

BIOEQUIVALENCE SUMMARY TABLES FOR AQUEOUS NASAL SPRAY PRODUCTS

Please note that the tables listed in this document only include the bioequivalence summary tables related to the **in vitro** tests recommended in the “Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (April 2003)”. For the bioequivalence summary tables related to the **in vivo** BE tests, the sponsor should refer to the Bioequivalence Summary Tables published on the Office of Generic Drugs website at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf>

Table 1. Formulation Table

| INGREDIENTS | TEST | | | REFERENCE | | |
|------------------------|----------------------|---------------|---------|----------------------|---------------|---------|
| | Amount per Actuation | Amount per mL | % (w/w) | Amount per Actuation | Amount per mL | % (w/w) |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| TOTALS | | | | | | |
| NET FILL WEIGHT | | | | | | |

Table 2. Batch Information

| Study Type | TEST | | | | REFERENCE | | | |
|-------------------------------------|---------|------------|----------------------------|--------------------|------------------|---------|------------|-----------------|
| | Lot No. | Potency*** | Lot Size (# of Bottles) | | Manufacture Date | Lot No. | Potency*** | Expiration Date |
| | | | Theoretical | # actually bottled | | | | |
| Bioequivalence study (PK study)* | | | | | | | | |
| In-Vitro equivalence studies ** | | | | | | | | |
| | | | | | | | | |

* If recommended

** Include lot numbers from each in vitro test

*** Data obtained from Certificate of Analysis

Table 3. Device Comparability

| | | TEST | REFERENCE |
|--|--------------------------|-------------|------------------|
| Container Description | | | |
| Protection Cap Description | | | |
| Pump (brand/ model/material) | | | |
| Actuator (brand/ model/material) | | | |
| Actuator Orifice Diameter | | | |
| Metering Valve (brand/ model/material) | | | |
| Volume of Metering Chamber | | | |
| Diptube | Internal Diameter | | |
| | Length | | |

Table 4. Actuation Methods

| | | | |
|--|----------------------|---|-----|
| Which tests (if any) used MANUAL actuation? | | | |
| If some tests used manual actuation(s), describe methods used to avoid T to RLD bias in dose release. | | | |
| Which tests (if any) used AUTOMATED actuation? | | | |
| What were the parameters of automated actuation? (units)* | | T | RLD |
| | Force | | |
| | Velocity | | |
| | Acceleration | | |
| | Initial Delay | | |
| | Hold Time | | |
| Final Delay | | | |
| Are the actuation parameters the same for the test and reference products? | Yes / No | | |

* Parameters may vary depending on the equipment used.

The Table 5 Series is for Single Actuation Content through Container Life Test

Table 5. 1. Study Information

| | |
|--|--|
| Study No. | |
| Study Site | |
| Principal Investigator | |
| Study Dates | |
| SOP No. | |
| SOP Effective Date | |
| SOP Title | |
| Test Method Description | |
| Testing Equipment Used (e.g., name, model, etc) | |
| Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..) | |
| Analytical Method Description | |
| Analytical Equipment Used (e.g., name, model, etc.) | |

Table 5. 2. Analytical Method Validation for HPLC

| | |
|---|--------------------|
| Information Requested | |
| Analytical method validation report location | |
| Study Report Number | |
| Analyte | |
| Internal Standard (IS) | Only If Applicable |
| Method description | |
| Selectivity or Specificity | |
| Limit of quantitation | |
| Detection Limit | |
| Linearity Range (ng, mcg/mL) | |
| Linearity (R²) | |
| Accuracy (% recovery at the high and low concentrations) | |
| Precision -- Repeatability | |
| Precision --Intermediate Precision | |
| Bench-top stability (hrs(CV%)) (working std solution) | |
| Refrigerator stability (hrs(CV%)) (working std solution) | Only If Applicable |

| | |
|--|--------------------|
| Stock solution stability (days (CV %)) | |
| Freeze-thaw stability (cycles (CV %)) | Only If Applicable |
| Robustness | |
| Dilution integrity | Only If Applicable |

Calibration of Manual and/or Automated Spray Pump Actuator (For Single Actuation Content and Priming/Repriming studies)

Table 5.3.1. Precision

| | Manual | | Automated | |
|-------------|--------------------|------------------|--------------------|------------------|
| | Content Assay (µg) | Shot Weight (mg) | Content Assay (µg) | Shot Weight (mg) |
| Mean | | | | |
| %RSD | | | | |

