CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 203760

Name: Albuterol Sulfate Inhalation Aerosol 0.09mg base/actuation

Sponsor: Perrigo Pharmaceutical Company

Approval Date: February 24, 2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA203760Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203760

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE REVIEW
FOR PRESSURIZED METERED DOSE INHALATION PRODUCTS

ANDA No.	203760		
Drug Product Name	Albuterol Sulfate Inhalation Aerosol		
Strength(s)	0.09 mg Base/Inhalation		
Applicant Name	Perrigo Pharmaceutical Company		
Applicant Address	515 Eastern Ave Allegan, MI, USA 49010		
US Contact Name and US Mailing Address	Matthew Popowski, Senior Regulatory Affairs Project Manager 3940 Quebec Ave North Minneapolis, MN, USA 55427		
US Contact Telephone Number	763-732-0481		
US Contact Fax Number	763-732-0509		
Original Submission Date(s)	12/16/2011		
Submission Date(s) of Amendment(s) Under Review	03/09/2012 Re-submission (SD2) 05/18/2012 Formulation Tablet (SD6) 07/03/2013 Major amendment to support the addition of an integrated dose counter to the metered dose inhaler (SD10) 04/24/2015 Post-CR meeting request (SD20) 07/01/2015 Response to complete response letter dated 04/13/2015 (SD22) 10/05/2015 Post-CR meeting request (SD24) 04/13/2017 Major amendment (SD29) 10/23/2017 Meeting Request (SD31) 12/29/2017 Major amendment (SD34) 04/26/2018 Response to IR request (SD37) 08/31/2018: Multiple Categories (SD 38) **11/30/2018: Multiple Categories (SD44)**		
Primary Assessor	Zhen Zhang, Ph.D.		
Secondary Assessor	Vipra Kundoor, Ph.D.		
Tertiary Assessor	Qing Liu, Ph.D.		
Study Number(s)	**10825302**		
Study Type(s)	**Fasting**		
Strength(s)	2 x 90 mcg actuations (total dose = 180 mcg)		
Clinical Site	Novum Pharmaceutical Research Services		
Clinical Site Address	Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712		
Analytical Site	(b) (4)		
Analytical Site Address			
Study Number(s)	**TTP-CBJ-M0050**	**TTP-CBJ-M00132**	**TTP-CBJ-0282**
Study Type(s)	**In vitro Bioequivalence Study**		
Strength(s)	90 mcg/ actuation		
***In Vitro* Test Site**	(b) (4)		

***In Vitro* Test Site Address**	(b) (4)
Study Number(s)	**PRG-723**
Study Type(s)	**Pharmacodynamic Bioequivalence Study**
Strength(s)	90 mcg/ actuation
Clinical Site	**Site 1** University of Florida Asthma Research Lab **Site 2** Roy J and Lucille A Carver College of Medicine Department of Pediatrics, Allergy/Pulmonary **Site 3** Allergy & Asthma Diagnostic Treatment Center **Site 4** California Allergy & Asthma Medical Group **Site 5** Clinical Research Atlanta **Site 6** Spartanburg Medical Research **Site 7** AARA Research Center
Clinical Site Address	**Site 1** 1600 SW Archer Road Gainesville, FL 32610-0486 **Site 2** The University of Iowa 200 Hawkins Drive Iowa City, Iowa 52242-1083 **Site 3** 2300 Centerville Road Tallahassee, FL 32308 **Site 4** 11645 Wilshire Blvd, Suite 1155 Los Angeles, CA 90025 **Site 5** 175 Country Club Drive, Suite 100A Stockbridge, GA 30281 **Site 6** 485 Simuel Road Spartanburg, SC 29303 **Site 7** 9900 N Central Expy, Suite 555 Dallas, TX 75231
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete** **Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete**
Formulation	☒ **Adequate** ☐ **Inadequate**

Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)		
Overall Review Result	☒ Adequate ☐ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study Tracking/Supporting Document #	**Study/Test Type**	**Strength (e.g., xx µg/inhalation)**	**Review Result**
1, 2, 6	**Fasting BE Study**	**0.09 mg Base/Inhalation**	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34, 37, 38, 44	**Pharmacodynamic BE Study**	**0.09 mg Base/Inhalation**	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29	**In vitro BE study # TTP-CBJ-M0050**	**0.09 mg Base/Inhalation**	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	**In vitro BE study # TTP-CBJ-M0282: Single Actuation Content through Container Life**	**0.09 mg Base/Inhalation**	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 34, 37	**In vitro BE study # TTP-CBJ-M0282: Priming and Repriming**	**0.09 mg Base/Inhalation**	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	**In vitro BE study # TTP-CBJ-M0282: Aerodynamic Particle Size Distribution by Cascade Impaction**	**0.09 mg Base/Inhalation**	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	**In vitro BE study # TTP-CBJ-M0282: Spray Pattern**	**0.09 mg Base/Inhalation**	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	**In vitro BE study # TTP-CBJ-M0282: Plume Geometry**	**0.09 mg Base/Inhalation**	☒ Adequate ☐ Inadequate ☐ Not Applicable

Addendum to the Bioequivalence Amendment Assessment Dated 1/29/2019

1 EXECUTIVE SUMMARY

This addendum is to update the cover page of the amendment assessment dated 1/29/2019[1]. The updates include: 1) 11/16/2011 was updated to 12/16/2011 in the Original Submission Date(s); 2) 03/09/2012 Re-submission (SD2) and 05/18/2012 Formulation Tablet (SD6) were added to Submission Date(s) of Amendment(s) Under Review.

The 12/16/2011, 3/9/2012 and 5/18/2012 submissions were assessed and documented in the assessment of 08/04/2014.[2]

The application remains **adequate**. No letter will be communicated to the applicant from this addendum.

[1] GDRP, ANDA 203760; A203760N000DB-Review01-Amend11302018.docx (Completed 1/29/2019); http://panorama.fda.gov/task/view?ID=5c0680e6002d64bd3a10d877129483fb

[2] DARRTS, ANDA 203760; Primary Review (REV-BIOEQ-21) dated 08/04/2014.

2 *COMPLETED ASSIGNMENT FOR 203760 ID: 38036*

Reviewer: Zhang, Zhen **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation - Addendum

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Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
38036	11/30/2018	BIO	Addendum [1]	0	0
38036	11/30/2018	Parallel	Addendum (for clarification or Error Correction [0]	0	0
				Total:	0

DIVISION OF BIOEQUIVALENCE REVIEW
FOR PRESSURIZED METERED DOSE INHALATION PRODUCTS

ANDA No.	203760		
Drug Product Name	Albuterol Sulfate Inhalation Aerosol		
Strength(s)	0.09 mg Base/Inhalation		
Applicant Name	Perrigo Pharmaceutical Company		
Applicant Address	515 Eastern Ave Allegan, MI, USA 49010		
US Contact Name and US Mailing Address	Matthew Popowski, Senior Regulatory Affairs Project Manager 3940 Quebec Ave North Minneapolis, MN, USA 55427		
US Contact Telephone Number	763-732-0481		
US Contact Fax Number	763-732-0509		
Original Submission Date(s)	11/16/2011		
Submission Date(s) of Amendment(s) Under Review	07/03/2013 Major amendment to support the addition of an integrated dose counter to the metered dose inhaler (SD10) 04/24/2015 Post-CR meeting request (SD20) 07/01/2015 Response to complete response letter dated 04/13/2015 (SD22) 10/05/2015 Post-CR meeting request (SD24) 04/13/2017 Major amendment (SD29) 10/23/2017 Meeting Request (SD31) 12/29/2017 Major amendment (SD34) 04/26/2018 Response to IR request (SD37) 08/31/2018: Multiple Categories (SD 38) **11/30/2018: Mutiple Categories (SD44)**		
Primary Assessor	Zhen Zhang, Ph.D.		
Secondary Assessor	Vipra Kundoor, Ph.D.		
Tertiary Assessor	Qing Liu, Ph.D.		
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Study Type(s)	**Fasting**		
Strength(s)	2 x 90 mcg actuations (total dose = 180 mcg)		
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Clinical Site Address	Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712		
Analytical Site	(b) (4)		
Analytical Site Address			
Study Number(s)	**TTP-CBJ-M0050**	**TTP-CBJ-M00132**	**TTP-CBJ-0282**
Study Type(s)	**In vitro Bioequivalence Study**		
Strength(s)	90 mcg/ actuation		
***In Vitro* Test Site**	(b) (4)		
***In Vitro* Test Site Address**			

	(b) (4)
Study Number(s)	**PRG-723**
Study Type(s)	**Pharmacodynamic Bioequivalence Study**
Strength(s)	90 mcg/ actuation
Clinical Site	**Site 1** University of Florida Asthma Research Lab **Site 2** Roy J and Lucille A Carver College of Medicine Department of Pediatrics, Allergy/Pulmonary **Site 3** Allergy & Asthma Diagnostic Treatment Center **Site 4** California Allergy & Asthma Medical Group **Site 5** Clinical Research Atlanta **Site 6** Spartanburg Medical Research **Site 7** AARA Research Center
Clinical Site Address	**Site 1** 1600 SW Archer Road Gainesville, FL 32610-0486 **Site 2** The University of Iowa 200 Hawkins Drive Iowa City, Iowa 52242-1083 **Site 3** 2300 Centerville Road Tallahassee, FL 32308 **Site 4** 11645 Wilshire Blvd, Suite 1155 Los Angeles, CA 90025 **Site 5** 175 Country Club Drive, Suite 100A Stockbridge, GA 30281 **Site 6** 485 Simuel Road Spartanburg, SC 29303 **Site 7** 9900 N Central Expy, Suite 555 Dallas, TX 75231
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete** **Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete**
Formulation	☒ **Adequate** ☐ **Inadequate**
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**

Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)		
Overall Review Result	☒ Adequate ☐ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study Tracking/Supporting Document #	**Study/Test Type**	**Strength (e.g., xx µg/inhalation)**	**Review Result**
1, 2, 6	Fasting BE Study	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34, 37, 38, 44	Pharmacodynamic BE Study	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29	In vitro BE study # TTP-CBJ-M0050	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Single Actuation Content through Container Life	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 34, 37	In vitro BE study # TTP-CBJ-M0282: Priming and Repriming	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Aerodynamic Particle Size Distribution by Cascade Impaction	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Spray Pattern	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Plume Geometry	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable

1 EXECUTIVE SUMMARY

This is a review of the amendment dated 11/30/2018.

In the original submission and subsequent amendments, the applicant submitted the results of the studies listed in the table below comparing the test product (Perrigo Pharmaceutical Company's Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation) to the corresponding reference product (Teva Global's ProAir® HFA (albuterol sulfate) Inhalation Aerosol, 0.09 mg Base/Inhalation). All the studies are adequate except the pharmacodynamic (PD) study # PRG-723 due to deficiency related to the Office of Study Integrity and Surveillance (OSIS)'s inspection[1, 2, 3, 4, 5, 6].

	Test Batch #	**Reference Batch #**	**Dose counter?**	**Relevant to BE determination?**	**Review Results for the relevant BE studies**
Fasting Study # 10825302	08MM-050	AEA13B	No for both T and R	Yes	**Adequate**
PD Study # PRG-723	08MM-050	AEA13B	No for both T and R	Yes	**Inadequate**
In vitro bioequivalence (BE) study # TTP-CBJ-M0050	08MM-050, 08MM-034, 08MM-039	AEA13B, AEA12C, AEA14A	No for both T and R	Yes	**Adequate**
In vitro BE study # TTP-CBJ-0282	15MM-023, 16MM-002, 16MM-003	DAC23A, DAC34A, DAC36A	Yes for both T and R; T has optimized actuator	Yes	**Adequate**

In the current amendment dated 11/30/2018, the applicant provided the response to OSIS related BE deficiency. Per the Division of Bioequivalence I (DBI)'s consult request, OSIS evaluated the applicant's response and considered *the data in the study report for study PRG-723 are reliable to support a regulatory decision*[7]. The assessor re-evaluated the data of the PD study # PRG-723 and found it **adequate**.

The application is **adequate**.

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[1] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)
[2] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222
[3] GDRP, ANDA-203760; A203760N000DB_NA04132017 (Completed 09/08/2017); http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88147efa5
[4] GDRP, ANDA-203760; A203760N000DPM-MeetingMinutes03.doc (Completed 12/14/2017); http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f8817ec1af
[5] GDRP, ANDA 203760; A203760N000DB-Review01-AMEND12292017.docx (Completed 05/17/2018); http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881ae8679
[6] GDRP, ANDA 203760; A203760N000DB-Review01-Amend08312018.docx (Completed 10/26/2018); http://panorama.fda.gov/task/view?ID=5b8fc23200f01deb2a746fc266654760
[7] GDRP, ANDA 203760; OSIS memo 2019-01-8.pdf (Completed 01/08/2019); http://panorama.fda.gov/task/view?ID=5c12a35e00d018462807b37e0cb7cd3d

2 REVIEW OF THE APPLICANT'S RESPONSE TO BIOEQUIVALENCE DEFICIENCY

2.1 Evaluation of the impact of revised Product-Specific Guidance (PSG) for Albuterol Sulfate Inhalation Aerosol on the BE studies of the current application

The original assessments of the pharmacokinetic (PK) study # 10825302, in vitro BE studies # TTP-CBJ-M0050 and pharmacodynamic (PD) study # PRG-723 were conducted based on the PSG for Albuterol Sulfate Inhalation Aerosol dated Jun 2013[8]. The PSG was then revised in Dec 2016[9]. The evaluation of the impact of the revised PSG dated Dec 2016 is as follows:

Recommendations	Difference between the PSGs dated Jun 2013 and Dec 2016[10]	Assessor's Comments
PD study	The PSG dated Dec 2016 removed the following recommendation: *Baseline PC20 or PD20 on each study day should be within a two-fold dilution (i.e., within 50-200 %) of the value measured on the qualifying day.*	The PD study # PRG-723 in the current application did not measure baseline PC20 challenge on each study day, which is in line with the current PSG dated Dec 2016. This was also discussed in the review of controlled correspondence (CC) # 42715[11]. Therefore, the revised PSG dated Dec 2016 has no impact on the PD study # PRG-723.
	Other minor edits to be consistent with other PSG for MDI products	No impact
PK study	Remain the same	No impact
In vitro BE studies	The PSG dated Dec 2016 changed the term from "actuator tip" to "actuator mouthpiece" for plume geometry study.	Both in vitro BE study # TTP-CBJ-M0050[12] and in vitro BE study # TTP-CBJ-0282[13] measured plume geometry at a single delay time while the fully developed plume is still in contact with the 'actuator mouthpiece'. Therefore, the revised PSG dated Dec 2016 has no impact on in vitro BE studies

Conclusion: The revised PSG for Albuterol Albuterol Sulfate Inhalation Aerosol dated Dec 2016 has no impact on the current application.

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[8] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)

[9] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf

[10] http://panorama.fda.gov/task/view?ID=54ee35f40008767878f9a2eaafab4564

[11] http://panorama.fda.gov/task/view?ID=546669ea0017fdd5cca5e468b8b066ca

[12] GlobalSubmit Review; ANDA 203760; Module 5.3.1.2 Test Methods (Page 5 of 52); Submitted 03/09/2012; \\cdsesub1\evsprod\anda203760\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\in-vitro-bio-study\methods.pdf

[13] GlobalSubmit Review; ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Page 21 of 407); Submitted 04/13/2017; \\cdsesub1\evsprod\anda203760\0028\m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\characterization-study\invitro-be-m0282.pdf

2.2 BE Deficiency

Deficiency Related to the Pharmacodynamic Study (PRG-723)

The Office of Study Integrity and Surveillance (OSIS) evaluated your response to the bioequivalence deficiency, amendment dated August 31, 2018, and has the following comments.

Please provide the audit trails from (b) (4) related to the Master Randomization Code (MRC) and scratch-off labels. The audit trails should include all activity related to the MRCs and scratch-off labels prior to the enrollment of the first study subject and until the date of the last FDA inspection (January 9, 2015).

2.3 Applicant's Response

As requested, Perrigo submits the audit trails of the Master Randomization Code (MRC) and the audit trails from the production of the clinical labeling, inclusive of the scratch-off kit labels, downloaded by (b) (4) and supplied to us. The audit trails show all activity related to the MRCs and scratch-off labels from prior to enrollment of the first study subject through 2018. The documents demonstrate that:

- (b) (4) *used two MRCs to print two batches of clinical labeling for Perrigo's study, as described in Perrigo's ANDA.*
- *The two MRCs used to print Perrigo's clinical labels match the MRCs in Perrigo's ANDA.*
- (b) (4) *printed labels for Perrigo's study only in January 2010 (for MRC #1) and April 2010 (for MRC #2).*
- *MRC #1 and MRC #2 were never modified.*
- *No activity occurred for the MRCs between April 2010 and August 2018.*
- *No activity occurred related to label printing between April 2010 and October 2015.*

In the sections below, for ease of understanding, Perrigo describes the organization of the audit trail documents and the specific data supporting the above conclusions.

i. Audit Trails for Master Randomization Codes

(b) (4)

Assignment Set #1

Assignment Set #1 was created on December 29, 2009 with Transaction #1 and includes Transactions #1 and #2. It was never used in the Perrigo study. As previously described in Perrigo's response to CRL#4 (Affidavit from (b) (4) *in Sequence 0037),* (b) (4) *generated Assignment Set #1 as a preliminary MRC with 10 treatment sequences. Prior to study enrollment, however, Perrigo reduced the number of treatment sequences from 10 to 5.*

The transactions in the audit trail for Assignment Set #1 show the following:

- *Transaction #1 (December 29, 2009) - Creation of this preliminary MRC with 10 treatment sequences*
- *Transaction #2 (January 14, 2010) - Quarantine of Assignment Set #1, noting that it was retained as an "unused entity" and therefore not a viable MRC used in the Perrigo study*

Assignment Set #2

Assignment Set #2 was created on January 14, 2010 with Transaction #3 and includes Transaction #3, #4, #8 and #9.1 Assignment Set #2 contains 5 treatment sequences and corresponds to MRC #1 for subjects 001-100 in the Perrigo study.

The transactions in the audit trail for Assignment Set #2 show the following:

- *Transaction #3 (January 14, 2010) – Creation of MRC #1 with 5 treatment sequences*
- *Transaction #4 (January 18, 2010) - Approval of MRC #1 prior to the production of clinical study materials commencing on January 21, 2010*
- *Transactions #8 and #9 (August 2, 2018) - Query of MRC #1 at Perrigo's request to retrieve information to respond to CRL #4.*

Assignment Set #3

Assignment Set #3 was created on April 12, 2010 with Transaction #5 and includes Transaction #5, #6, #7, and #10. Assignment Set #3 contains 5 treatment sequences and corresponds to MRC #2 for subjects 101-210 in the Perrigo study.

The transactions in the audit trail for Assignment Set #3 show the following:

- *Transaction #5 (April 12, 2010) – Creation of MRC #2 with 5 treatment sequences*
- *Transaction #6 (April 12, 2010) – Modification of number of subjects in MRC #2 from 265 to 210*
- *Transaction #7 (April 21, 2010) - Approval of MRC #2 prior to the production of clinical study materials commencing on April 22, 2010*
- *Transaction #10 (August 2, 2018) - Query of MRC #2 at Perrigo's request to retrieve information to respond to CRL #4*

The MRCs provided in the audit trails correspond to the MRCs in Perrigo's ANDA. The (b) (4) *audit trails demonstrate that the MRCs for Perrigo's*

study remained the same from their initial generation in January and April 2010 (shown in Transaction 3 and Transaction 5), through the FDA inspection on January 9, 2015, and indeed through 2018 (shown in Transaction 9 and Transaction 10). The last substantive transaction was the approval of MRC #2 in April 2010 (Transaction 7). The audit trail then shows no activity until Transactions 8, 9 and 10, which were queries of the MRCs in August 2018 to retrieve information for the response to CRL #4.

ii. Audit Trails for Scratch-Off Labels

The (b) (4) *system also provides a comprehensive audit trail of the production of scratch-off labels, canister labels and actuator labels printed from the Perrigo Model in a document titled "Model Log Report." Page 1 of the Model Log Report identifies the model as PRR PRG-723 (the Perrigo Model). In total, there are 197 'Transactions' in the Model Log Report. The breakdown of Transactions is as follows:*

Page #	Assignment Set #	Transaction #	Transaction Date	Purpose
1 - 4	2	1 – 30	Dec 29, 2009 – Jan 19, 2010	Creation/finalization of Assignment Set #2 Label proofs
4 - 24	2	31 – 90	Jan 21, 2010 – Jan 22, 2010	Assignment Set #2 label printing
24 – 27	3	91 - 117	Apr 09, 2010 – Apr 22, 2010	Creation/finalization of Assignment Set #3 Label proofs
28 – 53	3	118 - 195	Apr 22, 2010 – Apr 29, 2010	Assignment Set #3 label printing
53	n/a	196	Oct 02, 2015	Query at Perrigo's request to retrieve information to respond to CRL #2
53	n/a	197	Aug 02, 2018	Query at Perrigo's request to retrieve information to respond to CRL #4

The final 3 Transactions of the Model Log Report audit trail record the following:

- *Transaction #195 (April 29, 2010), last clinical supply produced at the end of the production run (sample reprint)*
- *Transaction #196, (October 2, 2015), query at Perrigo's request to retrieve information to respond to CRL #2.*
- *Transaction #197, (August 2, 2018), query at Perrigo's request to retrieve information to respond to CRL #4.*

The audit trail shows there was no access to the scratch-off labels or any clinical supplies between the period of April 29, 2010 and January 9, 2015. After the printing of the labels in 2010 for the study, the only access to the (b) (4) *system occurred on October 2, 2015 and August 2, 2018 after the date of the last FDA inspection at Perrigo's request to retrieve information to respond to CRL#2 and CRL#4 respectively.*

Perrigo is confident the audit trails provided in this Bioequivalence response establish without question the integrity of Pharmacodynamic study PRG-723 and fully addresses the request of the Office of Study Integrity and Surveillance.

2.4 Assessor's Comment

Per the Division of Bioequivalence I (DBI)'s consult request, the Office of Study Integrity and Surveillance (OSIS) evaluated the applicant's response as follows[14]:

> *In the documentation provided in Perrigo's complete response amendment dated August 31, 2018, I was previously unable to verify the sequence of treatments actually administered to subjects in study PRG723. Using the audit trails provided in the current response amendment, I was able to confirm that the sequence of treatments in the original randomization schedule and the treatment assignments in each kit are consistent with the sequence of treatments (i.e., DECAB, CDBEA, BCADE, EADBC, and ABECD) in the study report for study PRG-723 supporting ANDA 203760.*

OSIS's Recommendations:

> *Based on the audit trails provided in the complete response amendment dated November 30, 2018,* ***the data in the study report for study PRG-723 are reliable to support a regulatory decision****.*

Therefore, all PD study related deficiencies have been addressed except for the data reliability from the California Allergy & Asthma Medical Group. The assessor copies the deficiency issued on 09/21/2015, applicant's response on 04/13/2017 and BE assessor's comment on 09/08/2017 below for the reference[15]:

> ***BE Deficiency***
>
> *Investigational records were not retained. Specifically, three randomized subjects' and ten screen-failed subjects' bioequivalence study Source Records, Informed Consent Forms and Case Report Form Files were missing and could not be located during the inspection. The following subjects' entire study records were missing:*
>
> *Screening Number / Randomization Number*
> (b) (6)

[14] GDRP, ANDA 203760; OSIS memo 2019-01-8.pdf (Completed 01/08/2019); http://panorama.fda.gov/task/view?ID=5c12a35e00d018462807b37e0cb7cd3d

[15] GDRP, ANDA-203760; A203760N000DB_NA04132017 (Completed 09/08/2017); http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88147efa5

(b) (6)

Applicant's Response

Perrigo acknowledges the above comment. The attached statistical report (Attachment F, provided in section 5.3.4.1) demonstrates that, when the 3 randomized subjects referenced above, as well as the entire clinical site's data, are removed from the study analysis, the 90% CI is still contained entirely between 67-150%.

Assessor's Comment

Since the PD study is not acceptable per the evaluation in Section 4.5, the recalculation is not performed at this time by the reviewer.

The original BE assessment already deemed the PD study met the BE criteria of 67% - 150% when all data were included in the dose-scale analysis. Here, the BE assessor re-evaluated the PD study data by 1) excluding 3 affected subjects (b) (6) and 2) excluding all the data from the California Allergy & Asthma Medical Group (Site 4). The results are shown below:

Data	Assessor's Results			Applicant's Results[16]		
	N	F (T/R)	90% CI	N	F (T/R)	90% CI
All[17]	93	1.17	102.68% - 132.85%	93	1.16	102.3% - 133.0%
Excluding 3 subjects	90	1.16	101.83% - 132.71%	90	1.16	102.8% - 133.2%
Excluding all subjects from Site 4	66	1.12	98.33% - 125.46%	66	1.14	100.4% - 128.4%

The assessor's results are similar to the applicant's results for all three datasets above. The minor difference could be caused by that the assessor bootstrapped the data 10,000 times whereas the applicant only bootstrapped the data 2,000 times[16]. Nevertheless, both the assessor and applicant's results meet the BE criteria of 67.00% - 150.00%.

[16] GlobalSubmit Review; ANDA 203760; Module 5.3.4.1 Attachment F –Dose Scale Model Report; Submitted 04/13/2017; \\cdsesub1\evsprod\anda203760\0028\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\study-prg-723\model-rpt-attach-f.pdf

[17] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)

The PD study # PRG723 is **adequate**.

2.5 R Output

Study	Dataset	R Code	R Output
PD Study # PRG723	exclude 3 subjects	R Code	Output
	exclude site 4	R code	Output

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 203760

APPLICANT: Perrigo Pharmaceutical Company

DRUG PRODUCT: Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation

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

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

3 *COMPLETED ASSIGNMENT FOR 203760 ID: 37658*

Reviewer: Zhang, Zhen **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation (SD44)

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
37658	11/30/2018	BIO	ANDA Amendment [1]	1	1
37658	11/30/2018	BIO	Consult Review (For Consults to Other Office) [1]	1	1
37658	11/30/2018	Parallel	Minor Amendment (Original or Supplement) [1]	1	1
37658	11/30/2018	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
37658	11/30/2018	Parallel	Pre-Screening [0.25]	0.25	0.25
				Total:	4.25

DIVISION OF BIOEQUIVALENCE REVIEW
FOR PRESSURIZED METERED DOSE INHALATION PRODUCTS

ANDA No.	203760		
Drug Product Name	Albuterol Sulfate Inhalation Aerosol		
Strength(s)	0.09 mg Base/Inhalation		
Applicant Name	Perrigo Pharmaceutical Company		
Applicant Address	515 Eastern Ave Allegan, MI, USA 49010		
US Contact Name and US Mailing Address	Matthew Popowski, Senior Regulatory Affairs Project Manager 3940 Quebec Ave North Minneapolis, MN, USA 55427		
US Contact Telephone Number	(b) (6)		
US Contact Fax Number	763-732-0509		
Original Submission Date(s)	11/16/2011		
Submission Date(s) of Amendment(s) Under Review	07/03/2013 Major amendment to support the addition of an integrated dose counter to the metered dose inhaler (SD10) 04/24/2015 Post-CR meeting request (SD20) 07/01/2015 Response to complete response letter dated 04/13/2015 (SD22) 10/05/2015 Post-CR meeting request (SD24) 04/13/2017 Major amendment (SD29) 10/23/2017 Meeting Request (SD31) 12/29/2017 Major amendment (SD34) 04/26/2018 Response to IR request (SD37) **08/31/2018: Multiple Categories (SD 38)**		
Primary Reviewer	Zhen Zhang, Ph.D.		
Secondary Reviewer	Vipra Kundoor, Ph.D.		
Tertiary Reviewer	Qing Liu, Ph.D.		
Study Number(s)	**10825302**		
Study Type(s)	**Fasting**		
Strength(s)	2 x 90 mcg actuations (total dose = 180 mcg)		
Clinical Site	Novum Pharmaceutical Research Services		
Clinical Site Address	Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712		
Analytical Site	(b) (4)		
Analytical Site Address			
Study Number(s)	**TTP-CBJ-M0050**	**TTP-CBJ-M00132**	**TTP-CBJ-0282**
Study Type(s)	**In vitro Bioequivalence Study**		
Strength(s)	90 mcg/ actuation		
***In Vitro* Test Site**	(b) (4)		
***In Vitro* Test Site Address**			

Study Number(s)	**PRG-723**	
Study Type(s)	**Pharmacodynamic Bioequivalence Study**	
Strength(s)	90 mcg/ actuation	
Clinical Site	**Site 1** University of Florida Asthma Research Lab **Site 2** Roy J and Lucille A Carver College of Medicine Department of Pediatrics, Allergy/Pulmonary **Site 3** Allergy & Asthma Diagnostic Treatment Center **Site 4** California Allergy & Asthma Medical Group **Site 5** Clinical Research Atlanta **Site 6** Spartanburg Medical Research **Site 7** AARA Research Center	
Clinical Site Address	**Site 1** 1600 SW Archer Road Gainesville, FL 32610-0486 **Site 2** The University of Iowa 200 Hawkins Drive Iowa City, Iowa 52242-1083 **Site 3** 2300 Centerville Road Tallahassee, FL 32308 **Site 4** 11645 Wilshire Blvd, Suite 1155 Los Angeles, CA 90025 **Site 5** 175 Country Club Drive, Suite 100A Stockbridge, GA 30281 **Site 6** 485 Simuel Road Spartanburg, SC 29303 **Site 7** 9900 N Central Expy, Suite 555 Dallas, TX 75231	
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete**
Formulation	☒ **Adequate** ☐ **Inadequate**	
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☒ **No** ☐ **N/A**	
Deficiency Classification	☐ **Major**	

	☒ Minor ☐ N/A (Review is Adequate)		
Overall Review Result	☐ Adequate ☒ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study Tracking/Supporting Document #	**Study/Test Type**	**Strength (e.g., xx µg/inhalation)**	**Review Result**
1, 2, 6	Fasting BE Study	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34, 37 38	Pharmacodynamic BE Study	0.09 mg Base/Inhalation	☐ Adequate ☒ Inadequate ☐ Not Applicable
1, 2, 6, 29	In vitro BE study # TTP-CBJ-M0050	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Single Actuation Content through Container Life	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 34, 37	In vitro BE study # TTP-CBJ-M0282: Priming and Repriming	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Aerodynamic Particle Size Distribution by Cascade Impaction	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Spray Pattern	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Plume Geometry	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable

1 EXECUTIVE SUMMARY

This is a review of the amendment dated 08/31/2018 of ANDA 203760.

In the original submission and subsequent amendments, the applicant submitted the results of the following studies comparing the test product (Perrigo Pharmaceutical Company's Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation) to the corresponding reference product (Teva Global's ProAir® HFA (albuterol sulfate) Inhalation Aerosol, 0.09 mg Base/Inhalation). All the studies are adequate except pharmacodynamic study # PRG-723 due to deficiency related to the Office of Study Integrity and Surveillance (OSIS)'s inspection as shown in the table below[1, 2, 3, 4, 5].

	Test Batch #	Reference Batch #	Dose counter?	Relevant to BE determination?	Review Results for the relevant BE studies
Fasting Study # 10825302	08MM-050	AEA13B	No for both T and R	Yes	**Adequate**
Pharmacodynamic Study # PRG-723	08MM-050	AEA13B	No for both T and R	Yes	**Inadequate**
In vitro BE study # TTP-CBJ-M0050	08MM-050, 08MM-034, 08MM-039	AEA13B, AEA12C, AEA14A	No for both T and R	Yes	**Adequate**
In vitro BE study # TTP-CBJ-0282	15MM-023, 16MM-002, 16MM-003	DAC23A, DAC34A, DAC36A	Yes for both T and R; T has optimized actuator	Yes	**Adequate**

In the current amendment dated 08/31/2018, the applicant provided response to OSIS related BE deficiency. Per the Division of Bioequivalence I (DBI)'s consult request, OSIS evaluated the applicant's response and has the following recommendations: *OSIS recommends OGD request the sponsor provide the audit trails from [redacted] related to the Master Randomization Code (MRC) and scratch-off labels. The audit trails should include all activity related to the MRCs and scratch-off labels prior to the enrollment of the first study subject and until the date of the last FDA inspection (January 9, 2015).*

Therefore, pharmacodynamic study # PRG-723 remains inadequate due to OSIS related deficiency.

The application is **inadequate**.

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[1] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)
[2] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222
[3] GDRP, ANDA-203760; A203760N000DB_NA04132017 (Completed 09/08/2017); http://panorama fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88147efa5
[4] GDRP, ANDA-203760; A203760N000DPM-MeetingMinutes03.doc (Completed 12/14/2017); http://panorama fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f8817ec1af
[5] GDRP, ANDA 203760; A203760N000DB-Review01-AMEND12292017.docx (Completed 05/17/2018); http://panorama fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881ae8679

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3 REVIEW OF THE APPLICANT'S RESPONSE TO BIOEQUIVALENCE DEFICIENCY

3.1 BE Deficiency

Deficiency Related to the Pharmacodynamic Study (PRG-723)

The Office of Study Integrity and Surveillance (OSIS) evaluated your responses to Bioequivalence deficiencies #1 and #2 and has the following comments:

OSIS acknowledges that Perrigo considers the scratch-off labels as secondary documentation. However, OSIS considers the information on the scratch-off labels as the primary documentation to confirm the treatment a subject received. While the master randomization code identifies the treatment a subject was intended to receive, we consider the scratch-off label as primary documentation that identifies the treatment a subject actually received.

The original scratch-off labels were blinded when photocopied, and thus the copies do not provide information regarding the treatment each subject received during the study. Because the original scratch-off labels were not maintained at the clinical site and the appearance of the copies of the copy of the scratch-off labels maintained at the clinical site versus the copies of the original scratch-off labels provided during the inspection are different, the original scratch-off labels cannot be used as documentation to confirm the treatment each subject received in each sequence. Thus, OSIS is still interested in any primary documentation that positively indicates what treatment each subject received that remained at the clinical site.

