# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*
75-759

# BIOEQUIVALENCE REVIEW

# OFFICE OF GENERIC DRUGS
# DIVISION OF BIOEQUIVALENCE

**ANDA # 75-759** **SPONSOR: ESI LEDERLE**
**DRUG AND DOSAGE FORM: Butorphanol Tartrate Nasal Spray**
**STRENGTH(S): 10 mg/mL**
**TYPES OF STUDIES:** ***In vitro***

TESTING LABORATORIES: _____
STUDY SUMMARY: Acceptable

DISSOLUTION: NA

**DSI INSPECTION STATUS**

| Inspection needed: NO | Inspection status: | Inspection results: |
|---|---|---|
| First Generic YES<br>New facility NO<br>For cause _____<br>Other _____ | Inspection requested: (date)<br>Inspection completed: (date) | |

PRIMARY REVIEWER: Nhan L. Tran BRANCH: II

INITIAL: _____ DATE: _____

TEAM LEADER: Shriniwas Nerurkar BRANCH: II

INITIAL: _____ /S/ DATE: 7/17/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

for

INITIAL: _____ /S/ DATE: 7/18/2001

**Butorphanol Tartrate**
**Nasal Spray, 10 mg/mL**
**ANDA # 75-759**
Reviewer: Nhan L. Tran
**MSWord: 75759SW.D99**

**ESI LEDERLE**
**2 Esterbrook Lane**
Cherry Hill, NJ
**Submission Date:**
**December 22, 1999**
**May 15, 2001**

# Review of A Submission

## I. Objective:

This submission is for butorphanol tartrate nasal spray. The firm conducted comparative *in vitro testing based on recommendations from the DBE on the protocol submitted earlier* (August 5, 1999). A request for a waiver for in-vivo BE study is submitted in the present submission.

## II. Submission History:

The firm submitted a protocol on August 5, 1999(P # 99-032) for this drug product. The DBE reviewed the protocol and sent comments to the firm. The firm submitted an ANDA (75-759) on December 22, 1999. Based on review (review date: April 16, 2001) of the ANDA, the firm was informed of deficiencies in [redacted] data. The present amendment, has firm's responses to the deficiencies.
The arrangement of the review is as follows:

- review of the amendment
- review of in-vitro data
- Appendices including results of the statistical analysis from [redacted]

## III. Review of the firm's responses

[redacted]

Firm's response: The firm's response is summarized in the [redacted] section of in-vitro testing.

[redacted]

[redacted]

**FDA Comment:** Information provided is acceptable

<u>Comment 3</u>: Please submit representative (≥ 20%) plots of obscuration vs. time with D10, D50 and D90 data on the same plot.

**Firm's response:** Data were provided as requested. The graphs show stable D50 and D90 profiles for the fully formed plume.

**FDA Comment:** Acceptable.

## IV. Review of the overall in-vitro testing data

1. **Formulations** (Not to be released under FOI)

| Ingredient | Reference* | Test |
|---|---|---|
| | g/L | |
| Butorphanol Tartrate | [redacted] | [redacted] |
| Sodium Chloride | [redacted] | [redacted] |
| Citric Acid | [redacted] | [redacted] |
| Benzethonium Chloride | [redacted] | [redacted] |
| Sodium Hydroxide | [redacted] | [redacted] |
| Hydrochloric Acid | [redacted] | [redacted] |
| Water, Purified | [redacted] | [redacted] |
| pH | [redacted] | [redacted] |

*Based on the FDA COMIS database, the amount of sodium hydroxide in the reference product is not specified. Composition of the proposed test product is qualitatively and quantitatively the same as in the reference product.

2. **Container and closure Parameters**

Comparison of container and closure parameters for the test and reference product is given

Redacted _____

pages of trade

secret and/or

confidential

commercial

information

the end of the review) is the photocopy of the drawing along with its specifications.

3. **In-Vitro Tests**

**Test product:**

One batch of the test product manufactured under production conditions was used for this study. Of total o' [illegible] bottles filled, [illegible] samples were taken from the beginning, [illegible] from the middle and [illegible] from the end of filling process. These samples were packaged into 3 sublots, each using a different batch of the same model pump/actuator [illegible]. Each sublot contained samples from the beginning, middle, and end of filling process and the identification is as follows:

[illegible]

**Reference product:**

3 batches with different expiry dates used in this study:

9F04645, expiry date: 04/01
9C12417, expiry date: 02/01
9C15231, expiry date: 03/01

**Tests conducted:**

To demonstrate equivalent in-vitro performance of the test and reference products, the following tests were performed at different laboratories as follows:

| Test | Laboratory |
|---|---|
| Emitted dose | [illegible] |
| Priming and repriming | [illegible] |
| Tail off profile | [illegible] |
| Droplet size distribution: | |
| [illegible] | [illegible] |
| [illegible] | [illegible] |
| Plume geometry | [illegible] |
| Spray pattern | [illegible] |

For the test product, each test used 10 units (bottles) obtained from each of the 3 sublots of the test products. Of these 10 units, 3 were collected from the beginning, 4 from the middle, and 3 from the end of the production run. For the reference product, 3 different lots were collected, and

for each lot, 10 units (bottles) were used in each test.

## 4. Design of In-Vitro Tests

### a. Emitted dose, priming, repriming, and tail off profile

As recommended in the FDA comments, emitted dose, priming, repriming, and tail off profile were combined into one study. For each sample unit, spray samples were collected and analyzed for butorphanol content to a) determine the minimum number of actuations required before the pump delivered the labeled dose of drug (spray #1-8) and b) to characterize emitted dose uniformity at the beginning of unit life (spray #9, corresponding to dose #1 after priming). After 48 hours, the doses emitted by sprays #10, 11, 12, corresponding to dose #2, 3, 4 after priming, were collected, weighed, and assayed to characterize repriming pattern. The doses emitted by spray #23 (last dose, corresponding to dose #15 after priming, based on the label claim) were collected, weighed, and assayed to characterize emitted dose uniformity at the end of unit life. Additional sprays were collected and analyze to characterize the tail off profile.

### b. Spray pattern

Spray patterns were measured at 3 distances of 2, 4, and 6 cm from the actuator tip to the thin layer chromatography plate, at both the beginning (dose 9, 10, and 11) and at the end (dose 21, 22, and 23) of unit life according to the in-house method (CTMLP-226). A [redacted] scanner was used to scan the outline of the spot on a [redacted] plate ([redacted] plate in [redacted] chamber with iodine solution on the bottom of chamber for 25 minutes). A total of six pray patterns were collected for each sample unit. The longest internal diameter (Dmax) and the shortest internal diameter (Dmin) of each spot were with a caliper to the nearest hundredth of a millimeter. The spray pattern results include the widest (Dmax) and shortest (Dmin) diameters and the ovality ratio (Dmax/Dmin). Original photos are included in this submission (Vol. 1.2 pages 1870 – 1990).

### c. Droplet size distribution (DSD) by [redacted]

[redacted], used to measure droplet size distribution. The [redacted] equipped with a spray sizer adapter was used for this study. Prior to measuring the droplet size distribution, each spray unit was primed by actuating 8 times and the measurement was determined at the beginning, middle and end of the label claim corresponding to spray number 9-11, 15-17 and 21-23 respectively. For each spray unit, measurements were made at 2, 4, and 6 cm between the [redacted] and at three delay times, 10, 35 and 70 milliseconds, for each distance. The firm has conducted extensive studies for evaluation of the method for determination of droplet size distribution. All important validation information is submitted in Vol. 1.2, pages 1554-1632 for reference. The data were reviewed and found appropriate. Based on preliminary studies, 70 ms was chosen as the last portion because it represents the beginning of the dissipation of the plume, while 35 ms was chosen as midpoint because it represents the halfway portion to the maximum obscuration value, and 10 ms was chosen as the first portion because it is consistently distinguishable from the noise at the beginning of the

plume. The initial detection conditions, e.g., duration of sampling at each delay time (50 ms), used in this submission were recommended by the instrument manufacturer [redacted] Representative plots were submitted (Vol. 4.1).

Ten bottles from each of three test sublots and three batches of the reference product were used. The droplet size distribution data (D50) and span [(D90-D10)/D50] of the test and reference products were compared. Computer outputs are included in this submission, Vol. 1.2 pages 1992 – 2060.

**d. Droplet size distribution (DSD) by** [redacted]

Sizing of droplets by [redacted] measures [redacted] diameter based on inertial impaction. Ten bottles from each of the 3 test product sublots and 3 batches of the reference were tested at the beginning and end of label number of doses. Droplet size distribution of the test and reference products which were grouped into 3 groups (group 1:> 9 $\mu$m, group 2:> 5.8 $\mu$m, and group 3:> 4.7 $\mu$m) were compared for equivalence determination. The method for determination of droplet size distribution by [redacted] for butorphanol tartrate nasal spray was fully validated.

**e. Plume geometry**

Using an automatic actuation station, each sample unit was first primed by actuating 8 times, and the plume geometry was determined at the beginning of the life of the bottle. A fast speed video camera was positioned level to the spray unit and to one side to record plume images from 3 sequential sprays. The spray unit was rotated 90° clockwise and recorded plume images of 3 additional sprays.

## V. Results:

All calculation performed by the reviewer employed Microsoft Excel. Data tables given in the review represent overall summary statistics. Reviewer's conclusions are supported by Walter Hauck's analyses in the attached tables in the Appendix.

### 1. Randomization

The test and the reference products were distinguished from each other due to the size difference, and therefore, in-vitro tests were performed in a blinded manner by removing the original labels and replaced them with randomly generated numbers without identifying the source.

### 2. Automated actuation station validation

An automated actuation station was used with the following parameters: Dose time: 16ms; return time: 65 ms; hold time: 2 s, and actuation force: [redacted] The automated actuation station was validated (Vol. 1.2 pages 1743-1750) in terms of precision, ruggedness, and accuracy. Data

submitted indicated that the automated nasal spray station is reliable and rugged for standard testing of nasal bottles, and its performance is comparable to manual actuations.

**3. Emitted dose content uniformity through container life**

First and last emitted dose after priming were collected, weighed, and analyzed using an [redacted] method. The [redacted] Method was fully validated (Vol. 1.2 pages 1484-1512) and found appropriate for the study. Mean data given as percent label claim, and statistics are recalculated by the reviewer as shown below:

## Summary Statistics:

**Content uniformity**

**Overall**

| | Test | | | Reference | | | |
|---|---|---|---|---|---|---|---|
| N | Mean (%CV) | | N | Mean (%CV) | | T/R | |
| | Arithmetic | Geometric | | Arithmetic | Geometric | Arithmetic | Geometric |
| 60 | 111.91 (3.62) | 112.16 (2.22) | 60 | 108.98 (3.19) | 108.85 (2.0) | 1.027 | 1.030 |

***For each life stage (total all 3 lots combined)***

| | Test | | | Reference | | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean (%CV) | | N | Mean (%CV) | | T/R | | |
| | | Arithmetic | Geometric | | Arithmetic | Geometric | Arith. | Geo. | P |
| First dose | 30 | 111.13 (4.15) | 111.05 (2.51) | 30 | 108.05 (3.94) | 107.77 (2.34) | 1.028 | 1.03 | 0.026 |
| Last dose | 30 | 112.69 (2.92) | 112.16 (1.88) | 30 | 109.91 (1.96) | 109.94 (1.52) | 1.025 | 1.02 | 0.086 |

**Comments on UNIT SPRAY CONTENT AND CONTENT UNIFORMITY:**

For Lederle's Butorphanol Tartrate, the geometric mean values at beginning and end of life are approximately 3.0% higher, than the corresponding reference product values. Based on the mean values, there was no change in the unit dose determined at the beginning and end sectors. The test and the reference products exhibited approximately same variability (%CV) with regard to the unit dose data. The test/ref ratios are within the [redacted], limits, used hitherto by DBE for acceptance of in vitro studies on butorphanol tartrate nasal sprays. The unit spray content data also meet the content uniformity criteria (means within [redacted], and no unit outside [redacted]

**Priming and Repriming**

**Summary Statistics:**

**Priming:**

TEST REFERENCE

| Act.# | N | Mean (CV) Arithmetic | Mean (CV) Geometric | Act.# | N | Mean (%CV) Arithmetic | Mean (%CV) Geometric | P |
|---|---|---|---|---|---|---|---|---|
| 1 | 30 | 0 | | 1 | 30 | 0 | | |
| 2 | 30 | 15.09 (63.38) | 14.01 (20.7) | 2 | 30 | 13.67 (64.73) | 12.3 (25.7) | 0.380 |
| 3 | 30 | 67.35 (15.30) | 66.7 (4.02) | 3 | 30 | 63.63 (18.02) | 62.8 (4.8) | 0.221: |
| 4 | 30 | 96.76 (9.96) | 96.5 (2.32) | 4 | 30 | 91.83 (10.25) | 90.9 (2.4) | 0.062 |
| 5 | 30 | 103.39 (5.28) | 103.5 (1.19) | 5 | 30 | 101.45 (6.96) | 101.5 (1.6) | 0.027( |
| 6 | 30 | 105.79 (5.37) | 105.6 (1.02) | 6 | 30 | 104.39 (6.73) | 104.6 (1.6) | 0.051: |
| 7 | 30 | 108.29 (5.86) | 107.8 (1.35) | 7 | 30 | 106.70 (5.19) | 106.7 (1.2) | 0.083: |
| 8 | 30 | 108.81 (6.04) | 108.9 (1.39) | 8 | 30 | 107.99 (3.15) | 107.8 (0.7) | 0.034: |
| 9 | 30 | 111.13 (4.15) | 111.0 (0.92) | 9 | 30 | 108.05 (3.94) | 107.8 (0.8) | 0.026( |

**Repriming**

Summary Statistics:

| TEST Act.# | N | Mean (CV) Arithmetic | Mean (CV) Geometric | REFERENCE Act.# | N | Mean (%CV) Arithmetic | Mean (%CV) Geometric | P |
|---|---|---|---|---|---|---|---|---|
| 10 | 30 | 106.8 (4.59) | 106.7 (0.99) | 10 | 30 | 101.2 (6.53) | 100.5 (1.44) | 0.02491 |
| 11 | 30 | 110.2 (3.72) | 109.9 (0.80) | 11 | 30 | 107.1 (5.83) | 106.7 (1.33) | 0.0701: |
| 12 | 30 | 110.6 (6.9) | 109.9 (1.62) | 12 | 30 | 107.8 (4.09) | 107.8 (0.90) | 0.26766: |

**Tail off profile**

Summary Statistics:

| Tail off Profile | N | Test Mean | %CV | N | Reference Mean | %CV |
|---|---|---|---|---|---|---|
| For each life stage | | | | | | |
| Actuation # | | | | | | |
| 24 | 30 | 109.86 | 4.41 | 30 | 106.78 | 5.05 |
| 25 | 30 | 89.88 | 21.67 | 30 | 96.25 | 14.63 |
| 26 | 30 | 51.68 | 49.61 | 30 | 75.01 | 30.15 |
| 27 | 30 | 21.33 | 101.1 | 30 | 43.39 | 59.09 |
| 28 | 21 | 9.14 | 139.8 | 30 | 24.01 | 74.87 |
| 29 | 6 | 7.15 | 83.58 | 22 | 15.50 | 86.40 |
| 30 | 2 | 14.75 | 56.06 | 11 | 13.30 | 62.53 |
| 31 | 1 | 9.71 | - | 4 | 12.09 | 27.11 |
| 32 | 1 | 3.93 | - | 3 | 2.68 | 54.45 |
| 33 | 0 | - | - | 0 | - | - |

Comments on PRIMING AND RE-PRIMING AND TAIL OFF:

Based on the data submitted the test product is fully primed at the 5th spray. The loss of prime retention is determined on the 10th spray by allowing the product to rest for a period of 48 hours, followed by collecting the next spray without priming. The test and reference products have same prime retention characteristics.
Tail off characteristics was determined by assaying the unit sprays starting with the labeled end actuation until depletion. The tail off data indicate that the test product delivers the labeled numbers of doses and its tail off is no more erratic than that of the reference product.

4. **Droplet size distribution by** [redacted]

Droplet size distribution (DSD) by [redacted] was determined at the beginning (spray # 9, 10, 11), middle (spray # 15, 16, 17) and end (spray # 21, 22, 23) of life of the product. The firm reported D50 and span as suggested in the draft guidance. The reviewer recalculated the data along with p values. Results are shown in tables in the Appendix. A summary result is shown below:

Summary Statistics: [redacted]

D50 (Overall)

| Test | | Mean (CV) | | Ref | | Mean (CV) | | T/R | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Arithmetic | Geometric | | N | Arithmetic | geometric | Arith. | Geo. |
| 10 msec | 270 | 75.04 (53.84) | 71.52 (5.51) | 10 msec | 270 | 84.27 (78.31) | 75.9 (8.44) | 0.89 | 0.94 |
| 35 msec | 270 | 59.50 (46.22) | 56.83 (6.36) | 35 msec | 270 | 62.33 (67.12) | 57.40 (8.04) | 0.95 | 0.99 |
| 70 msec | 270 | 73.11 (62.67) | 62.80 (12.57) | 70 msec | 270 | 66.98 (72.33) | 57.40 (12.94) | 1.09 | 1.09 |

SPAN (Overall)

| Test | | Mean (CV) | | Ref | | Mean (CV) | | T/R | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Arithmetic | Geometric | | N | arithmetic | geometric | Arith. | Geo. |
| 10 msec | 270 | 1.49 (49.30) | 1.43 (62.78) | 10 msec | 270 | 1.76 (84.94) | 1.54 (98.16) | 0.85 | 0.92 |
| 35 msec | 270 | 1.52 (13.12) | 1.51 (27.46) | 35 msec | 270 | 1.52 (34.58) | 1.49 (44.83) | 1.0 | 1.01 |
| 70 msec | 270 | 1.53 (15.96) | 1.52 (36.96) | 70 msec | 270 | 1.62 (32.54) | 1.58 (45.38) | 0.94 | 0.96 |

COMMENTS ON DROPLET SIZE DISTRIBUTION TESTING BY [redacted]

The T/R geometric mean ratios for D50 data for the fully formed plume (35 and 75 msec) were in the range of 0.94 - 1.09. The test product variability (%CV) was less than that of the reference product. The ratio of geometric means in the range of 0.9-1.11 is acceptable.

Based on the SPAN data for the fully formed plumes, the T/R geometric mean ratios were in the rage of in the acceptable range of 0.92 - 1.01.

5. **Droplet size distribution by** [redacted].

The reviewer recalculated the data along with p values. Results are shown in tables in the Appendix. Data are given as % mass balance. A summary result is shown below:

**Summary:** [redacted]

| Test | | | | Reference | | | | Test/Reference | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean (CV) | | | | Mean (CV) | | Ratio | |
| Group | N | Arithmetic | geometric | Group | N | Arithmetic | Geometric | Arith | geo |
| 1 | 59 | 99.03(0.55) | 99.4(0.12) | 1 | 60 | 99.14(0.58) | 99.5(0.13) | 0.99 | 0.99 |
| 2 | 59 | 0.11(110.7) | 0.19(24.4) | 2 | 60 | 0.12(125.7) | 0.21(40) | 0.92 | 0.90 |
| 3 | 59 | 0.84(58.56) | 0.85(281) | 3 | 60 | 0.74(65.29) | 0.73(172) | 1.13 | 1.16 |

COMMENTs ON DROPLET SIZE DISTRIBUTION TESTING BY [redacted]

The [redacted] results indicated that the amount of drug deposed in droplets >9 um (Group 1) is similar between test and reference products (T/R ratios based on geometric means = 1.00). Therefore, there is not an excess mass of fines in the test product relative to the reference product. The test product variability (%CV) was same as that of the reference product.