Table 5.3.2. Ruggedness (By Date)

| Day 1 | Manual | | Automated | |
|--|--------------------|------------------|--------------------|------------------|
| | Content Assay (µg) | Shot Weight (mg) | Content Assay (µg) | Shot Weight (mg) |
| Mean | | | | |
| %RSD | | | | |
| Day 2 | Manual | | Automated | |
| | Content Assay (µg) | Shot Weight (mg) | Content Assay (µg) | Shot Weight (mg) |
| Mean | | | | |
| %RSD | | | | |
| %Difference Between Content Assay Means (Day 1 vs. Day 2) | | | | |
| %Difference Between Shot Weight Means (Day 1 vs. Day 2) | | | | |

Table 5.3.3. Ruggedness (By Analyst)

| Analyst 1 | Manual | | Automated | |
|-------------|--------------------|------------------|--------------------|------------------|
| | Content Assay (µg) | Shot Weight (mg) | Content Assay (µg) | Shot Weight (mg) |
| Mean | | | | |
| %RSD | | | | |
| Analyst 2 | Manual | | Automated | |

| | | | | |
|--|--------------------|------------------|--------------------|------------------|
| | | | | |
| | Content Assay (µg) | Shot Weight (mg) | Content Assay (µg) | Shot Weight (mg) |
| Mean | | | | |
| %RSD | | | | |
| %Difference Between Content Assay Mean (Analyst 1 vs Analyst 2) | | | | |
| %Difference Between Shot Weight Means (Analyst 1 vs Analyst 2) | | | | |

Table 5.3.4. Ruggedness (Unit to Unit if more than one unit is used)

| | | | | |
|--|--------------------|------------------|--------------------|------------------|
| Unit 1 | Manual | | Automated | |
| | Content Assay (µg) | Shot Weight (mg) | Content Assay (µg) | Shot Weight (mg) |
| Mean | | | | |
| %RSD | | | | |
| Unit 2 | Manual | | Automated | |
| | Content Assay (µg) | Shot Weight (mg) | Content Assay (µg) | Shot Weight (mg) |
| Mean | | | | |
| %RSD | | | | |
| %Difference Between Content Assay Means (Unit 1 vs. Unit 2) | | | | |
| %Difference Between Shot Weight Means (Unit 1 vs. Unit 2) | | | | |

Table 5. 4. Results Summary

| SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE | | | | | | | | | | | | |
|---|-------------|-----------|-----|---------------|-----|-------------------|-------|-------|-------------------|--------------|------------------|------------|
| | Spray # | Mean | | | | Variability (%CV) | | | | | Mean Ratio (T/R) | |
| | | Drug Mass | | % label claim | | Within Lot (n=10) | | | Between Lot (n=3) | Total (n=30) | Arithm (n=30) | Geo (n=30) |
| | | Arith | Geo | Arith | Geo | Lot 1 | Lot 2 | Lot 3 | | | | |
| BEG | Test | | | | | | | | | | | |
| | Ref | | | | | | | | | | | |
| END | Test | | | | | | | | | | | |
| | Ref | | | | | | | | | | | |

The Table 6 Series is for Priming & Re-priming Test

Table 6.1. Study Information

| | |
|--|--|
| Study No. | |
| Study site | |
| Principal Investigator | |
| Study dates | |
| SOP No. | |
| SOP Effective Date | |
| SOP Title | |
| Test Method Description | |
| Testing Equipment Used (e.g., name, model, etc) | |
| Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..) | |
| Analytical Method Description | |
| Analytical Equipment Used (e.g., name, model, etc) | |

Table 6. 2. Analytical Method Validation for HPLC

To be completed only if different from Table 5.2

| | |
|---|--------------------|
| Information Requested | |
| Analytical method validation report location | |
| Study Report Number | |
| Analyte | |
| Internal Standard (IS) | Only If Applicable |
| Method description | |
| Selectivity or Specificity | |
| Limit of quantitation | |
| Detection Limit | |
| Linearity Range (ng, mcg/mL) | |
| Linearity (R²) | |
| Accuracy (% recovery at the high and low concentrations) | |
| Precision -- Repeatability | |
| Precision --Intermediate Precision | |
| Bench-top stability (hrs(CV%)) (working std solution) | |
| Refrigerator stability (hrs(CV%)) (working std solution) | Only If Applicable |

| | |
|---|--------------------|
| Stock solution stability (days (CV %)) | |
| Freeze-thaw stability (cycles (CV %)) | Only If Applicable |
| Robustness | |
| Dilution integrity | Only If Applicable |