3.2 Applicant's Response

In this response, Perrigo resolves this minor deficiency in multiple, independent ways:

- *First, by providing extensive documentation, including primary documentation, that remained at the clinical site and which evidences what treatment each Study subject received;*
- *Second, by providing an assessment of Study records by an independent third-party auditor, who visited a clinical site and concluded that "the results of this review determined that such documentation does exist to enable positively identifying the treatment each subject received";*
- *Third, by providing primary documentation from the clinical labeling vendor, an independent third party, which establishes the authenticity of treatment sequences in the original scratch-off labels and demonstrates the actual treatment each subject received;*
- *Fourth, by identifying documentary evidence confirming that Perrigo's receipt of the original scratch-off labels after ANDA submission could not possibly permit manipulation or alteration of the Study results;*

- *Fifth, by identifying a likely root cause – verified by an independent auditor – of the discrepancy FDA found in the appearance of photocopies of the original scratch-offlabels; and*
- *Sixth and finally, by showing that Perrigo complied with its own clinical protocol, ICH guidelines, and FDA guidelines related to the location of study blinding information, and that FDA previously accepted a study in circumstances similar to those here.*

Perrigo respectfully submits that this additional information, along with the verification by independent, third-party auditor [redacted] (b) (4) *resolves any remaining questions as to the validity of the data in Perrigo's ANDA demonstrating bioequivalence of Perrigo's albuterol sulfate inhalation product to the Reference Listed Drug, ProAir®. In light of information provided in past CRL responses and in this response, the Agency should consider this deficiency resolved.*

3.3 Reviewer's Comment

Per the Division of Bioequivalence I (DBI)'s consult request, the Office of Study Integrity and Surveillance (OSIS) evaluated the applicant's response as follows[6]:

> Study PRG-723 was a multicenter, randomized, double-blind, 5-way crossover, placebo-controlled study where each study subject received all five study treatments (i.e., vehicle, 90 mcg of Reference, 180 mcg of Reference, 90 mcg of Test, 180 mcg of Test) in one of five sequences (ABECD, BCADE, CDBEA, DECAB, or EADBC) determined by the MRC. While Perrigo feels that the documentation for study PRG-723 positively identifies the treatment kit each subject received, OSIS is unable to verify in that documentation the sequence of treatments actually administered.
>
> Perrigo does not believe that removal of the original scratch-off labels from the clinical site could have impacted the integrity of the data. However, OSIS considers the scratch-off labels as primary documentation to verify the treatment actually administered to study subjects. Thus, their removal from the clinical site and the finding that the message printed on the scratch-off labels appeared to be modified when they were returned to the site negatively impacts the integrity of the documents. [redacted] (b) (4) investigation into whether the photocopier settings could have resulted in the discrepancy doesn't provide any additional information and doesn't explain why the same copier settings resulted in a different outcome when copying a copy of the scratch-off labels that remained at the clinical site versus copying the original scratch-off labels that were returned to the site. Although the agency accepted the bioequivalence study supporting NDA 22341, OSIS's position has not changed and the sponsor should have procedures and controls to ensure the integrity of the blinding codes prior to, during, and after a bioequivalence study is conducted.

[6] GDRP, ANDA 203760; OSIS memo 2018-10-05.pdf (Completed 10/05/2018); http://panorama fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881c383cb

> Perrigo's statement that the treatments received by each subject in each period can be further supported by referencing the MRCs and blinding codes that remain in the control and possession of (b) (4), the independent third party should be further explored. Because (b) (4) stores the MRCs and blinding code for Perrigo's Study in a secure, proprietary software system, complete with a document audit trail, the Agency should be able to verify the original randomization schedule and blinding code. Evaluation of the audit trails will enable OSIS to confirm the intended treatments in the MRC as well as the identity of the actual treatments administered in each period.

OSIS's Recommendations:

> OSIS recommends OGD request the sponsor to provide the audit trails from (b) (4) related to the MRC and scratch-off labels. The audit trails should include all activity related to the MRCs and scratchoff labels prior to the enrollment of the first study subject and until the date of the last FDA inspection (January 9, 2015).

Therefore, the applicant will be asked to provide the aforementioned information.

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 203760

APPLICANT: Perrigo Pharmaceutical Company

DRUG PRODUCT: Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiency:

Deficiency Related to the Pharmacodynamic Study (PRG-723)

The Office of Study Integrity and Surveillance (OSIS) evaluated your response to Bioequivalence deficiency dated August 31, 2018, and has the following comments:

Please provide the audit trails from (b) (4) related to the Master Randomization Code (MRC) and scratch-off labels. The audit trails should include all activity related to the MRCs and scratch-off labels prior to the enrollment of the first study subject and until the date of the last FDA inspection (January 9, 2015).

Sincerely yours,

{See appended electronic signature page}

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4 *COMPLETED ASSIGNMENT FOR 203760 ID: 36829*

Reviewer: Zhang, Zhen **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation (SD38)

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
36829	8/31/2018	BIO	ANDA Amendment [1]	1	1
36829	8/31/2018	BIO	Consult Review (For Consults to Other Office) [1]	1	1
36829	8/31/2018	Parallel	Study Amendment [1]	1	1
36829	8/31/2018	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
36829	8/31/2018	Parallel	Pre-Screening [0.25]	0.25	0.25
				Total:	4.25

DIVISION OF BIOEQUIVALENCE REVIEW
FOR PRESSURIZED METERED DOSE INHALATION PRODUCTS

ANDA No.	203760		
Drug Product Name	Albuterol Sulfate Inhalation Aerosol		
Strength(s)	0.09 mg Base/Inhalation		
Applicant Name	Perrigo Pharmaceutical Company		
Applicant Address	515 Eastern Ave Allegan, MI, USA 49010		
US Contact Name and US Mailing Address	Matthew Popowski, Senior Regulatory Affairs Project Manager 3940 Quebec Ave North Minneapolis, MN, USA 55427 Matthew.Popowski@perrigo.com		
US Contact Telephone Number	763-732-0481		
US Contact Fax Number	763-732-0509		
Original Submission Date(s)	11/16/2011		
Submission Date(s) of Amendment(s) Under Review	07/03/2013 Major amendment to support the addition of an integrated dose counter to the metered dose inhaler (SD10) 04/24/2015 Post-CR meeting request (SD20) 07/01/2015 Response to complete response letter dated 04/13/2015 (SD22) 10/05/2015 Post-CR meeting request (SD24) 04/13/2017 Major amendment (SD29) 10/23/2017 Meeting Request (SD31) **12/29/2017 Major amendment (SD34)** **04/26/2018 Response to IR request (SD37)**		
Primary Reviewer	Zhen Zhang, Ph.D.		
Secondary Reviewer	Vipra Kundoor, Ph.D.		
Tertiary Reviewer	Qing Liu, Ph.D.		
Study Number(s)	**10825302**		
Study Type(s)	**Fasting**		
Strength(s)	2 x 90 mcg actuations (total dose = 180 mcg)		
Clinical Site	Novum Pharmaceutical Research Services		
Clinical Site Address	Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712		
Analytical Site	(b) (4)		
Analytical Site Address			
Study Number(s)	**TTP-CBJ-M0050**	**TTP-CBJ-M00132**	**TTP-CBJ-0282**
Study Type(s)	**In vitro Bioequivalence Study**		
Strength(s)	90 mcg/ actuation		
***In Vitro* Test Site**	(b) (4)		
***In Vitro* Test Site Address**			
Study Number(s)	**PRG-723**		

Study Type(s)	**Pharmacodynamic Bioequivalence Study**	
Strength(s)	90 mcg/ actuation	
Clinical Site	**Site 1** University of Florida Asthma Research Lab **Site 2** Roy J and Lucille A Carver College of Medicine Department of Pediatrics, Allergy/Pulmonary **Site 3** Allergy & Asthma Diagnostic Treatment Center **Site 4** California Allergy & Asthma Medical Group **Site 5** Clinical Research Atlanta **Site 6** Spartanburg Medical Research **Site 7** AARA Research Center	
Clinical Site Address	**Site 1** 1600 SW Archer Road Gainesville, FL 32610-0486 **Site 2** The University of Iowa 200 Hawkins Drive Iowa City, Iowa 52242-1083 **Site 3** 2300 Centerville Road Tallahassee, FL 32308 **Site 4** 11645 Wilshire Blvd, Suite 1155 Los Angeles, CA 90025 **Site 5** 175 Country Club Drive, Suite 100A Stockbridge, GA 30281 **Site 6** 485 Sinuel Road Spartanburg, SC 29303 **Site 7** 9900 N Central Expy, Suite 555 Dallas, TX 75231	
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete**
Formulation	☒ **Adequate** ☐ **Inadequate**	
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☒ **No** ☐ **N/A**	
Deficiency Classification	☐ **Major** ☒ **Minor**	

	☐ N/A (Review is Adequate)		
Overall Review Result	☐ Adequate ☒ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study Tracking/Supporting Document #	**Study/Test Type**	**Strength (e.g., xx µg/inhalation)**	**Review Result**
1, 2, 6	Fasting BE Study	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6	Pharmacodynamic BE Study	0.09 mg Base/Inhalation	☐ Adequate ☒ Inadequate ☐ Not Applicable
1, 2, 6, 29	In vitro BE study # TTP-CBJ-M0050	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Single Actuation Content through Container Life	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 34, 37	In vitro BE study # TTP-CBJ-M0282: Priming and Repriming	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Aerodynamic Particle Size Distribution by Cascade Impaction	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Spray Pattern	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29, 34	In vitro BE study # TTP-CBJ-M0282: Plume Geometry	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable

1 EXECUTIVE SUMMARY

This is a review of the amendments dated 12/29/2017 and 04/26/2018 of ANDA 203760, which is the *first generic drug application.*

In the original application, the applicant submitted the results of the following studies comparing the test product without dose counter (Perrigo Pharmaceutical Company's Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation) to the corresponding reference product without dose counter (Teva Global's ProAir® HFA (albuterol sulfate) Inhalation Aerosol, 0.09 mg Base/Inhalation): one single-dose fasting pharmacokinetic (PK) bioequivalence (BE) study (#10825302), one clinical pharmacodynamics (PD) study (#PRG-723), and five in vitro BE studies (TTP-CBJ-M0050; single actuation content, aerodynamic particle size distribution by cascade impactor, spray pattern, plume geometry and priming/re-priming). In addition, the applicant also submitted the particle size distribution by laser diffraction, which is not recommended per the Product-Specific BE Guidance of Albuterol Sulfate Metered Dose Inhalers[1]. All of the in vivo and in vitro BE studies were deemed inadequate due to multiple deficiencies by the Division of Bioequivalence I (DBI)[2]. Note that all the studies were conducted on the drug products without dose counter.

Due to the introduction of a dose counter on the reference product in 2013, the applicant conducted additional in vitro BE studies (TTP-CBJ-M00132) comparing the test product with dose counter with the reference product with dose counter. The applicant submitted its study results in an amendment dated 07/03/2013. On 07/01/2015, the applicant submitted its responses to the BE deficiencies identified in the original BE review. Both amendments were reviewed together in the first amendment BE review and deemed inadequate due to multiple deficiencies by DBI[3].

In the amendment dated 04/13/2017, the applicant responded to the deficiencies identified in the first amendment BE review and submitted additional in vitro testing results (study # TTP-CBJ-0282) using test product with optimized actuator. The applicant's responses were deemed inadequate by DBI due to deficiencies related to the Office of Study Integrity and Surveillance (OSIS) findings, method validation, and missing information[4]. These deficiencies were communicated to the applicant through the complete response letter (CRL) dated 10/13/2017. Subsequently, the applicant submitted a meeting request for deficiency clarification and the meeting was held on 11/16/2017[5].

In the current amendments dated 12/29/2017 and 04/26/2018, the applicant submitted requested information in response to the CRL dated 10/13/2017. The applicant satisfactorily addressed all the deficiencies except for the OSIS related questions. Per the Division of Therapeutic Performance (DTP)'s consult response, it is not necessary to ask the applicant to *repeat the in vivo*

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[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf
[2] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)
[3] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222
[4] GDRP, ANDA-203760; A203760N000DB_NA04132017 (Completed 09/08/2017); http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88147efa5
[5] GDRP, ANDA-203760; A203760N000DPM-MeetingMinutes03.doc (Completed 12/14/2017); http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f8817ec1af

PK and PD BE studies using its T product with dose counter and optimized actuator and the R product with dose counter (PROAIR HFA) currently in the market, provided that the ANDA sponsor submits adequate information by which the BE reviewers consider that all deficiencies are resolved, and all the BE studies (in vitro, in vivo PK and in vivo PD) are ultimately deemed adequate[6]. The evaluation summary of each required BE studies per teleconference meeting between the Office of Generic Drugs (OGD) and Perrigo Pharmaceutical Company on 08/26/2011[7] is as follows:

	Test Batch #	Reference Batch #	Dose counter?	Relevant to BE determination?	Review Results for the relevant BE studies
Fasting Study # 10825302	08MM-050	AEA13B	No for both T and R	Yes	**Adequate**
PD Study # PRG-723	08MM-050	AEA13B	No for both T and R	Yes	**Inadequate**
In vitro BE study # TTP-CBJ-M0050	08MM-050, 08MM-034, 08MM-039	AEA13B, AEA12C, AEA14A	No for both T and R	Yes	**Adequate**
In vitro BE study # TTP-CBJ-0282	15MM-023, 16MM-002, 16MM-003	DAC23A, DAC34A, DAC36A	Yes for both T and R; T has optimized actuator	Yes	**Adequate**

The Office of Study Integrity and Surveillance (OSIS) inspection status for the clinical (Novum Pharmaceutical Research Services, Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712) and analytical (b) (4) (b) (4) sites of the fasting study # 10825320 and for the analytical site (b) (4) (b) (4) of the in vitro BE studies # TTP-CBJ-M0050 and TTP-CBJ-M0282 are complete and adequate.

The OSIS inspection status for the clinical sites (multiple sites) of the PD study # PRG-723 is considered complete at this time, but the application is considered inadequate pending the firm's response to OSIS's deficiency.

The application is **inadequate**.

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[6] GDRP, ANDA 203760; C 20049603 - DTP Consult Response - ANDA 203760 - RLD ProAir HFA - Dose Counter.doc (Completed 04/06/2018); http://panorama.fda.gov/document/preview?versionID=5ac7dbba0070b32e636a087b3cbea2b8&ID=5ac295a7001f571983afd8c44d081e60

[7] GDRP, ANDA 203760; Appendix (pages 120 – 132 of 136) in A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222

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3 *THE FIRM'S RESPONSES TO BIOEQUIVALENCE DEFICIENCIES*

Deficiency Related to the Pharmacodynamic Study (PRG-723)

3.1 BE Deficiency #1

Deficiency Related to the Pharmacodynamic Study (PRG-723)

During the inspection conducted at the University of Florida, Asthma Research Lab, Gainesville, FL the FDA Investigator determined that the study monitor collected the original study drug dispensation records containing the blinded code-breaking scratch-off labels from the site. The site only maintained photocopies of the records containing the blinded code-breaking scratch-off labels. The original study drug dispensation records containing the blinded code-breaking scratch-off labels were also removed from the site by the study monitor at the other two inspected sites (University of Iowa Hospitals & Clinic and California Allergy & Asthma Medical Group). Please provide a description of the documentation that was provided to the sites prior to the conduct of the study and remained at the clinical site until after the sites were inspected that demonstrates the intended treatment for each subject.

Applicant's Response #1

Please refer to the Complete Response Amendment (033) for the full response. Below is the applicant's summary:

Integrity of PD study PRG-723 Results

Perrigo firmly believes the transfer of the IMP kit original scratch-off labels from the clinical sites after conclusion of PD study PRG-723, consistent with FDA and ICH guidelines, has no relevance to confirming a subject received their intended treatment. As a practical matter, only the primary source document, the master randomization code, can be used as the comparator of the treatment sequence and treatment identifiers against the clinical packaging batch record, case report form, and clinical study report to provide the totality of evidence that a subject correctly received their intended treatment.

Reviewer's Comment #1

Per DBI's request, the Office of Study Integrity and Surveillance (OSIS) evaluated the applicant's response as follows[8]:

OSIS acknowledges that Perrigo considers the scratch-off labels as secondary documentation. However, OSIS considers the information on the scratch-off labels as the primary documentation to confirm the treatment a subject received. While the master randomization code identifies the

[8] GDRP, ANDA-203760-ORIG-1-AMEND-34; OSIS memo 2018-03-16-A203760.pdf (Completed 03/16/2018); http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881a01817

treatment a subject was intended to receive, we consider the scratch-off label as primary documentation that identifies the treatment a subject actually received.

The original scratch-off labels were blinded when photocopied, and thus the copies do not provide information regarding the treatment each subject received during the study. Because the original scratch-off labels were not maintained at the clinical site and the appearance of the copies of the copy of the scratch-off labels maintained at the clinical site versus the copies of the original scratch-off labels provided during the inspection are different, the original scratch-off labels cannot be used as documentation to confirm the treatment each subject received in each sequence. Thus, OSIS is still interested in any primary documentation that positively indicates what treatment each subject received that remained at the clinical site.

3.2 BE Deficiency #2

During the inspection at the University of Iowa Hospital & Clinic, the FDA Investigator was provided with copies of the original blinded scratch-off labels (returned to the site during the inspection) and the copies maintained at the clinical site (made before the scratch-off labels were collected by the study monitor). However, the obscure part of the copies of the scratch-off labels returned to the site did not show a description stating "Drug Information Inside in Case of Emergency Scratch off the Surface of Blinded Area", while it was visible on the copy of the copies maintained at the site. Please provide an explanation for this discrepancy.

Applicant's Response #2

Please refer to the Complete Response Amendment (033) for the full response. Below is the applicant's summary:

Perrigo has not been successful in recreating a photocopy of the original scratch-off label that lacks the emergency statement. The photocopies of the original scratch-off labels that remained at the U of Iowa clinical site bear the clearly legible emergency statement that matches the original scratch-off label. No secondary photocopies replicating the photocopies provided to FDA were made by the clinical site. The content and format forensics of the Study Drug Dispensation – MDI Label, and of the hand-written fields (Subject Number (b) (6) *confirm that the photocopy retained at the clinical site and photocopy provided to FDA are a direct match of the original scratch-off label. In addition, the same forensics confirm that both photocopies match the photograph of original, intact scratch-off label which undeniably displays the emergency statement on the unscratched label. Perrigo's contract with* (b) (6) *demonstrated that copies of the original scratch-off label will still retain legibility of the emergency statement even after ten successive copies are made. The weight of the evidence confirms that the original scratch-off labels contain the statement "DRUG INFORMATION INSIDE IN CASE OF EMERGENCY SCRATCH OFF THE SURFACE OF BLINDED AREA" and that this statement was inexplicably obscured when the labels were copied for the investigator during the inspection. Potential root causes for the lack of the emergency statement could be improper photocopier settings (e.g., darkness, contrast, 'Economode' turned 'ON'), toner cartridge almost empty or other menu settings. However, these are only speculative causes and cannot be confirmed because we have no information regarding the settings or condition of the copiers when the aberrant copies were made for the FDA*

inspector. Perrigo firmly believes the weight of evidence presented in bioequivalency responses 1 and 2 clearly demonstrate the integrity of PD study PRG-723 that should not be dismissed by the poor quality of clinical label photocopies.

Reviewer's Comment # 2

Per DBI's request, the Office of Study Integrity and Surveillance (OSIS) evaluated the applicant's response as follows[9]:

Perrigo conducted an investigation to determine if improper copier settings may have resulted in the discrepancy between FDA's copy of the original scratch-off label returned to the site during the inspection and FDA's copy of the copy that remained at the clinical site. Unfortunately, the investigation did not yield an assignable cause to the photocopy in FDA's possession that lacks the emergency statement. While the cause of the discrepancy is unknown, it supports OSIS' response to bioequivalence deficiency #1.

3.3 BE Deficiency #3

15MM-023, 16MM-002 and 16MM-003 are canister lot numbers as stated in your report of Optimization of Integrated Dose Counter TTP-CBJ-M0099 (Page 20 of 27) (Module 3.2.P.2, Submitted 4/13/2017). However, you did not specify the optimized actuator lot numbers used for the Certificate of Analyses (COAs) of these three test product lots (canister lots). Please provide this information.

Applicant's Response #3

Canister lots are paired with actuators at the time of study protocol finalization prior to study initiation. Actuator lot numbers are included in the study report or the COA associated with each stability protocol. For lots 15MM-023, 16MM-002, and 16MM-003, two different stability studies were conducted, one with the original dose counter (DC) actuator and one with the final optimized actuator.

The IVBE study report (TTP-CBJ-M0282) and each of the stability COAs include the actuator lot numbers. The updated stability COAs are included in Section 3.2.P.8 of this submission. The final optimized DC actuator lots paired with the canister lots used for stability, IVBE, and reprime studies are the same. For the reviewer's convenience, Table 22 below summarizes the IVBE study and reprime study conducted with the final optimized DC actuator and the stability protocols with the associated actuator lot number for each canister lot.

Table 22. Study Descriptions, Protocols, and Actuator Lots for Each Canister Lot

Study Description	*Protocol/Report*	*Canister Lot*	*Actuator Lot*
Original DC Stability	*TTP-CBJ-M0179*	*15MM-023*	(b) (4)

[9] GDRP, ANDA-203760-ORIG-1-AMEND-34; OSIS memo 2018-03-16-A203760.pdf (Completed 03/16/2018); http://panorama fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881a01817

			(b) (4)
Final Optimized DC Stability	*TTP-CBJ-M0283*	*15MM-023*	
IVBE Study Final Optimized DC	*TTP-CBJ-M0282*	*15MM-023*	
Original DC Stability	*TTP-CBJ-M0203*	*16MM-002*	
Final Optimized DC Stability	*TTP-CBJ-M0269*	*16MM-002*	
IVBE Study Final Optimized DC	*TTP-CBJ-M0282*	*16MM-002*	
Reprime Study Final Optimized DC	*TTP-CBJ-M0325*	*16MM-002*	
Original DC Stability	*TTP-CBJ-M0216*	*16MM-003*	
Final Optimized DC Stability	*TTP-CBJ-M0270*	*16MM-003*	
IVBE Study Final Optimized DC	*TTP-CBJ-M0282*	*16MM-003*	
Reprime Study Final Optimized DC	*TTP-CBJ-M0325*	*16MM-003*	
Original DC Stability	*TTP-CBJ-M0217*	*16MM-004*	
Final Optimized DC Stability	*TTP-CBJ-M0271*	*16MM-004*	
Reprime Study Final Optimized DC	*TTP-CBJ-M0325*	*16MM-004*	

Reviewer's Comment # 3

The applicant verified that three test lots were equipped with three different actuator lots in the COAs as indicated in the table above.

The applicant's response #3 is acceptable.

3.4 BE Deficiency #4

Please provide COAs for the reference lots # DAC23A, DAC34A and DAC36A.

Applicant's Response #4

COAs for the reference lots# DAC23A, DAC34A, and DAC36A are provided in section 3.2.P.5.4.

Reviewer's Comment # 4

The applicant provided COAs for the reference lots # DAC23A, DAC34A and DAC36A.

The applicant's response #4 is acceptable.

3.5 BE Deficiency #5

Please provide the following standard operating procedures (SOPs) with the updated version:

- (b) (4) : HPLC Rapid Screen Assay Method for the determination of Albuterol Sulfate
- (b) (4) (b) (4) Pharmaceutical (b) (4)
- (b) (4) Actuation Stations

- [redacted] Imaging System
- [redacted] Plume Geometry for Albuterol Sulfate HF A Inhalation Aerosol with Integrated Dose Counter

Applicant's Response #5

The requested version of [redacted] *is provided in section 3.2.P.5.2.*

The requested version of [redacted] *is provided in section 3.2.P.5.2.*

The requested version of [redacted] *is provided in section 3.2.P.5.2.*

The requested version of [redacted] *is provided in section 3.2.P.5.2.*

The requested version of SOP [redacted] *is provided in section 3.2.P.5.2.*

Please note that SOP [redacted] *has subsequently been updated to* [redacted] *to accommodate some editorial changes and clarifications to the instructions. A copy of SOP* [redacted]*, which includes a revision history at the end of the document, is also included in section 3.2.P.5.2.*

Reviewer's Comment # 5

The applicant provided the requested SOPs.

The applicant's response #5 is acceptable.

3.6 BE Deficiency #6

Please indicate how the test and reference products were stored before the SAC test.

Applicant's Response #6

The test product lots were stored [redacted] *in controlled room temperature environment (20°C – 25°C) post manufacture, then transferred to the testing laboratory and stored* [redacted] *laboratory conditions during SAC testing.*

The reference product lots were commercially sourced and stored [redacted] *laboratory conditions from receipt and during SAC testing.*

It should be noted that, for both the test and reference products, SAC testing was conducted after the product lagering period and more than one month after the last actuation conducted as part of batch release testing. Immediately prior to SAC testing both the test and reference product inhalers were primed 3 times in accordance with the reference product's instructions for use.

Reviewer's Comment # 6

Per the RLD labeling[10], the drug product should be stored "*between 15° and 25°C (59° and 77°F). Contents under pressure. Do not puncture or incinerate. Protect from freezing temperatures and prolonged exposure to direct sunlight. Exposure to temperatures above 120°F may cause bursting*". Therefore, the test and reference products were stored in accordance with the RLD labeling before the SAC test.

The applicant's response #6 is acceptable.

3.7 BE Deficiency #7

Your calibration of manual metered dose inhaler (MDI) actuation used the lots manufactured without dose counter. Please repeat your method validation using the reference lot with dose counter.

Applicant's Response #7

Validation of the manual metered dose inhaler (MDI) actuation, using a reference product lot with a dose counter (DAC23A), was performed in a supplemental method validation for (b) (4) *. A copy of the validation report,* (b) (4) *, is located in section 3.2.P.5.3.*

Reviewer's Comment # 7

The applicant repeated the validation of the manual metered dose inhaler (MDI) actuation using an unexpired reference lot with a dose counter (DAC23A). The evaluation of the method validation is as follows:

Precision – Single Actuation Content

Lot ID	% Label Claim
R7 Shot 1	(b) (4)
R7 Shot 2	
R7 Shot 3	
R7 Shot 4	
R7 Shot 5	
R7 Shot 6	
Mean	97
%RSD	2.2
	(b) (4)

Intermediate Precision (By Date) – Single Actuation Content

[10] Drugs@FDA; Search Term: 021457; https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021457s026lbl.pdf ; last accessed 6/12/2017

Day 1	%LC
Mean	100
%RSD	2.6
Day 2	%LC
Mean	96
%RSD	4.5
Overall Mean (n=12)	98
Overall %RSD (n=12)	4.0

Intermediate Precision (By Analyst) – Single Actuation Content

	Analyst 1		Analyst 2	
	Sample Name	%LC	Sample Name	%LC
Day 1	D1	(b) (4)	D4	(b) (4)
	D2		D5	
	D3		D6	
Day 2	D4		D1	
	D5		D2	
	D6		D3	
	Mean	100	Mean	96
	%RSD	2.7	%RSD	4.2

Does Applicant's SOP include validation criteria?	☒ Yes ☐ No
Does the precision and ruggedness meet the acceptance criteria?	☒ Yes ☐ No
Was Reference product used in the method validation?	☒ Yes ☐ No
Is the method sufficiently sensitive?	☒ Yes ☐ No

The applicant provided the data in % of label claim instead of content assay and shot weight. The reviewer considers the validation of the manual MDI actuation acceptable and will not ask the applicant to provide data of content assay and shot weight for the following reasons: 1) the validation on the unexpired reference lot with dose counter met its acceptance criteria for both precision and intermediate precision; and 2) the validation on the unexpired reference lot without dose counter was deemed adequate by DBI[11].

The applicant's response #7 is acceptable.

3.8 BE Deficiency #8

Per the response to your Question # 10 in the meeting between the Office of Generic Drug (OGD) and your company (Perrigo Pharmaceutical Company) on August 26, 2011, OGD stated that '*currently, OGD are not aware of any data showing that any changes in an actuator will not affect the MDI priming and repriming. Thus the sponsor is recommended to provide priming and*

[11] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222

repriming data. The sponsor may use the single actuation content data at the beginning lifestage (i.e., the first actuation immediately following the specified number of priming actuations in the RLD labeling for the priming study'. The priming test on the new test and reference lots is acceptable based on your SAC data. However, please conduct repriming test on three test lots with dose counter and optimized actuator, comparing them with three reference lots with dose counter.

Applicant's Response #8

As noted by the Agency, the priming test on the new test and reference lots is acceptable based on Perrigo's SAC data. This was successfully conducted on three lots of test product with the final optimized dose counter actuator (i.e. 15MM-023, 16MM-002, 16MM-003) and three lots of reference product with a dose counter (i.e. DAC23A, DAC34A, DAC36A). Test product lot 15MM-023 is now expired. Therefore, the reprime study was performed with test product lot 16MM-004 in addition to lots 16MM-002 and 16MM-003. Table 23 highlights the product lots used in each study.

Table 23. Test with final optimized dose counter and reference product lots with dose counter used in Prime and Reprime studies.

TEST				***REFERENCE***	
PRIME		***REPRIME***		***PRIME & REPRIME***	
Lot No.	***Manufacture Date***	***Lot No.***	***Manufacture Date***	***Lot No.***	***Expiration Date***
15MM-023	*12 May 2015*	*16MM-004*	*25 January 2016*	*DAC23A*	*03/2018*
16MM-002	*13 January 2016*	*16MM-002*	*13 January 2016*	*DAC34A*	*05/2018*
16MM-003	*20 January 2016*	*16MM-003*	*20 January 2016*	*DAC36A*	*05/2018*

The reprime study comparing test product with the final optimized dose counter actuator to the reference product with dose counter actuator demonstrated bioequivalence using PBE statistics. The study report (TTP-CBJ-M0325: In-Vitro Bioequivalence Reprime Study on Albuterol Sulfate HFA Metered Dose Inhaler Product) is provided in section 3.2.P.2.

Reviewer's Comment # 8

The same actuation method was used for the new repriming study submitted in the current amendments dated 12/29/2017 and 04/26/2018 as that submitted in the amendment dated 4/13/2017, which has been deemed acceptable by DBI[12].

[12] GDRP, ANDA-203760-ORIG-1-AMEND-29; A203760N000DB_NA04132017 (Completed 09/08/2017); http://panorama fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88147efa5

The repriming study was conducted on the unexpired test lots with optimized dose counter and unexpired reference lots with dose counter. The test formulation remains the same.

Study Information

Study No.	TTP-CBJ-M0282
Study Site Name and address	(b) (4)
Principal Investigator	
Study Dates	
SOP No.	
SOP Effective Date	
SOP Title	Determination of Dose Content Uniformity, Shot Weight, and Number of Actuations from an Albuterol Sulfate HF A Inhalation Aerosol Product.
Test Method Description	HPLC Rapid Screen Assay Method for the Determination of Albuterol Sulfate
Testing Equipment Used (e.g., name, model, etc)	(b) (4)
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	
Analytical Method Description	(b) (4) HPLC Rapid Screen Assay Method for the Determination of Albuterol Sulfate
Analytical Equipment Used (e.g., name, model, etc.)	(b) (4)

RE – PRIMING	**Number of actuations required**	3
	Is re-priming conducted as per Reference Product label?	☒ Yes ☐ No
Is testing a single actuation per determination?		☒ Yes ☐ No
If yes, what is the actuation number tested?		#5 after priming for the re-priming test
Is the same actuation number tested for the test and RLD products?		☒ Yes ☐ No
Are studies performed on products stored per the RLD labeling?		☒ Yes ☐ No ☐ N/A

Analytical Method Validation for HPLC and 4Calibration of Manual MDI Actuation

The applicant stated that HPLC method used for the quantitation of dose content in the repriming study was the same HPLC method used to generate results for the SAC priming analysis, which

has been deemed acceptable in previous BE review[13]. The calibration of manual metered dose inhaler (MDI) actuation is also deemed acceptable as evaluated in the Reviewer's Comment #7.

Results Calculated by the Applicant, N=60 (Test=30 and RLD=30)

Table 6.3. Results Summary – Re-Priming (from Appendix 4, Table A.4.1. 'Summary Results – Reprime' on pdf page 27 of TTP-CBJ-M0325 full report)

RE-PRIMING												
Number of actuations used to prime each product = 3												
Actuation number used for testing each product = 5												
	Spray #	Mean				Variability (%CV)[1]					Mean Ratio (T/R)	
		Drug Mass		% label Claim		Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3			Arith (n=30)	Geo (n=30)
Test	5	87.433	87.294	97.167	97.010	0.0030 (5.52%)	0.0036 (6.02%)	0.0040 (6.30%)	0.000000 (0.00%)	0.0033 (5.76%)	0.97	0.97
Ref	5	90.067	90.002	100.100	100.027	0.0015 (3.81%)	0.0017 (4.10%)	0.0014 (3.76%)	0.000002 (0.12%)	0.0015 (3.90%)		

Test Lots: Lot 1 =16MM-002; Lot 2 =16MM-003; Lot 3 = 16MM-004
Reference Lots: Lot 1 =DAC23A; Lot 2 = DAC34A; Lot 3 = DAC36A

[1] Due to the nature of the algorithms used in PROC VARCOMP for the restricted maximum likelihood method, negative estimates are constrained to zero.

Results Calculated by the Reviewer, N=60 (Test=30 and RLD=30)

REPRIMING												
Period of time each product was stored in the valve upright position following priming = 14 days												
Number of actuations used to re-prime each product = 3												
Actuation number used for testing each product = #5												
	Spray #	Mean				Variability (% CV)					Mean Ratio (T/R)	
		Drug Mass (mg)		% label claim		Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	1	87.43	87.29	97.17	97.01	5.56	6.29	6.15	0.53	5.81	0.97	0.97
Ref	1	90.07	90.00	100.10	100.03	3.64	4.03	3.43	1.22	3.85		

Summary of PBE Results Calculated by the Applicant, N=60 (Test=30 and RLD=30)

[13] GDRP, ANDA-203760-ORIG-1-AMEND-29; A203760N000DB_NA04132017 (Completed 09/08/2017); http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88147efa5

Variable	Test Mean	Reference Mean	Ratio	Test Variance	Reference Variance	Constant Scaled Upper 95% CI Bound	PBE Criteria Met
Reprime (Emitted Dose, µg)[1]	87.3	90.0	0.9699	0.003266	0.001482	-0.015426	Pass
Reprime (%Label Claim)	97.0	100.0	0.9698	0.003313	0.001517	-0.015371	Pass

[1]Emitted Dose = dose emitted from the actuator.
Ref. TTP-CBJ-M0325 RePrime (b) (4)

Summary of PBE Results Calculated by the Reviewer, N=60 (Test=30 and RLD=30)

Variable	Mean (Original Scale)		Mean Ratio (Original Scale) %	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
Prime	87.29	90.00	96.99	0.057	0.038	1.485

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant-scaled	-0.0183	-0.0156	Pass

Was the Reference-scaled analysis used to determine PBE?	☐ YES ☒ NO
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ YES ☐ NO ☒ N/A
Was the Constant-scaled analysis used to determine PBE?	☒ YES ☐ NO
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ YES ☐ NO ☐ N/A

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

REPRIMING	**Is the geo-mean of the test product (% of label claim) within 95-105%?**	☒ Yes (97.01%) ☐ No ☐ N/A
Are the PBE results acceptable for repriming test? If No, please comment		☒ Yes ☐ No ☐ N/A

(b) (4)

The repriming study is adequate.

The applicant's response #8 is acceptable.

3.9 BE Deficiency #9

Please provide the calculation method for mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD).

Applicant's Response #9

Reviewer's Comment # 9

The applicant's calculation method for MMAD and GSD is acceptable.

The applicant's response #9 is acceptable.

3.10 BE Deficiency #10

Your method validation for cascade impaction used the lots manufactured without dose counter. Please repeat your method validation using the reference lot with dose counter.

Applicant's Response #10

A supplemental method validation for cascade impaction using (b) (4) *was performed using a reference product lot with a dose counter (DAC23A). A copy of the validation report,* (b) (4)*, is located in section 3.2.P.5.3.*

Reviewer's Comment # 10

The applicant repeated the validation of cascade impaction using an unexpired reference lot with a dose counter (DAC23A). The reviewer summarizes the applicant's method validation results based on the report and evaluates it as follows:

Precision

Intermediate Precision (By Analyst)

SOP for Cascade Impaction method validation submitted?	☒ Yes ☐ No
Number of canisters and/or lots used in the validation study	6 units from 1 reference lot
Does Applicant's SOP include validation criteria?	☒ Yes ☐ No
Do the precision and ruggedness meet the acceptance criteria?	☒ Yes ☐ No
Was Reference product used in the method validation?	☒ Yes ☐ No

The validation of cascade impaction is acceptable.

The applicant's response #10 is acceptable.

3.11 BE Deficiency #11

Please provide the actuation number after priming for both the test and reference products in the spray pattern test.

