Contains Nonbinding Recommendations

Draft Guidance on Budesonide

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Active ingredient: Budesonide

Form/Route: Suspension/Inhalation

Recommended studies:

1. Testing Requirements for the Highest Strength (1 mg/2 mL) Product:

The generic budesonide suspension/inhalation product must be qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug product (RLD).

Option A. In Vitro Bioequivalence Studies Alone:

The following in vitro comparative tests are recommended. Pari LC Plus Nebulizer/Pari Master compressor system is recommended for those tests requiring nebulization. The tests include:

1) Sameness of polymorphic form of the drug substance based on X-ray diffraction.

2) Sameness of shape (crystalline habit) of the drug substance.

3) Comparative Unit Dose Content (UDC) of drug in the ampules.

4) Comparative Mean Nebulization Time (MNT) and Mean Delivered Dose (MDD): The test should be conducted at the mouthpiece (% nominal dose) at the labeled flow rate of 5.5 L/min through such time that mist is no longer coming out of the mouthpiece.

5) Comparative drug particle and agglomerate Particle Size Distribution (PSD) in the suspension (in the ampoule): The PSD determination should be based on a validated method. Validation should demonstrate method sensitivity to drug particle size over the expected size range in the suspension.

6) Comparative drug particle and agglomerate PSD in the nebulized aerosol: Recommended method for this test is the aerodynamic particle size distribution (APSD) of the nebulized aerosol based on Apparatus 5 (USP <601>) at a flow rate of 15 L/min through the Apparatus. We recommend the study be conducted based on USP <1601> using the Pari LC Plus Nebulizer/Pari Master compressor system. The amount of drug deposited on the induction port, the seven stages of the cascade impactor, and the sum of the back-up filter and micro-orifice collector (MOC) should be submitted.

7) Comparative aqueous droplet size distribution of the nebulized aerosol by a Laser diffraction method.

Option B. Combination of In Vitro and In Vivo Bioequivalence Studies:

1) Tests should include all described above in 1. Option A, with the exception of comparative drug particle and agglomerate PSD in the nebulized aerosol referred in 1. Option A. 6)

2) A clinical endpoint bioequivalence study, with demonstration of acceptable dose-response for test and reference products to assure study sensitivity. At this time, the Agency has no recommendations regarding the clinical bioequivalence study design.

3) A systemic exposure (pharmacokinetic) bioequivalence study.

2. Testing Requirements for the Two Lower Strengths (0.5 mg/2 mL or 0.25 mg/2 mL) Products:

If the micronized budesonide (bulk drug) used in the lower strength product is the same as that used in the higher strength product, i.e., same particle size, PSD, polymorphic form, and shape, and the respective lower strength test and reference formulations are Q1 and Q2 the same, the Division of Bioequivalence (DB) recommends that the firm conduct the following tests for the lower strengths of the test product:

Option A. **In Vitro Bioequivalence Studies Alone**:

If the comparative drug particle and agglomerate PSD in the nebulized aerosol between the test and reference products for both the higher and lower strengths can be determined, the following in vitro testing should be sufficient to demonstrate the equivalence of the lower strengths:

1) Documentation of bioequivalence of the higher strength product based on acceptable comparative in vitro data outlined above.

2) Comparative drug particle and agglomerate PSD in the suspension (in the ampoule) between the respective lower strengths of the test and reference products: The PSD determination should be based on a validated method. Validation should demonstrate method sensitivity to drug particle size over the expected size range in the suspension.

3) Comparative drug particle and agglomerate PSD in the nebulized aerosol between the respective lower strengths of the test and reference products: Recommended method for this test is the aerodynamic particle size distribution (APSD) of the

nebulized aerosol based on Apparatus 5 (USP <601>) at a flow rate of 15 L/min through the Apparatus. We recommend the study be conducted based on USP <1601> using the Pari LC Plus Nebulizer/Pari Master compressor system. The amount of drug deposited on the induction port, the seven stages of the cascade impactor, and the sum of the back-up filter and micro-orifice collector (MOC) should be submitted.

4) Comparative Unit Dose Content (UDC) of drug between the respective lower strengths of the test and reference products.

5) Comparative Mean Nebulization Time (MNT) and Mean Delivered Dose (MDD): The test should be conducted at the mouthpiece (% nominal dose) at the labeled flow rate of 5.5 L/min through such time that mist is no longer coming out of the mouthpiece, between the respective lower strengths of the test and reference products.