Table 6. 3. Results Summary – Priming & Re-Priming

| PRIMING | | | | | | | | | | | | |
|--|---------|-----------|-----|---------------|-----|-------------------|-------|-------|-------------------|--------------|------------------|------------|
| Number of actuations used to prime each product = | | | | | | | | | | | | |
| Actuation number used for testing each product = | | | | | | | | | | | | |
| | Spray # | Mean | | | | Variability (%CV) | | | | | Mean Ratio (T/R) | |
| | | Drug Mass | | % label claim | | Within Lot (n=10) | | | Between Lot (n=3) | Total (n=30) | Arithm (n=30) | Geo (n=30) |
| | | Arith | Geo | Arith | Geo | Lot 1 | Lot 2 | Lot 3 | | | | |
| Test | | | | | | | | | | | | |
| Ref | | | | | | | | | | | | |

| RE-PRIMING | | | | | | | | | | | | |
|---|---------|-----------|-----|---------------|-----|-------------------|-------|-------|-------------------|--------------|------------------|------------|
| Period of time each product was stored in the vertical position following priming (nasal sprays only) = | | | | | | | | | | | | |
| Number of actuations used to re-prime each product = | | | | | | | | | | | | |
| Actuation number used for testing each product = | | | | | | | | | | | | |
| | Spray # | Mean | | | | Variability (%CV) | | | | | Mean Ratio (T/R) | |
| | | Drug Mass | | % label claim | | Within Lot (n=10) | | | Between Lot (n=3) | Total (n=30) | Arithm (n=30) | Geo (n=30) |
| | | Arith | Geo | Arith | Geo | Lot 1 | Lot 2 | Lot 3 | | | | |
| Test | | | | | | | | | | | | |
| Ref | | | | | | | | | | | | |

The Table 7 Series is for Droplet Size Distribution by Laser Diffraction Test

Table 7. 1. Study Information

| | |
|---|---------------|
| Study No. | |
| Study site | |
| Principal Investigator | |
| Study dates | |
| SOP No. | |
| SOP Effective Date | |
| SOP Title | |
| Testing Method Description (including DSD measurement over entire life of spray, fully developed phase, etc) | |
| Study Distances (distances from actuator orifice) | |
| Testing Equipment Used (e.g., name, model, etc) | |
| Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..) | |
| Analytical Method Description | If applicable |
| Analytical Equipment Used (e.g., name, model, etc) | If applicable |

Validation Summary Tables for Droplet Size Distribution by Laser Diffraction

Table 7.2.1. Precision

| | D10 | | D50 | | D90 | | Span | |
|--------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm |
| Mean | | | | | | | | |
| %RSD | | | | | | | | |
| Range | | | | | | | | |

Table 7.2.2. Intermediate Precision (By Date)

| Day 1 | D10 | | D50 | | D90 | | Span | |
|-------------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm |
| Mean | | | | | | | | |
| %RSD | | | | | | | | |
| Day 2 | D10 | | D50 | | D90 | | Span | |
| | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm |
| Mean | | | | | | | | |
| %RSD | | | | | | | | |
| %Difference (Day 1 vs Day 2) | | | | | | | | |
| Interday %RSD | | | | | | | | |

Table 7.2.3. Intermediate Precision (By Analyst)

| Analyst 1 | D10 | | D50 | | D90 | | Span | |
|---|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm |
| Mean | | | | | | | | |
| %RSD | | | | | | | | |
| Analyst 2 | D10 | | D50 | | D90 | | Span | |
| | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm |
| Mean | | | | | | | | |
| %RSD | | | | | | | | |
| %Difference (Analyst 1 vs Analyst 2) | | | | | | | | |

| | | | | | | | | | |
|--------------------|--|--|--|--|--|--|--|--|--|
| Inter analyst %RSD | | | | | | | | | |
|--------------------|--|--|--|--|--|--|--|--|--|

Table 7.3. Results Summary – Droplet Size Distribution by Laser Diffraction

| D ₅₀ Summary | | | | | | | | | | | |
|-------------------------|-----|----------------|--------|-----|-------------------|-------|-------|-------------------|--------------|------------------|------------|
| | | Test Dist (cm) | Mean | | Variability (%CV) | | | | | Mean Ratio (T/R) | |
| | | | | | Within Lot (n=10) | | | Between Lot (n=3) | Total (n=30) | Arithm (n=30) | Geo (n=30) |
| | | | Arithm | Geo | Lot 1 | Lot 2 | Lot 3 | | | | |
| Test | BEG | | | | | | | | | | |
| | END | | | | | | | | | | |
| Ref | BEG | | | | | | | | | | |
| | END | | | | | | | | | | |