Applicant's Response #11

Spray pattern testing was performed per method (b) (4) *version 6.0 on labeled actuation #4 for the 30 mm distance and on labeled actuation #11 for the 60 mm distance. Table 24 highlights exceptions to the target spray pattern actuation number. These exceptions are explained in detail in Sections VI.A and VI.C of the report* (b) (4) *and Table A.10.2 in Appendix 10 to the report (provided in complete response amendment dated April 13, 2017, sequence 0028).*

Table 24. Spray Pattern Actuation Number for Repeated Measurements.

PRODUCT	***LOT***	***Inhaler***	***Labeled Actuation #***	
			Spray Pattern (30 mm)	***Spray Pattern (60 mm)***
Test	*15MM-023*	*303*	*5*	*12*
Test	*16MM-002*	*69*	*4*	*15*
Test	*16MM-002*	*285*	*4*	*11*
Test	*16MM-002*	*226*	*12*	*19*
Test	*16MM-002*	*165*	*8*	*15*
Reference	*DAC23A*	*116*	*4*	*13*
Reference	*DAC23A*	*114*	*5*	*12*
Reference	*DAC23A*	*251*	*5*	*12*
Reference	*DAC23A*	*239*	*4*	*12*
Reference	*DAC34A*	*92*	*5*	*12*
Reference	*DAC34A*	*238*	*4*	*12*
Reference	*DAC36A*	*205*	*5*	*14*
Reference	*DAC36A*	*252*	*5*	*13*
Reference	*DAC36A*	*215*	*4*	*12*

Reviewer's Comment # 11

The applicant provided the actuation number after priming for both the test and reference products in the spray pattern test, which confirms that the spray pattern was conducted at the B life stage of the product.

The applicant's response #11 is acceptable.

3.12 BE Deficiency #12

You used test lot # 16MM-003 for the spray pattern method validation. Please revalidate your spray pattern method using the reference lot with dose counter.

Applicant's Response #12

A supplemental method validation for the spray pattern analytical method (b) (4) *version 6 used in the in-vitro bioequivalence study was performed using a reference product lot with a dose counter (DAC23A). A copy of the validation report* (b) (4) *is located in section 3.2.P.5.3.*

Reviewer's Comment # 12

The applicant repeated the spray pattern method validation using an unexpired reference lot with a dose counter (DAC23A). The reviewer summarizes the applicant's method validation results based on the report and evaluates it as follows:

Precision

	Area, mm^2		Ovality	
	30 mm	60 mm	30 mm	60 mm
Mean	188.5	437.3	1.117	1.161
%RSD	5	8	3	3
Range	(b) (4)			

Intermediate Precision (By Analyst)

Analyst 1	Area, mm^2		Ovality	
	30 mm	60 mm	30 mm	60 mm
Mean	187.0	403.5	1.114	1.133
%RSD	3	8	3	5
Analyst 2	Area, mm^2		Ovality	
	30 mm	60 mm	30 mm	60 mm
Mean	182.7	391.8	1.104	1.189
%RSD	4	8	2	2
% Difference (Analyst 1 vs. Analyst 2)	2.3	2.9	0.9	4.8
Inter Analyst % RSD	3.4	7.5	2.6	4.2

Intermediate Precision (By Day)

Day 1	Area, mm^2		Ovality	
	30 mm	60 mm	30 mm	60 mm
Mean	184.1	397.2	1.112	1.151
%RSD	3.5	8.7	1.8	3.9
Day 2	Area, mm^2		Ovality	
	30 mm	60 mm	30 mm	60 mm
Mean	185.6	398.1	1.106	1.171
%RSD	3.7	7.0	3.4	4.6
% Difference (Day 1 vs. Day 2)	0.8	0.2	0.5	1.7
Inter day % RSD	3.4	7.5	2.6	4.2

Does Applicant's SOP include validation criteria?	☒ Yes ☐ No

Does the precision and ruggedness meet the acceptance criteria?	☒ Yes ☐ No
Was Reference product used in the method validation?	☒ Yes ☐ No

The spray pattern method validation is acceptable.

The applicant's response #10 is acceptable.

3.13 BE Deficiency #13

Please provide the actuation number after priming for both the test and reference products in the plume geometry test.

Applicant's Response #13

Plume geometry testing was performed per method (b) (4) *version 6.0 on labeled actuation #4 after priming. Table 25 highlights exceptions to the target plume geometry. These exceptions are explained in detail in Sections VI.A and VI.C of the report* (b) (4) *and Table A.10.3 in Appendix 10 to the report (provided in complete response amendment dated April 13, 2017, sequence 0028).*

Table 25. Plume Geometry Actuation Number for Repeated Measurements

PRODUCT	***LOT (Batch)***	***Inhaler***	***Labeled Actuation #***
Reference	*DAC23A*	*351*	*5*
Reference	*DAC23A*	*160*	*5*
Reference	*DAC36A*	*74*	*5*
Reference	*DAC36A*	*16*	*5*

Reviewer's Comment # 13

The applicant provided the actuation number after priming for both the test and reference products in the plume geometry test, which confirms that the plume geometry was conducted at the B life stage of the product.

The applicant's response #13 is acceptable.

3.14 BE Deficiency #14

Your method validation for plume geometry used the lots manufactured without dose counter. Please repeat your method validation using the reference lots with dose counter.

Applicant's Response #14

A supplemental method validation for the plume geometry analytical method (b) (4) (b) (4) *was performed using a reference product lot with a dose counter (DAC23A). A copy of the method is provided in section 3.2.P.5.2, and the validation report T* (b) (4) *is located in section 3.2.P.5.3.*

Reviewer's Comment # 14

The applicant repeated the method validation for plume geometry using an unexpired reference lot with a dose counter (DAC23A). The reviewer summarizes the applicant's method validation results based on the report and evaluates it as follows:

Precision

	Pume Angle (degrees)	Plume Width (mm)
Mean	19.2	23.9
%RSD	4	4
Range	(b) (4)	

Intermediate Precision (By Analyst)

Analyst 1	Pume Angle (degrees)	Plume Width (mm)
Mean	19.6	24.3
%RSD	2	3
Analyst 2	**Pume Angle (degrees)**	**Plume Width (mm)**
Mean	19.8	24.5
%RSD	2	1
% Difference (Analyst 1 vs Analyst 2)	1.0	0.8
Inter analyst % RSD	1.7	1.9

Intermediate Precision (By Day)

Day 1	Pume Angle (degrees)	Plume Width (mm)
Mean	19.5	24.1
%RSD	1.4	1.4
Day 2	**Pume Angle (degrees)**	**Plume Width (mm)**
Mean	19.9	24.7
%RSD	1.7	1.7
% Difference (Day 1 vs Day 2)	2.0	2.5
Inter Day % RSD	1.7	1.9

Does Applicant's SOP include validation criteria?	☒ Yes ☐ No
Does the precision and ruggedness meet the acceptance criteria?	☒ Yes ☐ No
Was Reference product used in the method validation?	☒ Yes ☐ No

The applicant did not provide robustness for various parameters. However, the reviewer considers the method validation for plume geometry acceptable for the following reasons: 1) the validation on the unexpired reference lot with dose counter met its acceptance criteria for both precision and intermediate precision; and 2) the validation with robustness for various parameters on the unexpired reference lot without dose counter was deemed adequate by DBI[14].

The applicant's response #14 is acceptable.

3.15 OSIS Status

The Office of Study Integrity and Surveillance (OSIS) inspection status for the clinical (Novum Pharmaceutical Research Services, Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712) and analytical (b) (4) (b) (4) sites of the fasting study # 10825320 and for the analytical site (b) (4) (b) (4) of the in vitro BE studies # TTP-CBJ-M0050 and TTP-CBJ-M0282 are complete and adequate.

The OSIS inspection status for the clinical sites (multiple sites) of the PD study # PRG-723 is considered complete at this time, but the application is considered inadequate pending the firm's response to OSIS's deficiency (please see Section 3.1 and 3.2 for details).

4 APPENDIX

4.1 Additional Attachments

4.1.1 The Consult to the Division of Therapeutic Performance (DTP)[15]

DTP provides the following response to DB-I's question (in bold):

The Division of Bioequivalence I (DB-I) seeks the expert opinion of the Division of Therapeutic Performance (DTP) in the Office of Generic Drugs (OGD) on whether the actuator optimization is significant enough to ask the firm to repeat pharmacokinetic (PK) and pharmacodynamic (PD) BE studies provided that in vitro BE studies (TTP-CBJ-0282) are eventually deemed adequate. Note: PK and PD BE studies were conducted on the T product without dose counter and R product without dose counter.

DTP's Response: *Based on the BE reviews of ANDA 203760, along with the data provided by the NDA sponsor in the Supplement #26 (which provided for integration of dose counter to PROAIR HFA, the RLD product), DTP provides the following comments regarding the T optimized actuator with dose counter in the ANDA 203760:*

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[14] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222

[15] GDRP, ANDA 203760; C 20049603 - DTP Consult Response - ANDA 203760 - RLD ProAir HFA - Dose Counter.doc (Completed 04/06/2018); http://panorama.fda.gov/document/preview?versionID=5ac7dbba0070b32e636a087b3cbea2b8&ID=5ac295a7001f571983afd8c44d081e60

1) *The T product without dose counter has been demonstrated to be equivalent to the R product without dose counter in terms of in vitro, in vivo PK and PD studies, that is, regardless the deficiencies cited in the BE reviews, the BE criteria were met. Therefore, upon integration of dose counter in the R product, the ANDA sponsor would not need to repeat the in vivo PK and PD BE studies, but repeat only the in vitro BE studies using T and R products with dose counter.*

2) *The R product without dose counter (used to conduct the in vivo PK and PD BE studies) has been demonstrated to perform equivalently to the R product with dose counter (currently in the market).*

3) *The T product with dose counter and optimized actuator has been demonstrated to be equivalent to the R product with dose counter in terms of in vitro performance (priming, SAC, APSD, spray pattern and plume geometry; note that the ANDA sponsor still needs to submit repriming data and information to resolve deficiencies). It appears that the design changes in the T optimized actuator with dose counter* (b) (4) (b) (4) *did not impact the performance of the T product with dose counter in comparison with the R product with dose counter currently in the market. Thus, considering that both R products with and without dose counter have been demonstrated to have similar in vitro performance (bullet #2 above), it can generally be expected that the T product with dose counter and optimized actuator would have similar performance as that of the R product without dose counter, this latter used in the in vivo PK and BE studies along with the T product without dose counter (bullet #1 above).*

4.1.2 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Repriming	dataset	repriming.SAS	Output	

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:	203760
APPLICANT:	Perrigo Pharmaceutical Company
DRUG PRODUCT:	Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiencies:

Deficiency Related to the Pharmacodynamic Study (PRG-723)

The Office of Study Integrity and Surveillance (OSIS) evaluated your responses to Bioequivalence deficiencies #1 and #2 and has the following comments:

OSIS acknowledges that Perrigo considers the scratch-off labels as secondary documentation. However, OSIS considers the information on the scratch-off labels as the primary documentation to confirm the treatment a subject received. While the master randomization code identifies the treatment a subject was intended to receive, we consider the scratch-off label as primary documentation that identifies the treatment a subject actually received.

The original scratch-off labels were blinded when photocopied, and thus the copies do not provide information regarding the treatment each subject received during the study. Because the original scratch-off labels were not maintained at the clinical site and the appearance of the copies of the copy of the scratch-off labels maintained at the clinical site versus the copies of the original scratch-off labels provided during the inspection are different, the original scratch-off labels cannot be used as documentation to confirm the treatment each subject received in each sequence. Thus, OSIS is still interested in any primary documentation that positively indicates what treatment each subject received that remained at the clinical site.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I

Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 *COMPLETED ASSIGNMENT FOR 203760 ID: 34966*

Reviewer: Zhang, Zhen **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Albuterol Sulfate Inhalation Aerosol 0.09 mg Base/Inhalation (SD34)

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
34966	12/29/2017	BIO	ANDA Amendment [1]	1	1
34966	12/29/2017	BIO	Consult Review (For Consults to Other Office) [1]	1	1
34966	12/29/2017	BIO	Consult Review (For Consults to Other Office) [1]	1	1
34966	12/29/2017	Parallel	Study Amendment [1]	1	1
34966	12/29/2017	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
34966	12/29/2017	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
34966	12/29/2017	Parallel	Pre-Screening [0.25]	0.25	0.25
				Total:	6.25

DIVISION OF BIOEQUIVALENCE REVIEW
FOR PRESSURIZED METERED DOSE INHALATION PRODUCTS

ANDA No.	203760		
Drug Product Name	Albuterol Sulfate Inhalation Aerosol		
Strength(s)	0.09 mg Base/Inhalation		
Applicant Name	Perrigo Pharmaceutical Company		
Applicant Address	515 Eastern Ave Allegan, MI, USA 49010		
US Contact Name and US Mailing Address	Matthew Popowski, Senior Regulatory Affairs Project Manager 3940 Quebec Ave North Minneapolis, MN, USA 55427 Matthew.Popowski@perrigo.com		
US Contact Telephone Number	763-732-0481		
US Contact Fax Number	763-732-0509		
Original Submission Date(s)	11/16/2011		
Submission Date(s) of Amendment(s) Under Review	07/03/2013 Major amendment to support the addition of an integrated dose counter to the metered dose inhaler (SD10) 04/24/2015 Post-CR meeting request (SD20) 07/01/2015 Response to complete response letter dated 04/13/2015 (SD22) 10/05/2015 Post-CR meeting request (SD24) **04/13/2017 Major amendment (SD29)**		
Primary Reviewer	Zhen Zhang, Ph.D.		
Secondary Reviewer	Vipra Kundoor, Ph.D.		
Tertiary Reviewer	Qing Liu, Ph.D.		
Study Number(s)	**10825302**		
Study Type(s)	**Fasting**		
Strength(s)	2 x 90 mcg actuations (total dose = 180 mcg)		
Clinical Site	Novum Pharmaceutical Research Services		
Clinical Site Address	Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712		
Analytical Site	(b) (4)		
Analytical Site Address			
Study Number(s)	**TTP-CBJ-M0050**	**TTP-CBJ-M00132**	**TTP-CBJ-0282**
Study Type(s)	**In vitro Bioequivalence Study**		
Strength(s)	90 mcg/ actuation		
***In Vitro* Test Site**	(b) (4)		
***In Vitro* Test Site Address**			
Study Number(s)	**PRG-723**		
Study Type(s)	**Pharmacodynamic Bioequivalence Study**		

Strength(s)	90 mcg/ actuation	
Clinical Site	**Site 1** University of Florida Asthma Research Lab **Site 2** Roy J and Lucille A Carver College of Medicine Department of Pediatrics, Allergy/Pulmonary **Site 3** Allergy & Asthma Diagnostic Treatment Center **Site 4** California Allergy & Asthma Medical Group **Site 5** Clinical Research Atlanta **Site 6** Spartanburg Medical Research **Site 7** AARA Research Center	
Clinical Site Address	**Site 1** 1600 SW Archer Road Gainesville, FL 32610-0486 **Site 2** The University of Iowa 200 Hawkins Drive Iowa City, Iowa 52242-1083 **Site 3** 2300 Centerville Road Tallahassee, FL 32308 **Site 4** 11645 Wilshire Blvd, Suite 1155 Los Angeles, CA 90025 **Site 5** 175 Country Club Drive, Suite 100A Stockbridge, GA 30281 **Site 6** 485 Simuel Road Spartanburg, SC 29303 **Site 7** 9900 N Central Expy, Suite 555 Dallas, TX 75231	
OSIS Status	**Backlog, Year 1 and Year 2**	**Post October 1, 2014 ANDAs**

	ANDAs ☐ Pending ☒ Complete	☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete
Formulation	☒ Adequate ☐ Inadequate	
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A	
Deficiency Classification	☒ Major ☐ Minor ☐ N/A (Review is Adequate)	
Overall Review Result	☐ Adequate ☒ Inadequate	
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO	

Bioequivalence study Tracking/Supporting Document #	Study/Test Type	Strength (e.g., xx µg/inhalation)	Review Result
1, 2, 6	Fasting BE Study	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6	Pharmacodynamic BE Study	0.09 mg Base/Inhalation	☐ Adequate ☒ Inadequate ☐ Not Applicable
1, 2, 6, 29	In vitro BE study # TTP-CBJ-M0050	0.09 mg Base/Inhalation	☒ Adequate ☐ Inadequate ☐ Not Applicable
1, 2, 6, 29	In vitro BE study # TTP-CBJ-M0282: Single Actuation Content through Container Life	0.09 mg Base/Inhalation	☐ Adequate ☒ Inadequate ☐ Not Applicable
1, 2, 6	In vitro BE study # TTP-CBJ-M0282: Priming and Repriming	0.09 mg Base/Inhalation	☐ Adequate ☒ Inadequate ☐ Not Applicable
1, 2, 6, 29	In vitro BE study # TTP-CBJ-M0282: Aerodynamic Particle Size Distribution by Cascade Impaction	0.09 mg Base/Inhalation	☐ Adequate ☒ Inadequate ☐ Not Applicable
1, 2, 6, 29	In vitro BE study # TTP-CBJ-M0282: Spray Pattern	0.09 mg Base/Inhalation	☐ Adequate ☒ Inadequate ☐ Not Applicable
1, 2, 6, 29	In vitro BE study # TTP-CBJ-M0282: Plume Geometry	0.09 mg Base/Inhalation	☐ Adequate ☒ Inadequate ☐ Not Applicable

1 EXECUTIVE SUMMARY

This is a review of the amendment dated 04/13/2017 of ANDA 203760, which is the *first generic drug application.*

In the original application, the firm submitted the results of the following studies comparing the test product (Perrigo Pharmaceutical Company's Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation) to the corresponding reference product (Teva Global's ProAir® HFA (albuterol sulfate) Inhalation Aerosol, 0.09 mg Base/Inhalation): one single-dose fasting pharmacokinetic bioequivalence (BE) study (#10825302), one clinical pharmacodynamics (PD) study (#PRG-723), and five in vitro BE studies (TTP-CBJ-M0050; single actuation content, aerodynamic particle size distribution by cascade impactor, spray pattern, plume geometry and priming/re-priming). In addition, the firm also submitted the particle size distribution by laser diffraction, which is not recommended per the Product-Specific BE Guidance of Albuterol Sulfate MDI[1]. All of the in vivo and in vitro BE studies were deemed inadequate due to multiple deficiencies by the Division of Bioequivalence I (DBI)[2]. Note that all the studies were conducted on the drug products without dose counter.

Due to the introduction of a dose counter on the reference product in 2013, the firm conducted additional in vitro BE studies (TTP-CBJ-M00132) comparing the test product with dose counter with the reference product with dose counter, and the firm submitted its study results in an amendment dated 07/03/2013. On 07/01/2015, the firm submitted its responses to the BE deficiencies identified in the original BE review. Both amendments were reviewed together in the first amendment BE review and deemed inadequate due to multiple deficiencies by DBI[3].

Per teleconference meeting between the Office of Generic Drugs (OGD) and Perrigo Pharmaceutical Company on 08/26/2011[4] documented in the first amendment review, "*Perrigo should compare the in vitro performance of the proposed generic MDI product with a dose counter and the RLD with a dose counter. 10 units from each of the three batches for the test and reference products should be tested for each of the following in vitro BE studies: Priming and repriming, single actuation content through container life, aerodynamic particle size distribution, spray pattern, and plume geometry. **This recommendation is conditioned upon the firm having previously established BE of the test MDI product without a dose counter and the RLD without a dose counter through in vitro equivalence, pharmacokinetic BE and pharmacodynamics BE studies**.*"

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[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf

[2] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)

[3] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222

[4] GDRP, ANDA 203760; Appendix (pages 120 – 132 of 136) in A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222

In the current amendment of 04/13/2017, the firm responded to the deficiencies identified in the first amendment BE review and submitted additional in vitro testing results (study # TTP-CBJ-0282) using test product with optimized actuator. The results from the fasting Study # 10825302 (no dose counter), PD Study # PRG-723 (no dose counter), in vitro BE study # TTP-CBJ-M0050 (no dose counter) and in vitro BE study # TTP-CBJ-0282 (new dose counter) are required for the determination of BE between the test and reference products (please see the table below), which are evaluated in the current review as follows:

	Test Batch #	**Reference Batch #**	**Dose counter?**	**Relevant to BE determination?**	**Review Results for the relevant BE studies**
Fasting Study # 10825302	08MM-050	AEA13B	No for both T and R	Yes	**Adequate**
PD Study # PRG-723	08MM-050	AEA13B	No for both T and R	Yes	**Inadequate**
In vitro BE study # TTP-CBJ-M0050	08MM-050, 08MM-034, 08MM-039	AEA13B, AEA12C, AEA14A	No for both T and R	Yes	**Adequate**
In vitro BE study # TTP-CBJ-M00132	12MM-020, 12MM-021, 12MM-022	DAA15A, DAA16A, DAA18A	Yes for both T and R	No	Not relevant
In vitro BE study # TTP-CBJ-0282	15MM-023, 16MM-002, 16MM-003	DAC23A, DAC34A, DAC36A	Yes for both T and R; T has optimized actuator	Yes	**Inadequate due to multiple deficiencies**

The Office of Study Integrity and Surveillance (OSIS) inspection status for the clinical (Novum Pharmaceutical Research Services, Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712) and analytical (b) (4) (b) (4) sites of the fasting study # 10825320 and for the analytical site (b) (4) of the in vitro BE studies # TTP-CBJ-M0050 and TTP-CBJ-M0282 are complete and adequate.

The OSIS inspection status for the clinical sites (multiple sites) of the PD study # PRG-723 is considered complete at this time, but the application is considered inadequate pending the firm's response to OSIS's deficiencies.

The application is **inadequate** due to deficiencies.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[5]

Test Product	Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation
Reference Standard[6]/Product	ProAir® HFA (albuterol sulfate) Inhalation Aerosol, 0.09 mg Base/Inhalation
Reference Listed Drug (RLD)[7] Product	ProAir® HFA (albuterol sulfate) Inhalation Aerosol, 0.09 mg Base/Inhalation
RLD Manufacturer	TEVA BRANDED PHARMACEUTICAL PRODUCTS R AND D INC
RLD NDA No.	021457
RLD Approval Date	Oct 29, 2004

3.2 PK/PD Information

Please refer to the original BE review [DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)].

4 THE FIRM'S RESPONSES TO BIOEQUIVALENCE DEFICIENCIES

4.1 BE Deficiency #1

You mentioned that few deviations occurred during the conduct of Single actuation content (SAC), aerodynamic particle size distribution (APSD) by cascade impaction and plume geometry (study # TTP-CBJ-M0132) studies comparing the test product with dose counter with reference product with dose counter and the data has been excluded from statistical analysis. You only provided the excluded data and did not provide the data with which it was replaced with. Therefore, please provide a table with original excluded values and replaced values.

Firm's Response #1

A full, detailed study report for study # TTP-CBJ-M0132 was submitted in our 01 July 2015 CRL response (sequence number 0020). This report contains all the in-vitro BE data collected in this study including the values excluded from the statistical analysis and replacement values.

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[5] Orange Book, Search Term: Albuterol; https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021457 last accessed 6/21/2017

[6] As identified in the Agency's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book").

[7] 21CFR314.94(a)(3): *An ANDA must refer to a listed drug. Ordinarily, that listed drug will be the drug product selected by the Agency as the reference standard for conducting bioequivalence testing.*

Data that was included in the statistical analysis is contained in Appendix 6, Tables A.6.1. through A.6.5. (p. 53 – 70) of the report TTP-CBJ-M0132 (provided in sequence 0020).

Data that was excluded from the statistical analysis is in Appendix 7, Tables A.7.1 through A.7.4. (p. 72 – 74) of the report TTP-CBJ-M0132 (provided in sequence 0020).

For ease of review, Tables 35, 36, 37, 38, 39, 40, and 41 (provided below) include both the original excluded values and the replacement values. Original excluded values were not included in statistical analysis, whereas the replacement values were included.

Original Excluded Values and Replacement Values for the Single Actuation Content (SAC) Test Specific details pertaining to deviations, investigations, and justifications that led to the replacement of values and the reanalysis or retest of any original or replacement canisters is provided in Section IV.C. (p. 9 – 11) of the study report (TTP-CBJ-M0132, provided in sequence 0020).

Reviewer's Comment #1

The firm provided requested information. Since the firm repeated its in vitro BE studies on the new test lots with optimized actuator in in vitro BE study # TTP-CBJ-M0282, the information of in vitro BE study # TTP-CBJ-M0132 will not be evaluated.

The firm's response #1 is acceptable.

4.2 BE Deficiency #2

The spray pattern testing (study # TTP-CBJ-M0132) comparing the test product with dose counter with the reference product with dose counter fails to meet the Population Bioequivalence (PBE) criteria for spray area at 3 cm distance. Please repeat this test.

Firm's Response #2

Perrigo has optimized the actuator design to more closely match the performance characteristics of the RLD (please see the IDC Development report included in Section 3.2.P.2). Therefore, not only has the spray pattern testing at 3 cm distance been repeated, but single actuation content (SAC), aerodynamic particle size distribution (APSD), spray pattern area at 6 cm and ovality at both 3 cm and 6 cm, and plume geometry have all been repeated in accordance with the albuterol sulfate metered dose inhalation bioequivalence guidance. The results of the repeated IVBE testing are reported in study # TTP-CBJ-0282 (provided in section 5.3.1.3), and the data demonstrates that the test product with dose counter meets all of the Population Bioequivalence (PBE) criteria when compared to the reference product with dose counter.

The evaluation of the valve performance, through the priming and repriming test, was performed previously in study # TTP-CBJ-M0132, and the valve has not changed with the

optimization to the actuator. Please reference study # TTP-CBJ-M0132 in sequence 0020 for the priming and repriming data.

Reviewer's Comment # 2

The firm optimized the actuator design and repeated all in vitro BE tests except for priming and repriming test on the new test lots with optimized actuator design, comparing them with the reference lots with dose counter. The firm will be asked to provide repriming study results using test product with optimized actuator (See Section 4.7.2.2). The new in vitro BE study # TTP-CBJ-M0282 is evaluated in Section 4.7.

The firm's response is acceptable. However, the new in vitro BE study # TTP-CBJ-M0282) is not acceptable due to deficiencies described in the current deficiency letter.

4.3 BE Deficiency #3

According to the following Office of Pharmaceutical Quality (OPQ) review comments, your test product batch # 08MM-050 is not considered as representative of the commercial batch:

"The exhibit batch that was manufactured (b) (4) is batch # 08MM-050. This batch is not considered a successful batch manufactured at commercial scale".

Therefore, the pharmacokinetic (PK) (study # 10825302) and pharmacodynamic (PD) (study # PRG-723) BE studies conducted using batch # 08MM-050 are not acceptable. In addition, the Office of Study Integrity and Surveillance (OSIS) recommends that the data from PD study (# PRG-723) are not acceptable for further Agency review (please refer to deficiencies based on the inspection findings by the OSIS). Therefore, please repeat the pharmacokinetic (PK) and pharmacodynamic (PD) BE studies.

Firm's Response #3

On October 05, 2015, Perrigo submitted a Post CRL Teleconference Meeting Request after receipt of the CRL dated September 21, 2015. In the Meeting Request letter, Perrigo asked for clarification regarding Bioequivalence deficiency #3, considering that Perrigo will demonstrate to OPQ that the clinical supplies from batch # 08MM-050 were representative of a successful commercial scale batch. The Agency provided written responses to the Meeting Request on December 11, 2015, and the following passage is a complete excerpt of the response as it relates to Bioequivalence deficiency #3 in the CRL.

> ***Question 13****: As described above in our question to product quality deficiency #1, Perrigo proposes to adopt the original process, as suggested by the Agency*
> (b) (4)

- *After reviewing Perrigo's data and response to Product Quality deficiency #1, if the Office of Pharmaceutical Quality determines that the intended clinical portion of batch 08MM-050 is representative of the commercial manufacturing process suggested by the Agency, would the Division of Bioequivalence consider the clinical supplies of batch 08MM-050 a successful product batch suitable for establishing bioequivalence?*

Additionally, Perrigo can provide clear evidence to mitigate the concerns that the Office of Study Integrity and Surveillance (OSIS) has regarding the PK and PD studies. Please see the comments and questions for bioequivalence deficiencies #5 and #6 below.

***DBI's Response**: If the Office of Pharmaceutical Quality determines that the test product batch # 08MM-050 is representative of the commercial batch, then the pharmacokinetic study (study # 10825302) conducted using this batch is acceptable from a bioequivalence perspective since there are no other pending bioequivalence deficiencies for the pharmacokinetic study. However, the pharmacodynamic study (study # PRG-723) will be still unacceptable pending the concerns of Office of Study Integrity and Surveillance (OSIS).*

Perrigo acknowledges DBI's response that if the Office of Pharmaceutical Quality determines that the test product batch # 08MM-050 is representative of the commercial batch, then the pharmacokinetic study (study # 10825302) conducted using this batch is acceptable from a bioequivalence perspective, but that the pharmacodynamic study will still be unacceptable pending the concerns of OSIS (Bioequivalence deficiency #5). Regarding the pharmacodynamics study, Perrigo had also asked for clarification on the OSIS concerns in the same Meeting Request, and the following passage is a complete excerpt of the response as it relates to Bioequivalence deficiency #5 in the CRL.

***Question 14**: There is no discrepancy that exists between the randomization schedule created on January 15, 2010 (which directed execution of the clinical packaging, subject enrollment, and statistical analysis), and the treatment assignments in the clinical study report. While it is true that the treatment identifiers in Protocol amendments #1 and #2 differ from the clinical study report treatment assignments, the protocol amendments were intended to serve as an example of the randomized treatment schematic but were never intended to be, nor could they ever have been used as, the official set of treatment identifiers for the study. Perrigo can provide definitive information and documents to demonstrate that the integrity between the development of the randomization labels on January 15, 2010 through clinical packaging, subject enrollment, and statistical analysis was not and thus has not been compromised. All original code blinding scratch off stickers remain intact and can be uncovered at the Agency's will and shall definitively correlate with each subjects' treatment assignments denoted in the analysis of the clinical study report and not the protocol amendments.*

- *This observation was not part of OSIS clinical study site audit observations. Therefore, we wish to obtain clarification from the Agency that a response to Bioequivalence deficiency 5.a in our CRL amendment would be reviewed by the Agency.*

***DBI's Response**: We would like to clarify that response to Bioequivalence deficiency 5.a would be reviewed by the Agency.*

***Question 15**: Regarding questions 5.b and 5.c, it is not clear to Perrigo if these are questions to be addressed in our CRL response or simply a notification of clinical study site audit observations cited by OSIS. Nonetheless, Perrigo would like to have the opportunity to provide clear evidence through supporting documentation that, although the original codeblinding scratch-off stickers were not present at the clinical site(s) at the time of the OSIS inspection, at no time did Perrigo have possession of the original code-blinding scratch-off stickers prior to database lock, prior to statistical analysis, nor prior to the ANDA submission and that the integrity of these original code-blinding scratch-off stickers was and remains intact. Further, should the Agency wish to verify the integrity of these labels and confirm that the treatment assignments correlate with the data provided in the clinical study report, they may do so at will or Perrigo proposes to fund this activity using a designated vendor of the Agency's choice. Perrigo can provide complete information to verify the events and facts. We submit to the Agency the following clarifying questions.*

- *Will the Agency give consideration to a CRL response to questions 5.a through 5.c?*
- *If so, will this response be reviewed by the Division of Bioequivalence and the Office of Study Integrity and Surveillance?*

***DBI's Response**: Please submit all the necessary additional documentation you wish to submit in support of your response to questions 5.a through 5.c and the response would be reviewed by DBI is consultation with OSIS.*

Per DBI's instruction, Perrigo has submitted all of the necessary additional documentation to support Perrigo's response to questions 5.a through 5.c so that the response will be reviewed by DBI in consultation with OSIS. Please reference the response to Bioequivalence deficiency 5.a, the response to Bioequivalence deficiency 5.b, and the response to Bioequivalence deficiency 5.c in this document.

Reviewer's Comment # 3

The acceptability of batch # 08MM-050 is the only deficiency related to the fasting study # 10825302[8]. Per quality review by the Office of Pharmaceutical Quality (OPQ), batch #

[8] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222

08MM-050 is now acceptable[9]. Therefore, the firm's fasting study # 10825302 is adequate.

The PD study # PRG-723 is still NOT acceptable per the current reviewer's evaluation in the comment #5 based on the OSIS's recommendation (Section 4.5).

4.4 BE Deficiency #4

Following the inspection of the analytical site (b) (4) between (b) (4) by the Office of Study Integrity and Surveillance (OSIS) for the current ANDA, Form FDA-483 was issued. Subsequently, the analytical site provided its responses to Form 483 and those responses were included in the final evaluation by the OSIS.

The DBI reviewed the above OSIS inspection report and found that the following objectionable findings by the OSIS at the analytical site could potentially compromise the integrity of the study of the current application:

Finding # 1: *Not all original data were reported following reanalysis or retest. Specifically, Protocol TTP-CBJ-M0050 required any reanalysis or retest data to be reported along with the original data in the study report. However, the following tests were repeated and the original data were not reported with the retest data:*

1) *Aerodynamic Particle Size Distribution (APSD) by Cascade Impactor (CI) for Study TTP-CBJ-M0050, Part 1, conducted from 4/13/2009 to 4/17/2009.*
2) *Spray Pattern for Study TTP-CBJ-M0050, Part 1, conducted from 3/31/2009 to 4/3/2009.*
3) *Plume Geometry for Study TTP-CBJ-M0050, Part 1, conducted from 4/1/2009 to 4/2/2009.*

Finding # 2: *Out-of-specification (OOS) results were not reported in the study report for Protocols TTP-CBJ-M0050 and TTP-CBJ-M0132. Examples include, but are not limited to, canisters retested/replaced and tests rejected due to assignable causes (e.g., instrument failure, sample collection, or processing errors). Specifically,*

1) *APSD by CI for Study TTP-CBJ-M0132,* (b) (4) (b) (4).
2) *APSD by CI for Study TTP-CBJ-M0132,* (b) (4) (b) (4).
3) *APSD by CI for Study TTP-CBJ-M0132,* (b) (4) (b) (4).
4) *Spray Pattern for Study TTP-CBJ-M0050 Part 1, Book 21:* (b) (4) (b) (4).
5) *Plume Geometry for Study TTP-CBJ-M0050,* (b) (4), (b) (4)

[9] GDRP, ANDA-203760-ORIG-1-AMEND-29; 203760CR03_06072017.doc; http://panorama.fda.gov/task/view?ID=58f51f8f0064d3a1bdcb2e46c2d58a61

(b) (4)

Based on the above findings, the firm should submit the following information:

a. Please submit all the in vitro BE study data including original and reanalysis or retest and a detailed study summary report which includes all the tests conducted and the details of the investigations for retesting or reanalysis for study # TTP-CBJ-M0132 (comparing the test product with dose counter with the reference product with dose counter). Please provide the sas data (original and retested/ reanalyzed) in xpt format. Please note that you do not need to submit such data for the in vitro study Study # TTP-CBJ-M0050, since this study was conducted with the product without dose counter and the product is not intended to be the final commercial use.

b. Please submit all the in vitro BE study data including original data obtained with original canisters and retested data obtained with replaced canisters and a detailed study summary report which includes justification for the replacement of canisters study # TTP-CBJ-M0132 (comparing the test product with dose counter with the reference product with dose counter). Please provide the SAS data (data from original and replaced canisters) in xpt format. Please note that you do not need to submit such data for the in vitro study Study # TTP-CBJ-M0050, since this study was conducted with the product without dose counter and the product is not intended to be the final commercial use.

