaled						
Constant-scaled						