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

The Table 8 Series is for Drug in Small Particles / Droplets by Cascade Impactor (CI) Test

Table 8.1. Study Information

| | |
|--|--|
| Study No. | |
| Study site | |
| Principal Investigator | |
| Study dates | |
| SOP No. | |
| SOP Effective Date | |
| SOP Title | |
| Testing Method Description | |
| Testing Equipment Used (e.g., name, model, etc) | |
| Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..) | |
| Analytical Method Description | |
| Analytical Equipment Used (e.g., name, model, etc) | |

Validation Summary Table for Particle Size Distribution by Cascade Impactor

Table 8.2. Analytical Method Validation for HPLC

| | |
|---|--------------------|
| Information Requested | |
| Analytical method validation report location | |
| Study Report Number | |
| Analyte | |
| Internal Standard (IS) | Only If Applicable |
| Method description | |
| Selectivity or Specificity | |
| Limit of quantitation | |
| Detection Limit | |
| Linearity Range (ng, mcg/mL) | |
| Linearity (R²) | |
| Accuracy (% recovery at the high and low concentrations) | |
| Precision -- Repeatability | |
| Precision -- Intermediate Precision | |
| Bench-top stability (hrs) (working std solution) | |

| | |
|---|--------------------|
| Refrigerator stability (hrs) (working std solution) | Only If Applicable |
| Stock solution stability (days) | |
| Freeze-thaw stability (cycles) | Only If Applicable |
| Robustness | |
| Dilution integrity | Only If Applicable |

Validation Tables for Cascade Impaction

Note: Mass of drug above and below the top stage of the cascade impactor is requested. The 9.0 micron cut point for the top stage assumes use of the Andersen Cascade Impactor. The cut point may be different for other impactors.

Table 8.3.1. Precision

| | >9.0 um* | <9.0 um* | Sum | Mass Balance% |
|----------------------------|----------|----------|-----|---------------|
| Mean of n** (Amount/spray) | | | | |
| % RSD | | | | |

* Based on the cutpoint for the top stage of the USP Apparatus I (<601>) operated at 28.3 LPM.

** n is the number of runs in the validation study.

Table 8.3.2. Intermediate Precision (By Date)

| Day 1 | >9.0 um | <9.0 um | Sum | Mass Balance% |
|--------------------------------------|---------|---------|-----|---------------|
| Mean of n* (Amount/spray) | | | | |
| %RSD | | | | |
| Day 2 | | | | |
| Mean of n* (Amount/spray) | | | | |
| %RSD | | | | |
| % Difference in RSD (Day 1 vs Day 2) | | | | |
| Interday %RSD | | | | |

* n is the number of runs in the validation study.

Table 8.3.3. Intermediate Precision (By Analyst)

| Analyst 1 | >9.0 um | <9.0 um | Sum | Mass Balance% |
|---|---------|---------|-----|---------------|
| Mean of n* (Amount/spray) | | | | |
| %RSD | | | | |
| Analyst 2 | | | | |
| Mean of n* (Amount/spray) | | | | |
| %RSD | | | | |
| %Difference in RSD (Analyst 1 vs Analyst 2) | | | | |
| Inter analyst %RSD | | | | |

* n is the number of runs in the validation study.

Table 8.4. Results Summary – Drug in Small Particles / Cascade Impactor (CI)

| DRUG MASS IN SMALL PARTICLES / DROPLETS PER GROUPING | | | | | | | | | | |
|--|------|-----------------|-----|-------------------|-------|-------|-------------------|--------------|------------------|------------|
| | | Drug Deposition | | Variability (%CV) | | | | | Mean Ratio (T/R) | |
| | | | | Within Lot (n=10) | | | Between Lot (n=3) | Total (n=30) | | |
| | | Arithm | Geo | Lot 1 | Lot 2 | Lot 3 | | | Arithm (n=30) | Geo (n=30) |
| Total A* (expressed as mass) | Test | | | | | | | | | |
| | Ref | | | | | | | | | |
| Total B** (expressed as mass) | Test | | | | | | | | | |
| | Ref | | | | | | | | | |
| Total B** (expressed as % of label claim) | Test | | | | | | | | | |
| | Ref | | | | | | | | | |