Firm's Response #4

Response to a:

A full detailed study report for study # TTP-CBJ-M0132 was submitted in our response, to the first CRL (sequence 0020 dated July 01, 2015). This report contains all in-vitro BE study data collected in this study inclusive of:

- *All original data collected with original canisters and replacement canisters,*
- *All retest data from original or replacement canisters*
- *All reanalysis data from original or replacement canisters*
- *Details of all investigations conducted during the study*
- *Justifications for the replacement of canisters or exclusion of data from statistical assessment*

Specific details pertaining to deviations, investigations, and the reanalysis or retest of any original or replacement canisters is provided in Section III.B (p. 4 – 6) and also the 'Study Events and Deviations' section of the report for each respective test: Single Actuation Content in Section IV.C. (p. 9 – 11), APSD in Section V.C. (p. 15 – 16), Spray Pattern in Section VI.C. (p. 22), Plume Geometry in Section VII.C. (p. 24), and Prime/Re-prime in Section VIII.C. (p. 27).

Data that was included in the statistical analysis is contained in Appendix 6, Tables A.6.A. through A.6.5. (p. 53 – 70)

Data that was excluded from the statistical analysis is in Appendix 7, Tables A.7.1 through A.7.4. (p. 72 – 74)

Per the instructions provided in the second CRL dated September 21, 2015, data from Study #TTP-CBJ-M0050 has been excluded from this response as this study was conducted with the product without a dose counter and the product is not intended for commercial use.

Response to b:

SAS data in .xpt format are provided as part of this response (in section 5.3.1.3) for both the original data used for statistical assessment (included in report as Appendix 6) as well as the retested/ reanalyzed data excluded from this assessment (original replaced canisters, original testing, included in report as Appendix 7).

Per the instructions provided in the second CRL dated September 21, 2015, data from Study #TTP-CBJ-M0050 has been excluded from this response as this study was conducted with the product without a dose counter and the product is not intended for commercial use.

It should be noted that due to a change in the sump geometry in the actuator used with the test product, an in-vitro BE study (TTP-CBJ-M0282, provided in section 5.3.1.3) has been conducted and the data from this study along with the full detailed study report is submitted for review as part of this response.

Reviewer's Comment # 4

- The firm provided requested information for in vitro BE study # TTP-CBJ-M0132. Since the firm repeated its in vitro BE study on the new test lots with optimized actuator in in vitro BE study # TTP-CBJ-M0282, the information related to in vitro BE study # TTP-CBJ-M0132 is not evaluated.

- The repeated in vitro BE study # TTP-CBJ-M0282 was conducted at the analytical site of (b) (4) (b) (4) after this analytic site was inspected by OSIS for in vitro BE study # TTP-CBJ-M0050 and study # TTP-CBJ-MJ0132 with voluntary action indicated (VAI) outcome[10]. Since DBI considered OSIS findings for in vitro BE study # TTP-CBJ-M0050 and study # TTP-CBJ-MJ0132 of the current

[10] GDRP, ANDA-203760-ORIG-1-AMEND-21, 203760 Alb Per.pdf (Date Uploaded 8/4/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4afbdc6f530d73e2d4e3

application at [redacted] (b) (4) were systemic[11], the current reviewer evaluates if the OSIS findings for study # TTP-CBJ-M0050 and study # TTP-CBJ-0132 also affect study # TTP-CBJ-0282 as follows:

The systemic OSIS findings are related to the original data for reanalysis, retest, and out-of-specification data. For in vitro BE study # TTP-CBJ-M0282, the firm provided information for the original and repeated data for sample reanalysis and out-of-specification results as evaluated in Section 4.7.2.1.5, Section 4.7.2.3.5, Section 4.7.2.4.4, and Section 4.7.2.5.4. The provided information did not include 100% raw numerical data (Analyst's printouts) for all analytical runs (accepted and rejected) for SAC and APSD tests. However, per the meeting request review from DBI[12], "*since there are no current issues for which the 100% raw numerical data needs to be looked at, the firm will be informed that the Division of Bioequivalence I (DBI) will not request the 100% raw numerical data at this time, but suggests the firm to keep the raw data available should that be needed in the future review processes.*" The current reviewer considers that the same situation also applies to study # TTP-CBJ-M0282. Therefore, the firm will not be asked to provide the 100% raw numerical data at this time.

The reviewer considers OSIS status is complete and adequate for the in vitro analytical site [redacted] (b) (4), [redacted] (b) (4) of in vitro BE study # TTP-CBJ-M0282.

- Per teleconference meeting between the Office of Generic Drugs (OGD) and Perrigo Pharmaceutical Company on 08/26/2011[13], "*Perrigo should compare the in vitro performance of the proposed generic MDI product with a dose counter and the RLD with a dose counter. 10 units from each of the three batches for the test and reference products should be tested for each of the following in vitro BE studies: Priming and repriming, single actuation content through container life, aerodynamic particle size distribution, spray pattern, and plume geometry. This recommendation is conditioned upon the firm having previously established BE of the test MDI product without a dose counter and the RLD without a dose counter through in vitro equivalence, pharmacokinetic BE and pharmacodynamics BE studies.*" Therefore, the results from the fasting Study # 10825302, pharmacodynamic Study # PRG-723, in vitro BE study # TTP-CBJ-M0050 and in vitro BE study # TTP-CBJ-0282 are required for the determination of BE between the test and reference products. As a result, even though the complete information for study # TTP-CBJ-M0050 was not requested by DBI, the current reviewer consider the in vitro BE study # TTP-CBJ-M0050 adequate for the following reasons:

[11] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222
[12] GDRP, ANDA-203760-GI-1-MEETING-20; 203760NA04242015 Post CR meeting response.doc (Date Uploaded 5/6/2015); http://panorama fda.gov/task/view?ID=5540186f00eabe8c3c77569ae2ba81e4
[13] GDRP, ANDA 203760; Appendix (pages 120 – 132 of 136) in A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015);
http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222

1) The batch # 08MM-050 used in the in vitro BE study # TTP-CBJ-M0050 is acceptable per OPQ's evaluation[9].

2) The only deficiency related to in vitro BE study # TTP-CBJ-M0050 from the original and subsequent amendment BE reviews is related to OSIS findings[14, 15]. Based on the information from relevant in vitro BE study # TTP-CBJ-M0132 and study # TTP-CBJ-M0282, the reviewer has no concern about the data integrity of in vitro BE study # TTP-CBJ-M0050 at this time.

The firm's response #4 is acceptable.

4.5 BE Deficiency #5

Following the inspection of the clinical sites (University of Florida, Gainesville; University of Iowa, Iowa City; California Allergy & Asthma Medical Group, Los Angeles) between 11/03/2014 – 01/09/2015 by the Office of Study Integrity and Surveillance (OSIS) for the current ANDA, Form FDA-483 was issued. Subsequently, the clinical sites provided its responses to Form 483 and those responses were included in the final evaluation by the OSIS.

The DBI reviewed the above OSIS inspection reports and found that the pharmacodynamic study (PRG-723) conducted is not acceptable based on the following OSIS findings. Please repeat the pharmacodynamic study.

a. There was a discrepancy in the assigned treatments between the randomization schedule in the study report and the protocol.
b. The original code-blinding scratch-off stickers were not maintained at the clinical site prior to subject enrollment and until the FDA inspection and their integrity cannot be assured.
c. Without the code-blinding scratch-off stickers, we are unable to confirm which treatments subjects received.

Firm's Response #5

Perrigo is confident that the integrity and credibility of the data from pharmacodynamics(PD) study PRG-723 remains intact and the information provided below demonstrates that there was no opportunity to manipulate the data to alter the outcome of the study. Perrigo followed ICH E6 (R2): Guideline For Good Clinical Practice, 2015 recommendations throughout the study. Provided below are general comments followed by detailed responses that will clarify OSIS observations.

[14] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)[14]
[15] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222

Perrigo would like to clarify the FDA inspector's use of the term "blinding code" in the Form 483 observation for the University of Iowa audit. Perrigo's interpretation of the "blinding code," is the study randomization code, which, in Perrigo's documentation, is referred to as the "Randomization Code" for the study. While the Randomization Code and the scratch-off sticker labels both contain information that can be used to determine which drug a specific subject received, their respective purposes are quite different.

- *The purpose of the Randomization Code is to enable the statistical analysis to be performed once the database has been locked.*
- *The code-blinding scratch-off stickers are intended only to provide a mechanism for rapid Investigational Medicinal Product (IMP) identification by study investigators in the event of an individual subject's medical emergency and not to be used in any way to support the statistical analysis as treatment identifiers.*

These scratch-off stickers remained at each of the clinical sites throughout the treatment portion of the clinical trial, fulfilling their sole purpose. The scratch-off stickers, in accordance with guidance in ICH E6(R2), were then sent to, and retained by the CRO (Attachment A). Perrigo would also like to note that none of the scratch-off stickers were unblinded during the study.

Finally, regarding the OSIS inspections of the three clinical study sites:

- *at University of Iowa site, Perrigo provided the original blinded scratch-off stickers to the inspector within 24 hours of notification.*
- *at the subsequent University of Florida site inspection, an affidavit (Attachment B) signed by the Principal Investigator was sufficient to address the inspector's question regarding the handling of the scratch-off stickers at the site, and no Form 483 was issued.*
- *at the final audit, at the California Allergy & Asthma Medical Group, OSIS completed their inspection and issued a Form 483 that included the absence of the scratch off labels on-site as an observation.*

Individual deficiencies itemized in Bioequivalence deficiency #5 are addressed below.

a. There was a discrepancy in the assigned treatments between the randomization schedule in the study report and the protocol.

The discrepancy noted in item 5.a was a transcription error, whereby the "Treatment Identifiers (the letter and the treatment)" from Attachment C were incorrectly written into the synopsis and body of the protocol, as well as the statistical analysis plan for efficacy analysis.

This occurred in the generation of Amendment #1 of the clinical protocol and had no impact on the preparation of the Investigational Medicinal Product (IMP), the integrity of the study, or the statistical analysis. The Randomization Code generated was properly used in the production of the blinded packaged IMP, and was the same schedule used

following database lock for assignment of IMP to treatment groups for statistical analysis.

Although there appears to be a discrepancy in the assigned treatments between the randomization schedule in the study report and the protocol, as explained below, that apparent discrepancy is due to a transcription error at the time of writing Protocol Amendment # 1 and was not material to the conduct of the study. Perrigo demonstrates, below, that the assigned treatments and randomization schedule used during the study were generated and approved prior to packaging the IMP. The randomization schedule was subsequently used to direct the packaging of the IMP which was completed prior to Protocol Amendment #1 being written.

To illustrate how and when the assigned treatments and randomization schedule were created, approved, and then used, the following information are provided:

- *copies of documentation from the vendor that created the randomization code (for the packaging service organization) confirming the assigned treatments listed in the randomization schedule in the final clinical study report were derived from the Treatment Sequence documents (Attachment C, Attachment D, and Attachment E). Attachment C, D, and E documents were used in the packaging of IMP that was then shipped to the clinical sites and either used by subjects throughout the study or randomly selected as "retention samples" at each clinical site as per 21 CFR 320.38.*
- *the timeline of events up to and including the finalization of Protocol Amendment # 1 which supports Perrigo's response.*

Attachment C contains the approved label forms for the treatment sequences used in Perrigo's PD study. Two important pieces of information for FDA review are:

- *the approval date of each of the sequences is January 11, 2010, and*
- *Treatment Identifiers A, B, C, D, and E are listed along with their associated treatments (see also Table 42 below).*

Table 42

Treatment identifier "A"	***Treatment identifier "B"***	***Treatment identifier "C"***	***Treatment identifier "D"***	***Treatment identifier "E"***
Placebo	*90mcg Test*	*90mcg RLD*	*180mcg Test*	*180mcg RLD*

Attachment D and Attachment E contain two randomization schedules for the two clinical packaging operations that took place over the course of the study. Both documents use the same Treatment identifiers from Attachment C (approved label forms) (and Table 42) in the placement of the individual products that were used in Perrigo's study.

Table 43 provides the acronyms used in Attachments D and E to delineate which treatments are designated to a given product (placebo, Test product, or Reference Listed Drug (RLD)).

Table 43

Treatment acronym	***Product used in study***
PBO	*Placebo*
ALB	*Albuterol HFA (i.e. Test product)*
PRO	*ProAir (i.e. Reference drug)*

Table 44 links the treatment identifiers in Attachment C to Attachments D and E and demonstrates that the treatment identifiers as originally approved on January 11, 2010 were used for both clinical packaging operations.

Table 44

Treatment identifier	***Attachment C description***	***Attachment D description***	***Attachment E description***
A	*Placebo / Placebo*	*PBO / PBO*	*PBO / PBO*
B	*Albuterol HFA / Placebo*	*ALB / PBO*	*ALB / PBO*
C	*ProAir / Placebo*	*PRO / PBO*	*PRO / PBO*
D	*Albuterol HFA / Albuterol HFA*	*ALB / ALB*	*ALB / ALB*
E	*ProAir / ProAir*	*PRO / PRO*	*PRO / PRO*

Table 45 below demonstrates that the assigned treatments from Attachment D and Attachment E match those of the randomization schedule of the study report. For ease of review, the first 5 subjects randomized from each packaging operation are listed below. The randomization schedule in the study report and Attachments D and E, as described above, match each other, demonstrating that the depiction of lettered treatment identifiers described in Protocol Amendment # 1 were an inadvertent transcription error and had no influence on the conduct of the trial or assignment of treatment to the subjects.

Table 45

Randomized subject #	***Randomization schedule in Attachment D***	***Randomization schedule in study report***
(b) (6)	*D-E-C-A-B*	*D-E-C-A-B*
	C-D-B-E-A	*C-D-B-E-A*
	B-C-A-D-E	*B-C-A-D-E*
	E-A-D-B-C	*E-A-D-B-C*
	A-B-E-C-D	*A-B-E-C-D*
	Randomization schedule in Attachment E	***Randomization schedule in study report***
	D-E-C-A-B	*D-E-C-A-B*

(b) (6)	*C-D-B-E-A*	*C-D-B-E-A*
	A-B-E-C-D	*A-B-E-C-D*
	B-C-A-D-E	*B-C-A-D-E*
	E-A-D-B-C	*E-A-D-B-C*

It is clear from Tables 42 - 45 that Attachment C controlled the placement of the treatment identifiers in Attachments D and E. This demonstrates that the treatment identifiers were approved and in use 2 months prior to Protocol Amendment # 1 being effective. This demonstrates that the Treatment identifiers listed in Protocol Amendment # 1 were transcribed in error from the original approval documents (Attachment C) and that Protocol Amendment # 1 Treatment identifiers are not, in fact, Treatment identifiers of the study.

Table 46 depicts the timeline of events up to and including the finalization of Protocol Amendment # 1 which supports Perrigo's response.

Table 46

Action	*Date*	*Responsible Vendor*
Original protocol finalized	*11/30/2009*	*Sponsor*
Treatment identifiers finalized	*1/11/2010*	*Sponsor*
Randomization schedule created	*1/15/2010*	*Randomization creator*
Randomization schedule approved	*1/15/2010*	*Randomization approver*
Clinical packaging #1 complete	*2/4/2010*	*Clinical packager*
First subject enrolled	*2/24/2010*	*Clinical site*
First randomized subject used drug	*3/3/2010*	*Clinical site*
Protocol amendment # 1 finalized	*3/5/2010*	*Sponsor*

Finally, to definitively confirm that the correct Treatment Identifiers were used in the packaging of IMP, subject enrollment, and statistical analysis, FDA could: 1) scratch off the labels from the retention samples currently in its possession from the FDA inspection of Dr. Leslie Hendeles, principal clinical investigator at the University of Florida, and 2) be willing to receive the retention samples, with scratch-off sticker labels, from the other two clinical sites previously inspected (which were not collected). These retention samples were maintained at the other two clinical sites from prior to subject enrollment through the present day. Upon removing the blinding coating from scratch-off labels and comparing that information to Attachment D and/or E, the FDA will confirm that there is no discrepancy between the assigned treatments in Attachment C, Attachment D, and Attachment E and the clinical study report which ultimately confirms that the integrity of the study is intact.

b. The original code-blinding scratch-off stickers were not maintained at the clinical site prior to subject enrollment and until the FDA inspection and their integrity cannot be assured.

We acknowledge that the original code-blinding scratch-off stickers were not maintained at the clinical sites following the treatment portion of the clinical trial. However, Perrigo respectfully challenges the assertion that the integrity of those same labels, as well as maintenance of the blind cannot be assured. It was the CROs Standard Operating Procedure to follow ICH guideline E6(R2) (Attachment A), which calls for the unblinding information to be returned to the Sponsor upon completion of subject dosing and follow-up. As the memo states, the scratch off sticker labels were not returned to Perrigo, rather, they were held at the CROs facility (independent of Perrigo) in the study's Trial Master File. Only after the ANDA was submitted to FDA, was the study's Trial Master File (which contained the scratch-off sticker labels) sent to Perrigo for retention. This in no way compromises the integrity of the trial or the resultant statistical outputs.

Also, as per Perrigo's response to Bioequivalence deficiency #5a above, we demonstrated that Attachment C, Attachment D, and Attachment E, not Protocol Amendment # 1, are the documents that contained the official assigned treatments and the randomization schedule that directed the packaging of IMP and therefore used by specific subjects. Packaging of IMP occurred on two different occasions due to the expiry of the initial lot of RLD during the study. Table 47 below outlines the subject numbers that were incorporated in each clinical packaging of IMP.

Table 47

Packaging operation number	*Range of subject numbers packaged*
1	(b) (6)
2	

Table 48 outlines the IMP shipped to each clinical site and which packaging operation the IMP came from.

Table 48 IMP received at each site, and the source (packaging operation) for the IMP

Range of IMP received	***Packaging operation number***	***Site number***	***Principal Investigator***
(b) (6)	*1*	*1*	*Leslie Hendeles*
	1	*2*	*Richard Ahrens*
	1	*Not shipped **	*Not shipped**
	2	*1*	*Leslie Hendeles*
	2	*2*	*Richard Ahrens*
	2	*6*	*Charles Fogarty*
	2	*4*	*Sheldon Spector*
	2	*5*	*Nathan Segall*
	2	*7*	*William Lumry*
	2	*4*	*Sheldon Spector*
	2	*3*	*Ronald Saff*
	2	*Not shipped*	*Not shipped*

** IMP not shipped to clinic sites due to expiration of the initial lot of RLD*

Together, Tables 47 and 48 demonstrate that ALL IMP used by subjects as well as selected as retention samples came from the two packaging operations. In addition, the randomization schedule documents in Attachment D and Attachment E from Perrigo's response to Bioequivalence deficiency #5a demonstrate that the "Treatment Identifiers" in these two packaging operations are derived from Attachment C and all of these documents match the randomized subjects' assigned treatments in the clinical study report. Still further, the clinical sites selected their "retention samples" per FDA requirements, 21 CFR 320.63 and these retained samples, with the scratch-off sticker labels, remained at each clinical site from the time each clinic site received their shipments through the inspections carried out by FDA. It should be noted that, for the clinical sites inspected by FDA, the black scratch off labels for the retention samples selected were on site during the FDA inspections such that FDA could have scratched off the black part of the label to verify that the Treatment Identifiers matched that of the other subjects. By scratching off the labels and cross checking that this information matched, FDA could have verified the integrity of the study.

Based on the above, FDA would be able to discern that the retention samples do have integrity as they were packaged using Attachment C's approved labeling with treatment identifiers, Attachment D and Attachment E's randomization schedule, were packaged along with the IMP used by subjects, and remained at the clinic sites from receipt through the present day. Based on this demonstrated integrity of the retention samples, it can be concluded that the scratch off labels for IMP used by subjects, also have integrity as they came from the same clinical packaging operations (and therefore Attachments C, D, and E) as the retention samples.

Based on the demonstration of facts in Bioequivalence deficiency responses #5a and #5b, FDA should have no doubts about the integrity of the scratch off labels for either the IMP used by subjects during the study or that of the retention samples selected by the clinic sites. However, if FDA does still have questions about the integrity of the scratch-off labels for the IMP used by subjects in the study, FDA should be willing to receive the scratch off labels from the clinic sites that were inspected and unblind them to verify 100% agreement with the treatment identifiers (Attachment C) and randomization schedules (Attachments D and E) submitted in response to Bioequivalence deficiency #5a, as well as the clinical study report submitted in the original ANDA.

c. Without the code-blinding scratch-off stickers, we are unable to confirm which treatments subjects received.

Please refer to Perrigo's response to Bioequivalence deficiency response #5b above, which specifically addresses the handling of the code-blinding scratch-off stickers, and how the treatments subjects received may be verified.

Reviewer's Comment # 5

The OSIS reviewer provides the following evaluation of the firm's response[16]:

During the inspection conducted at the University of Florida, Asthma Research Lab, Gainesville, FL the ORA Investigator unblinded the code-breaking scratch-off labels that were returned to the site by the study monitor. Upon breaking the blind, the ORA investigator determined that the scratch-off labels on the study dispensation records were not consistent with the treatment assignments in the study protocol. However, the treatment assignments on the unblinded scratch-off labels matched those in the study report.

While it is possible that protocol amendment #1 contained a transcription error, the scratch-off labels that were removed from each clinical site and later returned identifies the treatment actually administered to each subject. Because the unblinded scratch-off labels were removed from the clinical site by the study monitor, the data integrity is significantly compromised and cannot be recovered.

During the inspection conducted at the University of Florida, Asthma Research Lab, Gainesville, FL the ORA Investigator determined that the study monitor collected the original study drug dispensation records containing the blinded code-breaking scratch-off labels from the site. The site only maintained photocopies of the records containing the blinded code-breaking scratch-off labels. The ORA investigator contacted the sponsor during the inspection and requested the study drug dispensation records containing the blinded code-breaking scratch-off stickers be returned to the site. The original study drug dispensation records containing the blinded code-breaking scratch-off labels were also removed from the site by the study monitor at the other two inspected sites (University of Iowa Hospitals & Clinic and California Allergy & Asthma Medical Group). Because the unblinded scratch-off labels were removed from the clinical site by the study monitor, the data integrity is significantly compromised.

The investigator at the University of Iowa Hospital & Clinic provided the ORA Investigator with copies of the original blinded scratch-off labels (that were returned to the site during the inspection) and the copies maintained at the clinical site (made before collection by the study monitor). However, the obscure part of the copies of the scratch-off labels returned to the site did not show a description stating "Drug Information Inside in Case of Emergency Scratch off the Surface of Blinded Area", while it was visible on the copy of the copies maintained at the site. Thus, OSIS is unable to ensure that there were no changes or substitutions made to the scratch-off labels while they were outside the control of the clinical site.

The OSIS reviewer recommends the following deficiency language to be communicated to the firm[17]:

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[16] GDRP, ANDA-203760-ORIG-1-AMEND-29; OSIS memo_A203760.pdf (6/20/2017); http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881315798

[17] V:\DIVISION\BIO\BIO1\Email Reference\A203760 Albuterol MDI\ RE Comment on Respond to Consult Request on ANDA-203760-ORIG-1-AMEND-29 (ref# 15736893).msg

Comment #1:

During the inspection conducted at the University of Florida, Asthma Research Lab, Gainesville, FL the ORA Investigator determined that the study monitor collected the original study drug dispensation records containing the blinded code-breaking scratch-off labels from the site. The site only maintained photocopies of the records containing the blinded code-breaking scratch-off labels. The original study drug dispensation records containing the blinded code-breaking scratch-off labels were also removed from the site by the study monitor at the other two inspected sites (University of Iowa Hospitals & Clinic and California Allergy & Asthma Medical Group). Please provide a description of the documentation that was provided to the sites prior to the conduct of the study and remained at the clinical site until after the sites were inspected that demonstrates the intended treatment for each subject.

Comment #2:

During the inspection at the University of Iowa Hospital & Clinic, the ORA Investigator was provided with copies of the original blinded scratch-off labels (returned to the site during the inspection) and the copies maintained at the clinical site (made before the scratch-off labels were collected by the study monitor). However, the obscure part of the copies of the scratch-off labels returned to the site did not show a description stating "Drug Information Inside in Case of Emergency Scratch off the Surface of Blinded Area", while it was visible on the copy of the copies maintained at the site. Please provide an explanation for this discrepancy.

The BE reviewer agrees with the OSIS's evaluation and considers the firm's response is not acceptable. The firm will be asked to provide further information regarding OSIS's concerns.

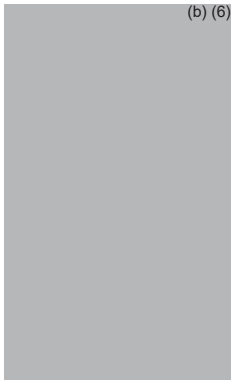
4.6 BE Deficiency #6

Please be informed that the case report forms for all the subjects in the pharmacodynamic study (PRG-723) were not retained based on the following OSIS finding for the California Allergy & Asthma Medical Group:

Investigational records were not retained. Specifically, three randomized subjects' and ten screen-failed subjects' bioequivalence study Source Records, Informed Consent Forms and Case Report Form Files were missing and could not be located during the inspection. The following subjects' entire study records were missing:

Screening Number / Randomization Number

(b) (6)



Firm's Response #6

Perrigo acknowledges the above comment. The attached statistical report (Attachment F, provided in section 5.3.4.1) demonstrates that, when the 3 randomized subjects referenced above, as well as the entire clinical site's data, are removed from the study analysis, the 90% CI is still contained entirely between 67-150%.

Reviewer's Comment # 6

Since the PD study is not acceptable per the evaluation in Section 4.5, the recalculation is not performed at this time by the reviewer.

4.7 *In Vitro* Equivalence Testing

4.7.1 Information Common to All in Vitro Equivalence Tests

4.7.1.1 Formulation

The test formulation in the current amendment dated 04/13/2017[18] is the same as that in the original submission, which has been deemed acceptable by DBI[19].

[18] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Page 6 of 407); Submitted 04/13/2017
[19] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)

4.7.1.2 Batch Information – For Repeated in vitro Equivalence Study

TEST								
Study Type	**Lot No.**	**Potency (%w/w)*****	**Lot Size (# of Canisaters)**		**Manufacture Date for Test Expiration Date for Reference**	**API lot(s)**	**Critical Excipient (e.g. surfactant, co-solvent, etc) Lot (s)**	**Container Closure System (e.g. Valve, Actuator[20], Canister) lot(s)**
			Theoretical	**Actual**				
In-Vitro* equivalence studies *	15MM-023	(b) (4)						
	16MM-002							
	16MM-003							

[20] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Page 7 of 407); Submitted 4/13/2017
[21] GlobalSubmit Review, ANDA 203760; Module 3.2.R Executed Production Records – Batch 15MM-023 (Page 24 of 120); Submitted 4/13/2017
Note: 8688540 was crossed out. There was a handwriting note cannot be read.
[22] GlobalSubmit Review, ANDA 203760; Module 3.2.R Executed Production Records – Batch 15MM-023 (Page 24 of 120); Submitted 4/13/2017
[23] GlobalSubmit Review, ANDA 203760; Module 3.2.R Executed Production Records – Batch 15MM-023 (Page 54 of 120); Submitted 4/13/2017
[24] GlobalSubmit Review, ANDA 203760; Module 3.2.R Executed Production Records – Batch 16MM-002 (Page 24 of 168); Submitted 4/13/2017
[25] GlobalSubmit Review, ANDA 203760; Module 3.2.R Executed Production Records – Batch 16MM-002 (Page 54 of 168); Submitted 4/13/2017
[26] GlobalSubmit Review, ANDA 203760; Module 3.2.R Executed Production Records – Batch 16MM-002 (Page 24 of 150); Submitted 4/13/2017

							(b) (4)		
REFERENCE									
In-Vitro* equivalence studies *	DAC23A	(b) (4)			03/2018				
	DAC34A				05/2018				
	DAC36A				05/2018				

* If recommended
** Include lot numbers from each *in vitro* test
*** Data obtained from Certificate of Analysis

Are the in vitro BE studies performed on samples from each of 3 or more batches of the test product and 3 or more batches of the reference product, with no fewer than 10 units from each batch?	☒ Yes ☐ No
For solution, is the test product manufactured from different batches of the same device (container/closure system) components?	☐ Yes ☐ No ☒ N/A
For suspension, is the test product manufactured from 3 different batches of the drug substance, different batches of critical excipients, and different batches of the same device (container/closure) components?	☐ Yes ☒ No ☐ N/A
Is the reference product expired at the time of studies?	☐ Yes ☒ No
Is same BE batch used in the *in vitro* and *in vivo* studies?	☐ Yes ☒ No ☐ N/A Lot # 08MM-050 was used for in vivo PK and PD study
Are the BE batches used in the *in vitro* and *in vivo* studies at least 1/3 of the production batch size?	☐ Yes ☒ No
Is difference of the potency values between Test and RLD within 5%?	☒ Yes ☐ No

Comments on Batch Information:

[27] GlobalSubmit Review, ANDA 203760; Module 3.2.R Executed Production Records – Batch 16MM-002 (Page 54 of 150); Submitted 4/13/2017

- 15MM-023, 16MM-002 and 16MM-003 are canister lot numbers[28]. The firm did not specify if the Certificate of Analyses (COAs) for three test product lots were from the aforementioned three canister lots with optimized actuator lots. The firm will be asked to provide this information.

- The firm did not provide COAs for the reference lots # DAC23A, DAC34A and DAC36A. The firm will be asked to provide this information.

- The in vivo PK and PD studies were both conducted on the test lot # 08MM-050 without dose counter, whose theoretical lot (b) (4) (b) (4) (b) (4) (b) (4). However, the test lot size for in vivo PK and PD studies is still considered acceptable (b) (4) Note: In the original quality review[29], the Office of Pharmaceutical Quality (OPQ) determined that *the test lot # 08MM-050 is not considered a successful batch manufactured at commercial scale*. The test lot # 08MM-050 is later deemed acceptable by OPQ after the firm provided further supporting documents[9].

- The drug product is suspension[30]. Per the current Product-Specific Guidance (PSG) for Albuterol Sulfate Inhalation, *the three batches of T product should be manufactured from, at minimum, three different batches of drug substance(s), excipient(s), and container/closure system*. The three new test lots (15MM-023, 16MM-002 and 16MM-003) in the current application were manufactured from the same lot of (b) (4). OPQ determined that the same lot of (b) (4) for the three new test lots (15MM-023, 16MM-002 and 16MM-003) is not a concern[9, 31].

Batch information is NOT acceptable.

[28] GlobalSubmit Review, ANDA 203760; Module 3.2.P.2 Optimization of Integrated Dose Counter TTP-CBJ-M0099 (Page 20 of 27); Submitted 4/13/2017
[29] GDRP, ANDA-203760-ORIG-1-AMED-21; 203760CR02_09182015.doc (Date Uploaded 9/18/2015); http://panorama.fda.gov/task/view?ID=559a876800fe4b85542609c7457a2e92
[30] GlobalSubmit Review, ANDA 203760; Module 2.3. Quality Overall Summary; Submitted 7/3/2017
[31] V:\DIVISION\BIO\BIO1\Email Reference\ANDA 203760 Albuterol MDI\RE Questions on exhibit batches for ANDA 203760 msg

4.7.1.3 Device Comparability

	TEST	REFERENCE
Canister		
Canister Supplier	(b) (4)	
Material		
Canister Volume	14 mL	14 mL
Valve		
Valve Supplier	(b) (4)	
Metering Volume		
Gasket and Seat Elastomers (material)		
Metering Chamber and Body (material)		
Core and Core Extension/Base		
Actuator		
Actuator Supplier	(b) (4)	
Actuator Orifice Diameter (μm)	0.17 to 0.21 mm	0.19 to 0.21 mm
Dose Counter	☒ Yes ☐ No	☒ Yes ☐ No
Number of Doses	200	200
Cleaning instructions (similar cleaning instruction and frequency? *)	Yes	Yes

*With alternate device design, the firm should provide justification and evidence to support that there will be no confusion with respect to cleaning.

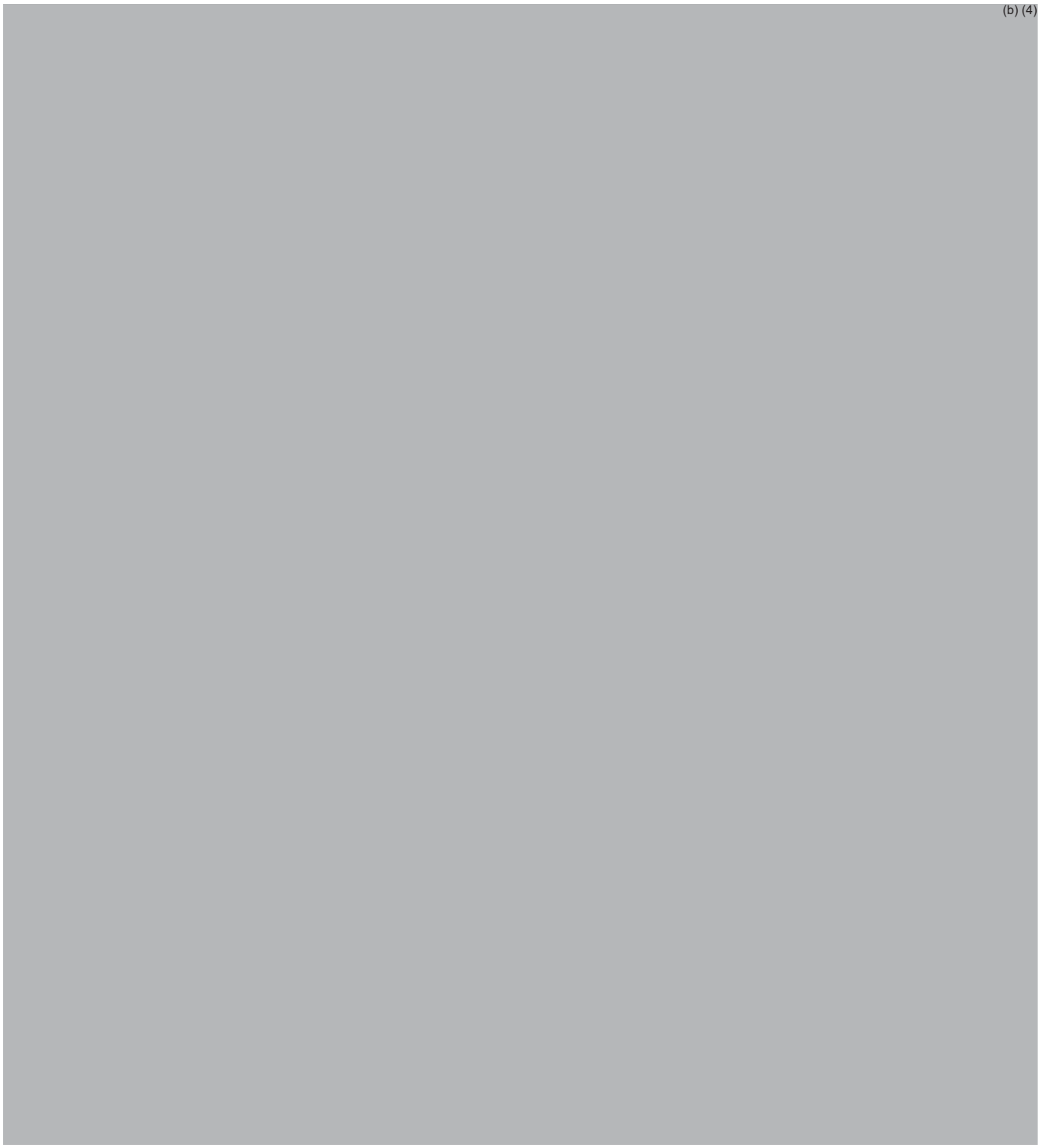
Has the firm submitted CC on its demo device to OGD?	☐ Yes ☒ No
If yes, please indicate the CC number and OGD evaluation result.	N/A
Is the device in the current application the same as that proposed in its CC?	☐ Yes ☐ No ☒ N/A
If no, please evaluate device suitability as per (1) external design (components, size, shape); (2) external operating principles	N/A

Reviewer's Comments

The original test device with dose counter was deemed comparable by DBI[32]. However, due to the failure to meet the Population Bioequivalence (PBE) criteria for spray area at 3 cm distance for the original test device with dose counter, the firm optimized the actuator design to more closely match the performance characteristics of the reference product[33].