The amount of drug collected in groups 2, and 3 4 constitutes <1.5% of the total drug collected from the [redacted] apparatus. This fraction represents fine particles (<9.0 um in diameter). The reviewer considers that the amount deposited in groups 2 and 3 is negligible compared with the quantity of drug received in group 1. Therefore, the test and reference equivalence is based on Group 1 data. Based on that data, the test/ref ratios were within the acceptable limits of [redacted].

6. **Spray pattern**

Spray patterns were measured at 3 distances of 2 cm, 4 cm, and 6 cm at both the beginning (spray 1-3 after priming) and end of unit life (spray 13-15 after priming). Data are presented in this submission (Vol 1.3, pages 2315-2336). The reviewer recalculated the data along with p values. Results are shown in tables in the Appendix. The overall means and standard deviations of Dmax, Dmin and ovality ratio (Dmax/Dmin) are shown below:

**Spray pattern –Overall**

| TEST | | | | REFERENCE | | | | Test/Ref. | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean (CV) | | | | Mean (CV) | | Ratio | |
| | N | arithmetic | geometric | | N | Arithmetic | geometric | Arith | geo |
| Dmax | 180 | 50.18(33.9) | 47.5(9.0) | Dmax | 180 | 46.23(31.2) | 43.8 (8.42) | 1.08 | 1.08 |
| Dmin | 180 | 41.66(32.4) | 39.6(9.0) | Dmin | 180 | 39.05(31.2) | 37.3(8.8) | 1.07 | 1.06 |
| Ovality | 180 | 1.20(11.0) | 1.2(55.0) | Ovality | 180 | 1.19(9.7) | 1.2(55.1) | 1.01 | 1.0 |

The spray patterns produced by the test and reference products were evaluated by comparative shape (based on ovality ratio) and size (based on Dmin and Dmax). The test/reference ratios for Dmin, Dmax, and ovality ratio were 1.06, 1.08, and 1.01 respectively

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7. Plume geometry:
Results can be summarized as follows:

**Data shown in parenthesis ( ) are test/reference ratios that are based on geometric means (calculated by reviewer)**

| Plume Geometry Data (N=30) | | | | | | |
|---|---|---|---|---|---|---|
| Time (msec) | View | Product | Statistic | Length (cm) | Width (cm) | Angle (°) |
| 2 | Front | Test | Mean | 8.07 | 3.84 | 42.90 |
| | | | %CV | 26.72 | 21.78 | 14.18 |
| | | Reference | Mean | 5.40 | 2.66 | 40.97 |
| | | | %CV | 29.04 | 34.76 | 17.58 |
| | | | T/R | 1.494 (1.507) | 1.44 (1.49) | 1.047 (1.05) |
| | | | *P* | *0.018* | *0.00566* | *0.2781* |
| | Side | Test | Mean | 8.20 | 4.10 | 44.30 |
| | | | %CV | 24.60 | 20.73 | 12.98 |
| | | Reference | Mean | 5.24 | 3.09 | 44.13 |
| | | | %CV | 24.89 | 37.93 | 20.03 |
| | | | T/R | 1.565 (1.56) | 1.326 (1.39) | 1.004 (1.01) |
| | | | *P* | *0.00884* | *0.02131* | *0.4862* |
| 105 | Front | Test | Mean | 32.79 | 14.97 | 42.83 |
| | | | %CV | 7.89 | 10.29 | 16.26 |
| | | Reference | Mean | 31.99 | 15.28 | 44.77 |
| | | | %CV | 9.86 | 13.21 | 20.37 |
| | | | T/R | 1.025 (1.03) | 0.98 (0.98) | 0.957 (0.96) |
| | | | *P* | *0.3497* | *0.3386* | *0.3713* |
| | Side | Test | Mean | 33.40 | 15.22 | 43.27 |
| | | | %CV | 11.14 | 10.36 | 16.74 |
| | | Reference | Mean | 31.28 | 15.34 | 44.27 |
| | | | %CV | 9.40 | 12.87 | 23.20 |
| | | | T/R | 1.06 (1.06) | 0.992 (1.00) | 0.977 (0.99) |
| | | | *P* | *0.09293* | *0.2980* | *0.4220* |
| 208 | Front | Test | Mean | 40.76 | 16.92 | 37.13 |
| | | | %CV | 6.72 | 8.99 | 10.65 |
| | | Reference | Mean | 40.82 | 17.97 | 40.50 |
| | | | %CV | 9.32 | 12.87 | 17.20 |
| | | | T/R | 0.998 (1.01) | 0.942 (0.94) | 0.917 (0.92) |
| | | | *P* | *0.4859* | *0.0987* | *0.2215* |
| | Side | Test | Mean | 40.19 | 16.95 | 38.43 |
| | | | %CV | 8.89 | 10.99 | 14.11 |
| | | Reference | Mean | 40.69 | 17.63 | 40.53 |
| | | | %CV | 8.90 | 12.42 | 20.08 |
| | | | T/R | 0.988 (1.00) | 0.961 (0.96) | 0.948 (0.96) |
| | | | *P* | *0.3052* | *0.1596* | *0.2933* |

COMMENTS ON GEOMETRY DATA:

Plume geometry was characterized at delay times of 2, 105 and 208 msec. The later two intervals represent fully formed plume. Therefore, plume height and plume width data for 105 and 208 msec delay times are appropriate for comparison of test and reference products. Plume angle, on the other hand, is best characterized at the beginning of the plume formation. Based on the plume angle data for the 2 msec delay time and plume height and plume width for the later delay times, the geometric means of the test and reference products were within the ' ——

## VI. Overall Comments:

- The composition of the test product formulation is Q1 and Q2 same as that of the reference product.

- The ratios of geometric means of test and reference products for the various parameters used to compare the Unit Spray Content, Droplet Size Distribution by ' —— —— Spray Pattern and plume geometry are within the acceptable range of 0.. —— —, used hitherto by DBE for acceptance of in vitro studies on butorphanol tartrate nasal sprays.

- The Unit Spray Content, Droplet Size Distribution by ' —— and Spray Patterns data were also analyzed using the population bioequivalence approach (PBE) for non-profile data outlined in the draft nasal BA/BE guidance. The PBE analyses were performed by ' —— —— group at the ' ——. Because the PBE methodology is under development, values of two parameters ($sigma_{T0}$ - the variance terms offset, and epsilon – the scaling variance) to be used in the method are still under consideration, Therefore, —— analyses utilized all possible combinations (i.e $sigma_{T0}$ values of 0.1 and 0.2, and epsilon values of 0.00, 0.01, 0.03, and 0.05, where 0.00 represents the most stringent criterion). In addition the average bioequivalence (ABE) limits of 1.11 and 1.25 were used. Based on the PBE analysis, the Unit Spray Content of the test spray is equivalent to that of the reference product. In addition, the test product's droplet size distribution and spray pattern are similar to those of the reference product.

- Plume geometry was characterized by plume angle, plume height, and plume width for the front and side views of the plume. Based on the test/reference geometric mean ratios, plume geometric characteristics of the test and reference products are similar.

## VII. Recommendation

Data submitted by ESI Lederle comparing its butorphanol tartrate nasal solution (10 mg/mL) with the reference listed drug, Stadol NS® manufactured by Bristol-Myers Squibb demonstrate that the formulation of the test and reference product is quantitatively and qualitatively same as that of the reference product. In addition, and the *in vitro* performance of nasal spray devices of

the test and the reference products are similar. Therefore, test products formulations and in vitro performance are acceptable.

Nhan L. Tran, Ph.D.
Review Branch II

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 7/17/2001

Concur: /S/ Date 7/18/2001
for Dale P. Conner, Pharm. D., Director
Division of Bioequivalence

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cc: ANDA 75-759 (original), HFD-655 (Tran, Nerurkar), Drug File, Division File

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-759 APPLICANT: ESI Lederle

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues.

Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75759
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Nerurkar/Tran

Endorsements: (Initial with Dates)
HFD-655/ Tran
HFD-655/ Singh 7/10/01
HFD-655/ Nerurkar
HFD-650/ D. Conner 7/18/2001

7/18/01

BIOEQUIVALENCY - ACCEPTABLE

Submission dates: December 22, 1999
May 15, 2001

1. In-Vitro study
Strength: 10 mg/mL

Outcome: AC

2. Amendment

Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments:

## APPENDICES

1. Additional individual data (pg. 20)
2. Drawing of the pump (pg. 36)
3. Results from ` , Statistical Analysis of the data (pg. 38):
   - Droplet Size Distribution by
   - Spray Pattern
   - Unit Dose

# Appendix I: Individual data

## 1. Priming

| | Test | | | | | Reference | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Act. # | N | Mean | CV | Overall Mean (CV) Arithmetic | Overall Mean (CV) Geometric | N | Mean | CV | Overall Mean (CV) Arithmetic | Overall Mean (CV) Geometric | P value |
| 1 | 10 | 0 | | | | 10 | 0 | | | | |
| 1 | 10 | 0 | | | | 10 | 0 | | | | |
| 1 | 10 | 0 | | | | 10 | 0 | | | | |
| 2 | 10 | 18.56 | 48.2 | 15.09 (63.4) | 14.01(20.7) | 10 | 10.98 | 61.84 | 13.67(64.7) | 12.3(25.7) | 0.3801 |
| 2 | 10 | 11 | 79.86 | | | 10 | 17.28 | 72.82 | | | |
| 2 | 10 | 15.7 | 65.25 | | | 10 | 12.73 | 38.58 | | | |
| 3 | 10 | 67.46 | 18.98 | 67.35(15.3) | 66.7(4.02) | 10 | 64.23 | 18.45 | 63.63(18.0) | 62.8(4.8) | 0.2213 |
| 3 | 10 | 62.15 | 15.57 | | | 10 | 64.96 | 18.93 | | | |
| 3 | 10 | 72.44 | 7 | | | 10 | 61.69 | 18.16 | | | |
| 4 | 10 | 98.48 | 7.05 | 96.76(9.96) | 96.5(2.32) | 10 | 90.83 | 9.85 | 91.83(10.5) | 90.9(2.4) | 0.0621 |
| 4 | 10 | 95.4 | 10.8 | | | 10 | 94.18 | 8.3 | | | |
| 4 | 10 | 96.39 | 12.25 | | | 10 | 90.48 | 12.85 | | | |
| 5 | 10 | 103.5 | 6.61 | 103.39(5.3) | 103.5(1.19) | 10 | 100.73 | 6.92 | 101.45(6.9) | 101.5(1.6) | 0.0270 |
| 5 | 10 | 101.77 | 5.56 | | | 10 | 100.63 | 9.04 | | | |
| 5 | 10 | 104.9 | 3.26 | | | 10 | 102.99 | 4.9 | | | |
| 6 | 10 | 105.18 | 7.67 | 105.79(5.4) | 105.6(1.20) | 10 | 104.58 | 4.41 | 104.39(6.7) | 104.6(1.6) | 0.0518 |
| 6 | 10 | 105.88 | 4.5 | | | 10 | 104.58 | 8.57 | | | |
| 6 | 10 | 106.3 | 3.71 | | | 10 | 104.02 | 7.28 | | | |
| 7 | 10 | 106.28 | 8.29 | 108.29(5.9) | 107.8(1.35) | 10 | 106.13 | 3.69 | 106.7(5.2) | 106.7(1.2) | 0.0832 |
| 7 | 10 | 108.97 | 4.9 | | | 10 | 106.33 | 8.08 | | | |
| 7 | 10 | 109.61 | 3.74 | | | 10 | 107.64 | 2.68 | | | |
| 8 | 10 | 107.59 | 6.97 | 108.81(6.0) | 108.9(1.39) | 10 | 107.22 | 3.71 | 107.99(3.1) | 107.8(0.7) | 0.0343 |
| 8 | 10 | 109.71 | 2.62 | | | 10 | 108.64 | 2.39 | | | |
| 8 | 10 | 109.14 | 7.78 | | | 10 | 108.1 | 3.4 | | | |
| 9 | 10 | 110.25 | 5.83 | 111.13(4.1) | 111.0(0.92) | 10 | 108.31 | 3.4 | 108.05(3.9) | 107.8(0.8) | 0.0260 |
| 9 | 10 | 110.86 | 3.97 | | | 10 | 108 | 5.33 | | | |
| 9 | 10 | 112.28 | 2.11 | | | 10 | 107.83 | 3.18 | | | |

| | Test | | | Reference | | |
|---|---|---|---|---|---|---|
| | N | Mean | %CV | N | Mean | %CV |
| For each life stage Actuation # | | | | | | |
| 1 | 30 | 0 | | 30 | 0 | |
| 2 | 30 | 15.09 | 63.38 | 30 | 13.67 | 64.73 |
| 3 | 30 | 67.35 | 15.30 | 30 | 63.63 | 18.02 |
| 4 | 30 | 96.76 | 9.96 | 30 | 91.83 | 10.25 |
| 5 | 30 | 103.39 | 5.28 | 30 | 101.45 | 6.96 |
| 6 | 30 | 105.79 | 5.37 | 30 | 104.39 | 6.73 |
| 7 | 30 | 108.29 | 5.86 | 30 | 106.70 | 5.19 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 8 | 30 | 108.81 | 6.04 | 30 | 107.99 | 3.15 |
| 9 | 30 | 111.13 | 4.15 | 30 | 108.05 | 3.94 |

For each lot & life stage

| Actuation # | Pump # V203978500 | | | Lot # 9F04645 | | |
|---|---|---|---|---|---|---|
| 1 | 10 | 0 | | 10 | 0 | |
| 2 | 10 | 18.56 | 48.20 | 10 | 10.98 | 61.84 |
| 3 | 10 | 67.46 | 18.98 | 10 | 64.23 | 18.45 |
| 4 | 10 | 98.48 | 7.05 | 10 | 90.83 | 9.85 |
| 5 | 10 | 103.50 | 6.61 | 10 | 100.73 | 6.92 |
| 6 | 10 | 105.18 | 7.67 | 10 | 104.58 | 4.41 |
| 7 | 10 | 106.28 | 8.29 | 10 | 106.13 | 3.69 |
| 8 | 10 | 107.59 | 6.97 | 10 | 107.22 | 3.71 |
| 9 | 10 | 110.25 | 5.83 | 10 | 108.31 | 3.40 |

| Actuation # | Pump # V203978400 | | | Lot # 9C12417 | | |
|---|---|---|---|---|---|---|
| 1 | 10 | 0 | | 10 | 0 | |
| 2 | 10 | 11.00 | 79.86 | 10 | 17.28 | 72,82 |
| 3 | 10 | 62.15 | 15.57 | 10 | 64.96 | 18.93 |
| 4 | 10 | 95.40 | 10.80 | 10 | 94.18 | 8.30 |
| 5 | 10 | 101.77 | 5.56 | 10 | 100.63 | 9.04 |
| 6 | 10 | 105.88 | 4.50 | 10 | 104.58 | 8.57 |
| 7 | 10 | 108.97 | 4.90 | 10 | 106.33 | 8.08 |
| 8 | 10 | 109.71 | 2.62 | 10 | 108.64 | 2.39 |
| 9 | 10 | 110.86 | 3.97 | 10 | 108.00 | 5.33 |

| Actuation # | | Pump # V203980000 | | Lot # 9C15231 | | |
|---|---|---|---|---|---|---|
| 1 | 10 | 0 | | 10 | 0 | |
| 2 | 10 | 15.70 | 65.25 | 10 | 12.73 | 38.58 |
| 3 | 10 | 72.44 | 7.00 | 10 | 61.69 | 18.16 |
| 4 | 10 | 96.39 | 12.25 | 10 | 90.48 | 12.85 |
| 5 | 10 | 104.90 | 3.26 | 10 | 102.99 | 4.90 |
| 6 | 10 | 106.30 | 3.71 | 10 | 104.02 | 7.28 |
| 7 | 10 | 109.61 | 3.74 | 10 | 107.64 | 2.68 |
| 8 | 10 | 109.14 | 7.78 | 10 | 108.10 | 3.40 |
| 9 | 10 | 112.28 | 2.11 | 10 | 107.83 | 3.18 |

## 2. Repriming

| Re-priming | N | Test Mean | %CV | N | Reference Mean | %CV |
|---|---|---|---|---|---|---|
| For each life stage | | | | | | |
| Actuation # | | | | | | |
| 10 | 30 | 106.84 | 4.59 | 30 | 101.15 | 6.53 |
| 11 | 30 | 110.20 | 3.72 | 30 | 107.13 | 5.83 |
| 12 | 30 | 110.56 | 6.89 | 30 | 107.78 | 4.09 |
| For each lot & life stage | | | | | | |
| Actuation # | Pump # V203978500 | | | Lot # 9F04645 | | |
| 10 | 10 | 107.59 | 4.65 | 10 | 98.70 | 4.90 |
| 11 | 10 | 110.64 | 4.48 | 10 | 106.61 | 4.05 |
| 12 | 10 | 110.09 | 8.54 | 10 | 107.69 | 2.28 |
| Actuation # | Pump # V203978400 | | | Lot # 9C12417 | | |
| 10 | 10 | 107.14 | 4.59 | 10 | 99.36 | 7.79 |
| 11 | 10 | 109.25 | 4.29 | 10 | 107.03 | 6.60 |
| 12 | 10 | 111.36 | 4.29 | 10 | 108.27 | 3.50 |
| Actuation # | Pump # V203980000 | | | Lot # 9C15231 | | |
| 10 | 10 | 105.79 | 4.85 | 10 | 105.39 | 4.94 |
| 11 | 10 | 110.70 | 2.22 | 10 | 107.75 | 6.96 |
| 12 | 10 | 110.23 | 7.84 | 10 | 107.38 | 6.03 |

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## 3. Tail off Profile

Tail off Profile

| Actuation | N | Test Mean | Test %CV | N | Ref. Mean | Ref. %CV | P Value |
|---|---|---|---|---|---|---|---|
| 24 | 10 | 109.16 | 5.39 | 10 | 106.43 | 6.13 | 0.031966 |
| 24 | 10 | 108.96 | 4.94 | 10 | 107.09 | 4.01 | |
| 24 | 10 | 111.47 | 2.5 | 10 | 106.83 | 5.32 | |
| 25 | 10 | 92.76 | 16.34 | 10 | 99.44 | 12.09 | 0.032255 |
| 25 | 10 | 90.07 | 24.86 | 10 | 99.24 | 11.26 | |
| 25 | 10 | 86.79 | 25.02 | 10 | 90.08 | 19.41 | |
| 26 | 10 | 54 | 56.48 | 10 | 84.09 | 21.32 | 0.010477 |
| 26 | 10 | 57.89 | 47.49 | 10 | 78.81 | 29.54 | |
| 26 | 10 | 43.16 | 40.32 | 10 | 62.12 | 35.72 | |
| 27 | 10 | 20.25 | 122.2 | 10 | 57.82 | 45.63 | 0.05335 |
| 27 | 10 | 27.36 | 97.24 | 10 | 43.72 | 58.8 | |
| 27 | 10 | 16.39 | 64.35 | 10 | 28.63 | 59.21 | |
| 28 | 7 | 12.18 | 162.3 | 10 | 40.8 | 42.9 | 0.081625 |
| 28 | 7 | 10.84 | 93.61 | 10 | 19.17 | 69.35 | |
| 28 | 7 | 4.41 | 73.02 | 10 | 12.06 | 64.49 | |
| 29 | 2 | 4.85 | 88.35 | 9 | 25.64 | 60.68 | 0.315538 |
| 29 | 3 | 5.46 | 89.24 | 8 | 9.41 | 59.45 | |
| 29 | 1 | 16.83 | - | 5 | 7 | 38.54 | |
| 30 | 0 | - | | 8 | 14.2 | 56.74 | |
| 30 | 1 | 8.9 | - | 3 | 10.93 | 94.79 | |
| 30 | 1 | 20.59 | - | 0 | - | - | |
| 31 | 0 | - | | 3 | 10.8 | 22.96 | |
| 31 | 0 | - | - | 1 | 15.96 | - | |
| 32 | 0 | - | | 2 | 3.49 | 18.46 | |
| 32 | 0 | - | - | 1 | 1.08 | - | |
| 33 | 0 | - | | 0 | - | - | |
| 33 | 0 | - | - | 0 | - | - | |