* **Total A** = Total mass of drug collected from stages and accessories **below stage 1 (e.g., < 9 µm in size)**

** **Total B** = Total mass (or % of label claim) of drug collected from **ALL stages and accessories** of cascade impactor

| MASS BALANCE (% of label claim) | | |
|--|------|--|
| Arithmetic Mean and Range (Min – Max) (n=30) | | |
| Mass Balance (%) | Test | |
| | Ref | |

The Table 9 Series is for Spray Pattern Test

Table 9.1. Study Information

| | |
|--|--|
| Study No. | |
| Study site | |
| Principal Investigator | |
| Study dates | |
| SOP No. | |
| SOP Effective Date | |
| SOP Title | |
| Testing Method Description | |
| Study Distances (distances from actuator orifice) | |
| Testing Equipment Used (e.g., name, model, etc) | |
| Image Analysis Apparatus Used | (i.e., automated = Laser Imaging; or manual = TLC) |
| Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..) | |
| Analytical Method Description | If applicable |
| Analytical Equipment Used (e.g., name, model, etc) | If applicable |

Validation Summary Tables for Spray Pattern

Table 9.2.1. Precision

| | Area* | | Ovality Ratio | |
|--------------|---------------------|---------------------|---------------------|---------------------|
| | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm |
| Mean | | | | |
| %RSD | | | | |
| Range | | | | |

*This parameter varies with the type of spray pattern analysis. If it is an automated analysis, e.g., Laser imaging, “area” should be used. If it is a manual analysis, e.g., TLC, “Dmax” should be used.

Table 9.2.2. Intermediate Precision (By Date)

| Day 1 | Area* | | Ovality Ratio | |
|---------------------------------------|---------------------|---------------------|---------------------|---------------------|
| | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm |
| Mean | | | | |
| %RSD (Precision/Repeatability) | | | | |
| Day 2 | Area | | Ovality Ratio | |
| | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm |
| Mean | | | | |
| %RSD (Precision/Repeatability) | | | | |
| %Difference (Day 1 vs. Day 2) | | | | |
| Interday %RSD** | | | | |

*This parameter varies with the type of spray pattern analysis. If it is an automated analysis, e.g., Laser imaging, “area” should be used. If it is a manual analysis, e.g., TLC, “Dmax” should be used.

** RSD of all day 1 and day 2 data.

Table 9.2. 3. Intermediate Precision (By Analyst)

| Analyst 1 | Area* | | Ovality Ratio | |
|---------------------------------------|---------------------|---------------------|---------------------|---------------------|
| | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm |
| Mean | | | | |
| %RSD (Precision/Repeatability) | | | | |
| Range | | | | |
| | Area* | | Ovality Ratio | |
| Analyst 2 | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm | Dist1 e.g., 3 cm | Dist2 e.g., 6 cm |
| Mean | | | | |
| %RSD (Precision/Repeatability) | | | | |
| Range | | | | |

| | | | | |
|--|--|--|--|--|
| %Difference (Analyst 1 vs. Analyst 2) | | | | |
| Inter analyst %RSD** | | | | |

*This parameter varies with the type of spray pattern analysis. If it is an automated analysis, e.g., Laser imaging, “area” should be used. If it is a manual analysis, e.g., TLC, “Dmax” should be used.

** RSD of all Chemist 1 and Chemist 2 data.

Table 9.3. Results Summary – Spray Pattern

| Area* – Spray Pattern Summary | | | | | | | | | | |
|--------------------------------------|------------------|-------------|-----|--------------------------|-------|-------|-------------------|--------------|-------------------------|------------|
| | Dist (cm) | Mean | | Variability (%CV) | | | | | Mean Ratio (T/R) | |
| | | | | Within Lot (n=10) | | | Between Lot (n=3) | Total (n=30) | | |
| | | Arithm | Geo | Lot 1 | Lot 2 | Lot 3 | | | Arithm (n=30) | Geo (n=30) |
| Test | | | | | | | | | | |
| Ref | | | | | | | | | | |

*This parameter varies with the type of spray pattern analysis. If it is an automated analysis, e.g., Laser imaging, “area” should be used. If it is a manual analysis, e.g., TLC, “Dmax” should be used.