[32] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)
[33] GlobalSubmit Review, ANDA 203760; Module 3.2.P.2 Optimization of Integrated Dose Counter TTP-CBJ-M0099; Submitted 04/13/2017

(b) (4)



Based on the information above, the reviewer considers the new test device is comparable to the reference device.

4.7.1.4 Actuation Methods

Which tests (if any) used MANUAL actuation?	Aerodynamic Particle Size Distribution by Cascade Impaction (APSD by CI), Single Actuation Content Uniformity Through Life (DTL)

<table>
<tr><td>If some tests used manual actuation(s), describe methods used to avoid Test to RLD bias in dose release.</td><td colspan="4">• Study design -T and R product inhalers were tested in pairs on same day using same test equipment.
• For each test to be performed, the inhalers were analyzed in a random order.
• On any given day, an analyst tested an equal number of T and R products across each product lot.
• To blind the study all data analyses (i.e., post-actuation evaluations of the collected data) were performed by another analyst</td></tr>
<tr><td>Which tests (if any) used AUTOMATED actuation?</td><td colspan="4">Spray Pattern, Plume Geometry</td></tr>
<tr><td rowspan="6">What were the parameters of automated actuation? (units)*</td><td></td><td></td><td>Test</td><td>RS</td></tr>
<tr><td rowspan="5">Velocity Driven Actuator [e.g., Vereo Actuator SFMDx, SPRAYTEC with SPRAYER module, etc.]</td><td>Velocity (mm/s)</td><td rowspan="5">(b) (4)</td><td rowspan="5"></td></tr>
<tr><td>Initial Hold Time (msec)</td></tr>
<tr><td>Hold Time (msec)</td></tr>
<tr><td>Final Delay (msec)</td></tr>
<tr><td>Acceleration (mm/s^2)</td></tr>
<tr><td>Are the actuation parameters the same for the test and reference products? If No, please comment</td><td colspan="4">☒ Yes ☐ No</td></tr>
</table>

Comments on Actuation Methods:

Manual actuation was used for conducting Aerodynamic Particle Size Distribution by Cascade Impaction (APSD by CI) and Single Actuation Content Uniformity Through Life (SAC). The following actions were taken to avoid test to reference bias in dose release[34]:

The individual canister and dose counter actuator for each inhaler designated for testing and reserve from the T and R products were individually numbered to assure the same canister and actuator (canister and actuator combination hereafter referred to as 'inhaler') remained paired throughout the testing. For each inhaler all available information was recorded, including point of batch (i.e.: beginning (B), middle (M), or end (E)), assigned inhaler number, imprinted canister number, lot, and whether the product is T or R. Once all information was recorded, ten inhalers from each lot were allocated for the individual in-vitro BE testing (e.g., single actuation content, spray pattern, etc.) and placed into separate containers labeled with test to be performed. Reserve inhalers were held in separate containers segregated by lot number.

For each test to be performed, the inhalers were analyzed in a random order.

[34] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 7-8 of 407); Submitted 04/13/2017

On any given day, an analyst tested an equal number of T and R products across each product lot……

To blind the study all data analyses (i.e., post-actuation evaluations of the collected data) were performed by another analyst who did not perform any of the testing, and who only had access to the blinded sample number so the identity of the sample data (i.e., test or reference) was not known to that person prior to data work up. This assured the samples remained blinded and did not introduce a bias during the analysis, effectively assuring the study integrity.

The firm's actuation methods are acceptable.

4.7.2 Individual *In Vitro*-Test Reviews

4.7.2.1 Single Actuation Content through Container Life

4.7.2.1.1 Study Information

Study No.	TTP-CBJ-M0282
Study Site Name and address	(b) (4)
Principal Investigator	
Study Dates	
SOP No.	
SOP Effective Date	
SOP Title	Determination of Dose Content Uniformity, Shot Weight, and Number of Actuations from an Albuterol Sulfate HF A Inhalation Aerosol Product.
Test Method Description	(b) (4)
Testing Equipment Used (e.g., name, model, etc)	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	
Analytical Method Description	
Analytical Equipment Used (e.g., name, model, etc.)	

Is testing performed as per RLD labeling?	☒ Yes ☐ No
Are data measured at beginning, middle & end lifestages?	☒ Yes ☐ No

Is testing a single actuation per determination?	☒ Yes ☐ No
If yes, what is the actuation number tested?	#s 1, 100 and 200 after priming (3 primings)
Are the same actuation numbers tested for the test and RLD products?	☒ Yes ☐ No
Is testing conducted using USP <601> Apparatus A at a flow rate of 28.3 L/min (±5%)? If no, please comment.	☒ Yes[35] ☐ No
Are studies performed on products stored per the RLD labeling?	☐ Yes ☐ No ☒ Not Provided

Comments on Study Methods:

- Per RLD labeling[36], the drug product should be stored "*between 15° and 25°C (59° and 77°F). Contents under pressure. Do not puncture or incinerate. Protect from freezing temperatures and prolonged exposure to direct sunlight. Exposure to temperatures above 120°F may cause bursting*". However, the firm did not indicate how the test and reference products were stored before the study. The firm will be asked to provide this information.

- The HPLC assay to analyze SAC samples follows SOP (b) (4) (b) (4) (b) (4) However, the firm only provided SOP (b) (4) The firm will be asked to provide SOP (b) (4)

The study method is not acceptable.

4.7.2.1.2 Analytical Method Validation for HPLC

[35] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Page 10 of 407); Submitted 04/13/2017
[36] Drugs@FDA; Search Term: 021457; https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021457s026lbl.pdf ; last accessed 6/12/2017
[37] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Page 10 of 407); Submitted 04/13/2017
[38] GlobalSubmit Review, ANDA 203760; Module 3.2.P.5.2 Analytical Procedure (b) (4) (b) (4)

Information Requested	(b) (4)
Analytical method validation report location	
Project Number	
Analyte	
Internal Standard (IS)	
Method description (Current Version)	
Selectivity or Specificity	
Limit of Quantitation	
Detection Limit	
Linearity Range (ng, mcg/mL)	
Linearity (R^2)	
Accuracy (% recovery at the high and low concentrations)	
Precision- Repeatability	
Precision - Intermediate Precision (Dose Content Uniformity)	
Benchtop Stability (working std solution)	
Stock Solution Stability (days)	
Robustness (HPLC)	
Robustness (Dose Content)	

SOP for analytical method validation submitted?	☒ Yes[39, 40] ☐ No
Was the pre-study validation of the analytical method used for the *in vitro* single actuation content and priming/repriming studies acceptable?	☒ Yes ☐ No

Comments on Method Validation for HPLC:

The same method validation for HPLC has been deemed adequate by DBI[41].

4.7.2.1.3 Calibration of Manual and/or Automated MDI Actuation (For Single Actuation Content)

(b) (4)

[redacted]

Intermediate Precision (By Analyst) – Single Actuation Content

[39] GlobalSubmit Review, ANDA 203760; Module 3.2.P.5.3. Validation of Analytical Procedure (b) (4) [redacted]; Submitted 12/16/2011

[40] GlobalSubmit Review, ANDA 203760; Module 3.2.P.5.3. Validation of Analytical Procedure (b) (4) [redacted] 1; Submitted 12/16/2011

[41] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222

Comments on Method Validation:

Per the previous BE review, the same method validation using the reference lots # AEA13B and AEF75A has been deemed adequate by DBI[42]. However, the reference lots # AEA13B and AEF75A were manufactured without dose counter[43], which cannot be applied to the current SAC study on the drug product with dose counter. Therefore, the firm will be asked to repeat its calibration of manual MDI actuation for SAC using the reference product with dose counter.

The method validation is inadequate.

[42] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222
[43] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)

4.7.2.1.4 Results Summary – Single Actuation Content

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE														
		Spray #	Mean				Variability (%CV)					Mean Ratio (T/R)	
			Drug Mass (mg)		% label claim		Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
BEG	Test	1	89.37	89.20	99.30	99.11	4.75	6.20	6.42	3.48	6.37	1 01	1.00
	Ref	1	88.90	88.86	98.80	98.76	3.69	1.77	2.81	0.22	2.88		
MID	Test	100	90.30	90.23	100.30	100.22	5.15	3.69	3.09	1.06	4.01	0 99	0.99
	Ref	100	90.97	90.92	101.00	100.95	3.53	2.91	2.12	1.89	3.29		
END	Test	200	92.50	92.46	102.80	102.75	4.21	3.07	2.20	0.50	3.18	1 01	1.02
	Ref	200	91.13	91.07	101.33	101.26	4.04	2.47	3.14	2.41	3.86		

Table 11. Summary of PBE Results Calculated by the Firm, N=60 (Test=30 and RLD=30)

Variable	Geometric Mean, Drug Mass, mcg		Geometric Mean Ratio	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
SAC Through Life	91	90	1.00	0.0482	0.0352	1.3670

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant- scaled	-0.019798	-0.018905	Pass

Was the Reference-scaled analysis used to determine PBE?	☐ **YES** ☒ **NO**
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ **YES** ☐ **NO** ☒ **N/A**
Was the Constant-scaled analysis used to determine PBE?	☒ **YES** ☐ **NO**
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ **YES** ☐ **NO** ☐ **N/A**

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

Table 12. Summary of PBE Results Calculated by the Reviewer, N=60 (Test=30 and RLD=30)

Variable	Mean (Original Scale)		Mean Ratio (Original Scale), %	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
SAC	90.62	90.28	100.38	0.048	0.035	1.381

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant-scaled	-0.0198	-0.0189	Pass

Was the Reference-scaled analysis used to determine PBE?	☐ **YES** ☒ **NO**
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ **YES** ☐ **NO** ☒ **N/A**
Was the Constant-scaled analysis used to determine PBE?	☒ **YES** ☐ **NO**

If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ **YES** ☐ **NO** ☐ **N/A**

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

Are data expressed as actual amount and % of label claim? If No, please comment		☒ Yes ☐ No
Is the geo-mean of the test product (% of label claim) within 95-105%?*	**Beginning**	☒ Yes (97.01%) ☐ No ☐ N/A
	Middle	☒ Yes (99.02%) ☐ No ☐ N/A
	End	☒ Yes (100.11%) ☐ No ☐ N/A
Are the PBE results acceptable? If No, please comment		☒ Yes ☐ No

* Reviewer's calculation based on the firm's data

4.7.2.1.5 Overall Comments

- The firm did not provide SAC data in .xpt file for the study # TTP-CBJ-M0282. The reviewer used the dataset provided in the firm's study report[44]. The reviewer's PBE calculation matches the firm's PBE calculation.

- The firm submitted 20% of the HPLC chromatograms from the SAC testing[45]. The firm's HPLC chromatograms are acceptable.

- The firm did not provide 100% raw numerical data (Analyst's printouts) for all analytical runs (accepted and rejected) conducted during the HPLC sample analysis of the SAC study. Per the meeting request review from DBI[46], "*since there are no current issues for which the 100% raw numerical data needs to be looked at, the firm will be informed that the Division of Bioequivalence I (DBI) will not request the 100% raw numerical data at this time, but suggests the firm to keep the raw data available should that be needed in the future review processes.*" The reviewer considers the same situation also applies to study # TTP-CBJ-M0282. Therefore, the firm will not be asked to provide the 100% raw numerical data at this time.

- The firm stated the following study events and deviations[47]:

  1) At beginning of life stage, inhaler # 319 (R) was replaced with inhaler #54 (R) from the same lot (DAC34A) due to the leak of the collection tube for inhaler #319.

[44] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 51-56 of 407); Submitted 04/13/2017
[45] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 11, 92-367 of 407); Submitted 04/13/2017
[46] GDRP, ANDA-203760-GI-1-MEETING-20; 203760NA04242015 Post CR meeting response.doc (Date Uploaded 5/6/2015); http://panorama.fda.gov/task/view?ID=5540186f00eabe8c3c77569ae2ba81e4
[47] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 11-12 of 407); Submitted 04/13/2017

2) In the middle of life stage, inhaler #17 (T) and its paired inhaler 97 (R) was retested due to the leak of the dose tube for inhaler #17 (R). Actuation #104 was used after the delivery of three repriming actuations.

The reviewer considers these study events and deviations will not affect the final BE analysis.

The SAC testing is **inadequate**.

4.7.2.2 Priming & Re-priming

- Due to the failure to meet the PBE criteria for spray area at 3 cm distance for the original test device with dose counter, the firm optimized the actuator design to more closely match the performance characteristics of the reference product[48]. (b) (4)

(b) (4)

The firm did not conducted new priming and re-priming tests on the new test product with optimized actuator for the following reasons[49]:

- Prime and re-prime test is a measure of metering valve performance consistency and its interaction with the formulation. Equivalency to the RLD has been demonstrated in two prior IVBE studies (TTP-CBJ-M0050 and TTP-CBJ-M0132).

(b) (4)

- Since SAC test at the beginning (#1 actuation) is the same as the priming test, the reviewer evaluates the priming using the SAC data from in vitro BE study # TTP-CBJ-M00282 in the current amendment dated 04/13/2017. The test product passes the PBE analysis on priming test as follows:

PRIMING							
Number of actuations used to **prime** each product = 3							
Actuation number used for testing each product = 1							
	Spray #	**Mean**		**Variability (%CV)**			**Mean Ratio (T/R)**
		Drug Mass	**% label**	Within Lot (n=10)	Between	Total	

[48] GlobalSubmit Review, ANDA 203760; Module 3.2.P.2 Optimization of Integrated Dose Counter TTP-CBJ-M0099; Submitted 04/13/2017

[49] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Page 5 of 407); Submitted 04/13/2017

		(mg)		claim					Lot (n=3)	(n=30)		
		Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	1	89.37	89.20	99.30	99.11	4.75	6.20	6.42	3.48	6.37	1.01	1.00
Ref	1	88.90	88.86	98.80	98.76	3.69	1.77	2.81	0.22	2.88		

Summary of PBE Results Calculated by the Reviewer, N=60 (Test=30 and RLD=30)

Variable	Mean (Original Scale)		Mean Ratio (Original Scale) %	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
Prime	89.20	88.86	100.37	0.063	0.029	2.183

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant-scaled	-0.0179	-0.0154	Pass

Was the Reference-scaled analysis used to determine PBE?	☐ **YES** ☒ **NO**
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ **YES** ☐ **NO** ☒ **N/A**
Was the Constant-scaled analysis used to determine PBE?	☒ **YES** ☐ **NO**
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ **YES** ☐ **NO** ☐ **N/A**

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

PRIMING	**Is the geo-mean of the test product (% of label claim) within 95-105%?**	☒ Yes (99.11%) ☐ No ☐ N/A
Are the PBE results acceptable for priming test? If No, please comment		☒ Yes ☐ No ☐ N/A

- Per the response to the firm's Question # 10 in the meeting between Perrigo and OGD on August 26, 2011[50], OGD stated that '*currently, OGD are not aware of any data showing that any changes in an actuator will not affect the MDI priming and repriming. Thus the sponsor is recommended to provide priming and repriming data. The sponsor may use the single actuation content data at the beginning lifestage (i.e., the first actuation immediately following the specified number of priming actuations in the RLD labeling for the priming study*'. Therefore, the firm's priming result based on the SAC study is acceptable. However, the firm will be asked to conduct repriming study on three test lots with optimized actuator comparing them with three reference lots.

The priming and repriming test is **inadequate**.

[50] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222

4.7.2.3 Aerodynamic Particle Size Distribution (APSD) by Cascade Impaction

4.7.2.3.1 Study Information

Study No.	TTP-CBJ-M0282 SA
Study Site Name and address	(b) (4)
Principal Investigator	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	(b) (4) Impactor
Testing Method Description [Eg. Test batches, B and E Lifestages, Number of canisters/batch, CI set up, flow rate determination, plate/cup coating, priming regimen, actuation method, filter, extraction diluent]	(b) (4) Assessment of the Aerodynamic Particle Size Distribution from an Albuterol Sulfate HF A Inhalation Aerosol by Cascade Impaction
Testing Equipment Used [e.g., name, model, etc, equipment includes but not limited to USP Apparatus (b) (4) (b) (4)	(b) (4)
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	
Analytical Method Description	
Analytical Equipment Used (e.g., name, model, etc)	

Is testing conducted as per RLD labeling?	☒ Yes ☐ No
Is the actuation procedure (priming, waste shot, auto/ manual actuation, actuator and actuation #) defined and provided?	☒ Yes ☐ No If No, comment:
Is the APSD test performed at both B and E lifestages?	☒ Yes ☐ No
Is the APSD determination of each unit performed with a minimum number of inhalations justified by the sensitivity of the validated assay?	☒ Yes ☐ No Actuation #1 after priming for B life stage Actuation #192 after priming for E life stage
If >1 actuation, what is the # of actuations used?	N/A
Have the drug deposition data on individual sites, including mouthpiece adapter, induction port, each stage of the impactor and the filter been submitted?	☒ Yes ☐ No If No, comment:
Are the ISM, FPM, and Mass Balance defined?	☒ Yes ☐ No If No, comment:
Is the calculation method for MMAD and GSD defined? (Eg. CITDAS for Compendial)	☐ Compendial ☐ Non-Compendial ☒unknown

How are the above parameters defined?	(b) (4)

Comments on Study Methods:

- The APSD study was conducted per SOP (b) (4) However, the firm did not provide this SOP. The firm will be asked to provide this information.
- The HPLC assay to analyze APSD samples follows SOP (b) (4). However, the firm only provided SOP (b) (4). The firm will be asked to provide SOP (b) (4)
- The firm did not provide the calculation method for MMAD and GSD. The firm will be asked to provide this information.

The study method is **inadequate**.

4.7.2.3.2 Analytical Method Validation for HPLC

All attributes identical to information in Section 4.7.2.1.2 except for the following details for accuracy, intermediate precision, stability, and robustness.

(b) (4)

[51] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282; Submitted 04/13/2017

[52] GlobalSubmit Review, ANDA 203760; Module 3.2.P.5.2 Analytical Procedure (b) (4) Submitted 12/16/2011

SOP for analytical method validation submitted?	☒ Yes[53, 54] ☐ No
Is the method sufficiently sensitive?	☒ Yes ☐ No
Is the pre-study validation of the analytical method used for APSD acceptable?	☒ Yes ☐ No

Comments on the Pre-Study HPLC Method Validation:

[53] GlobalSubmit Review, ANDA 203760; Module 3.2.P.5.3. Validation of Analytical Procedure (b) (4) Submitted 12/16/2011
[54] GlobalSubmit Review, ANDA 203760; Module 3.2.P.5.3. Validation of Analytical Procedure (b) (4) Submitted 12/16/2011

The same method validation for HPLC has been deemed adequate by DBI[55].

4.7.2.3.3 Method Validation for Cascade Impaction

Comments on the Cascade Impaction Method Validation

Per the previous BE review, the same method validation using the reference lots # AEA13B and AEF75A has been deemed adequate by DBI[56]. However, the reference lots # AEA13B and AEF75A were manufactured without dose counter[57], which cannot be applied to the current APSD study on the drug product with dose counter. Therefore, the firm will be asked to repeat its method validation for cascade impaction using the reference product with dose counter.

[55] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222
[56] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222
[57] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)

4.7.2.3.4 Results Summary – Aerodynamic Particle Size Distribution by Cascade Impaction – Reviewer Calculated

(b) (4)

Table 15. Average (Arithmetic mean) Aerodynamic Particle Size Distribution Data

(b) (4)

(b) (4)

Currently, the FDA relies on a weight of evidence, including PBE analysis of certain key parameters which characterize the particle size distribution, together with a statistical approach for comparing the distribution profiles, namely modified Chi-square ratio method, [61] to determine

[61] A Stability Analysis of a Modified Version of the Chi-Square Ratio Statistic: Implications for Equivalence Testing of Aerodynamic Particel Size Distribution; Benjamin Weber, Guenther Hochhaus, Wallace Adams, Robert Lionberger, Bing Li, Yi Tsong, and Sau L. Lee; The AAPS Journal, Published online: 25 Sept. 2012.

(b) (4)

Was the Reference-scaled analysis used to determine PBE?	☐ **YES** ☒ **NO**
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ **YES** ☐ **NO** ☒ **N/A**
Was the Constant-scaled analysis used to determine PBE?	☒ **YES** ☐ **NO**
If reference-scaled analysis was used, is the estimate of Sigma R<T0	☒ **YES** ☐ **NO** ☐ **N/A**

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

(b) (4)

(b) (4)

Was the Reference-scaled analysis used to determine PBE?	☐ **YES** ☒ **NO**
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ **YES** ☐ **NO** ☒ **N/A**
Was the Constant-scaled analysis used to determine PBE?	☒ **YES** ☐ **NO**
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ **YES** ☐ **NO** ☐ **N/A**

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of

(b) (4)

AERODYNAMIC PARTICLE SIZE DISTRIBUTION BY CASCADE IMPACTION		
REVIEW OF TESTING METHODS		
Is the testing method for CI test validated?		No
STUDY RESULTS:		
Is drug deposition reported in mass units?		Yes
Is the mass balance data reported?		Yes
Results	**Does Impactor -Sized Mass data pass PBE?**	Yes
	Does APSD analysis pass modified chi-square ratio test?	Yes
	Are the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) supportive?*	Yes
Mass Balance	**Is the mean range for Total B between**	Yes

AERODYNAMIC PARTICLE SIZE DISTRIBUTION BY CASCADE IMPACTION		
	85-115% of the label claim? (on a per actuation basis)	
	Is PBE acceptable?	**Acceptable**
If not, why?		N/A

*Reviewer should perform PBE analysis to determine if parameters are supportive
Note: Please add comments for any irregularities.

4.7.2.3.5 Overall Comments

- The APSD results meet the following acceptance criteria:

  I. Pass PBE on SAC

  II. Pass PBE on Impactor Size Mass [redacted] (b) (4)).

  III. Pass [redacted] (b) (4) Chi-square ratio method analysis on Impactor Sized Mass stages [redacted] (b) (4)).

- The firm did not provide 100% raw numerical data (Analyst's printouts) for all analytical runs (accepted and rejected) conducted during the HPLC sample analysis of the APSD study. Per the meeting request review from DBI[62], "*since there are no current issues for which the 100% raw numerical data needs to be looked at, the firm will be informed that the Division of Bioequivalence I (DBI) will not request the 100% raw numerical data at this time, but suggests the firm to keep the raw data available should that be needed in the future review processes.*" The reviewer considers the same situation also applies to the in vitro BE study # TTP-CBJ-M0282. Therefore, the firm will not be asked to provide the 100% raw numerical data at this time.

- The mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) all pass the PBE analysis, and thus are considered as supportive. The PBE analysis is as follows:

Summary of PBE on MMAD Results Calculated by the Reviewer, N=60 (Test=30 and

[redacted] (b) (4)

[62] GDRP, ANDA-203760-GI-1-MEETING-20; 203760NA04242015 Post CR meeting response.doc (Date Uploaded 5/6/2015); http://panorama.fda.gov/task/view?ID=5540186f00eabe8c3c77569ae2ba81e4

(b) (4)

Was the Reference-scaled analysis used to determine PBE?	☐ YES ☒ NO
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ YES ☐ NO ☒ N/A
Was the Constant-scaled analysis used to determine PBE?	☒ YES ☐ NO
If reference-scaled analysis was used, is the estimate of Sigma R<T0	☒ YES ☐ NO ☐ N/A

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

Summary of PBE on GSD Results Calculated by the Reviewer, N=60 (Test=30 and RLD=30)

(b) (4)

Was the Reference-scaled analysis used to determine PBE?	☐ YES ☒ NO
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ YES ☐ NO ☒ N/A
Was the Constant-scaled analysis used to determine PBE?	☒ YES ☐ NO
If reference-scaled analysis was used, is the estimate of Sigma R<T0	☒ YES ☐ NO ☐ N/A

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

Summary of PBE on FPM Results Calculated by the Reviewer, N=60 (Test=30 and

(b) (4)

Was the Reference-scaled analysis used to determine PBE?	☐ YES ☒ NO
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ YES ☐ NO ☒ N/A
Was the Constant-scaled analysis used to determine PBE?	☒ YES ☐ NO

If reference-scaled analysis was used, is the estimate of Sigma R<T0	☒ **YES** ☐ **NO** ☐ **N/A**

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

- The firm stated the following study events and deviations[63]:

  1) Failed to record the weight of the inhaler # 250 prior to priming;

  2) At beginning of life stage, inhaler # 53 (R) was replaced with inhaler #345 (R) from the same lot (DAC23A) due to uncoated NGI stage cup 7 at the analysis of inhaler 345 (R);

  3) At the end of life stage, APSD samples for inhaler 236 were repeated due to atypical chromatogram. The firm stated that atypical chromatogram was caused by the overfill of APSD samples for inhaler 236. The firm provided both original and repeated chromatograms[64].

  4) APSD samples for Inhaler #4 were reinjected due to the autosampler injector malfunction. The firm submitted the sample peak areas for the original sample injections and repeated sample injections for inhaler #4.

  5) At the end of life stage, one mass balance (b) (4) for inhaler # 250 (R) was out of range of (b) (4) of label claim. Inhaler #250 (R) was retested with its paired inhaler # 129 (T) and the repeated values (b) (4) for inhaler #250(R) and (b) (4) for inhaler # 129 (T)) were within the range of (b) (4) of label claim. The repeated values were used for the final BE analysis.

- The firm did not provide APSD data in .xpt file for the study # TTP-CBJ-M0282. The reviewer used the dataset provided in the firm's study report[65].

  The reviewer considers the aforementioned study events and deviations will not affect the final BE analysis.

The APSD test is **inadequate**.

[63] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 16-17 of 407); Submitted 04/13/2017
[64] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Page 86 of 407); Submitted 04/13/2017
[65] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 57-60 of 407); Submitted 04/13/2017

4.7.2.4 Spray Pattern

4.7.2.4.1 Study Information

Study No.	TTP-CBJ-M0282 SA
Study Site Name and Address	(b) (4)
Principal Investigator	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	(b) (4) Actuation Stations (b) (4) Imaging System
Testing Method Description	(b) (4) Evaluation of Spray Pattern for an Albuterol Sulfate HF A Inhalation Aerosol
Testing Equipment Used (e.g., name, model, etc)	(b) (4)
Image Analysis Apparatus Used (i.e., automated = Laser Imaging; or manual = TLC)	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	

Is testing conducted as per RLD labeling?	☒ Yes ☐ No
Is testing a single actuation per determination at beginning lifestage of the product?	☒ Yes ☐ No
If yes, what is the actuation number tested?	Not provided
Is the actuation number same for T and R? (If not, justification needs to be provided)	☐ Yes ☐ No ☒ Unknown
Data measured at two distances from reference product actuator mouthpiece?	☒ Yes ☐ No
If yes, distances 3 – 7 cm from reference product actuator mouthpiece?	Yes, 3 cm and 6 cm
If yes, distances separated by 3 cm or more?	Yes, 3 cm
If yes, is it feasible to accurately capture the spray pattern image at these 2 distances (e.g. Is it too far from the orifice? Is it too close to the mouthpiece)?	☒ Yes ☐ No (please comment below)
Is the distance between the actuator orifice and point of spray pattern measurement same for T and R?	☒ Yes (5.5 cm and 8.5 cm) ☐ No
Does the firm submit representative spray pattern images?	☒ Yes[66] (20%) ☐ No
Does the firm submit intensity profile of the spray?	Yes

[66] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 368 - 392); Submitted 04/13/2017

Did the firm perform manual or automated analysis?	automated analysis
Was the analysis based upon the *true shape* (to include a high proportion, e.g., 95% of the total pattern) of the Spray Pattern?	☒ Yes ☐ No
Do Dmax and Dmin pass through the center of gravity (COG) or center of mass (COM) as appropriate in extent to the parameter of the true shape?	☒ Yes ☐ No

Comments on Study Methods:

- The spray pattern test was conducted at a distance of 3 cm and 6 cm from the actuator mouthpiece. The firm also mentioned that the distance from the spray orifice to the actuator mouthpiece was (b) (4) for both test and reference products. Therefore, based on the information provided by the firm, the spray pattern testing was conducted at a distance of (b) (4) from the actuator orifice for both test and reference products.

- The firm stated that *the spray pattern test was performed at the B life stage of canister life*[67]. However, the firm did not specify the actual number of actuation after priming for both T and R. Therefore, the firm will be asked to provide this information.

- The firm stated in the summary table above that (b) (4) Actuation Stations and (b) (4) Imaging System were used for the spray pattern test. However, the firm only submitted (b) (4) and (b) (4) The firm will be asked to provide the aforementioned SOPs in the updated versions.

The study method is **inadequate**.

4.7.2.4.2 Validation Summary Table for Spray Pattern

Precision – Spray Pattern

	Area, mm^2		Ovality	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean	173.9	362.0	1.117	1.142
%RSD	4%	5%	4%	3%
Range	(b) (4)			

Intermediate Precision (By Day) - Spray Pattern

[67] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Page 18); Submitted 04/13/2017

Day 1	Area, mm^2		Ovality	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	173.9	362.0	1.117	1.142
%RSD (Precision / Repeatability)	4%	5%	4%	3%
Day 2	**Area, mm^2**		**Ovality**	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	175.9	347.0	1.090	1.165
%RSD (Precision / Repeatability)	3%	4%	2%	4%
% Difference (Day 1 vs. Day 2)	1%	4%	2%	2%
Interday %RSD**	4%	5%	3%	4%

**RSD of all Day 1 and Day 2 data

Intermediate Precision (By Analyst) - Spray Pattern

Analyst 1	Area, mm^2		Ovality	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	173.9	362.0	1.117	1.142
%RSD	4%	5%	4%	3%
Analyst 2	**Area, mm^2**		**Ovality**	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	175.9	347.0	1.090	1.165
%RSD	3%	4%	2%	4%
% Difference (Analyst 1 vs. Analyst 2)	1%	4%	2%	2%
Interday %RSD	4%	5%	3%	4%

Robustness: End of Stroke Force on Spray Pattern Measured 30 mm and 60 mm from the End of Actuator Mouthpiece

	Ovality 30 mm			Area (mm^2) 30 mm		
	(b) (4)					
Mean, n = 5	1.131	1.110	1.117	171.8	166.1	167.4
%RSD	2.3%	1.6%	1.8%	5.8%	3.7%	2.4%

	Ovality 60 mm			Area (mm^2) 60 mm		
	(b) (4)					
Mean, n = 5	1.127	1.158	1.161	380.8	390.3	386.1
%RSD	4.7%	3.0%	4.6%	4.9%	5.6%	5.7%

Robustness: Actuation Velocity on Spray Pattern Measured 30 mm and 60 mm from the End of Actuator Mouthpiece

	Ovality 30 mm			Area (mm^2) 30 mm		
	(b) (4)					
Mean, n = 5	1.110	1.110	1.129	164.8	166.1	168.9
%RSD	3.4%	1.6%	1.3%	5.8%	3.7%	3.6%

	Ovality 60 mm			Area (mm^2) 60 mm		
	(b) (4)					
Mean, n = 5	1.129	1.158	1.163	393.4	390.3	393.4
%RSD	1.1%	3.0%	2.6%	6.5%	5.6%	2.8%

Robustness: Camera Distance on Spray Pattern Measured 30 mm and 60 mm from the End of Actuator Mouthpiece

	Ovality 30 mm			Area (mm^2) 30 mm		
	(b) (4)					
Mean, n = 5	1.098	1.117	1.121	173.4	173.9	175.7
%RSD	3%	4%	1%	4%	4%	4%

* n=10 measurements (nominal camera distance, used precision data)

	Ovality 60 mm			Area (mm^2) 60 mm		
	(b) (4)					
Mean, n = 5	1.149	1.142	1.172	353.6	362.0	382.2
%RSD	4%	3%	3%	2%	5%	3%

* n=10 measurements (nominal camera distance, used precision data)

Acceptance criteria defined by SOP	The method validation report includes the following acceptance criteria. **Method Precision and Intermediate Precision** For each spray pattern characteristic measured, the %RSD for each analyst's data set were required to meet the following limits: Characteristic / RSD Limit Area / NMT (b) (4)% Dmax / NMT Dmin / NMT Ovality / NMT **Method Repeatability** The RSD for each spray pattern characteristic must be no greater than (b) (4)% **Method Robustness** For each spray pattern characteristic measured, the %RSD for each data set was required to meet the following limits: Characteristic / RSD Limit Area / NMT (b) (4)% Dmax / NMT

	Dmin	NMT (b) (4)%
	Ovality	NMT %
RLD lot numbers	Test Lot 16MM-003	
Number of units	10 replicate from 1 unit for method precision and intermediate precision 5 replicates from 1 unit for robustness	
Number of sprays/unit	1	
Automated or manual actuation used	automated	

Does Firm's SOP include validation criteria?[68]	☒ Yes ☐ No
Does the precision and ruggedness meet the acceptance criteria?	☒ Yes ☐ No
Was RLD product used in the method validation?	☐ Yes ☒ No

Comments on Method Validation:

- Per COA for Batch 16MM-002, for spray pattern test, (b) (4) (b) (4) (b) (4) The firm provided revalidated spray pattern method as listed above.

- The firm used test lot # 16MM-003 for the spray pattern method validation. The firm will be asked to revalidate its spray pattern method using the reference lot with dose counter.

- The firm provided the summary tables for "Robustness: End of Stroke Force on Spray Pattern Measured 30 mm and 60 mm from the End of Actuator Mouthpiece" and "Robustness: Actuation Velocity on Spray Pattern Measured 30 mm and 60 mm from the End of Actuator Mouthpiece" in the study #TTP-CBJ-M0282[70]. However, the firm did not provide the individual data for these two summary tables[71]. In addition, these data are exactly the same as those conducted on different lot for the study # TTP-CBJ-M0132 submitted in the amendment dated 07/01/2015[72]. Since the firm will be asked to repeat its method validation, the firm will not be asked to explain this discrepancy.

The method validation is **inadequate**.