6) The Mean Delivered Dose (MDD) ratio of the higher to lower strength of the test product should be similar to that of the reference product.

Option B. Combination of In Vitro and In Vivo Bioequivalence Studies:

If the drug particle and agglomerate PSD in the nebulized aerosols of the higher and lower strengths of the test and reference products cannot be determined as described above, the following testing should be sufficient to demonstrate the equivalence of the lower strengths:

1) Documentation of bioequivalence of the higher strength product based on acceptable comparative in-vivo and in-vitro data outlined in 1, option B.

2) Comparative Unit Dose Content (UDC) of drug between the respective lower strengths of the test and reference products.

3) Comparative Mean Nebulization Time (MNT) and Mean Delivered Dose (MDD) at the mouthpiece (% nominal dose) at the labeled flow rate of 5.5 L/min through such time that mist is no longer coming out of the mouthpiece, between the respective lower strengths of the test and reference products.

4) The Mean Delivered Dose (MDD) ratio of the higher to lower strength of the test product should be similar to that of the reference product.

3. Recommendations Related to the Batch Size Recommendation for In Vitro BE Studies:

1) In vitro BE studies for Budesonide Inhalation Suspension should generally be performed on samples from each of three or more batches of the test product and three or more batches of the reference listed drug.

2) The number of units per batch to be studied should not be fewer than 30 for each strength of the test and reference products (i.e., no fewer than 10 from each of three batches).

4. Recommendations Related to the Number of Retention Samples of Test Article from the In Vivo and In Vitro BE Studies:

According to 21 CFR 320.63, the applicant and the contract research organization "shall retain reserved samples for any test article and reference standard used in conducting an in vivo or in vitro bioequivalence study required for approval of the abbreviated application or supplemental application."

A. If the BE studies are conducted at one site, the number of BE retention samples for Budesonide Inhalation Suspension drug product is recommended as follows:

At least 50 units for each batch of test and reference products, including placebos (if applicable), must be retained for BE studies for Budesonide Inhalation Suspension drug product, in line with the FDA draft Guidance for Industry "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (April 2003), for multi-unit nasal aerosols and nasal sprays delivering 30 or more actuations per canister or bottle.

B. If the BE studies are conducted at multiple sites, the number of BE retention samples for Budesonide Inhalation Suspension drug product is recommended as follows:

At least 50 units for each batch of test and reference products, including placebos (if applicable), with not less than 10 units per each batch per site, be retained for the BE studies. For instance, if a BE study is conducted at 6 sites, using 1 batch of the test and reference products, the total number of reserve samples to be retained for the test and reference products must be at least 60, with at least 10 units per each batch per site (10 units/batch/site X 1 batch/product X 6 sites = at least 60 units/product).

5. Recommendation Related to the Population Bioequivalence (PBE) Statistical Analysis Procedure Used in Bioequivalence Determination of Budesonide Suspension Inhalation Product:

A. Step-wise Procedure of the PBE Computation:

Step 1. Establish population BE criterion:

Population BE criterion:

$$\frac{(\mu_T-\mu_R)^2+\left(\sigma_T{}^2-\sigma_R{}^2\right)}{\sigma_R{}^2}\le\theta \quad \textbf{or} \quad \frac{(\mu_T-\mu_R)^2+\left(\sigma_T{}^2-\sigma_R{}^2\right)}{\sigma_{T0}{}^2}\le\theta$$

Linerarized Criteria:

$\eta_1=(\mu_T-\mu_R)^2+\left(\sigma_T{}^2-\sigma_R{}^2\right)-\theta_p\bullet\sigma_R{}^2<0$ **for** $\sigma_R>\sigma_{T0}$

$\eta_2=(\mu_T-\mu_R)^2+\left(\sigma_T{}^2-\sigma_R{}^2\right)-\theta_p\bullet\sigma_{T0}{}^2<0$ **for** $\sigma_R\le\sigma_{T0}$

Where,

$\mu_T-\mu_R$: Mean difference of T (log scale) and R (log scale) products

$\sigma_T{}^2,\sigma_R{}^2$: Total variance of T and R products

σ_{TO} : Regulatory constant (σ_{TO}= 0.1)