| OVALITY RATIO – Spray Pattern Summary | | | | | | | | | | |
|--|------------------|-------------|-----|--------------------------|-------|-------|-------------------|--------------|-------------------------|------------|
| | Dist (cm) | Mean | | Variability (%CV) | | | | | Mean Ratio (T/R) | |
| | | | | Within Lot (n=10) | | | Between Lot (n=3) | Total (n=30) | | |
| | | Arithm | Geo | Lot 1 | Lot 2 | Lot 3 | | | Arithm (n=30) | Geo (n=30) |
| Test | | | | | | | | | | |
| Ref | | | | | | | | | | |

The Table 10 Series is for Plume Geometry Test

Table 10.1. Study Information

| | |
|--|---------------|
| | |
| Study No. | |
| Study site | |
| Principal Investigator | |
| Study dates | |
| SOP No. | |
| SOP Effective Date | |
| SOP Title | |
| Testing Method Description | |
| Criteria for defining plume angle, width, & height borders | |
| Testing Equipment Used (e.g., name, model, etc) | |
| Image Analysis Apparatus Used | |
| Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..) | |
| Analytical Method Description | If applicable |
| Analytical Equipment Used (e.g., name, model, etc) | If applicable |

Validation Summary Tables for Plume Geometry

Table 10.2.1. Precision

| | Plume Width | Plume Angle |
|-------|-------------|-------------|
| Mean | | |
| %RSD | | |
| Range | | |

Table 10.2.2. Intermediate Precision (By Date)

| Day 1 | Plume Width | Plume Angle |
|---------------------------------------|-------------|-------------|
| Mean | | |
| %RSD (Precision/Repeatability) | | |
| Range | | |
| Day 2 | | |
| Mean | | |
| %RSD (Precision/Repeatability) | | |
| Range | | |
| %Difference (Analyst 1 vs. Analyst 2) | | |
| Inter day %RSD* | | |

** RSD of all day 1 and day 2 data.

Table 10.2.3. Intermediate Precision (By Analyst)

| Analyst 1 | | |
|--------------------------------------|--|--|
| Mean | | |
| %RSD (Precision/Repeatability) | | |
| Range | | |
| Analyst 2 | | |
| Mean | | |
| %RSD (Precision/Repeatability) | | |
| Range | | |
| %Difference (Analyst 1 vs Analyst 2) | | |
| Inter Analyst %RSD* | | |

* RSD of all analyst 1 and analyst 2 data.

Table 10.2.4. Robustness for varies parameters (the selection of parameters is optional)

| | Plume Width | | | | Plume Angle | | | |
|--------------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| Parameter* | camera distance 1* | camera distance 2* | camera distance 3* | camera distance 4* | camera distance 1* | camera distance 2* | camera distance 3* | camera distance 4* |
| Mean | | | | | | | | |
| %RSD (Precision/Repeatability) | | | | | | | | |

* The selection of parameters is optional. Examples of parameters of robustness study include camera distance, delay time, velocity, acceleration, etc...

Table 10. 3. Results – Plume Geometry

| | Mean | | Variability (%CV) | | | | | Mean Ratio (T/R) | |
|------------------------|-------|-----|-------------------|-------|-------|-------------------|--------------|------------------|-----|
| | | | Within Lot (n=10) | | | Between Lot (n=3) | Total (n=30) | | |
| | Arith | Geo | Lot 1 | Lot 2 | Lot 3 | | | Arith | Geo |
| Plume Angle (°) | | | | | | | | | |
| Test | | | | | | | | | |
| Ref | | | | | | | | | |
| Plume Width | | | | | | | | | |
| Test | | | | | | | | | |
| Ref | | | | | | | | | |
| Plume Height | | | | | | | | | |
| Test | | | | | | | | | |
| Ref | | | | | | | | | |

SAS Data Tables for Aqueous Nasal Spray Product In Vitro Bioequivalence Study Data Submission

Data in these tables should be arranged in columns as shown in examples. Data sets should be submitted as SAS Transport files.