[68] GlobalSubmit Review, ANDA 203760; Module 3.2.P.5.3 Validation of Analytical Procedure Spray Pattern (b) (4) ; Submitted 04/13/2017
[69] GlobalSubmit Review, ANDA 203760; mOdule 3.2.P.5.4 Certificate of Analysis Batch 16MM-002 (Page 10 of 24); Submitted 4/13/2017
[70] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 47-48 of 407); Submitted 04/13/2017
[71] GlobalSubmit Review, ANDA 203760; Module 3.2.P.5.3 Validation of Analytical Procedure Spray Pattern (b) (4) ; Submitted 04/13/2017
[72] GlobalSubmit Review,ANDA 203760; Module 3.2.P.5.3 In-Vitro BE Study – Dose Counter Comparison with RLD (Pages 52-53 of 401); Submitted 7/1/2015

4.7.2.4.3 Results Summary – Spray Pattern

AREA* – SPRAY PATTERN SUMMARY										
	Dist (cm)	Mean (mm^2)		Variability (%CV)					Mean Ratio (T/R)	
				Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arithm	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	3	181.25	180.87	3.63	3.77	3.23	6.81	6.62	1.048	1.047
	6	384.97	384.05	4.03	8.95	4.65	4.44	7.23	1.024	1.026
Ref	3	172.91	172.90	3.58	4.14	6.77	1.51	4.99		
	6	376.08	374.39	14.64	7.09	5.17	4.37	10.43		

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

OVALITY RATIO – SPRAY PATTERN SUMMARY										
	Dist (cm)	Mean		Variability (%CV)					Mean Ratio (T/R)	
				Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arithm	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	3	1.11	1.11	2.39	3.08	1.61	0.99	2.46	1.004	1.004
	6	1.17	1.17	4.38	4.82	3.02	2.02	4.35	1.015	1.015
Ref	3	1.10	1.10	2.09	1.65	2.30	0.43	1.99		
	6	1.16	1.15	6.27	2.24	3.09	0.96	4.19		

Table 18. Summary of PBE Results Calculated by the Firm
Spray Pattern – Area* (mm^2) at 3 cm, N=60 (Test=30 and RLD=30)

Variable	Mean (Origial Scale)		Mean Ratio (Original Scale)	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
Area	180.9	172.7	1.05	0.0651	0.0509	1.2798

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant-scaled	-0.017099	-0.012996	Pass

Was the Reference-scaled analysis used to determine PBE?	☐ **YES** ☒ **NO**
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ **YES** ☐ **NO** ☒ **N/A**
Was the Constant-scaled analysis used to determine PBE?	☒ **YES** ☐ **NO**
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ **YES** ☐ **NO** ☐ **N/A**

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

Spray Pattern – Area* (mm^2) at 6 cm, N=60 (Test=30 and RLD=30)

Variable	Mean (Original Scale)		Mean Ratio (Original Scale)	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
Area	384.0	374.4	1.03	0.0695	0.0935	0.7434

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant-scaled	-0.024149	-0.018985	Pass

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

Was the Reference-scaled analysis used to determine PBE?	☐ **YES** ☒ **NO**
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ **YES** ☐ **NO** ☒ **N/A**
Was the Constant-scaled analysis used to determine PBE?	☒ **YES** ☐ **NO**
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ **YES** ☐ **NO** ☐ **N/A**

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

Spray Pattern – Ovality Ratio at 3 cm, N=60 (Test=30 and RLD=30)

Variable	Mean (Original Scale)		Mean Ratio (Original Scale)	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
Ovality Ratio	1.109	1.102	1.01	0.0263	0.0198	1.3303

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant-scaled	-0.020552	-0.020042	Pass

Was the Reference-scaled analysis used to determine PBE?	☐ **YES** ☒ **NO**
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ **YES** ☐ **NO** ☒ **N/A**
Was the Constant-scaled analysis used to determine PBE?	☒ **YES** ☐ **NO**
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ **YES** ☐ **NO** ☐ **N/A**

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

Spray Pattern – Ovality Ratio at 6 cm, N=60 (Test=30 and RLD=30)

Variable	Mean (Original Scale)		Mean Ratio (Original Scale)	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
Ovality Ratio	1.170	1.154	1.01	0.0420	0.0408	1.0279

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant-scaled	-0.020615	-0.019137	Pass

Was the Reference-scaled analysis used to determine PBE?	☐ **YES** ☒ **NO**
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ **YES** ☐ **NO** ☒ **N/A**
Was the Constant-scaled analysis used to determine PBE?	☒ **YES** ☐ **NO**
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ **YES** ☐ **NO** ☐ **N/A**

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

Table 19. Summary of PBE Results Calculated by the Reviewer

Spray Pattern – Area* (mm^2) at 3 cm, N=60 (Test=30 and RLD=30)

Variable	Mean (Original Scale)		Mean Ratio (Original Scale) %	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
Area	180.87	172.70	104.73	0.065	0.051	1.280

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant-scaled	-0.0173	-0.0133	Pass

Was the Reference-scaled analysis used to determine PBE?	☐ YES ☒ NO
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ YES ☐ NO ☒ N/A
Was the Constant-scaled analysis used to determine PBE?	☒ YES ☐ NO
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ YES ☐ NO ☐ N/A

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

Spray Pattern – Area* (mm^2) at 6 cm, N=60 (Test=30 and RLD=30)

Variable	Mean (Original Scale)		Mean Ratio (Original Scale) %	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
Area	384.05	374.39	102.58	0.069	0.093	0.743

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant-scaled	-0.0246	-0.0194	Pass

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

Was the Reference-scaled analysis used to determine PBE?	☐ YES ☒ NO
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ YES ☐ NO ☒ N/A
Was the Constant-scaled analysis used to determine PBE?	☒ YES ☐ NO
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ YES ☐ NO ☐ N/A

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

Spray Pattern – Ovality Ratio at 3 cm, N=60 (Test=30 and RLD=30)

Variable	Mean (Original Scale)		Mean Ratio (Original Scale) %	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
Ovality Ratio	1.11	1.10	100.41	0.025	0.020	1.241

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant-scaled	-0.0207	-0.0202	Pass

Was the Reference-scaled analysis used to determine PBE?	☐ YES ☒ NO
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ YES ☐ NO ☒ N/A
Was the Constant-scaled analysis used to determine PBE?	☒ YES ☐ NO
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ YES ☐ NO ☐ N/A

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

Spray Pattern – Ovality Ratio at 6 cm, N=60 (Test=30 and RLD=30)

Variable	Mean (Original Scale)		Mean Ratio (Original Scale) %	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
Ovality Ratio	1.17	1.15	101.49	0.043	0.041	1.056

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
Reference-scaled	N/A	N/A	N/A
Constant-scaled	-0.0206	-0.0190	Pass

Was the Reference-scaled analysis used to determine PBE?	☐ **YES** ☒ **NO**
If reference-scaled analysis was used, is the estimate of Sigma R>T0	☐ **YES** ☐ **NO** ☒ **N/A**
Was the Constant-scaled analysis used to determine PBE?	☒ **YES** ☐ **NO**
If constant-scaled analysis was used, is the estimate of Sigma R<T0	☒ **YES** ☐ **NO** ☐ **N/A**

Note to reviewer: If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

T and R with similar qualitative visual shapes?				☒ Yes ☐ No
Equivalence is based upon acceptable PBE results from **EITHER** Automated **OR** Manual Analysis				
Are PBE results acceptable? **If No, please comment**	**Automated**	**Ovality Ratio**	**3 cm**	☒ Yes ☐ No
			6 cm	☒ Yes ☐ No
		AREA	**3 cm**	☒ Yes ☐ No
			6 cm	☒ Yes ☐ No

4.7.2.4.4 Overall Comments

- The firm did not provide spray pattern data in .xpt file for the in vitro BE study # TTP-CBJ-M0282. The reviewer used the dataset provided in the firm's study report[73]. The PBE results for the parameters calculated by both the firm and reviewer passed the PBE acceptance criteria.

- The firm stated the following study events and deviations[74]:

  1) Spray pattern measurements for Inhalers # 165 (T), 226 (T), 69 (T) were repeated due to actuator reflection. The firm provided original images for these measurements[75]. The repeated values were used for the final BE analysis.

[73] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 61-62 of 407); Submitted 04/13/2017
[74] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 20-21 of 407); Submitted 04/13/2017
[75] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 404-407 of 407); Submitted 04/13/2017

2) System Suitability: At the 30 mm distance, characterizations of the following inhalers were affected by stroke length exceeding the acceptance limit of (b) (4): #114, #251, #205, #92, #252, and #303. At the 60 mm distance, characterizations of the following inhalers were affected by stroke length exceeding the acceptance limit of (b) (4): #116, #205, #238, #215, #252, and #239. Device characterization was repeated until the requirement was met before performing the analysis. The firm provided spray pattern characterization data[76].

The reviewer verified that these repeats followed SOP (b) (4) (b) (4) and considers these study events and deviation will not affect the final BE analysis.

The spray pattern test is **inadequate**.

4.7.2.5 Plume Geometry

4.7.2.5.1 Study Information

Study No.	(b) (4)
Study Site Name and Address	
Principal Investigator	
Study dates	
SOP No.	(b) (4) Actuation Station (b) (4) Imaging System
SOP Effective Date	(b) (4)
SOP Title	(b) (4) Actuation Stations (b) (4) Imaging System
Testing Method Description (e.g., Actuation distance; criteria for defining the plume angle and width, etc.**)**	(b) (4) Plume Geometry for Albuterol Sulfate HF A Inhalation Aerosol with Integrated Dose Counter
Criteria for defining plume angle and width borders	(b) (4)
Testing Equipment Used (e.g., name, model, etc)	
Image Analysis Apparatus Used	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	

Note to the Reviewer: The firm needs to submit representative photographs (manual) or digital images (automated) as supportive data.

[76] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Page 89 of 407); Submitted 04/13/2017
[77] GlobalSubmit Review, ANDA 203760; Module 3.2.P.5.2. Analytical Procedure PDF-ATM-CBJ-0054 Spray Pattern; Submitted 04/13/2017

Is testing conducted as per RLD labeling?	☒ Yes ☐ No
Is the image a snapshot? **In No, please comment**	☒ Yes ☐ No
Are representative photographs/digital images provided?	☒ Yes ☐ No
Is plume geometry measured at a single delay time while the fully-developed phase of the plume is still in contact with actuator mouthpiece?	☒ Yes ☐ No
Are plume width measurements made at a distance equal to the greater of the two distances selected for characterization of the spray pattern? (e.g., is plume width measured at 6 cm if spray pattern were measured at 3cm and 6 cm from reference product actuator mouthpiece)	☒ Yes ☐ No
Is plume geometry measured at:	
1) beginning lifestage	☒ Yes ☐ No
If yes, what is the actuation number tested?	Not Provided
Is the actuation number same for T and R? (If not, justification needs to be provided)	☐ Yes ☐ No ☒ Unknown
2) one side view only	☒ Yes ☐ No
Are plume angle and width all quantitated using same method?	☒ Yes ☐ No

Comments on Study Methods:

- The firm stated that *the plume geometry test was performed at the beginning of life stage at a single distance from the actuator orifice.*[78]. However, the firm did not specify the actual number of actuation after priming for both T and R. Therefore, the firm will be asked to provide this information.

- The firm stated in the summary table above that SOP [redacted] (b) (4) Actuation Stations and SOP [redacted] (b) (4) Imaging System were used for the spray pattern test. However, the firm only submitted SOP [redacted] (b) (4) and SOP [redacted] (b) (4) The firm will be asked to provide the aforementioned SOPs in the updated versions.

- The firm did not provide SOP [redacted] (b) (4): Plume Geometry for Albuterol Sulfate HF A Inhalation Aerosol with Integrated Dose Counter. The firm will be asked to provide this information.

The study methods are **inadequate**.

4.7.2.5.2 Validation Summary Table for Plume Geometry

[78] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Page 21 of 407); Submitted 04/13/2017

Precision

	Plume Angle	Plume Width
Mean	18.7°	23.1 mm
%RSD	8.2%	8.5%
Range	(b) (4)	

Intermediate Precision (By Date)

Day 1	Plume Angle	Plume Width
Mean, mm	18.7°	23.1 mm
%RSD (Precision / Repeatability)	8.2%	8.5%
Range, mm	(b) (4)	
Day 2	Plume Angle	Plume Width
Mean, mm	20.2°	25.0 mm
%RSD (Precision / Repeatability)	17.6%	17.9%
Range, mm	(b) (4)	
% Difference (Day 1 vs. Day 2)	8%	7%
Inter Day %RSD**	14.0%	14.2%

**RSD of all Day 1 and Day 2 data

Intermediate Precision (By Analyst)

Analyst 1	Plume Angle	Plume Width
Mean, mm	18.7°	23.1 mm
%RSD	8.2%	8.5%
Range, mm	(b) (4)	
Analyst 2	Plume Angle	Plume Width
Mean, mm	20.2°	25.0 mm
%RSD	17.6%	17.9%
Range, mm	(b) (4)	
% Difference (Analyst 1 vs. Analyst 2)	8%	7%
Inter Analyst %RSD	14.0%	14.2%

Robustness: Actuation Force at 60 mm from the End of Actuator Mouthpiece

MDI Number	Plume Angle (degrees)			Plume Width (mm)		
	(b) (4)					
Mean	15.2	16.4	18.4	18.8	20.2	19.0
%RSD	15.6%	14.2%	1.6%	15.8%	14.4%	1.9%

Robustness: Actuation Velocity at 60 mm from the End of Actuator Mouthpiece

MDI Number	Plume Angle (degrees)			Plume Width (mm)		
	(b) (4)					
Mean	14.8	16.4	17.1	18.3	20.2	21.1
%RSD	10.0%	14.2%	11.7%	10.4%	14.4%	12.2%

Comments on Method Validation:

- Per the previous BE review, the same method validation using the reference lots # AEA13B and AEF75A has been deemed adequate by DBI[79]. However, the reference lots # AEA13B and AEF75A were manufactured without dose counter[80], which cannot be applied to the current plume geometry study on the drug product with dose counter. Therefore, the firm will be asked to repeat its method validation using the reference product with dose counter.

The method validation is **inadequate**.

4.7.2.5.3 Results – Plume Geometry

	Mean Width (mm) or Mean Angle (°)		Variability (%CV)					Mean Ratio (T/R)	
			Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
	Arith	Geo	Lot 1	Lot 2	Lot 3			Arith	Geo
Plume Angle (°)									
Test	20.73	20.61	11/16	8.65	9.37	6.08	10.65	0.958	0.955
Ref	21.63	21.59	6.35	6.83	4.66	3.19	6.39		
Plume Width (mm)									
Test	25.66	25.51	11.41	8.74	9.53	6.19	10.84	0.955	0.952
Ref	26.86	26.80	6.41	6.80	4.92	3.16	6.44		

Is the Plume Angle T/R geo mean ratio between 0.90-1.11?	☒ Yes (0.955) ☐ No
Is the Width T/R geo mean ratio between 0.90-1.11?	☒ Yes (0.952) ☐ No
Are the (point estimate) results acceptable? **In No, please comment**	☒ Yes ☐ No

4.7.2.5.4 Overall Comments

- The firm did not provide plume geometry data in .xpt file for the in vitro BE study # TTP-CBJ-M0282. The reviewer used the dataset provided in the firm's study report[81]. The PBE results for the parameters calculated by both the firm and reviewer passed the PBE acceptance criteria.

- The firm stated the following study events and deviations[82]:

  1) Testing conducted on inhaler #282 was mistakenly performed using the first not the second characterization as defined per method. The difference between the first and

[79] GDRP, ANDA 203760; A203760N000DB_NA07012015_GDRP version.doc (Date Uploaded 9/11/2015); http://panorama.fda.gov/task/view?ID=559a876700fe4b13ce9f1ec18609f222
[80] DARRTS, ANDA 203760; KUNDOOR, VIPRA R 08/04/2014 REV-BIOEQ-21(Primary Review)
[81] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 64-65 of 407); Submitted 04/13/2017
[82] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Pages 23-24 of 407); Submitted 04/13/2017

second characterized stroke lengths for inhaler #282 was (b) (4) meeting the acceptance criteria of "no greater than (b) (4) difference" and indicated the device was properly seated in the actuator cradle. The results from inhaler #282 was used for the final BE analysis.

2) System suitability: The following inhalers were affected by stroke length exceeding the acceptance limit of (b) (4): #351, #160, #74, and #16. Device characterization was repeated until the requirement was met before performing the analysis. The firm provided spray pattern characterization data[83].

The reviewer considers these study events and deviation will not affect the final BE analysis.

The plume geometry test is **inadequate**.

4.8 OSIS Update (For in vivo and in vitro BE studies)

The Office of Study Integrity and Surveillance (OSIS) inspection status for the clinical (Novum Pharmaceutical Research Services, Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712) and analytical (b) (4) (b) (4) sites of the fasting study # 10825320 and for the analytical site (b) (4) (b) (4) of the in vitro BE studies # TTP-CBJ-M0050 and TTP-CBJ-M0282 are complete and adequate.

The OSIS inspection status for the clinical sites (multiple sites) of the PD study # PRG-723 is considered complete at this time, but the application is considered inadequate pending the firm's response to OSIS's deficiencies (please see Section 4.5 for details).

5 APPENDIX

5.1 Additional Attachments

5.1.1 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
PD	N/A	N/A	N/A	N/A
PK	N/A	N/A	N/A	N/A

[83] GlobalSubmit Review, ANDA 203760; Module 5.3.1.3 In-Vitro BE Study Report TTP-CBJ-M0282 (Page 90 of 407); Submitted 04/13/2017

Single Actuation Content	 SAC Dataset	 SAC.SAS	 SAS Stat and Output
Priming	 Priming Dataset	 priming.SAS	 Priming Stat and Output
Aerodynamic Particle Size Distribution	 APSD	 CI for APSD.SAS	 ISM  MMAD  GSD  FPM  TotalMass
	 APSD	 MmCSRS_MH.R	 Final_Outcome.html  MmCSRS.html
Spray Pattern	 Spray Pattern Dataset	 spray pattern spray.SAS	 Area_3 cm  Area_6 cm  Ovality_3 cm  Ovality_6 cm

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 203760

APPLICANT Perrigo Pharmaceutical Company

DRUG PRODUCT: Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiencies:

Deficiencies Related to the Pharmacodynamic Study (PRG-723)

1. During the inspection conducted at the University of Florida, Asthma Research Lab, Gainesville, FL the FDA Investigator determined that the study monitor collected the original study drug dispensation records containing the blinded code-breaking scratch-off labels from the site. The site only maintained photocopies of the records containing the blinded code-breaking scratch-off labels. The original study drug dispensation records containing the blinded code-breaking scratch-off labels were also removed from the site by the study monitor at the other two inspected sites (University of Iowa Hospitals & Clinic and California Allergy & Asthma Medical Group). Please provide a description of the documentation that was provided to the sites prior to the conduct of the study and remained at the clinical site until after the sites were inspected that demonstrates the intended treatment for each subject.

2. During the inspection at the University of Iowa Hospital & Clinic, the FDA Investigator was provided with copies of the original blinded scratch-off labels (returned to the site during the inspection) and the copies maintained at the clinical site (made before the scratch-off labels were collected by the study monitor). However, the obscure part of the copies of the scratch-off labels returned to the site did not show a description stating “Drug Information Inside in Case of Emergency Scratch off the Surface of Blinded Area”, while it was visible on the copy of the copies maintained at the site. Please provide an explanation for this discrepancy.

General Deficiencies

3. 15MM-023, 16MM-002 and 16MM-003 are canister lot numbers as stated in your report of Optimization of Integrated Dose Counter TTP-CBJ-M0099 (Page 20 of 27) (Module 3.2.P.2, Submitted 4/13/2017). However, you did not specify the optimized actuator lot numbers used for the Certificate of Analyses (COAs) of these three test product lots (canister lots). Please provide this information.

4. Please provide COAs for the reference lots # DAC23A, DAC34A and DAC36A.

5. Please provide the following standard operating procedures (SOPs) with the updated version:

   - [redacted]: HPLC Rapid Screen Assay Method for the determination of Albuterol Sulfate
   - [redacted] Impactor
   - [redacted] Actuation Stations
   - [redacted] Imaging System
   - [redacted] Plume Geometry for Albuterol Sulfate HF A Inhalation Aerosol with Integrated Dose Counter

Deficiencies Related to Single Actuation Content through Container Life (SAC)

6. Please indicate how the test and reference products were stored before the SAC test.

7. Your calibration of manual metered dose inhaler (MDI) actuation used the lots manufactured without dose counter. Please repeat your method validation using the reference lot with dose counter.

Deficiencies Related to Priming/Repriming

8. Per the response to your Question # 10 in the meeting between the Office of Generic Drug (OGD) and your company (Perrigo Pharmaceutical Company) on August 26, 2011, OGD stated that '*currently, OGD are not aware of any data showing that any changes in an actuator will not affect the MDI priming and repriming. Thus the sponsor is recommended to provide priming and repriming data. The sponsor may use the single actuation content data at the beginning lifestage (i.e., the first actuation immediately following the specified number of priming actuations in the RLD labeling for the priming study*'. The priming test on the new test and reference lots is acceptable based on your SAC data. However, please conduct repriming test on three test lots with dose counter and optimized actuator, comparing them with three reference lots with dose counter.

Deficiencies Related to Aerodynamic Particle Size Distribution (APSD) by Cascade Impaction

9. Please provide the calculation method for mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD).

10. Your method validation for cascade impaction used the lots manufactured without dose counter. Please repeat your method validation using the reference lot with dose counter.

Deficiencies Related to Spray Pattern

11. Please provide the actuation number after priming for both the test and reference products in the spray pattern test.

12. You used test lot # 16MM-003 for the spray pattern method validation. Please revalidate your spray pattern method using the reference lot with dose counter.

Deficiencies Related to Plume Geometry

13. Please provide the actuation number after priming for both the test and reference products in the plume geometry test.

14. Your method validation for plume geometry used the lots manufactured without dose counter. Please repeat your method validation using the reference lots with dose counter.

Sincerely yours,

{See appended electronic signature page}

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

6 *COMPLETED ASSIGNMENT FOR 203760 ID: 31925*

Reviewer: Zhang, Zhen

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation

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Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
31925	4/13/2017	BIO	ANDA Nasal [2]	2	2
31925	4/13/2017	BIO	Consult Review (For Consults to Other Office) [1]	1	1
31925	4/13/2017	BIO	OSIS Inspection Report Review [1]	1	1
31925	4/13/2017	Parallel	Study Amendment [1]	1	1
31925	4/13/2017	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	2.5	2.5
31925	4/13/2017	Parallel	OSIS Inspection Report: Review of Systemic Observations Identified by the Parent Reviewer [0.25]	0.25	0.25
31925	4/13/2017	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
				Total:	8.75

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203760
Drug Product Name	Albuterol Sulfate Inhalation Aerosol
Strength(s)	0.09 mg Base/Inhalation
Applicant Name	Perrigo Pharmaceuticals Company
Applicant Address	515 Eastern Ave., Allegan, MI 49010
Contact's Name and the mailing address	Matt Popowski, Senior Regulatory Affairs Project Manager 3940 Quebec Avenue North, Minneapolis, MN 55427
Contact's Telephone Number	763-732-0481
Contact's Fax Number	763-732-0509
Contact's Email Address	Mathew.Popowski@perrigo.com RegulatoryAffairs.USA@perrigo.com
Original Submission Date(s)	December 16, 2011
Submission Date(s) of Amendment(s) Under Review	07/03/2013 (Major amendment to support the addition of an integrated dose counter to the metered dose inhaler) 07/01/2015 (Response to complete response letter dated 04/13/2015) **October 05, 2015 post-CR meeting request (Current Review)**
Reviewer	Vipra Kundoor, Ph.D.
Overall Review Result	**ADEQUATE**

REVIEW OF A POST-CR MEETING REQUEST

This is a review of a post-CR (Complete Response) meeting request.

This is the *first generic drug application*. This application references NDA 021457, ProAir® HFA (albuterol sulfate) Inhalation Aerosol, Metered, 0.09 mg Base/Inhalation from Teva.

In the original submission dated 12/06/2011, the firm Perrigo Pharmaceuticals Company submitted the results of the following studies comparing the Test and Reference products: one single-dose fasting pharmacokinetic bioequivalence (BE) study (#10825302), one clinical pharmacodynamics study (#PRG-723), and five types of in vitro bioequivalence studies (single actuation content, aerodynamic particle size distribution by cascade impactor, spray pattern, plume geometry and priming/re-priming). In addition, the firm also submitted the particle size distribution by laser diffraction, which is not required per Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI[1]. The studies were inadequate due to deficiencies. A complete response letter was sent to the firm on 04/13/2015[2].

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[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf

[2] DARRTS, ANDA 203760, COR-ANDAACTION-09 (Complete Response), 04/13/2015

In an amendment dated 07/01/2015, the firm responded to the deficiencies stated in the complete response letter dated 04/13/2015. The firm's responses were still inadequate and a second complete response letter was sent to the firm on 09/21/2015[3].

In the current post-CR meeting request dated 10/05/2015, the firm is requesting a face-to-face meeting to clarify the following specific bioequivalence deficiencies (Bioequivalence deficiency #s 2, 3, 5 and 6) received in the complete response letter dated 09/21/2015:

Deficiency # 2: *The spray pattern testing (study # TTP-CBJ-M0132) comparing the test product with dose counter with the reference product with dose counter fails to meet the Population Bioequivalence (PBE) criteria for spray area at 3 cm distance. Please repeat this test.*

Firm's Comment:
While Perrigo acknowledges that the spray pattern area at 3 cm did not meet the PBE criteria, Perrigo also notes that primary measurements from which area is derived (i.e. Dmax and Dmin) did meet the PBE criteria for spray pattern at 3 cm. Because area is a derived value calculated from the two primary measurements, any small differences in Dmax and Dmin are magnified through the calculation of area. As such the comparison of the primary measurements provides a more direct discerning assessment of this attribute.

Additionally for the plume characteristics, Ovality at 3cm, Ovality at 6 cm, Area at 6 cm, Plume Width at 6 cm and Plume Angle at 6 cm, along with the primary measurements of Dmax and Dmin at 3 cm, all meet the PBE statistic comparison demonstrating bioequivalence; hence, the weight of evidence for plume characteristics demonstrate bioequivalence of the test and reference products.

- Please confirm if the Agency would support demonstration of equivalence of spray pattern area using primary measurements (i.e. Dmax and Dmin) for the 3 cm spray pattern analysis?

- If the Agency does not accept equivalence based on the use of the primary measures (i.e. Dmax and Dmin and weight of evidence for plume characteristics), would the Agency accept a comparison of the 3 cm spray pattern area data derived from the IVBE study for the reference product lots to the (b) (4) (b) (4) set for the test product lots used in the IVBE study as an acceptable approach to provide a supplemental body of evidence to support the demonstration of equivalence for spray pattern area at 3 cm?

Perrigo notes that because the test and reference lots used in this study are no longer in date, it would not be possible to repeat the evaluation of this attribute using the same product lots.

[3] DARRTS, ANDA 203760, COR-ANDAACTION-09 (Complete Response), 09/21/2015

- If the Agency still maintains that the spray pattern area at 3 cm for the demonstration of bioequivalence must be repeated would the Agency accept data from three new lots of both the Test and Reference products for this single test?

Reviewer's Comment:

- DBI would like to inform that currently FDA considers area and ovality ratio at 2 distances as the BE matrix for automated analysis of spray pattern test, and the primary measurements of Dmax and Dmin are not considered as the BE matrix to support equivalence for automated analysis of spray pattern test.

- Assuming the term, (b) (4) mentioned in the firm's response letter, refers to (b) (4) lots of the test product, the Office of Bioequivalence at OGD considers it acceptable to conduct spray pattern test at 3 cm distance using reference lots and 26 month stability lots of the test product, provided that 26 month stability lots of the test product meet the quality standard and is deemed acceptable by the Office of Product Quality. The firm is recommended to submit pertaining information regarding the quality of (b) (4) lots of the test product to Office of Product Quality for evaluation.

- The firm should be informed that it is also acceptable to conduct the spray pattern test using three new lots of both test and reference products, provided the new test product lots used for testing are deemed acceptable by the Office of Product Quality. The firm is recommended to submit pertaining information regarding the quality of new test product lots to Office of Product Quality for evaluation.

- It should be noted that the firm used three test product lots (#s 08MM-034, 08MM-039 and 08MM-050) for conducting spray pattern test in the original submission dated 12/16/2011. However, the firm used **only one test product lot divided into three sub lots** (#s 12MM-020, 12MM-021 and 12MM-022) for repeating the spray pattern analysis comparing the test product with dose counter with the reference product with dose counter. Given the fact that the firm has done a set of spray pattern test on three test product lot (without dose counter), and the addition of dose counter is not considered as a major change affecting the product performance, the OB considers it acceptable for a subsequent spray pattern study be conducted on **one test product lot divided into three sub lots**.

Deficiency # 3: *According to the following Office of Pharmaceutical Quality (OPQ) review comments, your test product batch # 08MM-050 is not considered as representative of the commercial batch:*

(b) (4)

Therefore, the pharmacokinetic (PK) (study # 10825302) and pharmacodynamic (PD) (study # PRG-723) BE studies conducted using batch # 08MM-050 are not acceptable. In addition, the Office of Study Integrity and Surveillance (OSIS) recommends that the data

from PD study (# PRG-723) are not acceptable for further Agency review (please refer to deficiencies based on the inspection findings by the OSIS). Therefore, please repeat the pharmacokinetic (PK) and pharmacodynamic (PD) BE studies.

Firm's Comment:
As described above in our question to product quality deficiency #1, Perrigo proposes to adopt the original process, as suggested by the Agency (headspace correction only), and commits to manufacture (b) (4) batch. Full characterization of the batch (B, M, and E), with matching characterization of the first (b) (4) of the batch, will be provided for Agency review along with 6 months of stability data.

- After reviewing Perrigo's data and response to Product Quality deficiency #1, if the Office of Pharmaceutical Quality determines that the intended clinical portion of batch 08MM-050 is representative of the commercial manufacturing process suggested by the Agency, would the Division of Bioequivalence consider the clinical supplies of batch 08MM-050 a successful product batch suitable for establishing bioequivalence?

Additionally, Perrigo can provide clear evidence to mitigate the concerns that the Office of Study Integrity and Surveillance (OSIS) has regarding the PK and PD studies. Please see the comments and questions for bioequivalence deficiencies #5 and #6 below.

Reviewer's Comment:
If the Office of Pharmaceutical Quality determines that the test product batch # 08MM-050 is representative of the commercial batch, then the pharmacokinetic study (study # 10825302) conducted using this batch is acceptable from a bioequivalence perspective since there are no other pending bioequivalence deficiencies for the pharmacokinetic study. However, the pharmacodynamic study (study # PRG-723) will be still unacceptable pending the deficiencies identified by Office of Study Integrity and Surveillance (OSIS).

Deficiency # 5: *Following the inspection of the clinical sites (University of Florida, Gainesville; University of Iowa, Iowa City; California Allergy & Asthma Medical Group, Los Angeles) between 11/03/2014 – 01/09/2015 by the Office of Study Integrity and Surveillance (OSIS) for the current ANDA, Form FDA-483 was issued. Subsequently, the clinical sites provided its responses to Form 483 and those responses were included in the final evaluation by the OSIS.*

The DBI reviewed the above OSIS inspection reports and found that the pharmacodynamic study (PRG-723) conducted is not acceptable based on the following OSIS findings. Please repeat the pharmacodynamic study.

a. There was a discrepancy in the assigned treatments between the randomization schedule in the study report and the protocol.
b. The original code-blinding scratch-off stickers were not maintained at the clinical site prior to subject enrollment and until the FDA inspection and their integrity cannot be assured.

c. *Without the code-blinding scratch-off stickers, we are unable to confirm which treatments subjects received.*

Firm's Comment for 5a:
There is no discrepancy that exists between the randomization schedule created on January 15, 2010 (which directed execution of the clinical packaging, subject enrollment, and statistical analysis), and the treatment assignments in the clinical study report. While it is true that the treatment identifiers in Protocol amendments #1 and #2 differ from the clinical study report treatment assignments, the protocol amendments were intended to serve as an example of the randomized treatment schematic but were never intended to be, nor could they ever have been used as, the official set of treatment identifiers for the study. Perrigo can provide definitive information and documents to demonstrate that the integrity between the development of the randomization labels on January 15, 2010 through clinical packaging, subject enrollment, and statistical analysis was not and thus has not been compromised. All original code blinding scratch off stickers remain intact and can be uncovered at the Agency's will and shall definitively correlate with each subjects' treatment assignments denoted in the analysis of the clinical study report and not the protocol amendments.

- This observation was not part of OSIS clinical study site audit observations. Therefore, we wish to obtain clarification from the Agency that a response to Bioequivalence deficiency 5.a in our CRL amendment would be reviewed by the Agency.

Reviewer's Comment:
Division of Bioequivalence I (DBI) would like to clarify the firm that response to Bioequivalence deficiency 5.a would be reviewed by the Agency.

Firm's Comment for 5b-c:
Regarding questions 5.b and 5.c, it is not clear to Perrigo if these are questions to be addressed in our CRL response or simply a notification of clinical study site audit observations cited by OSIS. Nonetheless, Perrigo would like to have the opportunity to provide clear evidence through supporting documentation that, although the original code blinding scratch-off stickers were not present at the clinical site(s) at the time of the OSIS inspection, at no time did Perrigo have possession of the original code-blinding scratch-off stickers prior to database lock, prior to statistical analysis, nor prior to the ANDA submission and that the integrity of these original code-blinding scratch-off stickers was and remains intact. Further, should the Agency wish to verify the integrity of these labels and confirm that the treatment assignments correlate with the data provided in the clinical study report, they may do so at will or Perrigo proposes to fund this activity using a designated vendor of the Agency's choice. Perrigo can provide complete information to verify the events and facts. We submit to the Agency the following clarifying questions.

- Will the Agency give consideration to a CRL response to questions 5.a through 5.c?

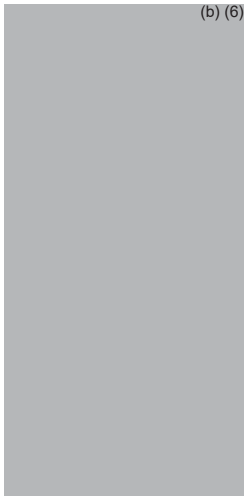
- If so, will this response be reviewed by the Division of Bioequivalence and the Office of Study Integrity and Surveillance?

Reviewer's Comment:
DBI would like to inform the firm to submit all the necessary additional documentation it wishes to submit in support of its response to questions 5.a through 5.c and the response would be reviewed by DBI is consultation with OSIS.

Deficiency # 6: *Please be informed that the case report forms for all the subjects in the pharmacodynamic study (PRG-723) were not retained based on the following OSIS finding for the California Allergy & Asthma Medical Group:*

Investigational records were not retained. Specifically, three randomized subjects' and ten screen-failed subjects' bioequivalence study Source Records, Informed Consent Forms and Case Report Form Files were missing and could not be located during the inspection. The following subjects' entire study records were missing:

Screening Number / Randomization Number



Firm's Comment:
Although this does not provide for locating the missing investigational records, Perrigo can provide new statistical analysis that demonstrates that the study continues to meet the OGD BE guidance requirement of 90% CI 67-150% when 1) the three randomized subjects are removed and 2) when the entire clinical site's data is removed from the statistical analysis.

- Will the Agency give consideration to a CRL response to question 6?

- If so, will this response be reviewed by the Division of Bioequivalence and the Office of Study Integrity and Surveillance?

Reviewer's Comment:

The firm should be informed that DBI would give consideration to the firm's response to bioequivalence deficiency # 6 and the response will be reviewed by DBI in consultation with OSIS.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	203760
APPLICANT:	Perrigo Pharmaceuticals Company
DRUG PRODUCT:	Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation

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

Comment #1:

While Perrigo acknowledges that the spray pattern area at 3 cm did not meet the PBE criteria, Perrigo also notes that primary measurements from which area is derived (i.e. Dmax and Dmin) did meet the PBE criteria for spray pattern at 3 cm. Because area is a derived value calculated from the two primary measurements, any small differences in Dmax and Dmin are be magnified through the calculation of area. As such the comparison of the primary measurements provides a more direct discerning assessment of this attribute.