θ_p: Regulatory constant (θ_p= 2.0891) calculated as following:

$$\frac{[\ln(1.11)]^2+0.01}{0.1^2}=2.089$$

Estimating the Linerarized Criteria:

$$\hat{\eta}_1=\hat{\Delta}^2+\frac{MSB_T}{m}+\frac{(m-1)MSW_T}{m}-(1+\theta_p)\frac{MSB_R}{m}-(1+\theta_p)\frac{(m-1)MSW_R}{m} \quad \textbf{for } \sigma_R>\sigma_{T0}$$

$$\hat{\eta}_2=\hat{\Delta}^2+\frac{MSB_T}{m}+\frac{(m-1)MSW_T}{m}-\frac{MSB_R}{m}-\frac{(m-1)MSW_R}{m}-\theta_p\sigma_{T0}{}^2 \quad \textbf{for } \sigma_R\le\sigma_{T0}$$

Where,

$$\hat{\Delta} = \overline{X}_{..T.} - \overline{X}_{..R.}$$

m: number of life stages
MSW_T : within-bottle variability for test product
MSW_R : within-bottle variability for reference product
$(MSB_T - MSW_T)/m$: between-bottle variability for test product
$(MSB_R - MSW_R)/m$: between-bottle variability for reference product

Step 2. Calculate MSB and MSW:

Calculation for MSW_T, MSW_R, MSB_T and MSB_R can be conducted as follows.

$$\boldsymbol{MSB_k} = \frac{\boldsymbol{m} \cdot \sum_{\boldsymbol{j}=1}^{\ell_k} \sum_{\boldsymbol{i}=1}^{\boldsymbol{n_k}} (\overline{\boldsymbol{X}}_{\boldsymbol{ijk}\cdot} - \overline{\boldsymbol{X}}_{\boldsymbol{..k}\cdot})^2}{\boldsymbol{n_k} \cdot \ell_{\boldsymbol{k}} - 1}$$ k refers to either test or reference product

$$\boldsymbol{MSW_k} = \frac{\sum_{\boldsymbol{j}=1}^{\ell_k} \sum_{\boldsymbol{i}=1}^{\boldsymbol{n_k}} \sum_{\boldsymbol{s}=1}^{\boldsymbol{m}} (\boldsymbol{X}_{\boldsymbol{ijks}} - \overline{\boldsymbol{X}}_{\boldsymbol{ijk}\cdot})^2}{\boldsymbol{n_k} \cdot \ell_{\boldsymbol{k}} \cdot (\boldsymbol{m} - 1)}$$

$$\overline{\boldsymbol{X}}_{\boldsymbol{ijk}\cdot} = \frac{\sum_{\boldsymbol{s}=1}^{\boldsymbol{m}} \boldsymbol{X}_{\boldsymbol{ijks}}}{\boldsymbol{m}}; \quad \overline{\boldsymbol{X}}_{\boldsymbol{..k}\cdot} = \frac{\sum_{\boldsymbol{i}=1}^{\ell_k} \sum_{\boldsymbol{j}=1}^{\boldsymbol{n_k}} \overline{\boldsymbol{X}}_{\boldsymbol{ijk}\cdot}}{\boldsymbol{n_k} \cdot \ell_{\boldsymbol{k}}}$$

n_T, n_R : Number of canisters or bottles per batch, for T and R products

ℓ_T, ℓ_R : Number of batches of T and R products

X_{ijks} is the i^{th} bottle in batch # j at life stage s for test or reference product;

$\overline{X}_{ijk\cdot}$ is the average m life stages for i^{th} bottle in batch # j;

$\overline{X}_{..k\cdot}$ is the population mean for the reference or test products.

Step 3. Calculate σ_R and σ_T

1) σ_R can be conducted as follow:

$$\sigma_R = \sqrt{\frac{MSB_R}{m} + \frac{(m-1)MSW_R}{m}}$$

a. If $\sigma_R > \sigma_{TO}$ (regulatory constant, 0.1), using the reference-scaled procedure to determine BE for the measured parameter(s)

b. If $\sigma_R \leq \sigma_{T0}$ (regulatory constant, 0.1), using the constant-scaled procedure to determine BE for the measured parameter(s)

2) σ_T can be conducted as follow:

$$\sigma_T = \sqrt{\frac{MSB_T}{m} + \frac{(m-1)MSW_T}{m}}$$

Step 4. Calculate linearized point estimate and 95% upper confidence bound:

1) Reference-scaled Criterion ($\hat{\eta}_1$): Use α=0.05 for a 95% upper confidence bound:

Equation for Linearized Point Estimate:

$Eq = E_D + E1 + E2 + E3s + E4s$

95% upper confidence bound ($H\eta_1$):

$H\eta_1 = (E_D + E1 + E2 + E3s + E4s) + (U_D + U1 + U2 + U3s + U4s)^{1/2}$

Following are the equations to compute each component:

E_q= Point Estimate	H_q= Confidence Bound	$U_q=(H_q- E_q)^2$
$E_D = \hat{\Delta}^2$	$\boldsymbol{H_D} = \left(\left\|\hat{\Delta}\right\| + \boldsymbol{t}_{1-\boldsymbol{\alpha},\boldsymbol{n_T}\cdot\ell_T+\boldsymbol{n_R}\cdot\ell_R-2} \left(\frac{\boldsymbol{MSB_T}}{\boldsymbol{n_T}\cdot\ell_T\cdot\boldsymbol{m}} + \frac{\boldsymbol{MSB_R}}{\boldsymbol{n_R}\cdot\ell_R\cdot\boldsymbol{m}} \right)^{1/2} \right)^2$	U_D
$\boldsymbol{E}1 = \frac{\boldsymbol{MSB_T}}{\boldsymbol{m}}$	$\boldsymbol{H}1 = \frac{(\ell_T\cdot\boldsymbol{n_T}-1)\cdot\boldsymbol{E}1}{\boldsymbol{\chi}^2_{\ell_T\cdot\boldsymbol{n_T}-1,\boldsymbol{\alpha}}}$	$U1$
$\boldsymbol{E}2 = \frac{(\boldsymbol{m}-1)\cdot\boldsymbol{MSW_T}}{\boldsymbol{m}}$	$\boldsymbol{H}2 = \frac{\ell_T\cdot\boldsymbol{n_T}\cdot(\boldsymbol{m}-1)\cdot\boldsymbol{E}2}{\boldsymbol{\chi}^2_{\ell_T\cdot\boldsymbol{n_T}\cdot(\boldsymbol{m}-1),\boldsymbol{\alpha}}}$	$U2$
$\boldsymbol{E}3\boldsymbol{s} = -(1+\boldsymbol{\theta_p})\frac{\boldsymbol{MSB_R}}{\boldsymbol{m}}$	$\boldsymbol{H}3\boldsymbol{s} = \frac{(\ell_R\cdot\boldsymbol{n_R}-1)\cdot\boldsymbol{E}3\boldsymbol{s}}{\boldsymbol{\chi}^2_{\ell_R\cdot\boldsymbol{n_R}-1,1-\boldsymbol{\alpha}}}$	$\boldsymbol{U}3\boldsymbol{s}$
$\boldsymbol{E}4\boldsymbol{s} = -(1+\boldsymbol{\theta_p})\frac{(\boldsymbol{m}-1)\boldsymbol{MSW_R}}{\boldsymbol{m}}$	$\boldsymbol{H}4\boldsymbol{s} = \frac{\ell_R\cdot\boldsymbol{n_R}\cdot(\boldsymbol{m}-1)\cdot\boldsymbol{E}4\boldsymbol{s}}{\boldsymbol{\chi}^2_{\ell_R\cdot\boldsymbol{n_R}\cdot(\boldsymbol{m}-1),1-\boldsymbol{\alpha}}}$	$\boldsymbol{U}4\boldsymbol{s}$

Where $\boldsymbol{\chi}^2_{\ell_T\cdot\boldsymbol{n_T}-1,\boldsymbol{\alpha}}$ is from the cumulative distribution function of the chi-square distribution with $\ell_T\cdot\boldsymbol{n_T}-1$ degrees of freedom, i.e. $\Pr(\boldsymbol{\chi}^2_{\ell_T\cdot\boldsymbol{n_T}-1} \le \boldsymbol{\chi}^2_{\ell_T\cdot\boldsymbol{n_T}-1,\boldsymbol{\alpha}}) = \boldsymbol{\alpha}$

For data collected on one life stage (m=1), ignore E2 and E4s and their corresponding H and U terms in the calculation. For data collected on more than one stage (m≥2), use the equations listed above.