For each lot & life stage

| Tail off Profile | N | Test Mean | %CV | N | Reference Mean | %CV |
|---|---|---|---|---|---|---|
| Actuation # | Pump # V203978500 | | | Lot # 9F04645 | | |
| 24 | 10 | 109.16 | 5.39 | 10 | 106.43 | 6.13 |
| 25 | 10 | 92.76 | 16.34 | 10 | 99.44 | 12.09 |
| 26 | 10 | 54.00 | 56.48 | 10 | 84.09 | 21.32 |
| 27 | 10 | 20.25 | 122.2 | 10 | 57.82 | 45.63 |
| 28 | 7 | 12.18 | 162.3 | 10 | 40.80 | 42.90 |
| 29 | 2 | 4.85 | 88.35 | 9 | 25.64 | 60.68 |
| 30 | 0 | - | - | 8 | 14.20 | 56.74 |
| 31 | 0 | - | - | 3 | 10.80 | 22.96 |
| 32 | 0 | - | - | 2 | 3.49 | 18.46 |
| 33 | 0 | - | - | 0 | - | - |

| Actuation # | Pump # V203978400 | | | Lot # 9C12417 | | |
|---|---|---|---|---|---|---|
| 24 | 10 | 108.96 | 4.94 | 10 | 107.09 | 4.01 |
| 25 | 10 | 90.07 | 24.86 | 10 | 99.24 | 11.26 |
| 26 | 10 | 57.89 | 47.49 | 10 | 78.81 | 29.54 |
| 27 | 10 | 27.36 | 97.24 | 10 | 43.72 | 58.80 |
| 28 | 7 | 10.84 | 93.61 | 10 | 19.17 | 69.35 |
| 29 | 3 | 5.46 | 89.24 | 8 | 9.41 | 59.45 |
| 30 | 1 | 8.90 | - | 3 | 10.93 | 94.79 |
| 31 | 0 | - | - | 1 | 15.96 | - |
| 32 | 0 | - | - | 1 | 1.08 | - |
| 33 | 0 | - | - | 0 | - | - |
| Actuation # | Pump # V203980000 | | | Lot # 9C15231 | | |
| 24 | 10 | 111.47 | 2.50 | 10 | 106.83 | 5.32 |
| 25 | 10 | 86.79 | 25.02 | 10 | 90.08 | 19.41 |
| 26 | 10 | 43.16 | 40.32 | 10 | 62.12 | 35.72 |
| 27 | 10 | 16.39 | 64.35 | 10 | 28.63 | 59.21 |
| 28 | 7 | 4.41 | 73.02 | 10 | 12.06 | 64.49 |
| 29 | 1 | 16.83 | - | 5 | 7.00 | 38.54 |
| 30 | 1 | 20.59 | - | 0 | - | - |

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## 4. Emitted dose content uniformity through container life

**Content uniformity**

**Overall**

| Test N | Test Mean (%CV) Arithmetic | Test Mean (%CV) Geometric | Reference N | Reference Mean (%CV) Arithmetic | Reference Mean (%CV) Geometric | T/R Arithmetic | T/R Geometric |
|---|---|---|---|---|---|---|---|
| 60 | 111.91 (3.62) | 112.16 (2.22) | 60 | 108.98 (3.19) | 108.85 (2.0) | 1.027 | 1.030 |

**For each life stage (total all 3 lots combined)**

| | Test N | Test Mean (%CV) Arithmetic | Test Mean (%CV) Geometric | Reference N | Reference Mean (%CV) Arithmetic | Reference Mean (%CV) Geometric | T/R Arithmetic | T/R Geometric |
|---|---|---|---|---|---|---|---|---|
| First dose | 30 | 111.13 (4.15) | 111.05 (2.51) | 30 | 108.05 (3.94) | 107.77 (2.34) | 1.028 | 1.03 |
| Last dose | 30 | 112.69 (2.92) | 112.16 (1.88) | 30 | 109.91 (1.96) | 109.94 (1.52) | 1.025 | 1.02 |

**For each lot & life stage**

| | Test N | Test Mean (%CV) Arithmetic | Test Mean (%CV) Geometric | Reference N | Reference Mean (%CV) Arithmetic | Reference Mean (%CV) Geometric | T/R Arithmetic | T/R Geometric |
|---|---|---|---|---|---|---|---|---|
| First dose | 10 | 110.25 (5.83) | 109.94 (3.63) | 10 | 108.31 (3.40) | 107.77 (2.07) | 1.028 | 1.03 |
| Last dose | 10 | 113.19 (2.85) | 113.29 (1.84) | 10 | 108.18 (2.06) | 107.77 (1.55) | 1.025 | 1.02 |
| First dose | 10 | 110.86 (3.97) | 111.05 (2.36) | 10 | 108.00 (5.33) | 107.77 (3.13) | 1.026 | 1.03 |
| Last dose | 10 | 111.54 (3.39) | 111.05 (2.12) | 10 | 111.15 (1.09) | 111.05 (1.26) | 1.00 | 1.00 |
| First dose | 10 | 112.28 (2.11) | 112.16 (1.57) | 10 | 107.83 (3.18) | 107.77 (1.99) | 1.04 | 1.04 |
| Last dose | 10 | 113.36 (2.46) | 113.29 (1.70) | 10 | 110.41 (1.61) | 109.94 (1.42) | 1.026 | 1.03 |

| | Test N | Test Mean | Test %CV | Reference N | Reference Mean | Reference %CV |
|---|---|---|---|---|---|---|
| First dose | 10 | 110.25 | 5.83 | 10 | 108.31 | 3.4 |
| First dose | 10 | 110.86 | 3.97 | 10 | 108 | 5.33 |
| First dose | 10 | 112.28 | 2.11 | 10 | 107.83 | 3.18 |

| | T | R | T/R | P |
|---|---|---|---|---|
| Mean | 111.130 | 108.047 | 1.029 | 0.026 |
| %CV | 0.94 | 0.23 | | |

| | Test N | Test Mean | Test %CV | Reference N | Reference Mean | Reference %CV |
|---|---|---|---|---|---|---|
| Last dose | 10 | 111.54 | 3.39 | 10 | 111.15 | 1.09 |
| Last dose | 10 | 113.19 | 2.85 | 10 | 108.18 | 2.06 |
| Last dose | 10 | 113.36 | 2.46 | 10 | 110.41 | 1.61 |

| | T | R | T/R | P |
|---|---|---|---|---|
| Mean | 112.697 | 109.913 | 1.025 | 0.086 |
| %CV | 0.89 | 1.41 | | |

## 5. Droplet size distribution by '

10 msec. TEST Reference

| SPRAY | N | MEAN | CV | OVERALL MEAN | MEAN | CV | OVERALL MEAN | P value |
|---|---|---|---|---|---|---|---|---|
| 9 | 30 | 74.29 | 14.64 | 73.79 | 79.38 | 42.206 | 80.025 | 0.026756 |
| 10 | 30 | 70.95 | 14.34 | | 82.67 | 64.25 | | |
| 11 | 30 | 73.29 | 17.05 | | 80.67 | 53.21 | | |
| 15 | 30 | 78.05 | 47.02 | 83.74 | 76.47 | 39.61 | 91.965 | 0.1106 |
| 16 | 30 | 72.16 | 32.07 | | 94.63 | 109.16 | | |
| 17 | 30 | 89.43 | 120.41 | | 107.46 | 103.34 | | |
| 21 | 30 | 73.45 | 28.6 | 74.605 | 69.01 | 16.22 | 76.065 | 0.198133 |
| 22 | 30 | 67.98 | 14.79 | | 84.98 | 97.51 | | |
| 23 | 30 | 75.76 | 27.59 | | 83.12 | 62.28 | | |

35 msec.

| SPRAY | N | TEST MEAN | CV | OVERALL MEAN | Reference MEAN | CV | OVERALL MEAN | |
|---|---|---|---|---|---|---|---|---|
| 9 | 30 | 60.99 | 16.28 | 56.85 | 59.29 | 15.66 | 60.225 | 0.138561 |
| 10 | 30 | 55.28 | 15.75 | | 63.11 | 74.45 | | |
| 11 | 30 | 52.71 | 15.13 | | 61.16 | 75.25 | | |
| 15 | 30 | 70.73 | 72.21 | 62.88 | 65.79 | 63.6 | 66 | 0.264204 |
| 16 | 30 | 61.56 | 60.37 | | 65.92 | 81.89 | | |
| 17 | 30 | 55.03 | 27.13 | | 66.21 | 88.76 | | |
| 21 | 30 | 68.95 | 59.76 | 61.815 | 56.88 | 14.76 | 61.235 | 0.495934 |
| 22 | 30 | 55.61 | 33.21 | | 57 | 37.24 | | |
| 23 | 30 | 54.68 | 23.96 | | 65.59 | 84.34 | | |

70 msec.

| SPRAY | N | TEST MEAN | CV | OVERALL MEAN | Reference MEAN | CV | OVERALL MEAN | |
|---|---|---|---|---|---|---|---|---|
| 9 | 30 | 77.72 | 43.99 | 71.365 | 72.66 | 44.02 | 70.265 | 0.292182 |
| 10 | 30 | 70.43 | 47.73 | | 68.13 | 47.67 | | |
| 11 | 30 | 65.01 | 48.7 | | 67.87 | 73.52 | | |
| 15 | 30 | 85.55 | 75.8 | 76.065 | 75.34 | 78.36 | 71.58 | 0.252187 |
| 16 | 30 | 75.38 | 76.84 | | 75.52 | 97.53 | | |
| 17 | 30 | 66.58 | 64.05 | | 67.82 | 99.55 | | |
| 21 | 30 | 78.4 | 69.72 | 74.55 | 57.3 | 47.58 | 57.655 | 0.033744 |
| 22 | 30 | 68.23 | 58.78 | | 60.18 | 60.12 | | |
| 23 | 30 | 70.7 | 60.56 | | 58.01 | 61.38 | | |

--D50 (Overall)

| Test | | Mean (CV) | | Ref | | Mean (CV) | | T/R | |
|---|---|---|---|---|---|---|---|---|---|
| | N | arithmetic | geometric | | N | Arithmetic | geometric | Arith. | Geo. |
| 10 msec | 270 | 75.04 (53.84) | 71.52 (5.51) | 10 msec | 270 | 84.27 (78.31) | 75.9 (8.44) | 0.89 | 0.94 |
| 35 msec | 270 | 59.50 (46.22) | 56.83 (6.36) | 35 msec | 270 | 62.33 (67.12) | 57.40 (8.04) | 0.95 | 0.99 |
| 70 msec | 270 | 73.11 (62.67) | 62.80 (12.57) | 70 msec | 270 | 66.98 (72.33) | 57.40 (12.94) | 1.09 | 1.09 |

For each life stage:

10 msec.

| | TEST | | | | REFERENCE | | |
|---|---|---|---|---|---|---|---|
| SPRAY | N | MEAN | CV | | N | MEAN | CV |
| 9 | 30 | 74.29 | 14.64 | | 30 | 79.38 | 42.206 |
| 10 | 30 | 70.95 | 14.34 | | 30 | 82.67 | 64.25 |
| 11 | 30 | 73.29 | 17.05 | | 30 | 80.67 | 53.21 |
| 15 | 30 | 78.05 | 47.02 | | 30 | 76.47 | 39.61 |
| 16 | 30 | 72.16 | 32.07 | | 30 | 94.63 | 109.16 |
| 17 | 30 | 89.43 | 120.41 | | 30 | 107.46 | 103.34 |
| 21 | 30 | 73.45 | 28.60 | | 30 | 69.01 | 16.22 |
| 22 | 30 | 67.98 | 14.79 | | 30 | 84.98 | 97.51 |
| 23 | 30 | 75.76 | 27.59 | | 30 | 83.12 | 62.28 |

35 msec.

| | TEST | | | | REFERENCE | | |
|---|---|---|---|---|---|---|---|
| SPRAY | N | MEAN | CV | | N | MEAN | CV |
| 9 | 30 | 60.99 | 16.28 | | 30 | 59.29 | 15.66 |
| 10 | 30 | 55.28 | 15.75 | | 30 | 63.11 | 74.45 |
| 11 | 30 | 52.71 | 15.13 | | 30 | 61.16 | 75.25 |
| 15 | 30 | 70.73 | 72.21 | | 30 | 65.79 | 63.60 |
| 16 | 30 | 61.56 | 60.37 | | 30 | 65.92 | 81.89 |
| 17 | 30 | 55.03 | 27.13 | | 30 | 66.21 | 88.76 |
| 21 | 30 | 68.95 | 59.76 | | 30 | 56.88 | 14.76 |
| 22 | 30 | 55.61 | 33.21 | | 30 | 57.00 | 37.24 |
| 23 | 30 | 54.68 | 23.96 | | 30 | 65.59 | 84.34 |

70 msec.

| | TEST | | | | REFERENCE | | |
|---|---|---|---|---|---|---|---|
| SPRAY | N | MEAN | CV | | N | MEAN | CV |
| 9 | 30 | 77.72 | 43.99 | | 30 | 72.66 | 44.02 |
| 10 | 30 | 70.43 | 47.73 | | 30 | 68.13 | 47.67 |
| 11 | 30 | 65.01 | 48.70 | | 30 | 67.87 | 73.52 |
| 15 | 30 | 85.55 | 75.80 | | 30 | 75.34 | 78.36 |
| 16 | 30 | 75.38 | 76.84 | | 30 | 75.52 | 97.53 |
| 17 | 30 | 66.58 | 64.05 | | 30 | 67.82 | 99.55 |
| 21 | 30 | 78.40 | 69.72 | | 30 | 57.30 | 47.58 |
| 22 | 30 | 68.23 | 58.78 | | 30 | 60.18 | 60.12 |
| 23 | 30 | 70.70 | 60.56 | | 30 | 58.01 | 61.38 |

Summary Statistics:

10 msec

| SPR AY | N | Test MEAN | Test CV | MEAN Overall | Reference MEAN | Reference CV | MEAN Overall | P value |
|---|---|---|---|---|---|---|---|---|
| 9 | 30 | 74.29 | 14.64 | 73.79 | 79.38 | 42.206 | 80.025 | 0.026756 |
| 10 | 30 | 70.95 | 14.34 | | 82.67 | 64.25 | | |
| 11 | 30 | 73.29 | 17.05 | | 80.67 | 53.21 | | |
| 15 | 30 | 78.05 | 47.02 | 83.74 | 76.47 | 39.61 | 91.965 | 0.1106 |
| 16 | 30 | 72.16 | 32.07 | | 94.63 | 109.16 | | |
| 17 | 30 | 89.43 | 120.41 | | 107.46 | 103.34 | | |
| 21 | 30 | 73.45 | 28.6 | 74.605 | 69.01 | 16.22 | 76.065 | 0.198133 |
| 22 | 30 | 67.98 | 14.79 | | 84.98 | 97.51 | | |
| 23 | 30 | 75.76 | 27.59 | | 83.12 | 62.28 | | |

35 msec.

| SPR AY | N | TEST MEAN | TEST CV | MEAN overall | Reference MEAN | Reference CV | MEAN overall | P value |
|---|---|---|---|---|---|---|---|---|
| 9 | 30 | 60.99 | 16.28 | 56.85 | 59.29 | 15.66 | 60.225 | 0.138561 |
| 10 | 30 | 55.28 | 15.75 | | 63.11 | 74.45 | | |
| 11 | 30 | 52.71 | 15.13 | | 61.16 | 75.25 | | |
| 15 | 30 | 70.73 | 72.21 | 62.88 | 65.79 | 63.6 | 66 | 0.264204 |
| 16 | 30 | 61.56 | 60.37 | | 65.92 | 81.89 | | |
| 17 | 30 | 55.03 | 27.13 | | 66.21 | 88.76 | | |
| 21 | 30 | 68.95 | 59.76 | 61.815 | 56.88 | 14.76 | 61.235 | 0.495934 |
| 22 | 30 | 55.61 | 33.21 | | 57 | 37.24 | | |
| 23 | 30 | 54.68 | 23.96 | | 65.59 | 84.34 | | |

70 msec.

| SPR AY | N | TEST MEAN | TEST CV | MEAN overall | Reference MEAN | Reference CV | MEAN overall | P value |
|---|---|---|---|---|---|---|---|---|
| 9 | 30 | 77.72 | 43.99 | 71.365 | 72.66 | 44.02 | 70.265 | 0.292182 |
| 10 | 30 | 70.43 | 47.73 | | 68.13 | 47.67 | | |
| 11 | 30 | 65.01 | 48.7 | | 67.87 | 73.52 | | |
| 15 | 30 | 85.55 | 75.8 | 76.065 | 75.34 | 78.36 | 71.58 | 0.252187 |
| 16 | 30 | 75.38 | 76.84 | | 75.52 | 97.53 | | |
| 17 | 30 | 66.58 | 64.05 | | 67.82 | 99.55 | | |
| 21 | 30 | 78.4 | 69.72 | 74.55 | 57.3 | 47.58 | 57.655 | 0.033744 |
| 22 | 30 | 68.23 | 58.78 | | 60.18 | 60.12 | | |
| 23 | 30 | 70.7 | 60.56 | | 58.01 | 61.38 | | |

SPAN (Overall)

| Test | | Mean (CV) | | Ref | | Mean (CV) | | T/R | |
|---|---|---|---|---|---|---|---|---|---|
| | N | arithmetic | geometric | | N | arithmetic | geometric | Arith. | Geo. |
| 10 msec | 270 | 1.49 (49.30) | 1.43 (62.78) | 10 msec | 270 | 1.76 (84.94) | 1.54 (98.16) | 0.85 | 0.92 |
| 35 msec | 270 | 1.52 (13.12) | 1.51 (27.46) | 35 msec | 270 | 1.52 (34.58) | 1.49 (44.83) | 1.0 | 1.01 |
| 70 msec | 270 | 1.53 (15.96) | 1.52 (36.96) | 70 msec | 270 | 1.62 (32.54) | 1.58 (45.38) | 0.94 | 0.96 |

10 msec.

| | TEST | | | | REFERENCE | | |
|---|---|---|---|---|---|---|---|
| SPRAY | N | MEAN | CV | | N | MEAN | CV |
| 9 | 30 | 1.45 | 7.08 | | 30 | 1.70 | 53.63 |
| 10 | 30 | 1.44 | 7.50 | | 30 | 2.05 | 96.46 |
| 11 | 30 | 1.77 | 95.05 | | 30 | 2.05 | 114.46 |
| 15 | 30 | 1.46 | 5.41 | | 30 | 1.64 | 68.82 |
| 16 | 30 | 1.44 | 10.22 | | 30 | 1.37 | 6.26 |
| 17 | 30 | 1.46 | 65.33 | | 30 | 2.00 | 102.64 |
| 21 | 30 | 1.43 | 8.53 | | 30 | 1.44 | 4.93 |
| 22 | 30 | 1.42 | 9.35 | | 30 | 2.04 | 89.69 |
| 23 | 30 | 1.53 | 67.49 | | 30 | 1.55 | 64.30 |

35 msec.