Additionally for the plume characteristics, Ovality at 3cm, Ovality at 6 cm, Area at 6 cm, Plume Width at 6 cm and Plume Angle at 6 cm, along with the primary measurements of Dmax and Dmin at 3cm, all meet the PBE statistic comparison demonstrating bioequivalence; hence, the weight of evidence for plume characteristics demonstrate bioequivalence of the test and reference products.

- *Please confirm if the Agency would support demonstration of equivalence of spray pattern area using primary measurements (i.e. Dmax and Dmin) for the 3 cm spray pattern analysis?*

- *If the Agency does not accept equivalence based on the use of the primary measures (i.e. Dmax and Dmin and weight of evidence for plume characteristics), would the Agency accept a comparison of the 3 cm spray pattern area data derived from the IVBE study for the reference product lots to the* (b) (4) *data set for the test product lots used in the IVBE study as an acceptable approach to provide a supplemental body of evidence to support the demonstration of equivalence for spray pattern area at 3 cm?*

Perrigo notes that because the test and reference lots used in this study are no longer in date, it would not be possible to repeat the evaluation of this attribute using the same product lots.

- *If the Agency still maintains that the spray pattern area at 3 cm for the demonstration of bioequivalence must be repeated would the Agency accept data from three new lots of both the Test and Reference products for this single test?*

DBI's Response:
Please be informed that primary measurements of Dmax and Dmin **would not** support equivalence of spray pattern testing.

Assuming (b) (4) refers to (b) (4) lots of the test product; it is acceptable to conduct spray pattern analysis at 3 cm distance using reference lots and (b) (4) lots of the test product provided the (b) (4) lots of the test product is acceptable by the office of product quality. Please submit all the necessary information regarding the (b) (4) (b) (4) lots of the test product to office of product quality.

It is also acceptable to conduct the spray pattern testing using three new lots of both test and reference products provided the test product lots used for testing are acceptable by the office of product quality. Please submit all the necessary information regarding the new test product lots to office of product quality.

Comment #2:
As described above in our question to product quality deficiency #1, Perrigo proposes to adopt the original process, as suggested by the Agency (headspace correction only), and commits to manufacture (b) (4) batch. Full characterization of the batch (B, M, and E), with matching characterization of the first (b) (4) of the batch, will be provided for Agency review along with 6 months of stability data.

- *After reviewing Perrigo's data and response to Product Quality deficiency #1, if the Office of Pharmaceutical Quality determines that the intended clinical portion of batch 08MM-050 is representative of the commercial manufacturing process suggested by the Agency, would the Division of Bioequivalence consider the clinical supplies of batch 08MM-050 a successful product batch suitable for establishing bioequivalence?*

Additionally, Perrigo can provide clear evidence to mitigate the concerns that the Office of Study Integrity and Surveillance (OSIS) has regarding the PK and PD studies. Please see the comments and questions for bioequivalence deficiencies #5 and #6 below.

DBI's Response:
If the Office of Pharmaceutical Quality determines that the test product batch # 08MM-050 is representative of the commercial batch, then the pharmacokinetic study (study # 10825302) conducted using this batch is acceptable from a bioequivalence perspective since there are no other pending bioequivalence deficiencies for the pharmacokinetic study. However, the pharmacodynamic study (study # PRG-723) will be still unacceptable pending the concerns of Office of Study Integrity and Surveillance (OSIS).

Comment #3:
There is no discrepancy that exists between the randomization schedule created on January 15, 2010 (which directed execution of the clinical packaging, subject enrollment, and statistical analysis), and the treatment assignments in the clinical study report. While it is true that the treatment identifiers in Protocol amendments #1 and #2 differ from the clinical study report treatment assignments, the protocol amendments were intended to

serve as an example of the randomized treatment schematic but were never intended to be, nor could they ever have been used as, the official set of treatment identifiers for the study. Perrigo can provide definitive information and documents to demonstrate that the integrity between the development of the randomization labels on January 15, 2010 through clinical packaging, subject enrollment, and statistical analysis was not and thus has not been compromised. All original code blinding scratch off stickers remain intact and can be uncovered at the Agency's will and shall definitively correlate with each subjects' treatment assignments denoted in the analysis of the clinical study report and not the protocol amendments.

- *This observation was not part of OSIS clinical study site audit observations. Therefore, we wish to obtain clarification from the Agency that a response to Bioequivalence deficiency 5.a in our CRL amendment would be reviewed by the Agency.*

DBI's Response:
We would like to clarify that response to Bioequivalence deficiency 5.a would be reviewed by the Agency.

Comment #4:
Regarding questions 5.b and 5.c, it is not clear to Perrigo if these are questions to be addressed in our CRL response or simply a notification of clinical study site audit observations cited by OSIS. Nonetheless, Perrigo would like to have the opportunity to provide clear evidence through supporting documentation that, although the original codeblinding scratch-off stickers were not present at the clinical site(s) at the time of the OSIS inspection, at no time did Perrigo have possession of the original code-blinding scratch-off stickers prior to database lock, prior to statistical analysis, nor prior to the ANDA submission and that the integrity of these original code-blinding scratch-off stickers was and remains intact. Further, should the Agency wish to verify the integrity of these labels and confirm that the treatment assignments correlate with the data provided in the clinical study report, they may do so at will or Perrigo proposes to fund this activity using a designated vendor of the Agency's choice. Perrigo can provide complete information to verify the events and facts. We submit to the Agency the following clarifying questions.

- *Will the Agency give consideration to a CRL response to questions 5.a through 5.c?*

- *If so, will this response be reviewed by the Division of Bioequivalence and the Office of Study Integrity and Surveillance?*

DBI's Response:
Please submit all the necessary additional documentation you wish to submit in support of your response to questions 5.a through 5.c and the response would be reviewed by DBI is consultation with OSIS.

Comment #5:

Although this does not provide for locating the missing investigational records, Perrigo can provide new statistical analysis that demonstrates that the study continues to meet the OGD BE guidance requirement of 90% CI 67-150% when 1) the three randomized subjects are removed and 2) when the entire clinical site's data is removed from the statistical analysis.

- *Will the Agency give consideration to a CRL response to question 6?*

- *If so, will this response be reviewed by the Division of Bioequivalence and the Office of Study Integrity and Surveillance?*

DBI's Response:
Please be informed that DBI would give consideration to your response to bioequivalence deficiency # 6 and the response will be reviewed by DBI in consultation with OSIS.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Bing V. Li, Ph.D.
Acting Director, Division of Bioequivalence 1
Office of Generic Drugs
Center for Drug Evaluation and Research

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203760
Drug Product Name	Albuterol Sulfate Inhalation Aerosol
Strength(s)	0.09 mg Base/Inhalation
Applicant Name	Perrigo Pharmaceuticals Company
Applicant Address	515 Eastern Ave., Allegan, MI 49010
Applicant's Point of Contact	Matt Popowski 3940 Quebec Avenue North, Minneapolis, MN 55427
Contact's Telephone Number	763-732-0481
Contact's Fax Number	763-732-0509
Contact's Email Address	Mathew.Popowski@perrigo.com RegulatoryAffairs.USA@perrigo.com
Original Submission Date(s)	12/16/2011
Submission Date(s) of Amendment(s) Under Review	07/03/2013 (Major amendment to support the addition of an integrated dose counter to the metered dose inhaler) 07/01/2015 (Response to complete response letter dated 04/13/2015)
First Generic (Yes or No)	Yes
Reviewer	Vipra Kundoor, Ph.D
Study Number (s)	10825302
Study Type (s)	Fasting
Strength (s)	2 x 90 mcg actuations (total dose = 180 mcg)
Clinical Site	Novum Pharmaceutical Research Services
Clinical Site Address	Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712
Analytical Site	(b) (4)
Analytical Site Address	
Study Number (s)	TTP-CBJ-M0050
Study Type (s)	In Vitro Bioequivalence
Strength (s)	90 mcg/ actuation
Analytical Site (In Vitro Studies)	(b) (4)
Analytical Site Address (In Vitro Studies)	
Study Number (s)	PRG-723
Study Type (s)	Pharmacodynamic Bioequivalence Study
Strength (s)	90 mcg/ actuation
Clinical Sites	**Site 1** University of Florida Asthma Research Lab

	Site 2 Roy J and Lucille A Carver College of Medicine Department of Pediatrics, Allergy/Pulmonary **Site 3** Allergy & Asthma Diagnostic Treatment Center **Site 4** California Allergy & Asthma Medical Group **Site 5** Clinical Research Atlanta **Site 6** Spartanburg Medical Research **Site 7** AARA Research Center	
Clinical Site Address	**Site 1** 1600 SW Archer Road Gainesville, FL 32610-0486 **Site 2** The University of Iowa 200 Hawkins Drive Iowa City, Iowa 52242-1083 **Site 3** 2300 Centerville Road Tallahassee, FL 32308 **Site 4** 11645 Wilshire Blvd, Suite 1155 Los Angeles, CA 90025 **Site 5** 175 Country Club Drive, Suite 100A Stockbridge, GA 30281 **Site 6** 485 Simuel Road Spartanburg, SC 29303 **Site 7** 9900 N Central Expy, Suite 555 Dallas, TX 75231	
Analytical Site (for PD study)	N/A	
Analytical Site Address	N/A	
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs**	**Year 3 ANDAs** ☐ **To Be Determined by OSIS**

	☐ Pending x Complete	☐ Pending For Cause Inspection	
OVERALL REVIEW RESULT	**INADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		
COMMUNICATION	☐ ECD ☐ IR x NOT APPLICABLE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
21	**FASTING STUDY**	**0.09 mg Base/Inhalation**	**INADEQUATE**
21	**IN VITRO BIOEQUIVALENCE STUDIES**	**0.09 mg Base/Inhalation**	**INADEQUATE**
21	**PHARMACODYNAMIC STUDY**	**0.09 mg Base/Inhalation**	**INADEQUATE**

REVIEW OF TWO AMENDMENTS AND OSIS INSPECTION REPORTS

1 EXECUTIVE SUMMARY

This is the *first generic drug application.*

In the original application, the firm submitted the results of the following studies comparing the Test and Reference products: one single-dose fasting pharmacokinetic bioequivalence (BE) study (#10825302), one clinical pharmacodynamics study (#PRG-723), and five types of in vitro bioequivalence studies (single actuation content, aerodynamic particle size distribution by cascade impactor, spray pattern, plume geometry and priming/re-priming). In addition, the firm also submitted the particle size distribution by laser diffraction, which is not recommended per Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI[1]. The findings and outcome of the studies are summarized as follows:

Fasting study: The fasting BE study was designed as a single-dose, two-way crossover study on healthy subjects. The firm's fasting BE study was **inadequate** due to bioanalytical deficiencies. The results of the BE study are summarized in the table below:

Albuterol Sulfate Inhalation Aerosol Dose: 2 x 90 mcg/Inhalation

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf

Fasting Bioequivalence Study No. 10825302, N=24 (Male=17 and Female=7) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	3777.60	24	3883.57	24	0.97	91.67	103.21
AUC∞ (hr *pg/ml)	4027.62	24	4146.43	24	0.97	91.81	102.77
Cmax (pg/ml)	562.71	24	603.18	24	0.93	84.74	102.70

Five types of in vitro bioequivalence studies: All of the *in vitro* BE studies were found **inadequate** due to the multiple deficiencies.

Pharmacodynamics BE study: A bronchoprovocation pharmacodynamic study was conducted. The study was designed as a multi-center, randomized, double-blind, five-way crossover study comparing the test and reference products using a methacholine challenge design in asthmatic subjects. The 90% confidence interval for the relative bioavailability (F) falls within the 67.00 – 150.00% BE criteria. However, the firm's pharmacodynamics study was **inadequate** due to clinical deficiencies. The results of the pharmacodynamics study (reviewer calculated) are summarized in the table below:

Method	**N**	**F (Test/Reference)**	**90% CI**
Using both Doses (0.09 mg and 0.18 mg to calculate F)	93	1.17	102.68% – 132.85%

A complete response letter dated 04/13/2015 was sent to the firm[2].

In the current amendment dated 07/01/2015, the firm responded to the above mentioned deficiencies. The firm's responses are still **inadequate**.

Due to the introduction of a dose counter actuator on the RLD (ProAir HFA Inhalation Aerosol) in 2013, the firm conducted the additional in vitro BE studies comparing the test product with dose counter actuator with the reference product with dose counter actuator, and the firm submitted its study results in an amendment dated 07/03/2013. The current reviewer reviewed the amendment, and found these in vitro studies are inadequate.

There are no necessary or pending Office of Study Integrity and Surveillance (OSIS) inspections of the clinical or analytical sites used for the current ANDA. The inspections for the clinical sites and analytical site of the current application have been conducted.

Review of a 'New' inspection of the analytical and clinical sites: The OSIS inspection reports for the current ANDA as the parent application are reviewed in the current document. The reviewer has identified systemic deficiencies.

Impact of the OSIS Inspection on the Parent ANDA (current ANDA):

[2] DARRTS, ANDA 203760, COR-ANDACTION-09 (Complete Response), 04/13/2015

The OSIS report review is considered inadequate for the current ANDA due to the fact that the findings influenced the study results of the current study.

Analytical Site Findings Summary:

1) (b) (4)

2)

Clinical Sites Findings Summary:

1) The blinding codes were not kept at the site prior to subject enrollment and until the inspection. The data integrity is significantly compromised and there is no assurance that the labels came from the same kits used in the study.
2) There was a discrepancy in the assigned treatments between the randomization schedule in the study report and the protocol. It could not be confirmed if the subjects received the correct study treatment (i.e., test or reference product) as per the treatment randomization schedule.
3) Failed to retain some of the subjects' investigational records. This compromises the integrity of the data and raises concerns on the safety of the subjects enrolled in the study.

Following the inspections for the clinical sites, the OSIS reviewer recommends that data from study PRG-723 are NOT acceptable for further Agency review.

OSIS Inspectional Findings' Impact on Other Related ANDAs:

OSIS report contains systemic findings, and, therefore, should be reviewed separately for the impact on the related ANDAs.

The PM should assign all related ANDAs for review to determine the acceptability of respective studies conducted at the same analytical laboratories.

☐ **Isolated** ☒ **Systemic**

Deficiencies identified on Product Quality which effects the BE decision:

The Office of Pharmaceutical Quality (OPQ) concerns that the bio batch (08MM-50) used for clinical study was not representative of the whole batch. The Division of Bioequivalence concurs with the OPQ's recommendation that batch # 08MM-050 is not

representative of the commercial batch and since the pharmacokinetic (PK) and pharmacodynamic (PD) studies were conducted using this batch, both PK and PD studies are unacceptable and the firm will be asked to repeat these studies. (refer to deficiency # 24 for details).

The application is **inadequate** with deficiencies.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Responses from the firm in the current amendment

Deficiency # 1
Please provide the Certificate of Analysis (CoA) of the reference product lot # AEA13B.

Firm's Response:
The Certificate of Analysis for ProAir HFA Metered Dose Inhaler Reference Listed Drug Lot AEA13B is provided with this amendment.

Reviewer's Comments:

1. The firm provided the certificate of Analysis of the reference product lot # AEA13B (Please see appendix section of the current review). The assay testing was conducted on 02/03/2009 and the pivotal fasting study was initiated on 03/17/2009. Therefore, based on the above information the testing was conducted one month prior to the fasting study.

2. The potency of the test and reference products were comparable.

3. The firm's response to deficiency # 1 is **adequate**.

Deficiency # 2
Per your analytical report for the fasting study (# 10825302), there were seven rejected batch runs for albuterol (Run ID #s 1AFGI, 4AFGI, 7AFGI, 8AFGI, 9AFGI, 13AFGI and 14AFGI). You provided the specific reasons for rejection of the batch runs in the analytical report. However, you did not include the original data to support the reasons for batch rejections. Therefore, please submit the raw data for calibration standards,

quality control (QC) samples and study samples, such as peak area of analyte and internal standard, calculated concentration, etc. of the failed batches.

In addition, you did not include those rejected batches in the calculation of repeat percentage in the "Reanalysis of Study Samples" Table. For the future submissions, please include all analytical repeats, including failed repeat runs, in the "Reanalysis of Study Samples" Table.

Firm's Response:
Perrigo hereby submits the raw data (Section 5.3.1.2) for calibration standards, quality control (QC) samples and study samples, including the peak area of the analyte and internal standard, calculated concentration, response ratio, and other related raw results from the rejected batch runs.

Also, Perrigo acknowledges FDAs comment and in the future will submit all analytical repeats, including failed repeat runs, in the "Reanalysis of Study Samples" Table.

Reviewer's Comments:

1. The firm provided the original data for the rejected run #s 1AFGI, 4AFGI, 7AFGI, 8AFGI, 9AFGI, 13AFGI and 14AFGI. The data provided supports the reasons for batch rejections.

2. In addition, the firm also acknowledged that in future all analytical repeats including failed repeat runs will be included in the "reanalysis of study samples" summary table.

3. The firm's response to deficiency # 2 is **adequate**.

Deficiency # 3
Please provide detailed study reports for all the in vitro equivalence studies.

Firm's Response:
Detailed study reports for all the in vitro equivalence studies (Study TTP-CBJ-M0050 and Study TTP-CBJ-M0132) are provided in section 5.3.1.3.

Reviewer's Comments:

1. The firm provided the detailed study reports for all the in vitro bioequivalence studies.

2. The firm's response to deficiency # 3 is **adequate**.

Deficiency # 4
Manual actuation was used for conducting Single Actuation Content Test, Priming/Re-Priming, Aerodynamic Particle Size Distribution by Cascade Impaction and Particle Size

Distribution by Laser Diffraction. You only indicated that both test and reference products were tested under the same instrumental conditions. Please provide the information regarding whether the test was conducted under blinded conditions to avoid the operator's bias.

Firm's Response:
The details of the blinding conditions used to avoid operator bias in the conduct of the in vitro studies supporting ANDA 203760, are provided in the full detailed summary reports (Study TTP-CBJ-M0050 and Study TTP-CBJ-M0132) in Section 5.3.1.3 supplied in response to IVBE deficiency item 3. Information relating to blinding is contained in Section III.B of each report. The relevant excerpt from the report is reproduced below for the convenience of the assessor.

"T and R drug product inhalers were randomized and blinded prior to execution of this study. For each T product lot, an equal number of units were selected from the beginning (B), middle (M), and end (E) of batch. R product was obtained from commercial sources and therefore assumed to be representative of B, M, and E of drug product batch.

The individual canister and actuator for each inhaler from both the T and R products were individually numbered to assure the same canister and actuator (canister and actuator combination hereafter referred to as 'inhaler') remained together throughout all testing. Once all information was recorded, ten inhalers from each lot were selected for each in-vitro BE test (e.g. prime/reprime, single actuation content, etc) and placed into containers separated by test to be performed. Reserve inhalers were held in separate containers segregated by lot number.

For each test to be performed, the inhalers were analyzed in a random order. A single analyst tested an equal number of T and R inhalers across each product lot (e.g. if 6 tests were performed in a given day, the analyst tested 3 R and 3 T inhalers equally distributed across 3 lots of T and R, respectively) in a random manner (i.e. interdispersing R and T product) using the same testing apparatus. (b) (4)
For the APSD by CI test the same test equipment refers to the use of the same mouthpiece, induction port, (b) (4) and vacuum source. These controls were put in place to minimize any analytical bias and maximize the probability that true differences between the T and R products would be clearly discerned. In the event of a deviation from the testing routine (e.g, if an analyst tested a higher number of T inhalers relative to R inhalers, a system suitability failure, etc) the protocol requirement was for the unit(s) tested without a paired unit from the other product to be retested on a subsequent date with a paired unit from the other product to ensure that testing occurred in a balanced manner with minimal bias.

To blind the study, all data analyses (i.e post-actuation evaluations of the collected data) were performed separately from the sample analysis and by different people who only had knowledge of the blinded inhaler number so the actual inhaler identity, or source, of the data (i.e. T or R) was not known, hence the analysis was not biased. (b) (4)
(b) (4)

(b) (4)

Reviewer's Comments:

1. Though manual actuation was used for conducting Single Actuation Content Test, Priming/Re-Priming, Aerodynamic Particle Size Distribution by Cascade Impaction and Particle Size Distribution by Laser Diffraction, based on the information provided by the firm, both test and reference products were randomized. All data analyses were performed by different people who did not involve in the testing and sample collection thus preventing operator bias. Therefore, the use of manual actuation for the above mentioned tests is acceptable.

2. The firm's response to deficiency # 4 is **adequate**.

Deficiency # 5
For Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study you did not provide 100% raw numerical data (analyst's printouts) for all analytical runs (accepted and rejected) conducted during the HPLC sample analysis of these studies. The raw numerical data should include the data of peak area/height for the drug, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard concentration samples, and quality control samples.

Firm's Response:
In FDA's written responses received May 22, 2015 to Perrigo's Post Complete Response Teleconference Meeting Request dated April 24, 2015, FDA agreed that the firm need not provide 100% numerical data at this time. A copy of the relevant question and response is provided below:

Question 6: *Perrigo is requesting confirmation whether the agency wants to review the same raw numerical data that was reviewed during the IVBE audit, and clarification on the distinction between bioequivalence deficiencies #5 and #6 with regard to the number of chromatograms to be submitted.*

DBI's Response: *Please be advised that DBI is not requesting the 100% raw numerical data at this time, but suggests that you keep the raw data available should that be needed in the future review processes.*

We also would like to clarify that bioequivalence deficiency #5 is related to submission of 100% raw numerical data and bioequivalence deficiency #6 is related to submission of 20% of chromatograms. While it is not necessary at this time to submit the 100% raw numerical data, please submit 20% chromatograms from Single Actuation Content Study,

Priming and Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study.

Regarding the submission of 20% chromatograms from Single Actuation Content Study, Priming and Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study, please see the response to bioequivalence deficiency 6 below.

Reviewer's Comments:

1. The firm requested a post complete response meeting request to request confirmation from the agency for not providing 100% raw numerical data and the Division of Bioequivalence I agreed to the firm's request that it may not submit 100% raw numerical data at this time. However, suggested the firm to keep the raw data available should that be needed in the future review processes[3].

2. Therefore, it is acceptable that the firm did not submit the 100% raw numerical data at this time.

3. The firm's response to deficiency # 5 is **adequate**.

Deficiency # 6
Please submit 20% of the chromatograms from Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study.

Firm's Response:
20% of the chromatograms from Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study have been provided in Study TTP-CBJ-M0050 and Study TTP-CBJ-M0132 located in section 5.3.1.3.

Reviewer's Comments:

1. The firm submitted the 20% chromatograms from Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study and the chromatograms are acceptable.

2. The firm's response to deficiency # 6 is **adequate**.

Deficiency # 7
You did not provide the validation data for the manual spray pump actuator for the SAC testing. Please submit the data using formatted summary tables. You may reference the

[3] Panorama Database, Project # ANDA-203760-GI-1-Meeting-20, Discipline Response to Questions, Document # 203760NA04242015_post CR meeting response.doc, Author: Vipra Kundoor, Version: 04, Updated 05/06/2015

CTD tables designed for nasal spray drug products (where applicable) from the FDA's website at the following location:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf

Firm's Response:
Validation data for the manual spray pump actuator for the SAC testing are provided in the full detailed summary reports supplied in response to IVBE deficiency item 3. Information has been provided in the requested CTD format and can be found in Appendices of each report. An excerpt from the report is provided below for the convenience of the assessor.

(b) (4)

Reviewer's Comments:

1. The firm provided the manual actuation data for the Single Actuation Content testing and the data is acceptable.

2. The firm's response to deficiency # 7 is **adequate**.

Deficiency # 8
Please indicate if stock solutions and working standards underwent freeze-thaw cycles prior to use. If so, please submit the appropriate data to demonstrate stability.

Firm's Response:
The stock solutions and working standard utilized in both in-vitro bioequivalence studies are stable at ambient storage conditions. Stability of these solutions was established in the respective validation reports (b) (4) and (b) (4) provide in section 3.2.P.5.3 of sequence 0000). Stock solutions and working standards were stored at ambient conditions during the entirety of the study; (b) (4)

Reviewer's Comments:

1. The firm confirmed that neither the stock solutions nor the working standards underwent freeze-thaw cycles and were stored at ambient conditions during the entirety of the study. Therefore, it is acceptable that the firm did not provide the freeze-thaw stability data.

2. The firm's response to deficiency # 8 is **adequate**.

Deficiency # 9
Please provide working standards refrigerator stability data.

Firm's Response:
Please refer to response for Bioequivalence deficiency item 8 regarding working standard stability established during validation. Because the stability of the working standards was established at ambient storage, refrigerated storage was not required, and therefore refrigerated stability was not determined.

Reviewer's Comments:

1. The firm mentioned that the working standards were stored at ambient conditions during the entirety of the study. Therefore, it is acceptable that the firm did not conduct the refrigerator stability.

2. The firm's response to deficiency # 9 is **adequate**.

Deficiency # 10

As per the in vitro summary tables you submitted, the Priming and Re-priming study was conducted between February – April 2009. However, your SOP (b) (4) *for Priming and Re-priming testing was effective from* (b) (4) *Please justify how you objectively conducted the study without a pre-established SOP.*

Firm's Response:

The Priming and Re-priming study conducted between February – April 2009 utilized SOP# (b) (4) Testing was conducted for Prime on Feb 11, 2009 and for Reprime on April 3, 2009. This method was validated prior to the execution of the study. Prior to submission of ANDA 203760 all analytical test methods supporting the analysis of the drug product were assigned new method numbers to distinguish between the filed proposed commercial method and previous development method. No changes to the method instruction details were implemented as part of this change control, although safety information was added to this method. In the case of the method utilized for the Priming and Re-Priming study, (b) (4) was assigned new method number (b) (4) as part of a change control (b) (4)

The histories of changes to the method (b) (4) are provided in Section 3.2.P.8.3.2.1.5.1 of the original ANDA submission.

Reviewer's Comments:

1. The firm mentioned that Priming and Re-priming study was conducted as per SOP# (b) (4) This SOP was effective (b) (4) which was prior to the execution of the study. The firm updated this SOP with additional safety information in (b) (4) The firm also mentioned that prior to the submission of ANDA 203760, all analytical test methods were assigned new method numbers to distinguish between the filed proposed commercial method and previous development method. In this process SOP (b) (4) (b) (4) was assigned new number (b) (4) (b) (4) (b) (4)

2. The following table lists the summary of changes from (b) (4) of SOP # (b) (4)

Method History

3. There were no major procedural changes between (b) (4) methods. The firm's response to deficiency # 10 is **adequate**.

Deficiency # 11

You did not provide number of actuations (i.e., how many actuations were employed in the CI test) and the sequential number of actuation (e.g. the 6th-11th sprays/actuations) used in the Cascade Impaction test. Please provide this information.

Firm's Response:

Information on the number of actuations and sequence of actuations for the cascade impaction test are provided in the full detailed summary reports (Study TTP-CBJ-M0050 and Study TTP-CBJ-M0132 provided in section 5.3.1.3.) supplied in response to IVBE deficiency item 3. Information can be found in Section VI.A of each report. An excerpt of the relevant information from the report is provided below for convenience.

The APSD test was conducted at the B and E life stages of the inhaler using a flow rate of 30 L/min using USP <601> Apparatus 1, Apparatus 6 using validated test method (b) (4) for the collection of samples; validated test method (b) (4) for the HPLC analysis of the collected samples. Each APSD determination was conducted on a single collected actuation following three priming actuations which were sprayed to waste.

APSD by Cascade Impaction was performed at B (1st labeled dose) and E (dose 196) life stage. The E life stage dose was selected to allow for a retest of the canister at E life stage in the event of the first determination not meeting method mass balance criteria. The mass balance results for beginning of life were confirmed prior to proceeding with firing down the canister to obtain the end of life testing. After mass balance results were

confirmed for the beginning of life (b) (4), each product canister was fired to actuation 192 to reach the E life stage according to the procedures outlined in (b) (4). For end of life testing, an APSD by CI determination was performed on actuation 196 according to (b) (4) actuator after delivering three priming actuations (actuations 193 – 195) to waste. For mass balance re-tests at B life stage three priming shots (actuations 2 – 4) would be sprayed to waste prior to collecting the next labeled dose (actuation 5) for the mass balance.

Reviewer's Comments:

1. The firm provided the actuation #s used for conducting APSD testing. The beginning of life testing was conducted by priming 3 actuations (# 1 – 3) into waste and actuation # 4 was used for testing. The end of life testing was conducted by priming 3 actuations (# 193 – 195) into waste and actuation # 196 was used for testing.

2. Since, the number of actuations used for APSD testing is less than 10, the actuations used by the firm is acceptable.

3. The firm's response to deficiency # 11 is **adequate**.

Deficiency # 12
According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the APSD test should be performed at both beginning and end lifestages of the product. However, you only conducted the test at the beginning lifestage, indicated in your SAS dataset as "B". Please conduct the test at both beginning and end lifestages of the product as recommended by Albuterol Sulfate MDI guidance.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf

Firm's Response:
The *In-Vitro* Bioequivalence study submitted in ANDA 203760 was conducted in 2009 prior to the issuance of the Albuterol Sulfate MDI guidance. The 2009 study was executed according to guidance obtained in an Industry Meeting held between the FDA Office of Generic Drugs, the Perrigo Company (ANDA Sponsor), (b) (4) (b) (4) on May 5, 2008 in which only beginning life stage APSD testing was recommended.

Subsequent to the release of the Albuterol Sulfate MDI BE guidance in 2013, a second *in-vitro* BE study was performed to support the addition of a dose counter to the test product. This second study, TTP-CBJ-M0132 (in section 5.3.1.3) included APSD testing which included both beginning and end life stages.

Reviewer's Comments:

1. The firm mentioned that additional APSD testing was conducted at both beginning and end life stages of the product. The firm provided the study report of the new APSD study conducted at the beginning and end life stages of the product and did not provide the SAS data in xpt format. However, the firm provided the data in pdf format. The reviewer converted the pdf files to excel and run the SAS analysis. For detailed review of the new APSD testing conducted at beginning and end stages please refer to section # 4 of the current review.

2. The firm's response to deficiency # 12 is **adequate**.

Deficiency # 13

Please specify how many quality control samples were used in each analytical run and at what concentrations. According to the Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Actions (April 2003): "analytical runs include at least three or more concentrations of quality control samples that represent the entire range of the standard curve or the expected concentration range of samples from the various stages of the CI." This is also applicable to the same test of inhalation drug product.

Firm's Response:

A single quality control sample (b) (4) was used in the analysis of the cascade impaction samples in the *in-vitro* bioequivalence studies supporting the Albuterol Sulfate Inhalation Aerosol drug product. Validation data support that the HPLC analysis method is linear over a concentration range of (b) (4) (b) (4). Samples having concentrations within the established linear range of the method are therefore valid. A typical sample concentration range across the cascade impactor is (b) (4). Accuracy experiments supporting the validation of the method demonstrated accurate recovery (b) (4) concentration range.

The *in-vitro* BE studies supporting ANDA 207370 were conducted according to direction from the Agency given in a meeting held between the Office of Generic Drugs, the Perrigo Company (ANDA Sponsor), (b) (4) on May 5, 2008 (Meeting Minutes provided in this amendment for reviewer convenience).

Subsequently, the studies were conducted in accordance with the FDA Draft Guidance on Albuterol Sulfate published in April 2013 (revised in Jun 2013). (b) (4) (b) (4)

Nasal spray products are designed to avoid the delivery of drug to the lungs. As a result, the amount of small particles (b) (4) delivered to the cascade impactor for a nasal spray in proportion to the overall dose would be small and contrast from the amount of small particles delivered to the cascade impactor for an inhalation aerosol. In turn, the

concentration of drug in samples recovered from the deposition sites (i.e. cups) within the impactor for a nasal spray would be much lower relative to the concentration of drug in samples recovered from the external accessories (i.e. induction port, expansion globe, etc). This phenomenon would result in a wider concentration range needing to be examined for a nasal product compared to what would be observed for an inhalation aerosol.

Reviewer's Comments:

1. The firm mentioned that a single quality control sample (b) (4) was used in the analysis of cascade impaction samples. All the in vitro BE studies were conducted according to the direction from the Agency given in a meeting held between the Office of Generic Drugs, the Perrigo Company (ANDA Sponsor), (b) (4) on 05/05/2008 (please refer to appendix section of the current review for the meeting minutes) and in accordance with the FDA Draft Guidance on Albuterol Sulfate published in April 2013 (revised June 2013). (b) (4) (b) (4)

2. According to the HPLC method validation conducted by the firm, the method was (b) (4) (b) (4) (b) (4) Therefore, it is acceptable that the firm used only one quality control sample for the analysis of cascade impaction samples. Please refer to OSIS finding # 2 for the analytical site (b) (4) where the OSIS reviewer was also of the opinion that lack of designated QC samples should not impact the data integrity.

3. The firm's response to deficiency # 13 is **adequate**.

Deficiency # 14

According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the Spray Pattern should be performed at the beginning lifestage of the product at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm ***from the reference product mouthpiece****. It should also be noted that the* ***distance between the actuator orifice and the point of spray pattern measurement should be the same for test and reference products.***

In the current ANDA, you conducted spray pattern test at 3 cm and 6 cm from the actuator mouthpiece. However, it is not clear from your submission whether the selected 3 cm and 6 cm distances are from the actuator mouthpiece of ***the reference product.*** *Therefore, please clarify whether the 3 cm and 6 cm distances are from the reference product actuator mouthpiece. In addition, please confirm whether the distances between*

the actuator orifice to the point of spray pattern measurements are the same for the test and reference products.

Firm's Response:
A non-impaction [redacted] was used to determine the spray pattern at distances of 3cm (30 mm) and 6 cm (60 mm) from the R actuator mouthpiece. The distance from the spray orifice to the end of the actuator mouthpiece was the same [redacted] for both the R and T actuators.

Reviewer's Comments:

1. The firm confirmed that spray pattern testing was conducted at a distance of 3 cm and 6 cm from the actuator mouthpiece of the reference product. The firm also mentioned that the distance from the spray orifice to the actuator mouthpiece was [redacted] for both test and reference products. Therefore, based on the information provided by the firm, the spray pattern testing was conducted at a distance of [redacted] from the actuator orifice for both test and reference products.

2. The distance between the actuator orifice to the point of spray measurements are same for both the test and reference products.

3. The firm's response to deficiency # 14 is **adequate**.

Deficiency # 15
According to the in vitro summary table provided in Module 5.2, the effective date of both SOP #s [redacted]. *However, according to the SOP #s* [redacted] *the effective date of both the SOPs was* [redacted]. *Please clarify this discrepancy.*

Firm's Response:
SOP [redacted] and SOP [redacted]) were supplied to Perrigo in March of 2012 in response to a Telephone Request for Information from the Division of Bioequivalence on May 15, 2012 (responded to on May 18, 2012) relating to the review of ANDA 203760. The versions of the SOPs provided represented the current versions of these respective SOPs at the time of the request.

During the execution of the *in-vitro* BE study (TTP-CBJ-M0050 Part 1) SOP [redacted] and SOP [redacted]

There are no material differences between the version submitted in 2012 and those in effect at the time of the study. In both cases the SOPs were updated to include a reference to [redacted] No other changes were implemented. A copy of the versions

of the SOP's effective at the time the study was executed has been included with this response.