2) Constant-scaled Criterion ($\hat{\eta}_2$): Use α=0.05 for a 95% upper confidence bound:

Equation for Linearized Point Estimate:

$E_q = E_D + E1 + E2 + E3c + E4c - \theta_p\sigma_{T0}^2$

95% upper confidence bound ($H\eta_2$):

$H\eta_2 = (E_D + E1 + E2 + E3c + E4c - \theta_p\sigma_{T0}^2) + (U_D + U1 + U2 + U3c + U4c)^{½}$

Following are the equations to compute each component:

E_q= Point Estimate	H_q= Confidence Bound	$U_q=(H_q- E_q)^2$
$E_D = \hat{\Delta}^2$	$\boldsymbol{H_D} = \left(\left\|\hat{\Delta}\right\| + \boldsymbol{t}_{1-\boldsymbol{\alpha},\boldsymbol{n_T}\cdot\ell_T+\boldsymbol{n_R}\cdot\ell_R-2} \left(\frac{\boldsymbol{MSB_T}}{\boldsymbol{n_T}\cdot\ell_T\cdot\boldsymbol{m}} + \frac{\boldsymbol{MSB_R}}{\boldsymbol{n_R}\cdot\ell_R\cdot\boldsymbol{m}} \right)^{1/2} \right)^2$	U_D
$\boldsymbol{E}1 = \frac{\boldsymbol{MSB_T}}{\boldsymbol{m}}$	$\boldsymbol{H}1 = \frac{(\ell_T\cdot\boldsymbol{n_T}-1)\cdot\boldsymbol{E}1}{\boldsymbol{\chi}^2_{\ell_T\cdot\boldsymbol{n_T}-1,\boldsymbol{\alpha}}}$	$U1$
$\boldsymbol{E}2 = \frac{(\boldsymbol{m}-1)\cdot\boldsymbol{MSW_T}}{\boldsymbol{m}}$	$\boldsymbol{H}2 = \frac{\ell_T\cdot\boldsymbol{n_T}\cdot(\boldsymbol{m}-1)\cdot\boldsymbol{E}2}{\boldsymbol{\chi}^2_{\ell_T\cdot\boldsymbol{n_T}\cdot(\boldsymbol{m}-1),\boldsymbol{\alpha}}}$	$U2$
$E3c = -\frac{MSB_R}{m}$	$\boldsymbol{H}3\boldsymbol{c} = \frac{(\ell_R\cdot\boldsymbol{n_R}-1)\cdot\boldsymbol{E}3\boldsymbol{c}}{\boldsymbol{\chi}^2_{\ell_R\cdot\boldsymbol{n_R}-1,1-\boldsymbol{\alpha}}}$	$\boldsymbol{U}3\boldsymbol{c}$
$\boldsymbol{E}4\boldsymbol{c} = -\frac{(\boldsymbol{m}-1)\boldsymbol{MSW_R}}{\boldsymbol{m}}$	$H4c = \frac{\ell_R\cdot n_R\cdot(m-1)\cdot E4rc}{\chi^2_{\ell_R\cdot n_R\cdot(m-1),1-\alpha}}$	$\boldsymbol{U}4\boldsymbol{c}$

For data collected on one life stage (m=1), ignore E2 and E4c and their corresponding H and U terms in the calculation. For data collected on more than one stage (m≥2), use the equations listed above.

The method of obtaining the upper confidence bound is based on two FDA guidances: 1) Statistical Information from the June 1999 Draft Guidance and Statistical Information for In Vitro Bioequivalence Posted on August 18, 1999, accompanying to Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (April 2003); and 2) Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (Jan. 2001). The concept is adapted from the method for the two-sequence, four-period study design using T-distribution.

Step 5. For the test product to be bioequivalent to the reference product, the following condition must be satisfied:

The 95% upper confidence bound for linearlized criteria Hη must be ≤ 0.

B. An Example of PBE Computation:

Study Design: The data given in this example are simulated. A parallel design with two products (test or reference) including 3 batches and 10 bottles/containers per batch for each product with three life stages (beginning, middle and end).

Batches	Container	Stage	Product	In vitro measurement
1	31	B	REF	5.957211
1	31	M	REF	5.961802
1	31	E	REF	5.967178
1	32	B	REF	6.010251
1	32	M	REF	6.004711
1	32	E	REF	6.004797
1	33	B	REF	5.884161
1	33	M	REF	5.894085
1	33	E	REF	5.895977
1	34	B	REF	5.624705
1	34	M	REF	5.632991
1	34	E	REF	5.614428
1	35	B	REF	5.957329
1	35	M	REF	5.966059
1	35	E	REF	5.968143
1	36	B	REF	5.074298
1	36	M	REF	5.063063
1	36	E	REF	5.058519
1	37	B	REF	5.418587
1	37	M	REF	5.420591
1	37	E	REF	5.418178
1	38	B	REF	6.325178
1	38	M	REF	6.321954
1	38	E	REF	6.303148
1	39	B	REF	5.656286
1	39	M	REF	5.68025
1	39	E	REF	5.675036
1	40	B	REF	5.792299
1	40	M	REF	5.775161
1	40	E	REF	5.793083
2	41	B	REF	5.601033
2	41	M	REF	5.611223
2	41	E	REF	5.601142
2	42	B	REF	5.61553
2	42	M	REF	5.587412
2	42	E	REF	5.591004
2	43	B	REF	5.682466
2	43	M	REF	5.676472
2	43	E	REF	5.671434
2	44	B	REF	5.844336