| | TEST | | | | REFERENCE | | |
|---|---|---|---|---|---|---|---|
| SPRAY | N | MEAN | CV | | N | MEAN | CV |
| 9 | 30 | 1.62 | 6.85 | | 30 | 1.80 | 66.53 |
| 10 | 30 | 1.54 | 8.98 | | 30 | 1.50 | 5.67 |
| 11 | 30 | 1.48 | 10.11 | | 30 | 1.42 | 9.64 |
| 15 | 30 | 1.48 | 9.84 | | 30 | 1.53 | 16.70 |
| 16 | 30 | 1.54 | 10.90 | | 30 | 1.49 | 7.50 |
| 17 | 30 | 1.47 | 14.13 | | 30 | 1.39 | 9.85 |
| 21 | 30 | 1.63 | 24.58 | | 30 | 1.51 | 6.70 |
| 22 | 30 | 1.56 | 9.56 | | 30 | 1.67 | 54.74 |
| 23 | 30 | 1.46 | 9.24 | | 30 | 1.40 | 11.01 |

70 msec.

| | TEST | | | | REFERENCE | | |
|---|---|---|---|---|---|---|---|
| SPRAY | N | MEAN | CV | | N | MEAN | CV |
| 9 | 30 | 1.47 | 13.34 | | 30 | 1.71 | 50.88 |
| 10 | 30 | 1.57 | 15.69 | | 30 | 1.59 | 20.73 |
| 11 | 30 | 1.57 | 14.15 | | 30 | 1.55 | 8.83 |
| 15 | 30 | 1.53 | 14.86 | | 30 | 1.56 | 26.20 |
| 16 | 30 | 1.53 | 18.02 | | 30 | 1.68 | 27.43 |
| 17 | 30 | 1.60 | 15.73 | | 30 | 1.54 | 12.83 |
| 21 | 30 | 1.49 | 16.44 | | 30 | 1.58 | 12.70 |
| 22 | 30 | 1.53 | 17.33 | | 30 | 1.74 | 55.07 |
| 23 | 30 | 1.51 | 17.74 | | 30 | 1.65 | 32.09 |

Summary Statistics:

10 msec.

| SPRAY | N | TEST MEAN | CV | Overal mean | Ref MEAN | CV | Overal Mean | P value |
|---|---|---|---|---|---|---|---|---|
| 9 | 30 | 1.45 | 7.08 | 1.61 | 1.7 | 53.63 | 1.875 | 0.040532 |
| 10 | 30 | 1.44 | 7.5 | | 2.05 | 96.46 | | |
| 11 | 30 | 1.77 | 95.05 | | 2.05 | 114.46 | | |
| 15 | 30 | 1.46 | 5.41 | 1.46 | 1.64 | 68.82 | 1.82 | 0.172817 |
| 16 | 30 | 1.44 | 10.22 | | 1.37 | 6.26 | | |
| 17 | 30 | 1.46 | 65.33 | | 2 | 102.64 | | |
| 21 | 30 | 1.43 | 8.53 | 1.48 | 1.44 | 4.93 | 1.495 | 0.197553 |
| 22 | 30 | 1.42 | 9.35 | | 2.04 | 89.69 | | |
| 23 | 30 | 1.53 | 67.49 | | 1.55 | 64.3 | | |

35 msec

| SPRAY | N | TEST MEAN | CV | | Ref MEAN | CV | | P value |
|---|---|---|---|---|---|---|---|---|
| 9 | 30 | 1.62 | 6.85 | 1.55 | 1.8 | 66.53 | 1.61 | 0.380902 |
| 10 | 30 | 1.54 | 8.98 | | 1.5 | 5.67 | | |
| 11 | 30 | 1.48 | 10.11 | | 1.42 | 9.64 | | |
| 15 | 30 | 1.48 | 9.84 | 1.475 | 1.53 | 16.7 | 1.46 | 0.283705 |
| 16 | 30 | 1.54 | 10.9 | | 1.49 | 7.5 | | |
| 17 | 30 | 1.47 | 14.13 | | 1.39 | 9.85 | | |
| 21 | 30 | 1.63 | 24.58 | 1.545 | 1.51 | 6.7 | 1.455 | 0.383527 |
| 22 | 30 | 1.56 | 9.56 | | 1.67 | 54.74 | | |
| 23 | 30 | 1.46 | 9.24 | | 1.4 | 11.01 | | |

70 msec.

| SPRAY | N | TEST MEAN | CV | overal. mean | Ref MEAN | CV | Overa. Mean | P value |
|---|---|---|---|---|---|---|---|---|
| 9 | 30 | 1.47 | 13.34 | 1.52 | 1.71 | 50.88 | 1.63 | 0.213309 |
| 10 | 30 | 1.57 | 15.69 | | 1.59 | 20.73 | | |
| 11 | 30 | 1.57 | 14.15 | | 1.55 | 8.83 | | |
| 15 | 30 | 1.53 | 14.86 | 1.565 | 1.56 | 26.2 | 1.55 | 0.289181 |
| 16 | 30 | 1.53 | 18.02 | | 1.68 | 27.43 | | |
| 17 | 30 | 1.6 | 15.73 | | 1.54 | 12.83 | | |
| 21 | 30 | 1.49 | 16.44 | 1.5 | 1.58 | 12.7 | 1.615 | 0.025977 |
| 22 | 30 | 1.53 | 17.33 | | 1.74 | 55.07 | | |
| 23 | 30 | 1.51 | 17.74 | | 1.65 | 32.09 | | |

## 6. Droplet size distribution by

| Test | | | | Reference | | | | Test/Reference | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean (CV) | | | | Mean (CV) | | Ratio | |
| Group | N | arithmetic | geometric | Group | N | arithmetic | geometric | Arith | geo |
| 1 | 59 | 99.03(0.55) | 99.4(0.12) | 1 | 60 | 99.14(0.58) | 99.5(0.13) | 0.99 | 0.99 |
| 2 | 59 | 0.11(110.7) | 0.19(24.4) | 2 | 60 | 0.12(125.7) | 0.21(40) | 0.92 | 0.90 |
| 3 | 59 | 0.84(58.56) | 0.85(281) | 3 | 60 | 0.74(65.29) | 0.73(172) | 1.13 | 1.16 |

For each life stage

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Group 1 | | | | | | | |
| Beginning | 20 | 99.18 | 0.42 | 30 | 99.21 | 0.45 | 0.99 |
| End | 30 | 98.89 | 0.63 | 30 | 99.07 | 0.69 | 0.99 |
| Group 2 | | | | | | | |
| Beginning | 29 | 0.11 | 106.9 | 30 | 0.10 | 127.1 | 1.1 |
| End | 30 | 0.11 | 115.7 | 30 | 0.15 | 120.1 | 0.73 |
| Group 3 | | | | | | | |
| Beginning | 29 | 0.68 | 55.70 | 30 | 0.69 | 54.73 | 0.98 |
| End | 30 | 1 | 54.41 | 30 | 0.78 | 72.83 | 1.3 |

For each lot & life stage

| | | | | | | |
|---|---|---|---|---|---|---|
| Group 1 | Pump # V203978500 | | | Lot # 9F04645 | | |
| Beginning | 9 | 99.15 | 0.37 | 10 | 99.41 | 0.52 |
| End | 10 | 99.27 | 0.41 | 10 | 99.20 | 0.85 |
| | | Pump # V203978400 | | Lot # 9C12417 | | |
| Beginning | 10 | 99.32 | 0.40 | 10 | 99.22 | 0.35 |
| End | 10 | 98.62 | 0.70 | 10 | 98.92 | 0.64 |
| | | Pump # V203980000 | | Lot # 9C15231 | | |
| Beginning | 10 | 99.07 | 0.49 | 10 | 99 | 0.39 |
| End | 10 | 98.77 | 0.60 | 10 | 99.10 | 0.62 |
| Group 2 | Pump # V203978500 | | | Lot # 9F04645 | | |
| Beginning | 9 | 0.09 | 131.9 | 10 | 0.09 | 193.7 |
| End | 10 | 0.07 | 119.8 | 10 | 0.16 | 141.7 |
| | | Pump # V203978400 | | Lot # 9C12417 | | |
| Beginning | 10 | 0.11 | 97.35 | 10 | 0.11 | 91.81 |
| End | 10 | 0.13 | 110.3 | 10 | 0.11 | 129 |
| | | Pump # V203980000 | | Lot # 9C15231 | | |
| Beginning | 10 | 0.12 | 107 | 10 | 0.09 | 108 |
| End | 10 | 0.13 | 114.8 | 10 | 0.18 | 97 |
| Group 3 | Pump # V203978500 | | | Lot # 9F04645 | | |
| Beginning | 9 | 0.65 | 55 | 10 | 0.5 | 82 |
| End | 10 | 0.66 | 57 | 10 | 0.65 | 105 |
| | | Pump # V203978400 | | Lot # 9C012417 | | |
| Beginning | 10 | 0.57 | 67 | 10 | 0.67 | 46 |
| End | 10 | 1.25 | 49 | 10 | 0.97 | 55 |
| | | Pump # V203980000 | | Lot # 9C15231 | | |
| Beginning | 10 | 0.82 | 46 | 10 | 0.91 | 34 |
| End | 10 | 1.10 | 43 | 10 | 0.72 | 64 |

Summary Statistics:

Group 1

| | Test | | | | Reference | | | |
|---|---|---|---|---|---|---|---|---|
| Stage | N | Mean | CV | Ove. Mean | Mean | CV | Ove. Mean | P value |
| Beginning | 9 | 99.15 | 0.37 | 99.11 | 99.41 | 0.52 | 99.205 | 0.409547 |
| Beginning | 10 | 99.32 | 0.4 | | 99.22 | 0.35 | | |
| Beginning | 10 | 99.07 | 0.49 | | 99 | 0.39 | | |
| End | 10 | 99.27 | 0.41 | 99.02 | 99.2 | 0.85 | 99.15 | 0.141907 |
| End | 10 | 98.62 | 0.7 | | 98.92 | 0.64 | | |
| End | 10 | 98.77 | 0.6 | | 99.1 | 0.62 | | |

Group 2

| | Test | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Stage | N | Mean | CV | Ove. Mean | Mean | CV | Ove. Mean | |
| Beginning | 9 | 0.09 | 131.9 | 0.105 | 0.09 | 193.7 | 0.09 | 0.211325 |
| Beginning | 10 | 0.11 | 97.35 | | 0.11 | 91.81 | | |
| Beginning | 10 | 0.12 | 107 | | 0.09 | 108 | | |
| End | 10 | 0.07 | 119.8 | 0.1 | 0.16 | 141.7 | 0.17 | 0.169711 |
| End | 10 | 0.13 | 110.3 | | 0.11 | 129 | | |
| End | 10 | 0.13 | 114.8 | | 0.18 | 97 | | |

Group 3

| | Test | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Stage | N | Mean | CV | Ove. Mean | Mean | CV | Ove. Mean | |
| Beginning | 9 | 0.65 | 55 | 0.735 | 0.5 | 82 | 0.705 | 0.442693 |
| Beginning | 10 | 0.57 | 67 | | 0.67 | 46 | | |
| Beginning | 10 | 0.82 | 46 | | 0.91 | 34 | | |
| End | 10 | 0.66 | 57 | 0.88 | 0.65 | 105 | 0.685 | 0.090335 |
| End | 10 | 1.25 | 49 | | 0.97 | 55 | | |
| End | 10 | 1.1 | 43 | | 0.72 | 64 | | |

## 7. Spray pattern

### Spray pattern --Overall

| TEST | | | | REFERENCE | | | | Test/Ref. | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean (CV) | | | | Mean (CV) | | Ratio | |
| | N | arithmetic | geometric | | N | arithmetic | geometric | Arith | geo |
| Dmax | 180 | 50.18(33.9) | 47.5(9.0) | Dmax | 180 | 46.23(31.2) | 43.8 (8.42) | 1.08 | 1.08 |
| Dmin | 180 | 41.66(32.4) | 39.6(9.0) | Dmin | 180 | 39.05(31.2) | 37.3(8.8) | 1.07 | 1.06 |
| Ovality | 180 | 1.20(11.0) | 1.2(55.0) | Ovality | 180 | 1.19(9.7) | 1.2(55.1) | 1.01 | 1.0 |

Dmax

| | | Test | | | | | Ref | |
|---|---|---|---|---|---|---|---|---|
| Spray | Distance | Mean | CV | | Spray | Distance | Mean | CV |
| 9 | 2 | 31.62 | 12.16 | | 9 | 2 | 27.89 | 5.40 |
| 10 | 4 | 50.66 | 13.61 | | 10 | 4 | 40.43 | 6.56 |
| 11 | 6 | 73.23 | 13.62 | | 11 | 6 | 59.56 | 10.47 |
| 21 | 2 | 32.14 | 10.14 | | 21 | 2 | 28.91 | 5.07 |
| 22 | 4 | 49.91 | 13.23 | | 22 | 4 | 43.13 | 3.68 |
| 23 | 6 | 71.76 | 12.00 | | 23 | 6 | 60.45 | 10.18 |
| 9 | 2 | 29.46 | 6.61 | | 9 | 2 | 29.97 | 4.84 |
| 10 | 4 | 45.75 | 9.16 | | 10 | 4 | 45.17 | 5.00 |
| 11 | 6 | 67.53 | 10.69 | | 11 | 6 | 64.12 | 6.04 |
| 21 | 2 | 30.67 | 5.49 | | 21 | 2 | 31.30 | 3.78 |
| 22 | 4 | 46.44 | 8.17 | | 22 | 4 | 47.25 | 7.14 |
| 23 | 6 | 66.73 | 11.14 | | 23 | 6 | 65.06 | 7.25 |
| 9 | 2 | 30.66 | 5.62 | | 9 | 2 | 30.45 | 5.13 |
| 10 | 4 | 50.39 | 7.11 | | 10 | 4 | 46.60 | 12.23 |
| 11 | 6 | 71.53 | 7.15 | | 11 | 6 | 66.52 | 8.37 |
| 21 | 2 | 31.65 | 7.67 | | 21 | 2 | 31.78 | 5.90 |
| 22 | 4 | 52.13 | 8.67 | | 22 | 4 | 47.97 | 11.65 |
| 23 | 6 | 71.00 | 5.87 | | 23 | 6 | 65.54 | 10.56 |

Dmin

| | | Test | | | | | Ref | |
|---|---|---|---|---|---|---|---|---|
| Spray | Distance | Mean | CV | | Spray | Distance | Mean | CV |
| 9 | 2 | 27.51 | 9.72 | | 9 | 2 | 23.94 | 9.64 |
| 10 | 4 | 42.84 | 9.81 | | 10 | 4 | 35.02 | 12.14 |
| 11 | 6 | 58.47 | 10.72 | | 11 | 6 | 51.36 | 16.85 |
| 21 | 2 | 27.80 | 8.24 | | 21 | 2 | 24.82 | 9.62 |
| 22 | 4 | 40.75 | 11.53 | | 22 | 4 | 36.72 | 12.57 |
| 23 | 6 | 57.54 | 14.68 | | 23 | 6 | 51.73 | 16.53 |
| 9 | 2 | 25.32 | 9.48 | | 9 | 2 | 26.27 | 7.84 |
| 10 | 4 | 38.98 | 13.63 | | 10 | 4 | 38.78 | 5.31 |
| 11 | 6 | 56.47 | 14.19 | | 11 | 6 | 52.88 | 10.85 |
| 21 | 2 | 25.91 | 10.83 | | 21 | 2 | 26.83 | 7.62 |
| 22 | 4 | 39.36 | 11.10 | | 22 | 4 | 40.76 | 7.29 |
| 23 | 6 | 55.71 | 14.82 | | 23 | 6 | 55.07 | 10.41 |
| 9 | 2 | 25.92 | 5.6 | | 9 | 2 | 26.19 | 7.40 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 10 | 4 | 41.48 | 7.43 | | 10 | 4 | 38.81 | 16.00 |
| 11 | 6 | 58.00 | 10.42 | | 11 | 6 | 54.11 | 10.53 |
| 21 | 2 | 26.66 | 5.68 | | 21 | 2 | 26.97 | 8.47 |
| 22 | 4 | 43.59 | 8.74 | | 22 | 4 | 39.28 | 14.54 |
| 23 | 6 | 57.66 | 7.57 | | 23 | 6 | 53.29 | 10.61 |

Ovality

| | | Test | | | | | Ref | |
|---|---|---|---|---|---|---|---|---|
| Spray | Distance | Mean | CV | | Spray | Distance | Mean | CV |
| 9 | 2 | 1.15 | 5.57 | | 9 | 2 | 1.18 | 13.03 |
| 10 | 4 | 1.19 | 13.94 | | 10 | 4 | 1.17 | 9.60 |
| 11 | 6 | 1.26 | 17.66 | | 11 | 6 | 1.18 | 9.81 |
| 21 | 2 | 1.16 | 6.66 | | 21 | 2 | 1.18 | 14.40 |
| 22 | 4 | 1.23 | 15.75 | | 22 | 4 | 1.19 | 11.42 |
| 23 | 6 | 1.27 | 21.11 | | 23 | 6 | 1.18 | 9.61 |
| 9 | 2 | 1.17 | 8.50 | | 9 | 2 | 1.15 | 6.29 |
| 10 | 4 | 1.19 | 10.96 | | 10 | 4 | 1.17 | 6.81 |
| 11 | 6 | 1.21 | 10.56 | | 11 | 6 | 1.22 | 10.50 |
| 21 | 2 | 1.19 | 9.82 | | 21 | 2 | 1.17 | 7.65 |
| 22 | 4 | 1.19 | 10.32 | | 22 | 4 | 1.16 | 8.40 |
| 23 | 6 | 1.21 | 9.77 | | 23 | 6 | 1.19 | 7.31 |
| 9 | 2 | 1.18 | 5.55 | | 9 | 2 | 1.17 | 6.43 |
| 10 | 4 | 1.22 | 6.27 | | 10 | 4 | 1.21 | 11.57 |
| 11 | 6 | 1.24 | 9.02 | | 11 | 6 | 1.24 | 10.00 |
| 21 | 2 | 1.19 | 6.87 | | 21 | 2 | 1.18 | 7.92 |
| 22 | 4 | 1.20 | 4.45 | | 22 | 4 | 1.23 | 10.78 |
| 23 | 6 | 1.24 | 9.63 | | 23 | 6 | 1.24 | 10.70 |