Table 1. Single Actuation Content through Container Life

| Variable Name | Variable Label | Variable Type | Content | Notes |
|-----------------|---|----------------------------------|----------------------------------|--|
| PRODUCT | Product Name | Character | TEST or REF | Identifier for product |
| SECTOR | Lifestage | Character | B, or E | B=Beginning; E=End |
| LOT | Lot number | Alphanumeric/ Numeric | Alphanumeric/ Numeric | Identifier for product lot |
| CONTAIN | Bottle or container Number | Numeric | Numeric values | Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref). |
| <i>ACTUAT</i> | <i>Spray Number</i> | <i>Numeric</i> | <i>Numeric values</i> | <i>Actual spray number corresponding to B or E life stages.</i> |
| AMOUNT | Actual delivered amount of drug mass | Numeric | Numeric values | Drug mass per single actuation |
| PCTLABEL | Percentage of label claim | Numeric | Numeric values | Percentage of drug mass per single actuation |

Example

| PRODUCT | SECTOR | LOT | CONTAIN | ACTUAT | AMOUNT | PCTLABEL |
|----------------|---------------|------------|----------------|---------------|---------------|-----------------|
| TEST | B | 1234 | 1 | | | |
| | | | 2 | | | |
| | | | 3 | | | |
| | | | 4 | | | |
| | | | 5 | | | |
| | | | 6 | | | |
| | | | 7 | | | |
| | | | 8 | | | |
| | | | 9 | | | |
| | | | 10 | | | |

Table 2. Priming and Repriming

| Variable Name | Variable Label | Variable Type | Content | Notes |
|----------------------|---|----------------------------------|----------------------------------|--|
| PRODUCT | Product Name | Character | TEST or REF | Identifier for product |
| SECTOR | Lifestage | Character | B | B=Beginning. Lifestage not specified for repriming data. |
| LOT | Lot number | Alphanumeric/ Numeric | Alphanumeric/ Numeric | Identifier for product lot |
| CONTAIN | Bottle or container Number | Numeric | Numeric values | Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref). |
| ACTUAT | Spray Number | Numeric | Numeric values | Actual spray number |
| AMOUNT | Actual delivered amount of drug mass | Numeric | Numeric values | Drug mass per single actuation |
| PCTLABEL | Percentage of label claim | Numeric | Numeric values | Percentage of drug mass per single actuation |

Example

| PRODUCT | SECTOR | LOT | CONTAIN | ACTUAT | AMOUNT | PCTLABEL |
|----------------|---------------|------------|----------------|---------------|---------------|-----------------|
| TEST | B | 1234 | 1 | | | |
| | | | 2 | | | |
| | | | 3 | | | |
| | | | 4 | | | |
| | | | 5 | | | |
| | | | 6 | | | |
| | | | 7 | | | |
| | | | 8 | | | |
| | | | 9 | | | |
| | | | 10 | | | |

Table 3. Droplet Size Distribution by Laser Diffraction

| Variable Name | Variable Label | Variable Type | Content | Notes |
|----------------------|-----------------------------------|------------------------------|------------------------------|---|
| PRODUCT | Product Name | Character | TEST or REF | Identifier for product |
| SECTOR | Lifestage | Character | B, or E | B=Beginning; E=End |
| LOT | Lot number | Alphanumeric/N umeric | Alphanumeric/N umeric | Identifier for product lot |
| DISTANCE | Distance | Numeric | Numeric values | Distance from the actuator tip to the laser beam (cm) |
| CONTAIN | Bottle or container Number | Numeric | Numeric values | Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref at each distance). |
| <i>ACTUAT</i> | <i>Spray Number</i> | <i>Numeric</i> | <i>Numeric values</i> | <i>Actual spray number corresponding to B or E life stages.</i> |
| D10 | D10 | Numeric | Numeric values | D10 |
| D50 | D50 | Numeric | Numeric values | D50 |
| D90 | D90 | Numeric | Numeric values | D90 |
| SPAN | SPAN | Numeric | Numeric values | SPAN calculated as ((D90-D10)/D50) |

Example

| PRODUCT | SECTOR | LOT | DISTANCE | CONTAIN | ACTUAT | D10 | D50 | D90 | SPAN |
|----------------|---------------|------------|-----------------|----------------|---------------|------------|------------|------------|-------------|
| TEST | B | 1234 | | 1 | | | | | |
| | | | | 2 | | | | | |
| | | | | 3 | | | | | |
| | | | | 4 | | | | | |
| | | | | 5 | | | | | |
| | | | | 6 | | | | | |
| | | | | 7 | | | | | |
| | | | | 8 | | | | | |
| | | | | 9 | | | | | |
| | | | | 10 | | | | | |