2	44	M	REF	5.855172
2	44	E	REF	5.862329
2	45	B	REF	5.898151
2	45	M	REF	5.883657
2	45	E	REF	5.878956
2	46	B	REF	6.100662
2	46	M	REF	6.105463
2	46	E	REF	6.108098
2	47	B	REF	6.294753
2	47	M	REF	6.28534
2	47	E	REF	6.302333
2	48	B	REF	5.638072
2	48	M	REF	5.627372
2	48	E	REF	5.623516
2	49	B	REF	5.113562
2	49	M	REF	5.122454
2	49	E	REF	5.109271
2	50	B	REF	5.932752
2	50	M	REF	5.913438
2	50	E	REF	5.912427
3	51	B	REF	5.961947
3	51	M	REF	5.955332
3	51	E	REF	5.943721
3	52	B	REF	6.2334
3	52	M	REF	6.250689
3	52	E	REF	6.219668
3	53	B	REF	6.041431
3	53	M	REF	6.038234
3	53	E	REF	6.080464
3	54	B	REF	6.049713
3	54	M	REF	6.039759
3	54	E	REF	6.054218
3	55	B	REF	6.834563
3	55	M	REF	6.85264
3	55	E	REF	6.857395
3	56	B	REF	4.864966
3	56	M	REF	4.907521
3	56	E	REF	4.891049
3	57	B	REF	5.895176
3	57	M	REF	5.885851
3	57	E	REF	5.874895
3	58	B	REF	6.45826
3	58	M	REF	6.443113
3	58	E	REF	6.435882
3	59	B	REF	6.090533
3	59	M	REF	6.102835
3	59	E	REF	6.077606

3	60	B	REF	5.886724
3	60	M	REF	5.920949
3	60	E	REF	5.915749
4	1	B	TEST	6.894594
4	1	M	TEST	6.913011
4	1	E	TEST	6.895764
4	2	B	TEST	5.832334
4	2	M	TEST	5.846562
4	2	E	TEST	5.832269
4	3	B	TEST	6.235755
4	3	M	TEST	6.26231
4	3	E	TEST	6.245095
4	4	B	TEST	5.646185
4	4	M	TEST	5.635887
4	4	E	TEST	5.63034
4	5	B	TEST	5.960711
4	5	M	TEST	5.962902
4	5	E	TEST	5.961959
4	6	B	TEST	5.500354
4	6	M	TEST	5.508444
4	6	E	TEST	5.513115
4	7	B	TEST	6.663099
4	7	M	TEST	6.64733
4	7	E	TEST	6.651215
4	8	B	TEST	5.724774
4	8	M	TEST	5.72086
4	8	E	TEST	5.71411
4	9	B	TEST	6.183375
4	9	M	TEST	6.186433
4	9	E	TEST	6.182109
4	10	B	TEST	5.64053
4	10	M	TEST	5.648589
4	10	E	TEST	5.626395
5	11	B	TEST	6.69764
5	11	M	TEST	6.71128
5	11	E	TEST	6.699829
5	12	B	TEST	6.555609
5	12	M	TEST	6.549935
5	12	E	TEST	6.551611
5	13	B	TEST	5.009683
5	13	M	TEST	5.013969
5	13	E	TEST	5.010928
5	14	B	TEST	5.440976
5	14	M	TEST	5.42057
5	14	E	TEST	5.447687
5	15	B	TEST	6.477609
5	15	M	TEST	6.456082