Summary Statistics:

| Dmax | | Test | | | | Ref | | | |
|---|---|---|---|---|---|---|---|---|---|
| Spray | Distance | Mean | CV | Over.mean | Test/Refe. | Mean | CV | Over.mean | P value |
| 9 | 2 | 31.62 | 12.16 | 31.14 | 1.067535 | 27.89 | 5.4 | 29.17 | 0.237398 |
| 9 | 2 | 29.46 | 6.61 | | | 29.97 | 4.84 | | |
| 9 | 2 | 30.66 | 5.62 | | | 30.45 | 5.13 | | |
| 21 | 2 | 32.14 | 10.14 | 31.895 | 0.732966 | 40.43 | 6.56 | 43.515 | 0.013981 |
| 21 | 2 | 30.67 | 5.49 | | | 45.17 | 5 | | |
| 21 | 2 | 31.65 | 7.67 | | | 46.6 | 12.23 | | |
| 10 | 4 | 50.66 | 13.61 | 50.525 | 0.801475 | 59.56 | 10.47 | 63.04 | 0.018435 |
| 10 | 4 | 45.75 | 9.16 | | | 64.12 | 6.04 | | |
| 10 | 4 | 50.39 | 7.11 | | | 66.52 | 8.37 | | |
| 22 | 4 | 49.91 | 13.23 | 51.02 | 1.681331 | 28.91 | 5.07 | 30.345 | 0.00478 |
| 22 | 4 | 46.44 | 8.17 | | | 31.3 | 3.78 | | |
| 22 | 4 | 52.13 | 8.67 | | | 31.78 | 5.9 | | |
| 11 | 6 | 73.23 | 13.62 | 72.38 | 1.589023 | 43.13 | 3.68 | 45.55 | 0.00672 |
| 11 | 6 | 67.53 | 10.69 | | | 47.25 | 7.14 | | |
| 11 | 6 | 71.53 | 7.15 | | | 47.97 | 11.65 | | |
| 23 | 6 | 71.76 | 12 | 71.38 | 1.133106 | 60.45 | 10.18 | 62.995 | 0.079844 |
| 23 | 6 | 66.73 | 11.14 | | | 65.06 | 7.25 | | |
| 23 | 6 | 71 | 5.87 | | | 65.54 | 10.56 | | |

| Dmin | | Test | | | | Ref | | | |
|---|---|---|---|---|---|---|---|---|---|
| Spray | Distance | Mean | CV | Over.mean | Test/Refe. | Mean | CV | Over.mean | P value |
| 9 | 2 | 27.51 | 9.72 | 26.715 | 1.065829 | 23.94 | 9.64 | 25.065 | 0.316855 |
| 9 | 2 | 25.32 | 9.48 | | | 26.27 | 7.84 | | |
| 9 | 2 | 25.92 | 5.6 | | | 26.19 | 7.4 | | |
| 21 | 2 | 27.8 | 8.24 | 27.23 | 1.051554 | 24.82 | 9.62 | 25.895 | 0.338814 |
| 21 | 2 | 25.91 | 10.83 | | | 26.83 | 7.62 | | |
| 21 | 2 | 26.66 | 5.68 | | | 26.97 | 8.47 | | |
| 10 | 4 | 42.84 | 9.81 | 42.16 | 1.142083 | 35.02 | 12.14 | 36.915 | 0.126656 |
| 10 | 4 | 38.98 | 13.63 | | | 38.78 | 5.31 | | |
| 10 | 4 | 41.48 | 7.43 | | | 38.81 | 16 | | |
| 22 | 4 | 40.75 | 11.53 | 42.17 | 1.109737 | 36.72 | 12.57 | 38 | 0.169645 |
| 22 | 4 | 39.36 | 11.1 | | | 40.76 | 7.29 | | |
| 22 | 4 | 43.59 | 8.74 | | | 39.28 | 14.54 | | |
| 11 | 6 | 58.47 | 10.72 | 58.235 | 1.104295 | 51.36 | 16.85 | 52.735 | 0.024851 |
| 11 | 6 | 56.47 | 14.19 | | | 52.88 | 10.85 | | |
| 11 | 6 | 58 | 10.42 | | | 54.11 | 10.53 | | |
| 23 | 6 | 57.54 | 14.68 | 57.6 | 1.096934 | 51.73 | 16.53 | 52.51 | 0.072018 |
| 23 | 6 | 55.71 | 14.82 | | | 55.07 | 10.41 | | |
| 23 | 6 | 57.66 | 7.57 | | | 53.29 | 10.61 | | |

| Ovality | | Test | | | | Ref | | | |
|---|---|---|---|---|---|---|---|---|---|
| Spray | Distance | Mean | CV | Over.mean | Test/Refe. | Mean | CV | Over.mean | P value |
| 9 | 2 | 1.15 | 5.57 | 1.165 | 0.991489 | 1.18 | 13.03 | 1.175 | 0.5 |
| 9 | 2 | 1.17 | 8.5 | | | 1.15 | 6.29 | | |
| 9 | 2 | 1.18 | 5.55 | | | 1.17 | 6.43 | | |
| 21 | 2 | 1.16 | 6.66 | 1.175 | 0.987395 | 1.17 | 9.6 | 1.19 | 0.403775 |
| 21 | 2 | 1.19 | 9.82 | | | 1.17 | 6.81 | | |
| 21 | 2 | 1.19 | 6.87 | | | 1.21 | 11.57 | | |
| 10 | 4 | 1.19 | 13.94 | 1.205 | 0.995868 | 1.18 | 9.81 | 1.21 | 0.191393 |
| 10 | 4 | 1.19 | 10.96 | | | 1.22 | 10.5 | | |
| 10 | 4 | 1.22 | 6.27 | | | 1.24 | 10 | | |
| 22 | 4 | 1.23 | 15.75 | 1.215 | 1.029661 | 1.18 | 14.4 | 1.18 | 0.047733 |
| 22 | 4 | 1.19 | 10.32 | | | 1.17 | 7.65 | | |
| 22 | 4 | 1.2 | 4.45 | | | 1.18 | 7.92 | | |
| 11 | 6 | 1.26 | 17.66 | 1.25 | 1.033058 | 1.19 | 11.42 | 1.21 | 0.066667 |
| 11 | 6 | 1.21 | 10.56 | | | 1.16 | 8.4 | | |
| 11 | 6 | 1.24 | 9.02 | | | 1.23 | 10.78 | | |
| 23 | 6 | 1.27 | 21.11 | 1.255 | 1.03719 | 1.18 | 9.61 | 1.21 | 0.155577 |
| 23 | 6 | 1.21 | 9.77 | | | 1.19 | 7.31 | | |
| 23 | 6 | 1.24 | 9.63 | | | 1.24 | 10.7 | | |

# Appendix II: DRAWING OF THE PUMP

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information

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# III STATISTICAL ANALYSIS

## Summary Tables: Non-Profile Bioequivalence

- Droplet Size Distribution by
- Spray Pattern
- Unit Dose

**Non-Profile Bioequivalence**

**Droplet Size Distribution by**

**Summary Table**

| BE Measure | Distance (cm) | Delay (msec) | Geometric Mean | | Geometric Mean Ratio (%) | Standard Deviation | | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|
| | | | Test | Reference | | Reference | T/R Ratio | |
| D50 | 2 | 10 | 73.03 | 72.38 | 100.89 | 0.235 | 0.938 | -0.048 |
| | | 35 | 62.43 | 58.53 | 106.66 | 0.226 | 1.370 | 0.022 (-0.026) |
| | | 70 | 69.36 | 60.19 | 115.22 | 0.491 | 1.075 | -0.090 |
| | 4 | 10 | 69.14 | 75.87 | 91.14 | 0.411 | 0.432 | -0.255 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 35 | 55.14 | 56.81 | 97.06 | 0.338 | 0.731 | -0.132 |
| | | 70 | 61.40 | 57.25 | 107.26 | 0.557 | 0.961 | -0.224 |
| | 6 | 10 | 73.51 | 78.97 | 93.08 | 0.423 | 0.698 | -0.228 |
| | | 35 | 53.20 | 56.70 | 93.82 | 0.398 | 0.440 | -0.241 |
| | | 70 | 58.90 | 54.31 | 108.45 | 0.533 | 0.948 | -0.209 |
| Span | 2 | 10 | 1.44 | 1.51 | 95.52 | 0.265 | 0.253 | -0.121 |
| | | 35 | 1.53 | 1.55 | 98.33 | 0.225 | 0.590 | -0.074 |
| | | 70 | 1.48 | 1.56 | 94.71 | 0.234 | 0.631 | -0.072 |
| | 4 | 10 | 1.43 | 1.57 | 91.04 | 0.438 | 0.189 | -0.336 |
| | | 35 | 1.54 | 1.52 | 101.31 | 0.167 | 0.545 | -0.042 |
| | | 70 | 1.52 | 1.62 | 94.22 | 0.223 | 0.723 | -0.060 |
| | 6 | 10 | 1.41 | 1.52 | 93.29 | 0.516 | 0.727 | -0.338 |
| | | 35 | 1.46 | 1.40 | 104.56 | 0.107 | 0.994 | -0.005 |
| | | 70 | 1.54 | 1.56 | 99.05 | 0.158 | 0.970 | -0.020 |

† 95% upper confidence bound uses the regulatory constants

suggested in the draft guidance "Bioavailability
And Bioequivalence Studies for Nasal Aerosols and Nasal Sprays
for Local Action", June 1999

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PBE Results 15:19 Wednesday, March 21, 2001 173

---------- Distance (cm)=2 Delay (msec)=10 BE Measure=D50 ----------

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 10 | D50 | 0.1 | 0.00 | 1.11 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.0479 | -0.0034 | -0.04793 |
| 2 | 2 | 10 | D50 | 0.1 | 0.00 | 1.25 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.2392 | -0.0423 | -0.23919 |
| 3 | 2 | 10 | D50 | 0.2 | 0.00 | 1.11 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.0066 | -0.0034 | -0.00655 |
| 4 | 2 | 10 | D50 | 0.2 | 0.00 | 1.25 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.0557 | -0.0423 | -0.05572 |
| 5 | 2 | 10 | D50 | 0.1 | 0.01 | 1.11 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.0976 | -0.0134 | -0.09763 |
| 6 | 2 | 10 | D50 | 0.1 | 0.01 | 1.25 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.2879 | -0.0523 | -0.28790 |
| 7 | 2 | 10 | D50 | 0.2 | 0.01 | 1.11 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.0193 | -0.0134 | -0.01933 |
| 8 | 2 | 10 | D50 | 0.2 | 0.01 | 1.25 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.0682 | -0.0523 | -0.06818 |
| 9 | 2 | 10 | D50 | 0.1 | 0.03 | 1.11 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.1958 | -0.0334 | -0.19576 |
| 10 | 2 | 10 | D50 | 0.1 | 0.03 | 1.25 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.3852 | -0.0723 | -0.38515 |
| 11 | 2 | 10 | D50 | 0.2 | 0.03 | 1.11 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.0446 | -0.0334 | -0.04458 |
| 12 | 2 | 10 | D50 | 0.2 | 0.03 | 1.25 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.0930 | -0.0723 | -0 09297 |
| 13 | 2 | 10 | D50 | 0.1 | 0.05 | 1.11 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.2932 | -0.0534 | -0.29324 |
| 14 | 2 | 10 | D50 | 0.1 | 0.05 | 1.25 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.4823 | -0.0923 | -0.48228 |
| 15 | 2 | 10 | D50 | 0.2 | 0.05 | 1.11 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.0695 | -0.0534 | -0.06955 |
| 16 | 2 | 10 | D50 | 0.2 | 0.05 | 1.25 | 73.03 | 72.38 | 100.89 | 0.24 | 0.94 | -0.1176 | -0.0923 | -0.11763 |

---------- Distance (cm)=2 Delay (msec)=10 BE Measure=Span ----------

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 17 | 2 | 10 | Span | 0.1 | 0.00 | 1.11 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.1213 | -0.0653 | -0.12129 |
| 18 | 2 | 10 | Span | 0.1 | 0.00 | 1.25 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.3597 | -0.1042 | -0.35973 |
| 19 | 2 | 10 | Span | 0.2 | 0.00 | 1.11 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.0712 | -0.0653 | -0.07116 |
| 20 | 2 | 10 | Span | 0.2 | 0.00 | 1.25 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.1308 | -0.1042 | -0.13084 |
| 21 | 2 | 10 | Span | 0.1 | 0.01 | 1.11 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.1826 | -0.0753 | -0.18260 |
| 22 | 2 | 10 | Span | 0.1 | 0.01 | 1.25 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.4210 | -0.1142 | -0.42101 |
| 23 | 2 | 10 | Span | 0.2 | 0.01 | 1.11 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.0865 | -0.0753 | -0.08651 |

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---------- Distance (cm)=2 Delay (msec)=10 BE Measure=Span ----------
(continued)

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 24 | 2 | 10 | Span | 0.2 | 0.01 | 1.25 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.1462 | -0.1142 | -0.14617 |
| 25 | 2 | 10 | Span | 0.1 | 0.03 | 1.11 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.3052 | -0.0953 | -0.30518 |
| 26 | 2 | 10 | Span | 0.1 | 0.03 | 1.25 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.5436 | -0.1342 | -0.54357 |
| 27 | 2 | 10 | Span | 0.2 | 0.03 | 1.11 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.1172 | -0.0953 | -0.11719 |
| 28 | 2 | 10 | Span | 0.2 | 0.03 | 1.25 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.1768 | -0.1342 | -0.17682 |
| 29 | 2 | 10 | Span | 0.1 | 0.05 | 1.11 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.4277 | -0.1153 | -0.42774 |
| 30 | 2 | 10 | Span | 0.1 | 0.05 | 1.25 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.6661 | -0.1542 | -0.66612 |
| 31 | 2 | 10 | Span | 0.2 | 0.05 | 1.11 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.1479 | -0.1153 | -0.14785 |
| 32 | 2 | 10 | Span | 0.2 | 0.05 | 1.25 | 1.44 | 1.51 | 95.52 | 0.27 | 0.25 | -0.2075 | -0.1542 | -0.20747 |

---------- Distance (cm)=2 Delay (msec)=35 BE Measure=D50 ----------

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | 2 | 35 | D50 | 0.1 | 0.00 | 1.11 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | 0.0221 | 0.0644 | 0.02207 |
| 34 | 2 | 35 | D50 | 0.1 | 0.00 | 1.25 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | -0.1595 | 0.0255 | -0.15951 |
| 35 | 2 | 35 | D50 | 0.2 | 0.00 | 1.11 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | 0.0618 | 0.0644 | 0.06181 |
| 36 | 2 | 35 | D50 | 0.2 | 0.00 | 1.25 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | 0.0146 | 0.0255 | 0.01459 |
| 37 | 2 | 35 | D50 | 0.1 | 0.01 | 1.11 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | -0.0256 | 0.0544 | -0.02556 |
| 38 | 2 | 35 | D50 | 0.1 | 0.01 | 1.25 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | -0.2052 | 0.0155 | -0.20516 |
| 39 | 2 | 35 | D50 | 0.2 | 0.01 | 1.11 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | 0.0496 | 0.0544 | 0.04956 |
| 40 | 2 | 35 | D50 | 0.2 | 0.01 | 1.25 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | 0.0026 | 0.0155 | 0.00263 |
| 41 | 2 | 35 | D50 | 0.1 | 0.03 | 1.11 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | -0.1186 | 0.0344 | -0.11865 |
| 42 | 2 | 35 | D50 | 0.1 | 0.03 | 1.25 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | -0.2959 | -0.0045 | -0.29592 |
| 43 | 2 | 35 | D50 | 0.2 | 0.03 | 1.11 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | 0.0253 | 0.0344 | 0.02529 |
| 44 | 2 | 35 | D50 | 0.2 | 0.03 | 1.25 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | -0.0211 | -0.0045 | -0.02111 |
| 45 | 2 | 35 | D50 | 0.1 | 0.05 | 1.11 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | -0.2102 | 0.0144 | -0.21015 |

---------- Distance (cm)=2 Delay (msec)=35 BE Measure=D50 ----------
(continued)

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 46 | 2 | 35 | D50 | 0.1 | 0.05 | 1.25 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | -0.3862 | -0.0245 | -0.38624 |
| 47 | 2 | 35 | D50 | 0.2 | 0.05 | 1.11 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | 0.0013 | 0.0144 | 0.00132 |
| 48 | 2 | 35 | D50 | 0.2 | 0.05 | 1.25 | 62.43 | 58.53 | 106.66 | 0.23 | 1.37 | -0.0446 | -0.0245 | -0.04464 |

---------- Distance (cm)=2 Delay (msec)=35 BE Measure=Span ----------

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | 2 | 35 | Span | 0.1 | 0.00 | 1.11 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.0740 | -0.0365 | -0.07399 |
| 50 | 2 | 35 | Span | 0.1 | 0.00 | 1.25 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.2460 | -0.0754 | -0.24601 |
| 51 | 2 | 35 | Span | 0.2 | 0.00 | 1.11 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.0377 | -0.0365 | -0.03772 |
| 52 | 2 | 35 | Span | 0.2 | 0.00 | 1.25 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.0809 | -0.0754 | -0.08089 |
| 53 | 2 | 35 | Span | 0.1 | 0.01 | 1.11 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.1183 | -0.0465 | -0.11826 |
| 54 | 2 | 35 | Span | 0.1 | 0.01 | 1.25 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.2902 | -0.0854 | -0.29019 |
| 55 | 2 | 35 | Span | 0.2 | 0.01 | 1.11 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.0488 | -0.0465 | -0.04884 |
| 56 | 2 | 35 | Span | 0.2 | 0.01 | 1.25 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.0920 | -0.0854 | -0.09196 |
| 57 | 2 | 35 | Span | 0.1 | 0.03 | 1.11 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.2067 | -0.0665 | -0.20667 |
| 58 | 2 | 35 | Span | 0.1 | 0.03 | 1.25 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.3785 | -0.1054 | -0.37855 |
| 59 | 2 | 35 | Span | 0.2 | 0.03 | 1.11 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.0710 | -0.0665 | -0.07103 |
| 60 | 2 | 35 | Span | 0.2 | 0.03 | 1.25 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.1141 | -0.1054 | -0.11409 |
| 61 | 2 | 35 | Span | 0.1 | 0.05 | 1.11 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.2950 | -0.0865 | -0.29504 |
| 62 | 2 | 35 | Span | 0.1 | 0.05 | 1.25 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.4669 | -0.1254 | -0.46689 |
| 63 | 2 | 35 | Span | 0.2 | 0.05 | 1.11 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.0932 | -0.0865 | -0.09318 |
| 64 | 2 | 35 | Span | 0.2 | 0.05 | 1.25 | 1.53 | 1.55 | 98.33 | 0.23 | 0.59 | -0.1362 | -0.1254 | -0.13620 |

Distance (cm)=2 Delay (msec)=70 BE Measure=D50

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 65 | 2 | 70 | D50 | 0.1 | 0.00 | 1.11 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -0.0904 | 0.1391 | -0.09036 |
| 66 | 2 | 70 | D50 | 0.1 | 0.00 | 1.25 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -0.9063 | 0.1002 | -0.90629 |
| 67 | 2 | 70 | D50 | 0.2 | 0.00 | 1.11 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | 0.0889 | 0.1391 | 0.08885 |
| 68 | 2 | 70 | D50 | 0.2 | 0.00 | 1.25 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -0.1240 | 0.1002 | -0.12395 |
| 69 | 2 | 70 | D50 | 0.1 | 0.01 | 1.11 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -0.3039 | 0.1291 | -0.30394 |
| 70 | 2 | 70 | D50 | 0.1 | 0.01 | 1.25 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -1.1125 | 0.0902 | -1.11255 |
| 71 | 2 | 70 | D50 | 0.2 | 0.01 | 1.11 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | 0.0334 | 0.1291 | 0.03339 |
| 72 | 2 | 70 | D50 | 0.2 | 0.01 | 1.25 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -0.1776 | 0.0902 | -0.17760 |
| 73 | 2 | 70 | D50 | 0.1 | 0.03 | 1.11 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -0.7221 | 0.1091 | -0.72206 |
| 74 | 2 | 70 | D50 | 0.1 | 0.03 | 1.25 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -1.5237 | 0.0702 | -1.52370 |
| 75 | 2 | 70 | D50 | 0.2 | 0.03 | 1.11 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -0.0759 | 0.1091 | -0.07589 |
| 76 | 2 | 70 | D50 | 0.2 | 0.03 | 1.25 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -0.2840 | 0.0702 | -0.28399 |
| 77 | 2 | 70 | D50 | 0.1 | 0.05 | 1.11 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -1.1352 | 0.0891 | -1.13516 |
| 78 | 2 | 70 | D50 | 0.1 | 0.05 | 1.25 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -1.9338 | 0.0502 | -1.93381 |
| 79 | 2 | 70 | D50 | 0.2 | 0.05 | 1.11 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -0.1835 | 0.0891 | -0.18347 |
| 80 | 2 | 70 | D50 | 0.2 | 0.05 | 1.25 | 69.36 | 60.19 | 115.22 | 0.49 | 1.07 | -0.3895 | 0.0502 | -0.38947 |