Table 4. Plume Geometry

| Variable Name | Variable Label | Variable Type | Content | Notes |
|----------------------|---|----------------------------------|----------------------------------|--|
| PRODUCT | Product Name | Character | TEST or REF | Identifier for product |
| SECTOR | Lifestage | Character | B | B=Beginning |
| LOT | Lot number | Alphanumeric/N umeric | Alphanumeric/N umeric | Identifier for product lot |
| CONTAIN | Bottle or container Number | Numeric | Numeric values | Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref). |
| HEIGHT | Height | Numeric | Numeric values | Plume height |
| WIDTH | Width | Numeric | Numeric values | Plume width |
| ANGLE | Angle | Numeric | Numeric values | Cone angle of one side view at one delay time |

Example

| PRODUCT | SECTOR | LOT | CONTAIN | HEIGHT | WIDTH | ANGLE |
|----------------|---------------|------------|----------------|---------------|--------------|--------------|
| TEST | B | 1234 | 1 | | | |
| | | | 2 | | | |
| | | | 3 | | | |
| | | | 4 | | | |
| | | | 5 | | | |
| | | | 6 | | | |
| | | | 7 | | | |
| | | | 8 | | | |
| | | | 9 | | | |
| | | | 10 | | | |

Table 5. Spray Pattern

| Variable Name | Variable Label | Variable Type | Content | Notes |
|-----------------|---|----------------------------------|----------------------------------|---|
| PRODUCT | Product Name | Character | TEST or REF | Identifier for product |
| SECTOR | Lifestage | Character | B, or E | B=Beginning; E=End |
| LOT | Lot number | Alphanumeric/N umeric | Alphanumeric/N umeric | Identifier for product lot |
| DISTANCE | Distance | Numeric | Numeric values | Distance from the actuator tip to the laser beam (cm) |
| CONTAIN | Bottle or container Number | Numeric | Numeric values | Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref at each distance). |
| <i>ACTUAT</i> | <i>Spray Number</i> | <i>Numeric</i> | <i>Numeric values</i> | <i>Actual spray number corresponding to B or E life stages.</i> |
| DMAX | Dmax | Numeric | Numeric values | Dmax |
| DMIN | Dmin | Numeric | Numeric values | Dmin |
| OVALITY | Ovality | Numeric | Numeric values | Ovality ratio (Dmax divided by Dmin) |
| AREA | Pattern Area | Numeric | Numeric values | Pattern area |

Example

| PRODUCT | SECTOR | LOT | DISTANCE | CONTAIN | ACTUAT | DMAX | DMIN | OVALITY | AREA |
|---------|--------|------|----------|---------|--------|------|------|---------|------|
| TEST | B | 1234 | | 1 | | | | | |
| | | | | 2 | | | | | |
| | | | | 3 | | | | | |
| | | | | 4 | | | | | |
| | | | | 5 | | | | | |
| | | | | 6 | | | | | |
| | | | | 7 | | | | | |
| | | | | 8 | | | | | |
| | | | | 9 | | | | | |
| | | | | 10 | | | | | |

Table 6. Drug in Small Particles/Droplets by Cascade Impactor

| Variable Name | Variable Label | Variable Type | Content | Notes |
|---------------|---|----------------------|----------------------|---|
| PRODUCT | Product Name | Character | TEST or REF | Identifier for product |
| SECTOR | Lifestage | Character | B | B=Beginning |
| LOT | Lot number | Alphanumeric/Numeric | Alphanumeric/Numeric | Identifier for product lot |
| CONTAIN | Bottle or container Number | Numeric | Numeric values | Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref). |
| AMT_ACT | Actual Amount of drug | Numeric | Numeric value | Actual amount of drug per spray |
| AMT_TOT | Total Amount at all Stages and Accessories | Numeric | Numeric values | Drug mass collected on all Stages and Accessories |
| AMT_LT 9 | Amount for Equal or Less Than 9 μm | Numeric | Numeric values | Drug mass collected for particles equal or less than 9 μm |
| MB_TOTAL | Mass Balance Total | Numeric | Numeric value | Mass balance for total drug mass collected on all stages and accessories |

See an example below:

Table 6. Drug in Small Particles/Droplets by Cascade Impactor:

| PRODUCT | SECTOR | LOT | CONTAIN | AMT_ACT | AMT_TOT | AMT_LT 9 | MB_TOTAL |
|---------|--------|------|---------|---------|---------|----------|----------|
| TEST | B | 1234 | 1 | | | | |
| | | | 2 | | | | |
| | | | 3 | | | | |
| | | | 4 | | | | |
| | | | 5 | | | | |
| | | | 6 | | | | |
| | | | 7 | | | | |
| | | | 8 | | | | |
| | | | 9 | | | | |
| | | | 10 | | | | |