5	15	E	TEST	6.448981
5	16	B	TEST	6.442601
5	16	M	TEST	6.426217
5	16	E	TEST	6.436262
5	17	B	TEST	5.640496
5	17	M	TEST	5.63846
5	17	E	TEST	5.640755
5	18	B	TEST	6.597718
5	18	M	TEST	6.599232
5	18	E	TEST	6.609437
5	19	B	TEST	6.007241
5	19	M	TEST	5.990695
5	19	E	TEST	5.984292
5	20	B	TEST	6.781806
5	20	M	TEST	6.774386
5	20	E	TEST	6.784001
6	21	B	TEST	5.993852
6	21	M	TEST	5.994287
6	21	E	TEST	5.993541
6	22	B	TEST	6.012322
6	22	M	TEST	6.006182
6	22	E	TEST	6.017961
6	23	B	TEST	5.965969
6	23	M	TEST	5.97125
6	23	E	TEST	5.967839
6	24	B	TEST	5.592609
6	24	M	TEST	5.581154
6	24	E	TEST	5.588877
6	25	B	TEST	6.002182
6	25	M	TEST	6.011583
6	25	E	TEST	6.018746
6	26	B	TEST	5.267014
6	26	M	TEST	5.272291
6	26	E	TEST	5.265213
6	27	B	TEST	5.766104
6	27	M	TEST	5.786727
6	27	E	TEST	5.773194
6	28	B	TEST	6.054975
6	28	M	TEST	6.05232
6	28	E	TEST	6.061088
6	29	B	TEST	5.838689
6	29	M	TEST	5.837566
6	29	E	TEST	5.842508
6	30	B	TEST	5.784255
6	30	M	TEST	5.789891
6	30	E	TEST	5.788662

Following the step-wise PBE computation procedure outlined above, the following components can be determined:

Reference-scaled:

Eq related intermediate parameters	**Hq related intermediate parameters**	**U_q related intermediate parameters**	**Hη= Eq + (Uq)½**
E_D= 0.022094106	H_D= 0.113976896	U_D= 0.008442447	
E1= 0.219742944	H1= 0.359860715	U1= 0.01963299	
E2= 3.9108E-05	H2= 5.43319E-05	U2= 2.31765E-10	
E3s= -0.505515326	H3s= -0.344478125	U3= 0.02593298	
E4s= -0.000256672	H4s= -0.000194739	U4= 3.83572E-09	
Eq (linearized point estimate) = -0.26389584		**$U_q = (H_q - E_q)^2$ = 0.054008421**	**Hη = -0.031498721**

Constant-scaled:

Eq related intermediate parameters	**Hq related intermediate parameters**	**U_q related intermediate parameters**	**Hη= Eq + (Uq)½**
E_D = 0.022094106	H_D= 0.113976896	U_D = 0.008442447	
E1= 0.219742944	H1= 0.359860715	U1= 0.01963299	
E2=3.9108E-05	H2= 5.43319E-05	U2= 2.31765E-10	
E3c= -0.163644789	H3c= -0.111514028	U3= 0.002717616	
E4c= -8.30895E-05	H4c= -6.30405E-05	U4= 4.0196E-10	
Eq (linearized point estimate) = 0.057257267		**$U_q = (H_q - E_q)^2$ = 0.030793054**	**Hη = 0.232736764**

Calculate σ_R:

$\sigma_R = \sqrt{\frac{MSB_R}{m} + \frac{(m-1)MSW_R}{m}} = \sqrt{0.163727878} = 0.4046 > 0.1$ (regulatory constant), therefore, reference-scaled procedure applies.

Since the 95% upper confidence bound for linearized criteria of reference-scaled procedure is negative (-0.031498721), bioequivalence can be concluded.

C. Electronic Table Templates for BE Study Data

The following table templates have been developed in a concise format consistent with the Common Technical Document (CTD). For electronic submission of the individual data and summary data from the BE studies, please provide complete tables using the

formats indicated below, and send them as a part of the ANDA bioequivalence submission. Submission of these electronic summary tables is necessary for improving the efficiency of the review process.

Table 1. Individual Data of In Vitro Tests Using SAS Transport Format

Batches	Container	Stage	Product	In vitro measurement (original data)
1	1	Beginning	Reference	
1	1	Middle	Reference	
1	1	End	Reference	
2	2	Beginning	Test	
2	2	Middle	Test	
2	2	End	Test	

Table 2. Summary Tables of PBE Results Using Word and/or PDF Format

Variable	Geometric Mean		Geometric Mean Ratio	Standard Deviation		SigmaT/SigmaR Ratio
	Test	Reference		SigmaT	SigmaR	

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled			
Constant-scaled			