Distance (cm)=2 Delay (msec)=70 BE Measure=Span

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 81 | 2 | 70 | Span | 0.1 | 0.00 | 1.11 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.0720 | -0.0310 | -0.07205 |
| 82 | 2 | 70 | Span | 0.1 | 0.00 | 1.25 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.2548 | -0.0699 | -0.25476 |
| 83 | 2 | 70 | Span | 0.2 | 0.00 | 1.11 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.0332 | -0.0310 | -0.03324 |
| 84 | 2 | 70 | Span | 0.2 | 0.00 | 1.25 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.0794 | -0.0699 | -0.07940 |
| 85 | 2 | 70 | Span | 0.1 | 0.01 | 1.11 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.1192 | -0.0410 | -0.11917 |
| 86 | 2 | 70 | Span | 0.1 | 0.01 | 1.25 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.3816 | -0.0799 | -0.38161 |
| 87 | 2 | 70 | Span | 0.2 | 0.01 | 1.11 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.0452 | -0.0410 | -0.04517 |

---------- Distance (cm)=2 Delay (msec)=70 BE Measure=Span ----------
(continued)

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 88 | 2 | 70 | Span | 0.2 | 0.01 | 1.25 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.0912 | -0.0799 | -0.09120 |
| 89 | 2 | 70 | Span | 0.1 | 0.03 | 1.11 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.2130 | -0.0610 | -0.21304 |
| 90 | 2 | 70 | Span | 0.1 | 0.03 | 1.25 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.3953 | -0.0999 | -0.39527 |
| 91 | 2 | 70 | Span | 0.2 | 0.03 | 1.11 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.0689 | -0.0610 | -0.06889 |
| 92 | 2 | 70 | Span | 0.2 | 0.03 | 1.25 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.1147 | -0.0999 | -0.11474 |
| 93 | 2 | 70 | Span | 0.1 | 0.05 | 1.11 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.3067 | -0.0810 | -0.30675 |
| 94 | 2 | 70 | Span | 0.1 | 0.05 | 1.25 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.4889 | -0.1199 | -0.48890 |
| 95 | 2 | 70 | Span | 0.2 | 0.05 | 1.11 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.0925 | -0.0810 | -0.09249 |
| 96 | 2 | 70 | Span | 0.2 | 0.05 | 1.25 | 1.48 | 1.56 | 94.71 | 0.23 | 0.63 | -0.1382 | -0.1199 | -0.13824 |

---------- Distance (cm)=4 Delay (msec)=10 BE Measure=D50 ----------

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 97 | 4 | 10 | D50 | 0.1 | 0.00 | 1.11 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.2552 | -0.1105 | -0.25522 |
| 98 | 4 | 10 | D50 | 0.1 | 0.00 | 1.25 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.8079 | -0.1494 | -0.80791 |
| 99 | 4 | 10 | D50 | 0.2 | 0.00 | 1.11 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.1387 | -0.1105 | -0.13866 |
| 100 | 4 | 10 | D50 | 0.2 | 0.00 | 1.25 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.2774 | -0.1494 | -0.27739 |
| 101 | 4 | 10 | D50 | 0.1 | 0.01 | 1.11 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.3975 | -0.1205 | -0.39745 |
| 102 | 4 | 10 | D50 | 0.1 | 0.01 | 1.25 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.9499 | -0.1594 | -0.94986 |
| 103 | 4 | 10 | D50 | 0.2 | 0.01 | 1.11 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.1744 | -0.1205 | -0.17440 |
| 104 | 4 | 10 | D50 | 0.2 | 0.01 | 1.25 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.3130 | -0.1594 | -0.31296 |
| 105 | 4 | 10 | D50 | 0.1 | 0.03 | 1.11 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.6815 | -0.1405 | -0.68153 |
| 106 | 4 | 10 | D50 | 0.1 | 0.03 | 1.25 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -1.2337 | -0.1794 | -1.23372 |
| 107 | 4 | 10 | D50 | 0.2 | 0.03 | 1.11 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.2457 | -0.1405 | -0.24570 |
| 108 | 4 | 10 | D50 | 0.2 | 0.03 | 1.25 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.3841 | -0.1794 | -0.38405 |
| 109 | 4 | 10 | D50 | 0.1 | 0.05 | 1.11 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.9654 | -0.1605 | -0.96544 |

Distance (cm)=4 Delay (msec)=10 BE Measure=D50 (continued)

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 110 | 4 | 10 | D50 | 0.1 | 0.05 | 1.25 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -1.5176 | -0.1994 | -1.51756 |
| 111 | 4 | 10 | D50 | 0.2 | 0.05 | 1.11 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.3169 | -0.1605 | -0.31686 |
| 112 | 4 | 10 | D50 | 0.2 | 0.05 | 1.25 | 69.14 | 75.87 | 91.14 | 0.41 | 0.43 | -0.4551 | -0.1994 | -0.45511 |

Distance (cm)=4 Delay (msec)=10 BE Measure=Span

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 113 | 4 | 10 | Span | 0.1 | 0.00 | 1.11 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.3358 | -0.1627 | -0.33581 |
| 114 | 4 | 10 | Span | 0.1 | 0.00 | 1.25 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.9916 | -0.2016 | -0.99156 |
| 115 | 4 | 10 | Span | 0.2 | 0.00 | 1.11 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.1979 | -0.1627 | -0.19788 |
| 116 | 4 | 10 | Span | 0.2 | 0.00 | 1.25 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.3621 | -0.2016 | -0.36209 |
| 117 | 4 | 10 | Span | 0.1 | 0.01 | 1.11 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.5045 | -0.1727 | -0.50446 |
| 118 | 4 | 10 | Span | 0.1 | 0.01 | 1.25 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -1.1601 | -0.2116 | -1.16006 |
| 119 | 4 | 10 | Span | 0.2 | 0.01 | 1.11 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.2401 | -0.1727 | -0.24013 |
| 120 | 4 | 10 | Span | 0.2 | 0.01 | 1.25 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.4043 | -0.2116 | -0.40425 |
| 121 | 4 | 10 | Span | 0.1 | 0.03 | 1.11 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.8415 | -0.1927 | -0.84155 |
| 122 | 4 | 10 | Span | 0.1 | 0.03 | 1.25 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -1.4971 | -0.2316 | -1.49706 |
| 123 | 4 | 10 | Span | 0.2 | 0.03 | 1.11 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.3245 | -0.1927 | -0.32454 |
| 124 | 4 | 10 | Span | 0.2 | 0.03 | 1.25 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.4886 | -0.2316 | -0.48856 |
| 125 | 4 | 10 | Span | 0.1 | 0.05 | 1.11 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -1.1786 | -0.2127 | -1.17857 |
| 126 | 4 | 10 | Span | 0.1 | 0.05 | 1.25 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -1.8340 | -0.2516 | -1.83404 |
| 127 | 4 | 10 | Span | 0.2 | 0.05 | 1.11 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.4089 | -0.2127 | -0.40888 |
| 128 | 4 | 10 | Span | 0.2 | 0.05 | 1.25 | 1.43 | 1.57 | 91.04 | 0.44 | 0.19 | -0.5729 | -0.2516 | -0.57285 |

Distance (cm)=4 Delay (msec)=35 BE Measure=D50

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 129 | 4 | 35 | D50 | 0.1 | 0.00 | 1.11 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.1315 | -0.0384 | -0.13154 |
| 130 | 4 | 35 | D50 | 0.1 | 0.00 | 1.25 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.4972 | -0.0773 | -0.49717 |
| 131 | 4 | 35 | D50 | 0.2 | 0.00 | 1.11 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.0538 | -0.0384 | -0.05382 |
| 132 | 4 | 35 | D50 | 0.2 | 0.00 | 1.25 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.1463 | -0.0773 | -0.14626 |
| 133 | 4 | 35 | D50 | 0.1 | 0.01 | 1.11 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.2258 | -0.0484 | -0.22584 |
| 134 | 4 | 35 | D50 | 0.1 | 0.01 | 1.25 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.5989 | -0.0873 | -0.59892 |
| 135 | 4 | 35 | D50 | 0.2 | 0.01 | 1.11 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.0777 | -0.0484 | -0.07773 |
| 136 | 4 | 35 | D50 | 0.2 | 0.01 | 1.25 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.1699 | -0.0873 | -0.16986 |
| 137 | 4 | 35 | D50 | 0.1 | 0.03 | 1.11 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.4137 | -0.0684 | -0.41369 |
| 138 | 4 | 35 | D50 | 0.1 | 0.03 | 1.25 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.7783 | -0.1073 | -0.77834 |
| 139 | 4 | 35 | D50 | 0.2 | 0.03 | 1.11 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.1252 | -0.0684 | -0.12521 |
| 140 | 4 | 35 | D50 | 0.2 | 0.03 | 1.25 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.2170 | -0.1073 | -0.21697 |
| 141 | 4 | 35 | D50 | 0.1 | 0.05 | 1.11 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.6012 | -0.0884 | -0.60121 |
| 142 | 4 | 35 | D50 | 0.1 | 0.05 | 1.25 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.9657 | -0.1273 | -0.96571 |
| 143 | 4 | 35 | D50 | 0.2 | 0.05 | 1.11 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.1725 | -0.0884 | -0.17245 |
| 144 | 4 | 35 | D50 | 0.2 | 0.05 | 1.25 | 55.14 | 56.81 | 97.06 | 0.34 | 0.73 | -0.2640 | -0.1273 | -0.26400 |

Distance (cm)=4 Delay (msec)=35 BE Measure=Span

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 145 | 4 | 35 | Span | 0.1 | 0.00 | 1.11 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.0423 | -0.0261 | -0.04226 |
| 146 | 4 | 35 | Span | 0.1 | 0.00 | 1.25 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.1377 | -0.0650 | -0.13769 |
| 147 | 4 | 35 | Span | 0.2 | 0.00 | 1.11 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.0220 | -0.0261 | -0.02613 |
| 148 | 4 | 35 | Span | 0.2 | 0.00 | 1.25 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.0461 | -0.0650 | -0.06503 |
| 149 | 4 | 35 | Span | 0.1 | 0.01 | 1.11 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.0669 | -0.0361 | -0.06685 |
| 150 | 4 | 35 | Span | 0.1 | 0.01 | 1.25 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.1622 | -0.0750 | -0.16218 |
| 151 | 4 | 35 | Span | 0.2 | 0.01 | 1.11 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.0283 | -0.0361 | -0.03613 |

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Distance (cm)=4 Delay (msec)=35 BE Measure=Span
(continued)

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 152 | 4 | 35 | Span | 0.2 | 0.01 | 1.25 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.0523 | -0.0750 | -0.07503 |
| 153 | 4 | 35 | Span | 0.1 | 0.03 | 1.11 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.1159 | -0.0561 | -0.11589 |
| 154 | 4 | 35 | Span | 0.1 | 0.03 | 1.25 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.2111 | -0.0950 | -0.21113 |
| 155 | 4 | 35 | Span | 0.2 | 0.03 | 1.11 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.0406 | -0.0561 | -0.05613 |
| 156 | 4 | 35 | Span | 0.2 | 0.03 | 1.25 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.0645 | -0.0950 | -0.09503 |
| 157 | 4 | 35 | Span | 0.1 | 0.05 | 1.11 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.1649 | -0.0761 | -0.16487 |
| 158 | 4 | 35 | Span | 0.1 | 0.05 | 1.25 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.2601 | -0.1150 | -0.26008 |
| 159 | 4 | 35 | Span | 0.2 | 0.05 | 1.11 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.0529 | -0.0761 | -0.07613 |
| 160 | 4 | 35 | Span | 0.2 | 0.05 | 1.25 | 1.54 | 1.52 | 101.31 | 0.17 | 0.54 | -0.0768 | -0.1150 | -0.11503 |

Distance (cm)=4 Delay (msec)=70 BE Measure=D50

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 161 | 4 | 70 | D50 | 0.1 | 0.00 | 1.11 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -0.2236 | 0.0682 | -0.22364 |
| 162 | 4 | 70 | D50 | 0.1 | 0.00 | 1.25 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -1.2581 | 0.0293 | -1.25809 |
| 163 | 4 | 70 | D50 | 0.2 | 0.00 | 1.11 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | 0.0020 | 0.0682 | 0.00198 |
| 164 | 4 | 70 | D50 | 0.2 | 0.00 | 1.25 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -0.2660 | 0.0293 | -0.26597 |
| 165 | 4 | 70 | D50 | 0.1 | 0.01 | 1.11 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -0.4932 | 0.0582 | -0.49317 |
| 166 | 4 | 70 | D50 | 0.1 | 0.01 | 1.25 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -1.5210 | 0.0193 | -1.52095 |
| 167 | 4 | 70 | D50 | 0.2 | 0.01 | 1.11 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -0.0679 | 0.0582 | -0.06786 |
| 168 | 4 | 70 | D50 | 0.2 | 0.01 | 1.25 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -0.3336 | 0.0193 | -0.33360 |
| 169 | 4 | 70 | D50 | 0.1 | 0.03 | 1.11 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -1.0236 | 0.0382 | -1.02359 |
| 170 | 4 | 70 | D50 | 0.1 | 0.03 | 1.25 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -2.0456 | -0.0007 | -2.04562 |
| 171 | 4 | 70 | D50 | 0.2 | 0.03 | 1.11 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -0.2054 | 0.0382 | -0.20542 |
| 172 | 4 | 70 | D50 | 0.2 | 0.03 | 1.25 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -0.4680 | -0.0007 | -0.46795 |
| 173 | 4 | 70 | D50 | 0.1 | 0.05 | 1.11 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -1.5498 | 0.0182 | -1.54979 |

---------- Distance (cm)=4 Delay (msec)=70 BE Measure=D50 ----------
(continued)

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 174 | 4 | 70 | D50 | 0.1 | 0.05 | 1.25 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -2.5695 | -0.0207 | -2.56949 |
| 175 | 4 | 70 | D50 | 0.2 | 0.05 | 1.11 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -0.3410 | 0.0182 | -0.34101 |
| 176 | 4 | 70 | D50 | 0.2 | 0.05 | 1.25 | 61.40 | 57.25 | 107.26 | 0.56 | 0.96 | -0.6014 | -0.0207 | -0.60141 |

---------- Distance (cm)=4 Delay (msec)=70 BE Measure=Span ----------

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 177 | 4 | 70 | Span | 0.1 | 0.00 | 1.11 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.0599 | -0.0217 | -0.05988 |
| 178 | 4 | 70 | Span | 0.1 | 0.00 | 1.25 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.2311 | -0.0606 | -0.23114 |
| 179 | 4 | 70 | Span | 0.2 | 0.00 | 1.11 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.0233 | -0.0217 | -0.02325 |
| 180 | 4 | 70 | Span | 0.2 | 0.00 | 1.25 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.0668 | -0.0606 | -0.06681 |
| 181 | 4 | 70 | Span | 0.1 | 0.01 | 1.11 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.1042 | -0.0317 | -0.10416 |
| 182 | 4 | 70 | Span | 0.1 | 0.01 | 1.25 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.2750 | -0.0706 | -0.27496 |
| 183 | 4 | 70 | Span | 0.2 | 0.01 | 1.11 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.0345 | -0.0317 | -0.03454 |
| 184 | 4 | 70 | Span | 0.2 | 0.01 | 1.25 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.0779 | -0.0706 | -0.07789 |
| 185 | 4 | 70 | Span | 0.1 | 0.03 | 1.11 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.1921 | -0.0517 | -0.19210 |
| 186 | 4 | 70 | Span | 0.1 | 0.03 | 1.25 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.3625 | -0.0906 | -0.36254 |
| 187 | 4 | 70 | Span | 0.2 | 0.03 | 1.11 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.0569 | -0.0517 | -0.05691 |
| 188 | 4 | 70 | Span | 0.2 | 0.03 | 1.25 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.1000 | -0.0906 | -0.10000 |
| 189 | 4 | 70 | Span | 0.1 | 0.05 | 1.11 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.2798 | -0.0717 | -0.27977 |
| 190 | 4 | 70 | Span | 0.1 | 0.05 | 1.25 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.4501 | -0.1106 | -0.45008 |
| 191 | 4 | 70 | Span | 0.2 | 0.05 | 1.11 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.0791 | -0.0717 | -0.07911 |
| 192 | 4 | 70 | Span | 0.2 | 0.05 | 1.25 | 1.52 | 1.62 | 94.22 | 0.22 | 0.72 | -0.1220 | -0.1106 | -0.12204 |

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---------- Distance (cm)=6 Delay (msec)=10 BE Measure=D50 ----------

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 193 | 6 | 10 | D50 | 0.1 | 0.00 | 1.11 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.2278 | -0.0676 | -0.22777 |
| 194 | 6 | 10 | D50 | 0.1 | 0.00 | 1.25 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.8310 | -0.1065 | -0.83105 |
| 195 | 6 | 10 | D50 | 0.2 | 0.00 | 1.11 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.0998 | -0.0676 | -0.09981 |
| 196 | 6 | 10 | D50 | 0.2 | 0.00 | 1.25 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.2520 | -0.1065 | -0.25203 |
| 197 | 6 | 10 | D50 | 0.1 | 0.01 | 1.11 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.3833 | -0.0776 | -0.38328 |
| 198 | 6 | 10 | D50 | 0.1 | 0.01 | 1.25 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.9858 | -0.1165 | -0.98579 |
| 199 | 6 | 10 | D50 | 0.2 | 0.01 | 1.11 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.1391 | -0.0776 | -0.13914 |
| 200 | 6 | 10 | D50 | 0.2 | 0.01 | 1.25 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.2909 | -0.1165 | -0.29095 |
| 201 | 6 | 10 | D50 | 0.1 | 0.03 | 1.11 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.6932 | -0.0976 | -0.69325 |
| 202 | 6 | 10 | D50 | 0.1 | 0.03 | 1.25 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -1.2952 | -0.1365 | -1.29518 |
| 203 | 6 | 10 | D50 | 0.2 | 0.03 | 1.11 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.2173 | -0.0976 | -0.21734 |
| 204 | 6 | 10 | D50 | 0.2 | 0.03 | 1.25 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.3686 | -0.1365 | -0.36864 |
| 205 | 6 | 10 | D50 | 0.1 | 0.05 | 1.11 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -1.0028 | -0.1176 | -1.00278 |
| 206 | 6 | 10 | D50 | 0.1 | 0.05 | 1.25 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -1.6045 | -0.1565 | -1.60449 |
| 207 | 6 | 10 | D50 | 0.2 | 0.05 | 1.11 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.2952 | -0.1176 | -0.29521 |
| 208 | 6 | 10 | D50 | 0.2 | 0.05 | 1.25 | 73.51 | 78.97 | 93.08 | 0.42 | 0.70 | -0.4462 | -0.1565 | -0.44623 |

---------- Distance (cm)=6 Delay (msec)=10 BE Measure=Span ----------

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 209 | 6 | 10 | Span | 0.1 | 0.00 | 1.11 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -0.3376 | -0.0899 | -0.33761 |
| 210 | 6 | 10 | Span | 0.1 | 0.00 | 1.25 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -1.2490 | -0.1288 | -1.24897 |
| 211 | 6 | 10 | Span | 0.2 | 0.00 | 1.11 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -0.1442 | -0.0899 | -0.14421 |
| 212 | 6 | 10 | Span | 0.2 | 0.00 | 1.25 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -0.3743 | -0.1288 | -0.37428 |
| 213 | 6 | 10 | Span | 0.1 | 0.01 | 1.11 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -0.5726 | -0.0999 | -0.57258 |
| 214 | 6 | 10 | Span | 0.1 | 0.01 | 1.25 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -1.4827 | -0.1388 | -1.48270 |
| 215 | 6 | 10 | Span | 0.2 | 0.01 | 1.11 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -0.2037 | -0.0999 | -0.20366 |

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Distance (cm)=6 Delay (msec)=10 BE Measure=Span
(continued)

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 216 | 6 | 10 | Span | 0.2 | 0.01 | 1.25 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -0.4331 | -0.1388 | -0.43308 |
| 217 | 6 | 10 | Span | 0.1 | 0.03 | 1.11 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -1.0408 | -0.1199 | -1.04083 |
| 218 | 6 | 10 | Span | 0.1 | 0.03 | 1.25 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -1.9500 | -0.1588 | -1.94999 |
| 219 | 6 | 10 | Span | 0.2 | 0.03 | 1.11 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -0.3219 | -0.1199 | -0.32186 |
| 220 | 6 | 10 | Span | 0.2 | 0.03 | 1.25 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -0.5505 | -0.1588 | -0.55047 |
| 221 | 6 | 10 | Span | 0.1 | 0.05 | 1.11 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -1.5084 | -0.1399 | -1.50836 |
| 222 | 6 | 10 | Span | 0.1 | 0.05 | 1.25 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -2.4172 | -0.1788 | -2.41717 |
| 223 | 6 | 10 | Span | 0.2 | 0.05 | 1.11 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -0.4395 | -0.1399 | -0.43953 |
| 224 | 6 | 10 | Span | 0.2 | 0.05 | 1.25 | 1.41 | 1.52 | 93.29 | 0.52 | 0.73 | -0.6677 | -0.1788 | -0.66769 |

Distance (cm)=6 Delay (msec)=35 BE Measure=D50

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 225 | 6 | 35 | D50 | 0.1 | 0.00 | 1.11 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.2407 | -0.1068 | -0.24070 |
| 226 | 6 | 35 | D50 | 0.1 | 0.00 | 1.25 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.7555 | -0.1457 | -0.75548 |
| 227 | 6 | 35 | D50 | 0.2 | 0.00 | 1.11 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.1323 | -0.1068 | -0.13225 |
| 228 | 6 | 35 | D50 | 0.2 | 0.00 | 1.25 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.2613 | -0.1457 | -0.26134 |
| 229 | 6 | 35 | D50 | 0.1 | 0.01 | 1.11 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.3731 | -0.1168 | -0.37315 |
| 230 | 6 | 35 | D50 | 0.1 | 0.01 | 1.25 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.8877 | -0.1557 | -0.88772 |
| 231 | 6 | 35 | D50 | 0.2 | 0.01 | 1.11 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.1655 | -0.1168 | -0.16550 |
| 232 | 6 | 35 | D50 | 0.2 | 0.01 | 1.25 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.2945 | -0.1557 | -0.29446 |
| 233 | 6 | 35 | D50 | 0.1 | 0.03 | 1.11 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.6377 | -0.1368 | -0.63775 |
| 234 | 6 | 35 | D50 | 0.1 | 0.03 | 1.25 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -1.1522 | -0.1757 | -1.15117 |
| 235 | 6 | 35 | D50 | 0.2 | 0.03 | 1.11 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.2318 | -0.1368 | -0.23185 |
| 236 | 6 | 35 | D50 | 0.2 | 0.03 | 1.25 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.3607 | -0.1757 | -0.36067 |
| 237 | 6 | 35 | D50 | 0.1 | 0.05 | 1.11 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.9022 | -0.1568 | -0.90224 |



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---------- Distance (cm)=6 Delay (msec)=35 BE Measure=D50 ----------
(continued)

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 238 | 6 | 35 | D50 | 0.1 | 0.05 | 1.25 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -1.4166 | -0.1957 | -1.41660 |
| 239 | 6 | 35 | D50 | 0.2 | 0.05 | 1.11 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.2981 | -0.1568 | -0.29810 |
| 240 | 6 | 35 | D50 | 0.2 | 0.05 | 1.25 | 53.20 | 56.70 | 93.82 | 0.40 | 0.44 | -0.4268 | -0.1957 | -0.42684 |

---------- Distance (cm)=6 Delay (msec)=35 BE Measure=Span ----------

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 241 | 6 | 35 | Span | 0.1 | 0.00 | 1.11 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0049 | -0.0046 | -0.004935 |
| 242 | 6 | 35 | Span | 0.1 | 0.00 | 1.25 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0429 | -0.0435 | -0.042908 |
| 243 | 6 | 35 | Span | 0.2 | 0.00 | 1.11 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | 0.0034 | -0.0046 | -0.004607 |
| 244 | 6 | 35 | Span | 0.2 | 0.00 | 1.25 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0065 | -0.0435 | -0.043509 |
| 245 | 6 | 35 | Span | 0.1 | 0.01 | 1.11 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0149 | -0.0146 | -0.014876 |
| 246 | 6 | 35 | Span | 0.1 | 0.01 | 1.25 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0525 | -0.0535 | -0.052510 |
| 247 | 6 | 35 | Span | 0.2 | 0.01 | 1.11 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | 0.0008 | -0.0146 | -0.014607 |
| 248 | 6 | 35 | Span | 0.2 | 0.01 | 1.25 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0090 | -0.0535 | -0.053509 |
| 249 | 6 | 35 | Span | 0.1 | 0.03 | 1.11 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0343 | -0.0346 | -0.034332 |
| 250 | 6 | 35 | Span | 0.1 | 0.03 | 1.25 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0717 | -0.0735 | -0.071655 |
| 251 | 6 | 35 | Span | 0.2 | 0.03 | 1.11 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0043 | -0.0346 | -0.034607 |
| 252 | 6 | 35 | Span | 0.2 | 0.03 | 1.25 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0139 | -0.0735 | -0.073509 |
| 253 | 6 | 35 | Span | 0.1 | 0.05 | 1.11 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0536 | -0.0546 | -0.053563 |
| 254 | 6 | 35 | Span | 0.1 | 0.05 | 1.25 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0908 | -0.0935 | -0.090754 |
| 255 | 6 | 35 | Span | 0.2 | 0.05 | 1.11 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0093 | -0.0546 | -0.054607 |
| 256 | 6 | 35 | Span | 0.2 | 0.05 | 1.25 | 1.46 | 1.40 | 104.56 | 0.11 | 0.99 | -0.0189 | -0.0935 | -0.093509 |

---------- Distance (cm)=6 Delay (msec)=70 BE Measure=D50 ----------

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 257 | 6 | 70 | D50 | 0.1 | 0.00 | 1.11 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -0.2086 | 0.0545 | -0.20865 |
| 258 | 6 | 70 | D50 | 0.1 | 0.00 | 1.25 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -1.1456 | 0.0156 | -1.14564 |
| 259 | 6 | 70 | D50 | 0.2 | 0.00 | 1.11 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -0.0045 | 0.0545 | -0.00450 |
| 260 | 6 | 70 | D50 | 0.2 | 0.00 | 1.25 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -0.2469 | 0.0156 | -0.24695 |
| 261 | 6 | 70 | D50 | 0.1 | 0.01 | 1.11 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -0.4526 | 0.0445 | -0.45261 |
| 262 | 6 | 70 | D50 | 0.1 | 0.01 | 1.25 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -1.3839 | 0.0056 | -1.38392 |
| 263 | 6 | 70 | D50 | 0.2 | 0.01 | 1.11 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -0.0677 | 0.0445 | -0.06770 |
| 264 | 6 | 70 | D50 | 0.2 | 0.01 | 1.25 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -0.3082 | 0.0056 | -0.30816 |
| 265 | 6 | 70 | D50 | 0.1 | 0.03 | 1.11 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -0.9331 | 0.0245 | -0.93311 |
| 266 | 6 | 70 | D50 | 0.1 | 0.03 | 1.25 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -1.8596 | -0.0144 | -1.85961 |
| 267 | 6 | 70 | D50 | 0.2 | 0.03 | 1.11 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -0.1922 | 0.0245 | -0.19216 |
| 268 | 6 | 70 | D50 | 0.2 | 0.03 | 1.25 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -0.4298 | -0.0144 | -0.42977 |
| 269 | 6 | 70 | D50 | 0.1 | 0.05 | 1.11 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -1.4101 | 0.0045 | -1.41006 |
| 270 | 6 | 70 | D50 | 0.1 | 0.05 | 1.25 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -2.3346 | -0.0344 | -2.33464 |
| 271 | 6 | 70 | D50 | 0.2 | 0.05 | 1.11 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -0.3149 | 0.0045 | -0.31486 |
| 272 | 6 | 70 | D50 | 0.2 | 0.05 | 1.25 | 58.90 | 54.31 | 108.45 | 0.53 | 0.95 | -0.5506 | -0.0344 | -0.55062 |

---------- Distance (cm)=6 Delay (msec)=70 BE Measure=Span ----------

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 273 | 6 | 70 | Span | 0.1 | 0.00 | 1.11 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.0201 | -0.0058 | -0.02007 |
| 274 | 6 | 70 | Span | 0.1 | 0.00 | 1.25 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.1068 | -0.0447 | -0.10685 |
| 275 | 6 | 70 | Span | 0.2 | 0.00 | 1.11 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.0013 | -0.0058 | -0.00579 |
| 276 | 6 | 70 | Span | 0.2 | 0.00 | 1.25 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.0236 | -0.0447 | -0.04469 |
| 277 | 6 | 70 | Span | 0.1 | 0.01 | 1.11 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.0426 | -0.0158 | -0.04263 |
| 278 | 6 | 70 | Span | 0.1 | 0.01 | 1.25 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.1289 | -0.0547 | -0.12894 |
| 279 | 6 | 70 | Span | 0.2 | 0.01 | 1.11 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.0071 | -0.0158 | -0.01579 |

---------- Distance (cm)=6 Delay (msec)=70 BE Measure=Span ----------
(continued)

| Obs | Distance (cm) | Delay (msec) | BE Measure | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTR (Total R Std Dev) | Ratio: sigT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 280 | 6 | 70 | Span | 0.2 | 0.01 | 1.25 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.0293 | -0.0547 | -0.05469 |
| 281 | 6 | 70 | Span | 0.1 | 0.03 | 1.11 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.0871 | -0.0358 | -0.08714 |
| 282 | 6 | 70 | Span | 0.1 | 0.03 | 1.25 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.1730 | -0.0747 | -0.17304 |
| 283 | 6 | 70 | Span | 0.2 | 0.03 | 1.11 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.0185 | -0.0358 | -0.03579 |
| 284 | 6 | 70 | Span | 0.2 | 0.03 | 1.25 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.0405 | -0.0747 | -0.07469 |
| 285 | 6 | 70 | Span | 0.1 | 0.05 | 1.11 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.1314 | -0.0558 | -0.13136 |
| 286 | 6 | 70 | Span | 0.1 | 0.05 | 1.25 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.2171 | -0.0947 | -0.21709 |
| 287 | 6 | 70 | Span | 0.2 | 0.05 | 1.11 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.0299 | -0.0558 | -0.05579 |
| 288 | 6 | 70 | Span | 0.2 | 0.05 | 1.25 | 1.54 | 1.56 | 99.05 | 0.16 | 0.97 | -0.0517 | -0.0947 | -0.09469 |

APPEARS THIS WAY ON ORIGINAL

**Non-Profile Bioequivalence**

**Test: Spray Pattern**
**Summary Table**

| | | Geometric | | Geometric | Standard | | Upper |
|---|---|---|---|---|---|---|---|
| Distance | BE | Mean | | Mean | Deviation | | Confidence |
| (cm) | Variable | Test | Reference | Ratio (%) | Reference | T/R Ratio | Bound ↑ |
| 2 | $D_{max}$ | 30.93 | 29.99 | 103.14 | 0.066 | 1.248 | -0.004 |
| | $D_{min}$ | 26.42 | 25.73 | 102.68 | 0.095 | 0.950 | -0.007 |
| | Ovality Ratio | 1.17 | 1.17 | 100.45 | 0.089 | 0.797 | -0.011 |
| 4 | $D_{max}$ | 48.93 | 44.87 | 109.04 | 0.100 | 1.085 | **0.007** **(-0.002)** |
| | $D_{min}$ | 40.92 | 37.92 | 107.92 | 0.133 | 0.851 | -0.007 |
| | Ovality Ratio | 1.20 | 1.18 | 101.04 | 0.096 | 1.031 | -0.006 |
| 6 | $D_{max}$ | 69.92 | 63.25 | 110.54 | 0.099 | 1.071 | **0.009** **(-0.001)** |
| | $D_{min}$ | 56.90 | 52.63 | 108.11 | 0.134 | 0.913 | -0.004 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ovality Ratio | 1.23 | 1.20 | 102.26 | 0.094 | 1.275 | 0.002 |
| | | | | | | (-0.008) |

† 95% upper confidence bound uses the regulatory constants suggested in the draft guidance "Bioavailability And Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", June 1999; that is, average BE criterion (GMR) of 90/111, = 0, and $_0$ = 0.1. If the bioequivalence test fails using these constants, then the alternate values suggested in the guidance (i.e., = 0.01 and the other two unchanged) are reported in parentheses.

Dataset: asprptgjp.xls
3/6/2001





APPEARS THIS WAY ON ORIGINAL

distance=2 metric=Dmax

| Obs | metric | distance | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTT (Total T Std Dev) | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Dmax | 2 | 0.1 | 0.00 | 1.11 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | 0.0022 | -0.0043 | -0.004315 |
| 2 | Dmax | 2 | 0.1 | 0.00 | 1.25 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | -0.0121 | -0.0432 | -0.043217 |
| 3 | Dmax | 2 | 0.2 | 0.00 | 1.11 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | 0.0055 | -0.0043 | -0.004315 |
| 4 | Dmax | 2 | 0.2 | 0.00 | 1.25 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | 0.0016 | -0.0432 | -0.043217 |
| 5 | Dmax | 2 | 0.1 | 0.01 | 1.11 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | -0.0016 | -0.0143 | -0.014315 |
| 6 | Dmax | 2 | 0.1 | 0.01 | 1.25 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | -0.0157 | -0.0532 | -0.053217 |
| 7 | Dmax | 2 | 0.2 | 0.01 | 1.11 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | 0.0045 | -0.0143 | -0.014315 |
| 8 | Dmax | 2 | 0.2 | 0.01 | 1.25 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | 0.0007 | -0.0532 | -0.053217 |
| 9 | Dmax | 2 | 0.1 | 0.03 | 1.11 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | -0.0089 | -0.0343 | -0.034315 |
| 10 | Dmax | 2 | 0.1 | 0.03 | 1.25 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | -0.0227 | -0.0732 | -0.073217 |
| 11 | Dmax | 2 | 0.2 | 0.03 | 1.11 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | 0.0025 | -0.0343 | -0.034315 |
| 12 | Dmax | 2 | 0.2 | 0.03 | 1.25 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | -0.0012 | -0.0732 | -0.073217 |
| 13 | Dmax | 2 | 0.1 | 0.05 | 1.11 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | -0.0160 | -0.0543 | -0.054315 |
| 14 | Dmax | 2 | 0.1 | 0.05 | 1.25 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | -0.0297 | -0.0932 | -0.093217 |
| 15 | Dmax | 2 | 0.2 | 0.05 | 1.11 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | 0.0006 | -0.0543 | -0.054315 |
| 16 | Dmax | 2 | 0.2 | 0.05 | 1.25 | 30.9 | 30.0 | 103.14 | 0.08 | 0.07 | 1.25 | -0.0031 | -0.0932 | -0.093217 |

distance=2 metric=Dmin

| Obs | metric | distance | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTT (Total T Std Dev) | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 17 | Dmin | 2 | 0.1 | 0.00 | 1.11 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0043 | -0.0068 | -0.006824 |
| 18 | Dmin | 2 | 0.1 | 0.00 | 1.25 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0320 | -0.0457 | -0.045726 |
| 19 | Dmin | 2 | 0.2 | 0.00 | 1.11 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | 0.0019 | -0.0068 | -0.006824 |
| 20 | Dmin | 2 | 0.2 | 0.00 | 1.25 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0054 | -0.0457 | -0.045726 |
| 21 | Dmin | 2 | 0.1 | 0.01 | 1.11 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0116 | -0.0168 | -0.016824 |
| 22 | Dmin | 2 | 0.1 | 0.01 | 1.25 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0390 | -0.0557 | -0.055726 |
| 23 | Dmin | 2 | 0.2 | 0.01 | 1.11 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0000 | -0.0168 | -0.016824 |
| 24 | Dmin | 2 | 0.2 | 0.01 | 1.25 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0073 | -0.0557 | -0.055726 |
| 25 | Dmin | 2 | 0.1 | 0.03 | 1.11 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0258 | -0.0368 | -0.036824 |
| 26 | Dmin | 2 | 0.1 | 0.03 | 1.25 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0530 | -0.0757 | -0.075726 |
| 27 | Dmin | 2 | 0.2 | 0.03 | 1.11 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0038 | -0.0368 | -0.036824 |
| 28 | Dmin | 2 | 0.2 | 0.03 | 1.25 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0109 | -0.0757 | -0.075726 |
| 29 | Dmin | 2 | 0.1 | 0.05 | 1.11 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0398 | -0.0568 | -0.056824 |
| 30 | Dmin | 2 | 0.1 | 0.05 | 1.25 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0669 | -0.0957 | -0.095726 |
| 31 | Dmin | 2 | 0.2 | 0.05 | 1.11 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0075 | -0.0568 | -0.056824 |
| 32 | Dmin | 2 | 0.2 | 0.05 | 1.25 | 26.4 | 25.7 | 102.68 | 0.09 | 0.09 | 0.95 | -0.0145 | -0.0957 | -0.095726 |

distance=2 metric=OR

| Obs | metric | distance | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTT (Total T Std Dev) | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | OR | 2 | 0.1 | 0.00 | 1.11 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0072 | -0.0110 | -0.011029 |
| 34 | OR | 2 | 0.1 | 0.00 | 1.25 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0312 | -0.0499 | -0.049931 |
| 35 | OR | 2 | 0.2 | 0.00 | 1.11 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0019 | -0.0110 | -0.011029 |
| 36 | OR | 2 | 0.2 | 0.00 | 1.25 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0082 | -0.0499 | -0.049931 |
| 37 | OR | 2 | 0.1 | 0.01 | 1.11 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0134 | -0.0210 | -0.021029 |
| 38 | OR | 2 | 0.1 | 0.01 | 1.25 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0374 | -0.0599 | -0.059931 |
| 39 | OR | 2 | 0.2 | 0.01 | 1.11 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0036 | -0.0210 | -0.021029 |
| 40 | OR | 2 | 0.2 | 0.01 | 1.25 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0097 | -0.0599 | -0.059931 |
| 41 | OR | 2 | 0.1 | 0.03 | 1.11 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0258 | -0.0410 | -0.041029 |
| 42 | OR | 2 | 0.1 | 0.03 | 1.25 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0496 | -0.0799 | -0.079931 |
| 43 | OR | 2 | 0.2 | 0.03 | 1.11 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0068 | -0.0410 | -0.041029 |
| 44 | OR | 2 | 0.2 | 0.03 | 1.25 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0129 | -0.0799 | -0.079931 |
| 45 | OR | 2 | 0.1 | 0.05 | 1.11 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0380 | -0.0610 | -0.061029 |
| 46 | OR | 2 | 0.1 | 0.05 | 1.25 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0618 | -0.0999 | -0.099931 |
| 47 | OR | 2 | 0.2 | 0.05 | 1.11 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0099 | -0.0610 | -0.061029 |
| 48 | OR | 2 | 0.2 | 0.05 | 1.25 | 1.2 | 1.2 | 100.45 | 0.07 | 0.09 | 0.80 | -0.0160 | -0.0999 | -0.099931 |

---------- distance=4 metric=Dmax ----------

| Obs | metric | distance | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTT (Total T Std Dev) | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | Dmax | 4 | 0.1 | 0.00 | 1.11 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | 0.0069 | 0.0060 | 0.006893 |
| 50 | Dmax | 4 | 0.1 | 0.00 | 1.25 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | -0.0262 | -0.0329 | -0.026221 |
| 51 | Dmax | 4 | 0.2 | 0.00 | 1.11 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | 0.0144 | 0.0060 | 0.006043 |
| 52 | Dmax | 4 | 0.2 | 0.00 | 1.25 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | 0.0055 | -0.0329 | -0.032859 |
| 53 | Dmax | 4 | 0.1 | 0.01 | 1.11 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | -0.0019 | -0.0040 | -0.001918 |
| 54 | Dmax | 4 | 0.1 | 0.01 | 1.25 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | -0.0344 | -0.0429 | -0.034424 |
| 55 | Dmax | 4 | 0.2 | 0.01 | 1.11 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | 0.0120 | -0.0040 | -0.003957 |
| 56 | Dmax | 4 | 0.2 | 0.01 | 1.25 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | 0.0033 | -0.0429 | -0.042859 |
| 57 | Dmax | 4 | 0.1 | 0.03 | 1.11 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | -0.0189 | -0.0240 | -0.018853 |
| 58 | Dmax | 4 | 0.1 | 0.03 | 1.25 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | -0.0507 | -0.0629 | -0.050684 |
| 59 | Dmax | 4 | 0.2 | 0.03 | 1.11 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | 0.0075 | -0.0240 | -0.023957 |
| 60 | Dmax | 4 | 0.2 | 0.03 | 1.25 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | -0.0011 | -0.0629 | -0.062859 |
| 61 | Dmax | 4 | 0.1 | 0.05 | 1.11 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | -0.0353 | -0.0440 | -0.035321 |
| 62 | Dmax | 4 | 0.1 | 0.05 | 1.25 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | -0.0668 | -0.0829 | -0.066824 |
| 63 | Dmax | 4 | 0.2 | 0.05 | 1.11 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | 0.0030 | -0.0440 | -0.043957 |
| 64 | Dmax | 4 | 0.2 | 0.05 | 1.25 | 48.9 | 44.9 | 109.04 | 0.11 | 0.10 | 1.08 | -0.0054 | -0.0829 | -0.082859 |



---------- distance=4 metric=Dmin ----------

| | | | | | | | | | SigmaTT | SigmaTR | Ratio: | 95% UCL | 95% UCL | Upper |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

| Obs | metric | distance | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | (Total T Std Dev) | (Total R Std Dev) | sigTT / sigTR | R-scaled PBE Criterion | C-scaled PBE Criterion | Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 65 | Dmin | 4 | 0.1 | 0.00 | 1.11 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0068 | -0.0012 | -0.00676 |
| 66 | Dmin | 4 | 0.1 | 0.00 | 1.25 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0615 | -0.0401 | -0.06147 |
| 67 | Dmin | 4 | 0.2 | 0.00 | 1.11 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | 0.0055 | -0.0012 | -0.00116 |
| 68 | Dmin | 4 | 0.2 | 0.00 | 1.25 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0090 | -0.0401 | -0.04006 |
| 69 | Dmin | 4 | 0.1 | 0.01 | 1.11 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0212 | -0.0112 | -0.02117 |
| 70 | Dmin | 4 | 0.1 | 0.01 | 1.25 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0752 | -0.0501 | -0.07523 |
| 71 | Dmin | 4 | 0.2 | 0.01 | 1.11 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | 0.0017 | -0.0112 | -0.01116 |
| 72 | Dmin | 4 | 0.2 | 0.01 | 1.25 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0127 | -0.0501 | -0.05006 |
| 73 | Dmin | 4 | 0.1 | 0.03 | 1.11 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0492 | -0.0312 | -0.04917 |
| 74 | Dmin | 4 | 0.1 | 0.03 | 1.25 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.1026 | -0.0781 | -0.10263 |
| 75 | Dmin | 4 | 0.2 | 0.03 | 1.11 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0058 | -0.0312 | -0.03116 |
| 76 | Dmin | 4 | 0.2 | 0.03 | 1.25 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0198 | -0.0781 | -0.07006 |
| 77 | Dmin | 4 | 0.1 | 0.05 | 1.11 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0767 | -0.0512 | -0.07673 |
| 78 | Dmin | 4 | 0.1 | 0.05 | 1.25 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.1300 | -0.0981 | -0.12996 |
| 79 | Dmin | 4 | 0.2 | 0.05 | 1.11 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0131 | -0.0512 | -0.05116 |
| 80 | Dmin | 4 | 0.2 | 0.05 | 1.25 | 40.9 | 37.9 | 107.92 | 0.11 | 0.13 | 0.85 | -0.0269 | -0.0981 | -0.09006 |

---------- distance=4 metric=OR ----------

| Obs | metric | distance | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTT (Total T Std Dev) | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 81 | OR | 4 | 0.1 | 0.00 | 1.11 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0034 | -0.0057 | -0.005736 |
| 82 | OR | 4 | 0.1 | 0.00 | 1.25 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0316 | -0.0446 | -0.044638 |
| 83 | OR | 4 | 0.2 | 0.00 | 1.11 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | 0.0030 | -0.0057 | -0.005736 |
| 84 | OR | 4 | 0.2 | 0.00 | 1.25 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0045 | -0.0446 | -0.044638 |
| 85 | OR | 4 | 0.1 | 0.01 | 1.11 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0108 | -0.0157 | -0.015736 |
| 86 | OR | 4 | 0.1 | 0.01 | 1.25 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0388 | -0.0546 | -0.054638 |
| 87 | OR | 4 | 0.2 | 0.01 | 1.11 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | 0.0010 | -0.0157 | -0.015736 |
| 88 | OR | 4 | 0.2 | 0.01 | 1.25 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0064 | -0.0546 | -0.054638 |
| 89 | OR | 4 | 0.1 | 0.03 | 1.11 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0253 | -0.0357 | -0.035736 |
| 90 | OR | 4 | 0.1 | 0.03 | 1.25 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0529 | -0.0746 | -0.074638 |
| 91 | OR | 4 | 0.2 | 0.03 | 1.11 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0029 | -0.0357 | -0.035736 |
| 92 | OR | 4 | 0.2 | 0.03 | 1.25 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0101 | -0.0746 | -0.074638 |
| 93 | OR | 4 | 0.1 | 0.05 | 1.11 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0395 | -0.0557 | -0.055736 |
| 94 | OR | 4 | 0.1 | 0.05 | 1.25 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0671 | -0.0946 | -0.094638 |
| 95 | OR | 4 | 0.2 | 0.05 | 1.11 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0066 | -0.0557 | -0.055736 |
| 96 | OR | 4 | 0.2 | 0.05 | 1.25 | 1.2 | 1.2 | 101.04 | 0.10 | 0.10 | 1.03 | -0.0138 | -0.0946 | -0.094638 |

---------- distance=6 metric=Dmax ----------

| Obs | metric | distance | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTT (Total T Std Dev) | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 97 | Dmax | 6 | 0.1 | 0.00 | 1.11 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | 0.0103 | 0.0090 | 0.009048 |
| 98 | Dmax | 6 | 0.1 | 0.00 | 1.25 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | -0.0212 | -0.0299 | -0.029854 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99 | Dmax | 6 | 0.2 | 0.00 | 1.11 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | 0.0175 | 0.0090 | 0.009048 |
| 100 | Dmax | 6 | 0.2 | 0.00 | 1.25 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | 0.0090 | -0.0299 | -0.029854 |
| 101 | Dmax | 6 | 0.1 | 0.01 | 1.11 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | 0.0019 | -0.0010 | -0.000952 |
| 102 | Dmax | 6 | 0.1 | 0.01 | 1.25 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | -0.0290 | -0.0399 | -0.039854 |
| 103 | Dmax | 6 | 0.2 | 0.01 | 1.11 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | 0.0152 | -0.0010 | -0.000952 |
| 104 | Dmax | 6 | 0.2 | 0.01 | 1.25 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | 0.0068 | -0.0399 | -0.039854 |
| 105 | Dmax | 6 | 0.1 | 0.03 | 1.11 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | -0.0142 | -0.0210 | -0.020952 |
| 106 | Dmax | 6 | 0.1 | 0.03 | 1.25 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | -0.0443 | -0.0599 | -0.059854 |
| 107 | Dmax | 6 | 0.2 | 0.03 | 1.11 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | 0.0109 | -0.0210 | -0.020952 |
| 108 | Dmax | 6 | 0.2 | 0.03 | 1.25 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | 0.0027 | -0.0599 | -0.059854 |
| 109 | Dmax | 6 | 0.1 | 0.05 | 1.11 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | -0.0298 | -0.0410 | -0.040952 |
| 110 | Dmax | 6 | 0.1 | 0.05 | 1.25 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | -0.0595 | -0.0799 | -0.079854 |
| 111 | Dmax | 6 | 0.2 | 0.05 | 1.11 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | 0.0066 | -0.0410 | -0.040952 |
| 112 | Dmax | 6 | 0.2 | 0.05 | 1.25 | 69.9 | 63.2 | 110.54 | 0.11 | 0.10 | 1.07 | -0.0015 | -0.0799 | -0.079854 |

---------- distance=6 metric=Dmin ----------

| Obs | metric | distance | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTT (Total T Std Dev) | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 113 | Dmin | 6 | 0.1 | 0.00 | 1.11 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0039 | 0.0023 | -0.00392 |
| 114 | Dmin | 6 | 0.1 | 0.00 | 1.25 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0603 | -0.0366 | -0.06027 |
| 115 | Dmin | 6 | 0.2 | 0.00 | 1.11 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | 0.0088 | 0.0023 | 0.00228 |
| 116 | Dmin | 6 | 0.2 | 0.00 | 1.25 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0063 | -0.0366 | -0.03663 |
| 117 | Dmin | 6 | 0.1 | 0.01 | 1.11 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0188 | -0.0877 | -0.01882 |
| 118 | Dmin | 6 | 0.1 | 0.01 | 1.25 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0744 | -0.0466 | -0.07438 |
| 119 | Dmin | 6 | 0.2 | 0.01 | 1.11 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | 0.0048 | -0.0077 | -0.00772 |
| 120 | Dmin | 6 | 0.2 | 0.01 | 1.25 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0100 | -0.0466 | -0.04663 |
| 121 | Dmin | 6 | 0.1 | 0.03 | 1.11 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0476 | -0.0277 | -0.04764 |
| 122 | Dmin | 6 | 0.1 | 0.03 | 1.25 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.1025 | -0.0666 | -0.10245 |
| 123 | Dmin | 6 | 0.2 | 0.03 | 1.11 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0029 | -0.0277 | -0.02772 |
| 124 | Dmin | 6 | 0.2 | 0.03 | 1.25 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0174 | -0.0666 | -0.06663 |
| 125 | Dmin | 6 | 0.1 | 0.05 | 1.11 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0759 | -0.0477 | -0.07592 |
| 126 | Dmin | 6 | 0.1 | 0.05 | 1.25 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.1304 | -0.0866 | -0.13042 |
| 127 | Dmin | 6 | 0.2 | 0.05 | 1.11 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0104 | -0.0477 | -0.04772 |
| 128 | Dmin | 6 | 0.2 | 0.05 | 1.25 | 56.9 | 52.6 | 108.11 | 0.12 | 0.13 | 0.91 | -0.0247 | -0.0866 | -0.08663 |



---------- distance=6 metric=OR ----------

| Obs | metric | distance | Sigma T0 | epsilon | ABE | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTT (Total T Std Dev) | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 129 | OR | 6 | 0.1 | 0.00 | 1.11 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | 0.0037 | 0.0015 | 0.001533 |
| 130 | OR | 6 | 0.1 | 0.00 | 1.25 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | -0.0252 | -0.0374 | -0.037369 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 131 | OR | 6 | 0.2 | 0.00 | 1.11 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | 0.0102 | 0.0015 | 0.001533 |
| 132 | OR | 6 | 0.2 | 0.00 | 1.25 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | 0.0024 | -0.0374 | -0.037369 |
| 133 | OR | 6 | 0.1 | 0.01 | 1.11 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | -0.0040 | -0.0085 | -0.008467 |
| 134 | OR | 6 | 0.1 | 0.01 | 1.25 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | -0.0324 | -0.0474 | -0.047369 |
| 135 | OR | 6 | 0.2 | 0.01 | 1.11 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | 0.0082 | -0.0085 | -0.008467 |
| 136 | OR | 6 | 0.2 | 0.01 | 1.25 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | 0.0005 | -0.0474 | -0.047369 |
| 137 | OR | 6 | 0.1 | 0.03 | 1.11 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | -0.0188 | -0.0285 | -0.028467 |
| 138 | OR | 6 | 0.1 | 0.03 | 1.25 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | -0.0466 | -0.0674 | -0.067369 |
| 139 | OR | 6 | 0.2 | 0.03 | 1.11 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | 0.0042 | -0.0285 | -0.028467 |
| 140 | OR | 6 | 0.2 | 0.03 | 1.25 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | -0.0033 | -0.0674 | -0.067369 |
| 141 | OR | 6 | 0.1 | 0.05 | 1.11 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | -0.0332 | -0.0485 | -0.048467 |
| 142 | OR | 6 | 0.1 | 0.05 | 1.25 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | -0.0607 | -0.0874 | -0.087369 |
| 143 | OR | 6 | 0.2 | 0.05 | 1.11 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | 0.0003 | -0.0485 | -0.048467 |
| 144 | OR | 6 | 0.2 | 0.05 | 1.25 | 1.2 | 1.2 | 102.26 | 0.12 | 0.09 | 1.27 | -0.0071 | -0.0874 | -0.087369 |

APPEARS THIS WAY
ON ORIGINAL

**Non-Profile Bioequivalence**

**Test: Unit Dose**
**Summary Table**

| BE Variable | Geometric Mean | | Geometric Mean | Standard Deviation | | Upper Confidence Bound † |
|---|---|---|---|---|---|---|
| | Test | Reference | Ratio (%) | Reference | T/R Ratio | |
| % label | 104.82 | 106.86 | 98.10 | 0.044 | 1.033 | -0.0097 |

† A negative upper confidence bound means the test product passes this bioequivalence test. These 95% upper confidence bounds use the regulatory constants suggested in the draft guidance, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", June 1999; that is, average BE criterion (GMR) of 90/111, = 0, and $_0$ = 0.1. If the bioequivalence test fails using these constants, then the alternate values suggested in the guidance (i.e., = 0.01 and the other two unchanged) are reported in parentheses.

Dataset: aunitdose.xls
3/2/2001

| Obs | # Sectors | Sigma T0 | epsilon | ABE | FDA PBE limit | Geom Mean T | Geom Mean R | exp(DELTA)* 100 | SigmaTT (Total T Std Dev) | SigmaTR (Total R Std Dev) | Ratio: sigTT / sigTR | 95% UCL R-scaled PBE Criterion | 95% UCL C-scaled PBE Criterion | Upper Confidence Bound |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 0.1 | 0.00 | 1.11 | 1.09 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0006 | -0.0097 | -0.009675 |
| 2 | 2 | 0.1 | 0.00 | 1.25 | 4.98 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0069 | -0.0486 | -0.048577 |
| 3 | 2 | 0.2 | 0.00 | 1.11 | 0.27 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | 0.0007 | -0.0097 | -0.009675 |
| 4 | 2 | 0.2 | 0.00 | 1.25 | 1.24 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0009 | -0.0486 | -0.048577 |
| 5 | 2 | 0.1 | 0.01 | 1.11 | 2.09 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0023 | -0.0197 | -0.019675 |
| 6 | 2 | 0.1 | 0.01 | 1.25 | 5.98 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0085 | -0.0586 | -0.058577 |
| 7 | 2 | 0.2 | 0.01 | 1.11 | 0.52 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | 0.0003 | -0.0197 | -0.019675 |
| 8 | 2 | 0.2 | 0.01 | 1.25 | 1.49 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0013 | -0.0586 | -0.058577 |
| 9 | 2 | 0.1 | 0.03 | 1.11 | 4.09 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0055 | -0.0397 | -0.039675 |
| 10 | 2 | 0.1 | 0.03 | 1.25 | 7.98 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0116 | -0.0786 | -0.078577 |
| 11 | 2 | 0.2 | 0.03 | 1.11 | 1.02 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0005 | -0.0397 | -0.039675 |
| 12 | 2 | 0.2 | 0.03 | 1.25 | 1.99 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0021 | -0.0786 | -0.078577 |
| 13 | 2 | 0.1 | 0.05 | 1.11 | 6.09 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0086 | -0.0597 | -0.059675 |
| 14 | 2 | 0.1 | 0.05 | 1.25 | 9.98 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0148 | -0.0986 | -0.098577 |
| 15 | 2 | 0.2 | 0.05 | 1.11 | 1.52 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0013 | -0.0597 | -0.059675 |
| 16 | 2 | 0.2 | 0.05 | 1.25 | 2.49 | 104.82 | 106.86 | 98.10 | 0.045 | 0.044 | 1.033 | -0.0029 | -0.0986 | -0.098577 |





Residuals



| Obs | bottle | product | lot | spray | sector | label | loglabel | Pred | Resid |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 85 | REF | 6 | 23 | END | 89.484 | 4.49406 | 4.65309 | -0.15903 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 10 | REF | 5 | 9 | BEG | 91.920 | 4.52092 | 4.64896 | -0.12804 |
| 3 | 81 | REF | 4 | 9 | BEG | 93.357 | 4.53643 | 4.65626 | -0.11983 |
| 61 | 148 | TEST | 3 | 23 | END | 88.245 | 4.48012 | 4.62484 | -0.14472 |
| 62 | 88 | TEST | 1 | 9 | BEG | 90.501 | 4.50536 | 4.62710 | -0.12174 |

APPEARS THIS WAY
ON ORIGINAL

**Butorphanol Tartrate**
**Nasal Spray, 10 mg/mL**
**ANDA # 75-759**
Reviewer: Nhan L. Tran
**MSWord: 75759S.D99**

**ESI LEDERLE**
**2 Esterbrook Lane**
Cherry Hill, NJ
**Submission Date:**
**December 22, 1999**

# Review of A Submission

## I. Objective:

This submission is for butorphanol tartrate nasal spray. The firm conducted comparative *in vitro* testing based on recommendations from the DBE on the protocol submitted earlier (August 5, 1999). A request for a waiver for in-vivo BE study is submitted in the present submission.

## II. Submission History:

The firm submitted a protocol on August 5, 1999-Protocol # 99-032 for this drug product. The protocol was reviewed by the DBE and comments were sent to the firm. The present study was conducted based on the protocol submitted to the Agency on 8/5/1999.

## III. Background:

Butorphanol Tartrate Nasal Spray, 10 mg/mL, is indicated for the management of pain when the use of an opioid analgesic is appropriate. It is marketed as a solution provided in 2.5 mL fill bottles; one bottle delivers 14-15 sprays (1 spray = 100µL=1mg). The drug exerts effects through the systemic circulation following absorption from the nasal cavity. The reference listed drug is Stadol NS®, nasal solution by Bristol-Myers Squibb (BMS).

## IV. Comments on the in-vitro testing data

The in-vitro bioequivalence studies are under review. There are deficiencies to be conveyed to the firm for additional information as follows:

1. [redacted]

[ ]

2. In addition the firm should be requested to provide the following information:

   The sampling time duration in determination of droplet size distribution by ——— at beginning,

   Representative (≥ 20%) plots of obscuration vs. time with D10, D50 and D90 data on the same plot.

## V. Recommendation

The *in vitro* performance testing conducted by ESI Lederle on its Butorphanol Tartrate Nasal Spray, 10 mg/mL comparing it with the reference product, Stadol®, nasal solution (Bristol-Myers Squibb) has been found incomplete due to deficiencies above. The sponsor should be informed of the deficiency comments.

Nhan L. Tran, Ph.D. /S/ 4-10
Review Branch II
Division of Bioequivalence

/S/

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR Date 4/10/2001

Concur: /S/ Date 4/16/01
Dale P. Conner, Pharm. D., Director
Division of Bioequivalence

V:\FIRMSAM\ESILEDERLE\LTRS&REV\75759S.D99
cc: ANDA 75-759 (original), HFD-655 (Tran, Nerurkar), Drug File, Division File

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pages of trade secret and/or confidential commercial information