Reviewer's Comments:

1. The firm mentioned that the spray pattern testing was conducted as per SOP # [redacted] (b) (4) and SOP [redacted] (b) (4) However, in response to the telephone request for information from the Division of Bioequivalence on 05/15/2012, the firm provided the current versions [redacted] (b) (4) of the respective SOPs. This was the reason for the discrepancy in the effective date of the SOP.

2. The firm submitted the SOP [redacted] (b) (4) in the current amendment. There are no differences in method instruction details between [redacted] (b) (4)

3. The firm's response to deficiency # 15 is **adequate**.

Deficiency # 16

Please provide the Intermediate Precision (By Date) data for the validation of the spray pattern test.

Firm's Response:

The Intermediate Precision (By Date) data for the validation of the spray pattern test are provided in the full detailed summary reports (Study TTP-CBJ-M0050 and Study TTPCBJ-M0132, provided in section 5.3.1.3) supplied in response to IVBE deficiency item 3. Information has been provided in the requested CTD format and can be found in Appendices of each report. Because Analyst 1 and Analyst 2 each conducted their testing on separate dates, the data are identical to the previously submitted intermediate (By Analyst) data. The relevant information from the report is reproduced below for convenience.

Table 43Intermediate Precision (By Day) – Spray Pattern

Day 1	Area (mm^2)		Ovality	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	174.8	383.6	1.129	1.148
%RSD (Precision / Repeatability)	3.2%	3.1%	1.7%	3.2%
Day 2	**Area (mm^2)**		**Ovality**	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	169.4	383.8	1.147	1.157
%RSD (Precision / Repeatability)	4.1%	5.1%	2.8%	2.8%
% Difference (Day 1 vs. Day 2)	3.1%	0.0%	1.6%	0.7%
Interday %RSD**	3.9%	4.1%	2.4%	2.9%

**RSD of all Day 1 and Day 2 data

Table 44 Intermediate Precision (By Analyst) – Spray Pattern

Analyst 1	Area (mm^2)		Ovality	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	174.8	383.6	1.129	1.148
%RSD	3.2%	3.1%	1.7%	3.2%
Analyst 2	**Area (mm^2)**		**Ovality**	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	169.4	383.8	1.147	1.157
%RSD	4.1%	5.1%	2.8%	2.8%
% Difference (Analyst 1 vs. Analyst 2)	3.1%	0.0%	1.6%	0.7%
Interday %RSD	3.9%	4.1%	2.4%	2.9%

Reviewer's Comments:

1. The firm submitted the intermediate precision data for spray pattern testing and the data is acceptable.

2. The firm's response to deficiency # 16 is **adequate**.

Deficiency # 17
You provided the spray pattern images and the accompanying raw data for 20% samples at both 3 cm and 6 cm distances. However, it is not clear from your submission whether the images are of the test or reference product. Please clarify.

Firm's Response:
The spray pattern images have been updated and provided with this response (attachment 2 to Study TTP-CBJ-M0132 located in section 5.3.1.3) to indicate in the top right hand corner whether they relate to test to reference product.

Reviewer's Comments:

1. The firm updated the spray pattern images to indicate whether they relate to test or reference product.

2. The spray pattern images of the test and reference products were comparable.

3. The firm's response to deficiency # 17 is **adequate**.

Deficiency # 18
*Please clarify whether the 6 cm distance selected for the Plume Geometry test is from **the reference product actuator mouthpiece**. In addition, please confirm whether the distances between the actuator orifice to the point of spray pattern measurements are the same for the test and reference products.*

Firm's Response:
A non-impaction (b) (4) was used to determine the plume geometry at a distance of 6 cm (60 mm) from the R actuator mouthpiece (i.e. this distance is complementary to the farthest distance evaluated in the

spray pattern test). The distance from the spray orifice to the end of the actuator mouthpiece was the same for both the R and T actuators (b) (4) The time sequence (b) (4) was used to determine the plume geometry at a (b) (4) post actuation delay time, at which the plume is fully developed yet still in contact with the actuator orifice. Plume geometry sample images were collected (b) (4). Plume geometry was defined quantitatively in terms of plume angle and width.

Reviewer's Comments:

1. The firm confirmed that plume geometry testing was conducted at a distance of 6 cm from the actuator mouthpiece of the reference product. The firm also mentioned that the distance from the spray orifice to the actuator mouthpiece was (b) (4) for both test and reference products. Therefore, based on the information provided by the firm, the plume geometry testing was conducted at a distance of (b) (4) from the actuator orifice for both test and reference products.

2. The firm's response to deficiency # 18 is **adequate**.

Deficiency # 19
Please provide the Intermediate Precision (By Date) data for the validation of the plume geometry test.

Firm's Response:
The Intermediate Precision (By Date) data for the validation of the plume geometry test are provided in the full detailed summary reports (Study TTP-CBJ-M0050 and Study TTP-CBJ-M0132, provided in section 5.3.1.2) supplied in response to IVBE deficiency item 3. Information has been provided in the requested CTD format and can be found in Appendices of each report. Because Analyst 1 and Analyst 2 each conducted their testing on separate dates, the data are identical to the previously submitted intermediate (By Analyst) data. The relevant information from the report is reproduced below for the convenience of the reviewer.

Table 45 Intermediate Precision (By Date) – Plume Geometry

Day 1	**Plume Angle, °**	**Plume Width, mm**
Mean	18.7	23.1
%RSD (Precision / Repeatability)	8.2%	8.5%
Range	(b) (4)	
Day 2	**Plume Angle, °**	**Plume Width, mm**
Mean	20.2	25.0
%RSD (Precision / Repeatability)	17.6%	17.9%
Range	(b) (4)	
% Difference (Day 1 vs. Day 2)	8%	8%
Inter Day %RSD**	14.0%	14.2%

**RSD of all Day 1 and Day 2 data

Table 46. Intermediate Precision (By Analyst) – Plume Geometry

Analyst 1	Plume Angle, °	Plume Width, mm
Mean	18.7	23.1
%RSD	8.2%	8.5%
Range	(b) (4)	
Analyst 2	**Plume Angle, °**	**Plume Width, mm**
Mean	20.2	25.0
%RSD	17.6	17.9%
Range	(b) (4)	
% Difference (Analyst 1 vs. Analyst 2)	8%	8%
Inter Analyst %RSD	14.0%	14.2%

Reviewer's Comments:

1. The firm submitted the intermediate precision data for plume geometry testing and the data is acceptable.

2. The firm's response to deficiency # 19 is **adequate**.

Deficiency # 20
Please provide the certificate of analysis of the reference product lot # PAEF75A.

Firm's Response:
The Certificate of Analysis for ProAir HFA Metered Dose Inhaler Reference Listed Drug Lot PAEF75A is provided with this amendment.

Reviewer's Comments:

1. The firm provided the certificate of Analysis of the reference product lot # PAEF75A (Please see appendix section of the current review). The assay testing was conducted on 06/02/2010 and the pharmacodynamic study was initiated on 02/24/2010. Therefore, based on the above information the testing was conducted three months after the start of the pharmacodynamic study.

2. The potency of the test and reference products were comparable.

3. The firm's response to deficiency # 20 is **adequate**.

Deficiency # 21
You only provided the case report forms of subject #s (b) (6) *Please provide the case report forms of all subjects included in the pharmacodynamic study.*

Firm's Response:
All case report forms for all subjects randomized in the pharmacodynamic study have been submitted with this response. Please note the following transcription discrepancies in selected case report forms in the tables below.

In the table below, the investigator site staff mistakenly transcribed the randomization number of (b) (6) instead of (b) (6)" to a single page of the subject (b) (6) case report form.

Case report form #	Screening #	Randomization #	Transcription discrepancy page(s)	Transcription discrepancy
				(b) (6)

In the table below, the investigator site staff mistakenly transcribed each subject's screening number on the case report form pages mentioned below when they should have used the subjects' randomization (i.e. "drug kit number") number. The transcription discrepancy stems from the identification numbers associated to each subject during the study. During the study there were two unique identification numbers associated with each subject based on the extent of their participation in the study. The first identification number was a "screening number" which identified each subject during Visit 1 and 2. The second identification number was given to subjects when they were eligible to be randomized (Visit 3). This second number matched up to the drug kit number that contained the drug the subject used during the study.

Case report form #	Screening #	Randomization #	Transcription discrepancy page(s)	Transcription discrepancy
				(b) (6)

Reviewer's Comments:

1. The firm provided the case report forms. However, the case report forms of all the subjects were not provided. Please refer to OSIS finding # 2 for California Allergy & Asthma Medical Group clinical site for the subjects with missing investigational study records for the pharmacodynamic study (PRG-723). As per the OSIS findings, the pharmacodynamic study (PRG-723) is not acceptable and the firm will be asked to repeat the study; however, the firm will be informed that the case report forms for all the subjects in the pharmacodynamic study (PRG-723) were not submitted as requested.

2. The firm's response to deficiency # 21 is **inadequate**.

Deficiency # 22

In your submission (Module 5.3.4.1) for the study design of PD study (# PRG-723), you indicated that "placebo MDI" was used in treatments 1 through 5. However, you did not specify whether the "placebo MDI" is the test or reference product placebo. Please clarify which placebo, test or reference placebo, were used in each treatment in your PD study. In addition, please provide the formulation of the placebo product.

Firm's Response:

The placebo MDI that was used in PD study # PRG-723 consisted of the "test product" canister (b) (4) and the "test product"

actuator. Perrigo was able to source both the actuator and canister that were comparable to the RLD product. This similarity allowed the PD study to be double dummy, double blind in design. Please see the table below which more clearly explains the source of the canisters and actuators throughout the study.

DOSE LEVEL	PRODUCT	MDI COMPONENTS SUPPLIED BY	
		Canister	Actuator
90 mcg TEST	Test	PERRIGO	PERRIGO
	Placebo	PERRIGO	PERRIGO
90 mcg RLD	RLD	TEVA	TEVA
	Placebo	PERRIGO	PERRIGO
180 mcg TEST	Test	PERRIGO	PERRIGO
	Test	PERRIGO	PERRIGO
180 mcg RLD	RLD	TEVA	TEVA
	RLD	TEVA	TEVA
0 mcg	Placebo	PERRIGO	PERRIGO
	Placebo	PERRIGO	PERRIGO

The formulation of the placebo product is included in the table below.

Formulation Component	% w/w	Theoretical Quantity per MDI
(b) (4) Alcohol, USP	(b) (4)	(b) (4)
HFA-134a		
Total	**100**	

Reviewer's Comments:

1. The firm clarified that the placebo MDI used in the pharmacodynamic study is of the test product.

2. The firm also provided the composition of the placebo. The formulation of the placebo is same as the test product minus the active ingredient.

3. The firm's response to deficiency # 22 is **adequate**.

Deficiency # 23

Following the inspection of the analytical site (b) (4) (b) (4) *by the Office of Scientific Investigation (OSI) (for the BE studies from other applications), Form FDA-483 was issued. Subsequently, the analytical site provided its responses to Form 483 and those responses were included in the final evaluation by the OSI.*

For considering the impact of similar study conduct and site practices by the same analytical facility on the BE study of the current ANDA, the DBI reviewed the above OSI inspection report and found that the following objectionable finding by the OSI at the analytical site could potentially compromise the integrity of the study of the current application as well:

(b) (4)

Please address the above systemic finding by the OSI with respect to its impact on the fasting BE study (# 10825302) of the current ANDA.

Firm's Response:

(b) (4) was inspected by the FDA and Office of Scientific Investigation (OSI) issued a Form 483 finding for (b) (4) (b) (4) Specifically, the study samples were (b) (4)

(b) (4)

[redacted]

Reviewer's Comments:

1. For the fasting study (# 10825302) in the current ANDA, the analyte stability was demonstrated under the actual conditions of sample handling and storage. (b) (4)

   (b) (4)

   [redacted]

2. Since, the analyte stability was demonstrated under the actual conditions of sample handling and storage, the OSIS finding should not have an impact on the study outcome.

3. The firm's response to deficiency # 23 is **adequate**.

Deficiency # 24

Based on the following deficiency issued by Office of Pharmaceutical Quality (deficiency #34 in Product Quality Section), the Office of Pharmaceutical Quality (OPQ) concerns that the bio batch (08MM-50) used for clinical study was not representative of the whole batch.

*"We have significant concerns of the exhibit batches and regulatory batches you have provided. **The** (b) (4) **batch 08MM-50 which were used for clinical and stability tests were not representative of the whole batch.** (b) (4) (b) (4) (b) (4) Therefore we recommend you to manufacture another three batches* (b) (4) (b) (4) (b) (4) *Please include detail information of these commercial batches including drug substance COAs, executed batch record, drug product release tests, and accelerated and long term stability data. The stability data should include both valve up and valve down positions".*

Please provide justifications to OPQ to address their concerns. Please note that additional bioequivalence studies may be needed if OPQ determines your response is inadequate to address this issue.

Firm's Response:
Please refer to response for Product Quality deficiency item 34 regarding the OPQ's concerns.

Reviewer's Comments:

1. The drug product quality review is complete and the recommendation is **inadequate with major deficiency**[4].

2. The firm provided its response to Office of Pharmaceutical Quality (OPQ). However, as per the review, the firm's response is not adequate. The review had the following note to be sent to DB:

   (b) (4)

[4] Panorama Database, Project # ANDA-203760-ORIG-1-AMEND-21, Drug Product Primary Review, Document # 203760CR02_09102015.doc, Author: Xihao Li, Modified: 09/10/2015

(b) (4)

Therefore, the firm's response to demonstrate that the (b) (4) *canisters for clinical supplies of batch 08MM-050 are representative of the whole batch is not adequate."*

3. In its review, the OPQ has the following deficiency to be sent to the firm regarding the batch # 08MM-050[5]:

(b) (4)

4. The Division of Bioequivalence concurs with the OPQ's recommendation that batch # 08MM-050 is not representative of the commercial batch and since the pharmacokinetic (PK) and pharmacodynamic (PD) studies were conducted using this batch, both PK and PD studies are unacceptable and the firm will be asked to repeat these studies.

5. The firm's response to deficiency # 24 is **inadequate**.

4 ADDITIONAL NOTES FROM THE REVIEWER:

In its original application dated 12/16/2011, the firm submitted the results of the following studies comparing the test and reference products: one single-dose fasting pharmacokinetic bioequivalence (BE) study (#10825302), one clinical

[5] Panorama Database, Project # ANDA-203760-ORIG-1-AMEND-21, Drug Product Primary Review, Document # 203760CR02_09102015.doc, Author: Xihao Li, Modified: 09/10/2015

pharmacodynamics study (#PRG-723), and five types of in vitro bioequivalence studies (single actuation content, aerodynamic particle size distribution by cascade impactor, spray pattern, plume geometry and priming/re-priming). All the above mentioned studies were conducted with test product without a dose counter. The reference product used also did not have the commercial formulation device available with a dose counter at the time of these studies. The following lots of test and reference products were used:

Study Type	TEST					REFERENCE		
	Lot No.	Potency (%w/w)	Lot Size: Theoretical Quantity	Lot Size: Actual Quantity Used	Manufacture Date	Lot No.	Potency (%w/w)	Expiration Date
Bioequivalence study (PK and PD Study)	08MM-050	(b) (4)			12/11/2008	AEA13B	(b) (4)	6/2010
In-Vitro equivalence studies	08MM-034				11/11/2008	AEA13B		6/2010
	08MM-039				11/20/2008	AEA12C		7/2010
	08MM-050				12/11/2008	AEA14A		6/2010

Due to the introduction of a dose counter actuator on the RLD (ProAir HFA Inhalation Aerosol) in 2013, the firm conducted the following additional in vitro BE studies comparing the test product with dose counter actuator with the reference product with dose counter actuator[6]:

1. Single Actuation Content through container life
2. Priming and Re-priming
3. Aerodynamic Particle Size Distribution (APSD) by Cascade Impaction
4. Spray Pattern
5. Plume Geometry

As per the teleconference meeting with the Office of Generic Drugs (OGD) on August 26, 2011, the firm was informed of the following regarding the studies to be conducted for the addition of a dose counter (please refer to the appendix section of the current review for the meeting minutes dated August 26, 2011):

OGD suggests to refer to the 2003 draft Nasal BA/BE guidance for details. Perrigo should compare the in vitro performance of the proposed generic MDI product with a dose counter and the RLD with a dose counter. 10 units from each of the three batches for the test and reference products should be tested for each of the following in vitro BE studies[7]:

- Priming and repriming

[6] EDR, ANDA 203760, Sequence 0009, Module 5.3.1.2

[7] This recommendation is conditioned upon the firm having previously established BE of the test MDI product without a dose counter and the RLD without a dose counter through in vitro equivalence, pharmacokinetic BE and pharmacodynamics BE studies.

- Single actuation content through container life
- Aerodynamic particle size distribution (APSD)
- Spray pattern
- Plume geometry

These studies were submitted in an amendment dated 07/03/2013. The following lots of the test and reference products were used:

Table 3. Batch Information

(b) (4)

[redacted]

Table 4. Dose Counter Actuator Information for T Product

(b) (4)

[redacted]

Review of the new *in vitro* studies conducted comparing the test product with dose counter actuator with the reference product with dose counter actuator

4.1 In Vitro Equivalence Testing

4.1.1 Information Common to ALL *In Vitro* Equivalence Tests

4.1.1.1 Batch Information

Study Type	TEST					REFERENCE		
	Lot No.	Potency (%w/w)	Lot Size		Manufacture Date	Lot No.	Potency (%w/w)	Expiration Date
			Theoretical Quantity	Actual Quantity Used				
In-Vitro equivalence studies	12MM-020	(b) (4) [redacted]			12/13/2012	DAA15A	(b) (4) [redacted]	08/2014
	12MM-021				12/13/2012	DAA16A		08/2014
	12MM-022				12/13/2012	DAA18A		08/2014

Comments:

1. Per the current ANDA Filing Requirements for Nasal Products[8] , (b) (4) (b) (4) . The current reviewer applied the same criterion for Inhalation Products. Since the firm's theoretical lot (b) (4) , the test product lot size is acceptable.

2. For each in vitro test, ten (10) units from each of the three lots of the test product and each of the three lots of the reference product were tested for each. Therefore, for each test a total of 30 units of the test product and 30 units of the reference product were tested.

3. All the in vitro tests were performed on unexpired lots of reference products.

4. The batch information provided by the firm is **adequate**.

4.1.1.2 Device Comparability

(b) (4)

Comments:

- The firm submitted the comparative data for three device components: can, valve and actuator. The dimensions of the critical components such as actuator orifice diameter and metering volume are the same for the test and reference product.

[8] 2010 GPhA Annual Meeting, Title "The Orange Book, and ANDA Filing Requirements" presented by Martin Shimer

- According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the test product should have a dose counter if the reference product has a dose counter. Both the test and reference products have a dose counter. On November 15, 2013, the labeling reviewer requested a consult to the DCR regarding the dose counter system[9].

- There are two differences on the display of the dose counter system between test and reference products: 1) display of beginning number on the dose counter is different; and 2) refill dose reminder is different. Per DCR consult response, *the Perrigo's proposed dose counter system* (b) (4) *acceptable and not considered a safety concern*[10].

- The devices used for the test and reference products were comparable.

- The information provided by the firm is **adequate**.

Figure 1: Pump Drawing of Test Product

[9] DARRTS ANDA 203760 Vu, Thuyanh 11/15/2013 N/A 11/15/2013 FRM-CONSULT-01(General Consult Request)
[10] DARRTS ANDA 203760 Kim, Carol Y 01/13/2014 N/A 01/13/2014 CONSULT REV-CLINICAL-01(General Consult Review) Archive

4.1.1.3 Actuation Methods

Which tests (if any) used MANUAL actuation?	Dose Content Uniformity Through Life Prime/Re-prime (Dose Content Uniformity) Particle Size Distribution by Cascade Impaction	
If some tests used manual actuation(s), describe methods used to avoid T to RLD bias in dose release.	Study design – single analyst tests T and R in pairs on same day using same test equipment.	
Which tests (if any) used AUTOMATED actuation?	Spray Pattern Plume Geometry	
What were the parameters of automated actuation?		Automated Spray Pump Actuation Station
	Force (kg)	(b) (4)
	Velocity (mm/s)	
	Acceleration (mm/s^2)	
	Initial Delay (sec)	
	Hold Time (sec)	
	Final Delay (sec)	
Are the actuation parameters the same for the test and reference products?	Yes	

Reviewer Comments:

1. Manual actuation was used for conducting SAC, priming/re-Priming and particle size distribution by cascade impaction.

2. Though manual actuation was used for conducting Single Actuation Content Test, Priming/Re-Priming and Aerodynamic Particle Size Distribution by Cascade Impaction, based on the information provided by the firm, both test and reference products were randomized. All data analyses were performed by different people who did not involve in the testing and sample collection thus preventing operator bias. Therefore, the use of manual actuation for the above mentioned tests is acceptable.

3. The actuation methods used by the firm are **acceptable**.

4.1.2 Individual In Vitro Test reviews

4.1.2.1 Single Actuation Content through Container Life

4.1.2.1.1 Study Information

Study No.	TTP-CBJ-M0132
Study Site	(b) (4)
Principal Investigator	
Study Dates	
SOP No.	
SOP Effective Date	
SOP Title	Determination of Dose Content Uniformity, shot weight, and number of actuations from Albuterol Sulfate HFA Inhalation Aerosol Product
Test Method Description	(b) (4)
Testing Equipment Used **(e.g., name, model, etc)**	
Operating Conditions for Testing Equipment Used **(e.g., temperature, humidity, etc.)**	
Analytical Method Description	
Analytical Equipment Used **(e.g., name, model, etc.)**	

Comments:

- This is a metered dose inhaler, therefore, the single actuation content (SAC) at beginning, middle and end of the unit life are requested according to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI (recommended April 2003; Revised June 2013). The firm performed the test at the beginning, middle and end lifestages using flow rate 28.3 L/min. The USP <601> Apparatus A was used in the SAC testing.

4.1.2.1.1 Analytical Method Validation for HPLC

Information Requested	
Analytical method validation report location	Module 3.2.P.5.3
Study Report Number	TTP-CBJ-M0013 MQ TTP-CBJ-M0079 Std Stab (standard stability) TTP-CBJ-M0061 Phase 1 (Dose Content MV)
Analyte	Albuterol Sulfate
Internal Standard (IS)	N/A
Method description	(b) (4) HPLC Rapid Screen Assay Method for the Determination of Albuterol Sulfate
Selectivity or Specificity	(b) (4)
Limit of quantitation	
Detection Limit	
Linearity Range (µg/mL)	
Linearity (R^2)	
Accuracy (% recovery at the high and low concentrations)	
Precision -- Repeatability	
Precision --Intermediate Precision	
Bench-top stability (hrs(CV%)) (working std solution)	
Refrigerator stability (hrs(CV%)) (working std solution)	
Stock solution stability (days (CV %))	
Freeze-thaw stability (cycles (CV %))	
Robustness	

	(b) (4)
Dilution integrity	Not Provided

Does Firm's SOP include validation criteria? (Y/N) If so, list the criteria.	Yes (b) (4)
Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	Acceptable

Comments:

- The firm mentioned that the working standards were stored at ambient conditions during the entirety of the study. Therefore, it is acceptable that the firm did not conduct the refrigerator stability.

- The HPLC method validation conducted by the firm is acceptable.

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

4.1.2.1.3 Precision

Table 40. Precision – Single Actuation Content

(b) (4)

[redacted]

4.1.2.1.4 Ruggedness (by Date)

(b) (4)

[redacted]

Comments on Method Validation:

Did the firm provide a table of pump specific parameters of each actuator used for each in vitro test? (Y/N) **If yes, please include the table(s) above.**	Yes
Number of Bottles and/or Lots Used in the Validation Study	The reference lots# used in the validation report are AEA13B and AEF75A.
Does Firm's SOP include validation criteria? (Y/N)	**Yes**

Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	ACCEPTABLE

Comments: The method validation conducted by the firm is acceptable.

4.1.2.1.6 Results Summary

Reviewer Calculated Results:

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Spray #	Mean				Variability (%CV)					Mean Ratio (T/R)	
			Drug Mass		% label claim		Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
BEG	**Test**	1	107.9	107.45	100.06	99.64	9.76	10.07	7.10	NP	8.93	1.00	0.99
	Ref	1	108	107.83	100.03	99.91	3.18	3.76	6.15	NP	4.92		
MID	**Test**	124	103.9	103.71	96.2	96.03	6.13	5.75	5.84	NP	5.94	0.97	0.97
	Ref	124	106.86	106.75	98.9	98.8	4.26	4.25	4.24	NP	4.55		
END	**Test**	200	106	105.83	98.2	98.04	3.6	5.68	7.26	NP	5.68	1.01	1.01
	Ref	200	104.23	104.07	96.5	96.4	4.76	6.29	4.31	NP	5.64		

NOTE: The drug mass is expressed as Albuterol Sulfate and not the base.
NP – Not Provided

The firm did not provide the SAC results summary table. The reviewer calculated the results from the SAC data provided by the firm. Since the within lot and total variability is less, it is acceptable that the firm did not provide the between lot variability and therefore the firm will not be asked to provide the same.

The firm mentioned that few deviations occurred during the SAC testing and the data mentioned in the following table has been excluded from statistical analysis. The firm only provided the excluded data and did not provide the data with which it was replaced with (the firm only provided the replaced canister numbers). Therefore, the firm will be asked to provide a table with original values and replaced values, so that the reviewer can include the original values and run the statistical analysis.

Table A.7.1. Single Actuation Content Data

(b) (4)

NT = Not Tested

(b) (4)

(b) (4)

[redacted]

4.1.2.1.7 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE		
REVIEW OF TESTING METHODS:		
Is the testing method validated?		Yes
Is the Quantitative Analytical Method Validated? (e.g., HPLC)		Yes
Is the method sufficiently sensitive?		Yes
Is testing performed as per RLD labeling?		Yes
Are data measured at both beginning, middle & end lifestages?		Data are measured at beginning, middle and end stages. This is according to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI.
Is testing a single actuation per determination?		Yes
If yes, what is the actuation number tested?		**# 1 (beginning) after priming # 124 (middle) # 200 (end)**
Are the testing methods acceptable?		**ACCEPTABLE**
If not, why?		N/A
STUDY RESULTS:		
Are data expressed as actual amount and % of label claim?		Yes
Is the geo-mean of the test product (% of label claim) within 95-105%?	**Beginning**	Yes
	Middle	Yes
	End	Yes
Are the PBE results acceptable?		**Acceptable (pass PBE)**
If not, why?		N/A

Reviewer Comments on SAC:

1. The RLD labeling of Albuterol Sulfate Metered Dose Inhaler states the following regarding the priming of the inhaler[11]:
   "You must prime the inhaler to get the right amount of medicine. Prime the inhaler before you use it for the first time or if you have not used it for more than 14 days. To prime the inhaler, take the cap off the mouthpiece of the actuator. Then shake the inhaler well, and spray it into the air away from your face. Shake and spray the inhaler like this 2 more times to finish priming it".

2. In the current ANDA, both the test and reference products were primed three actuations and then performed the SAC testing. This is according to the RLD labeling. Actuation #1 actually is actuation #4. Actuation #124 actually is actuation #127. Actuation #200 actually is actuation #203.

3. After priming, the firm assayed actuation #1, actuation #124 and actuation #200 of the test product and reference products to represent the beginning, middle and end life stages respectively.

4. The test product passes the PBE analysis. The firm also provided the PBE analysis results for 95% upper bound. The 95% upper bound of drug mass calculated by the reviewer is same as the firm's calculations. Please see the summary results of 95% upper bounds.

Parameters	Firm's Calculation		Reviewer's Calculation	
	Reference-Scaled	Constant-Scaled	Reference-Scaled	Constant-Scaled
Drug Mass	(b) (4)			
Final BE Conclusion Based on	Constant-Scaled		Constant-Scaled	

5. The geo-mean of the test product (% of label claim) for the beginning, middle and end unit life is within 95-105%.

6. This study is **inadequate**.

4.1.2.1.8 Deficiencies / Recommendations

Please see deficiency comments section.

[11] Drugs@FDA, Keyword Search: Proair, RLD Label approved on 08/17/2010, last accessed date: 01/06/2013.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021457s021lbl.pdf

4.1.2.2 Priming & Re-priming

4.1.2.2.1 Study Information

Study No.	TTP-CBJ-M0132
Study site	(b) (4)
Principal Investigator	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	Determination of Dose Content Uniformity, shot Weight, and Number of actuations from an Albuterol Sulfate HFA Inhalation Aerosol Product.
Test Method Description	(b) (4)
Testing Equipment Used **(e.g., name, model, etc)**	
Operating Conditions for Testing Equipment Used **(e.g., temperature, humidity, etc..)**	
Analytical Method Description	
Analytical Equipment Used **(e.g., name, model, etc)**	

Comments:

1. The firm's labeled actuation #1 is actual actuation #4 (following 3 priming actuations as specified in the drug product label).

2. The RLD labeling of Albuterol Sulfate Inhalation Aerosol states that when 14 or more days have elapsed since the last use, the pump should be reprimed with 2 actuations. Therefore, a repriming study is necessary for the current application. The firm stored the products and then tested the repriming on Day 15.

3. The firm mentioned that because the reference product labeling does not specify specific storage orientation, the containers were stored in valve upright position without being actuated before priming and repriming. The bottles were shaken as per the RLD labeling prior to use.

4.1.2.2.2 Analytical Method Validation for HPLC

Please refer to the method validation for SAC test.

4.1.2.2.3 Results Summary – Priming & Re-Priming

Reviewer Calculated Results

PRIMING												
Number of actuations used to **prime** each product = 3												
Actuation number used for testing each product = # 1												
	Spray #	**Mean**				**Variability (%CV)**					**Mean Ratio (T/R)**	
		Drug Mass		**% label claim**		Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	1	107.9	107.46	100.06	99.64	9.76	10.07	7.10	NP	8.93	0.99	0.99
Ref	1	108	107.87	100.03	99.91	3.18	3.76	6.15	NP	4.92		

RE-PRIMING												
Period of time each product was stored in the vertical position following priming (nasal sprays only) = 14 days												
Number of actuations used to **re-prime** each product = 3												
Actuation number used for testing each product = # 5												
	Spray #	**Mean**				**Variability (%CV)**					**Mean Ratio (T/R)**	
		Drug Mass		**% label claim**		Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	5	98.36	98.20	91	90.83	3.73	6.58	7.45	NP	5.96	0.92	0.92
Ref	5	106.23	106.16	98.43	98.36	2.31	5.39	2.85	NP	3.75		

NOTE: The drug mass is expressed as Albuterol Sulfate and not the base.
NP – Not Provided

The firm did not provide the Priming and Repriming results summary table. The reviewer calculated the results from the Priming and Repriming data provided by the firm. Since the within lot and total variability is less, it is acceptable that the firm did not provide the between lot variability and therefore the firm will not be asked to provide the same.

ANDA 203760 Priming Test: Amount

Is the testing method validated?		**No**
PRIMING	**Number of actuations required**	3 priming actuations
	Is priming conducted as per RLD label?	Yes
RE – PRIMING	**Number of actuations required**	3 repriming actuations
	Is re-priming conducted as per RLD label?	Yes
Is testing a single actuation per determination?		Yes
If yes, what is the actuation number tested?		# 1 (after 3 priming actuations) for priming and # 5 (after 3 repriming actuations) for repriming
Are studies performed on products stored in the valve-upright position? (nasal spray only)		Yes
Are the testing methods acceptable?		**ACCEPTABLE**
If not, why?		N/A
STUDY RESULTS:		
PRIMING	**Is the geo-mean of the test product (% of label claim) within 95-105%?**	Yes
RE – PRIMING	**Is the geo-mean of the test product (% of label claim) within 95-105%?**	No
Are the PBE results acceptable?		**ACCEPTABLE (pass PBE)**
If not, why?		N/A

Reviewer Comments on Priming:

1. The RLD label states that *"You must prime the inhaler to get the right amount of medicine. Prime the inhaler before you use it for the first time or if you have not used it for more than 14 days. To prime the inhaler, take the cap off the mouthpiece of the actuator. Then shake the inhaler well, and spray it into the air away from your face. Shake and spray the inhaler like this 2 more times to finish priming it".*

2. For priming, the inhaler was primed by wasting the first 3 actuations for both the test and reference products and actuation # 4 (or actuation # 1 after priming) was used for testing.

3. For re-priming, the firm mentioned that the inhaler was stored for at least two weeks (14 days) valve upright position, without being actuated, prior to re-prime data collection. After 14 days, the inhaler was primed 3 times and actuation # 5 was used for re-priming testing.

4. The test product passes the PBE analysis. The firm also provided the PBE analysis results for 95% upper bound. The 95% upper bound of drug mass

calculated by the reviewer is same as the firm's calculations. Please see the summary results of 95% upper bounds.

4.1.2.2.5 Deficiencies / Recommendations – Priming & Re-Priming

None

4.1.2.3 Aerodynamic Particle Size Distribution (APSD) by [redacted] Cascade [redacted]

4.1.2.3.1 Study Information

Study No.	TTP-CBJ-M0132
Study site	[redacted]
Principal Investigator	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	Standard Operating Procedure for [redacted] Impactor
Testing Method Description	[redacted] Assessment of the Aerodynamic Particle Size Distribution from an Albuterol Sulfate HF A Inhalation Aerosol by Cascade Impaction
Testing Equipment Used **(e.g., name, model, etc)**	[redacted]
Operating Conditions for Testing Equipment Used **(e.g., temperature, humidity, etc..)**	
Analytical Method Description	
Analytical Equipment Used **(e.g., name, model, etc)**	

Comments:

1. The APSD testing was conducted as per the RLD labeling. The beginning of life testing was conducted by priming 3 actuations (# 1 – 3) into waste and actuation # 4 was used for testing. The end of life testing was conducted by priming 3 actuations (# 193 – 195) into waste and actuation # 196 was used for testing.

4.1.2.3.2 Validation Summary Table for Particle Size Distribution by Cascade Impactor

4.1.2.3.2.1 Analytical Method Validation for HPLC

Information Requested	
Analytical method validation report location	Module 3.2.P.5.3
Study Report Number	(b) (4)
Analyte	Albuterol Sulfate
Internal Standard (IS)	N/A
Method description	(b) (4) HPLC Rapid Screen Assay Method for the Determination of Albuterol Sulfate
Selectivity or Specificity	(b) (4)
Limit of quantitation	
Detection Limit	
Linearity Range (mcg/mL)	
Linearity (R^2)	
Accuracy (% recovery at the high and low concentrations)	
Precision -- Repeatability	
Precision --Intermediate Precision	
Bench-top stability (hrs) (working std solution)	
Refrigerator stability (hrs) (working std solution)	

Stock solution stability (days)	(b) (4)
Freeze-thaw stability (cycles)	
Robustness	
Dilution integrity	Not Provided

Does Firm's SOP include validation criteria? (Y/N)	The firm's method validation report includes the validation criteria
Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	Acceptable

Comments:

- The firm mentioned that the working standards were stored at ambient conditions during the entirety of the study. Therefore, it is acceptable that the firm did not conduct the refrigerator stability.
- The HPLC method validation conducted by the firm is acceptable.

4.1.2.3.2.2 Validation Table for Cascade Impaction

4.1.2.3.2.2.1 Precision

(b) (4)

4.1.2.3.2.2.3 Intermediate Precision (By Analyst)

(b) (4)

Number of Bottles and/or Lots Used in the Validation Study	Reference lot #AEA13B Reference lot #PAEF75A
Does Firm's SOP include validation criteria? (Y/N)	Yes
Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	Acceptable

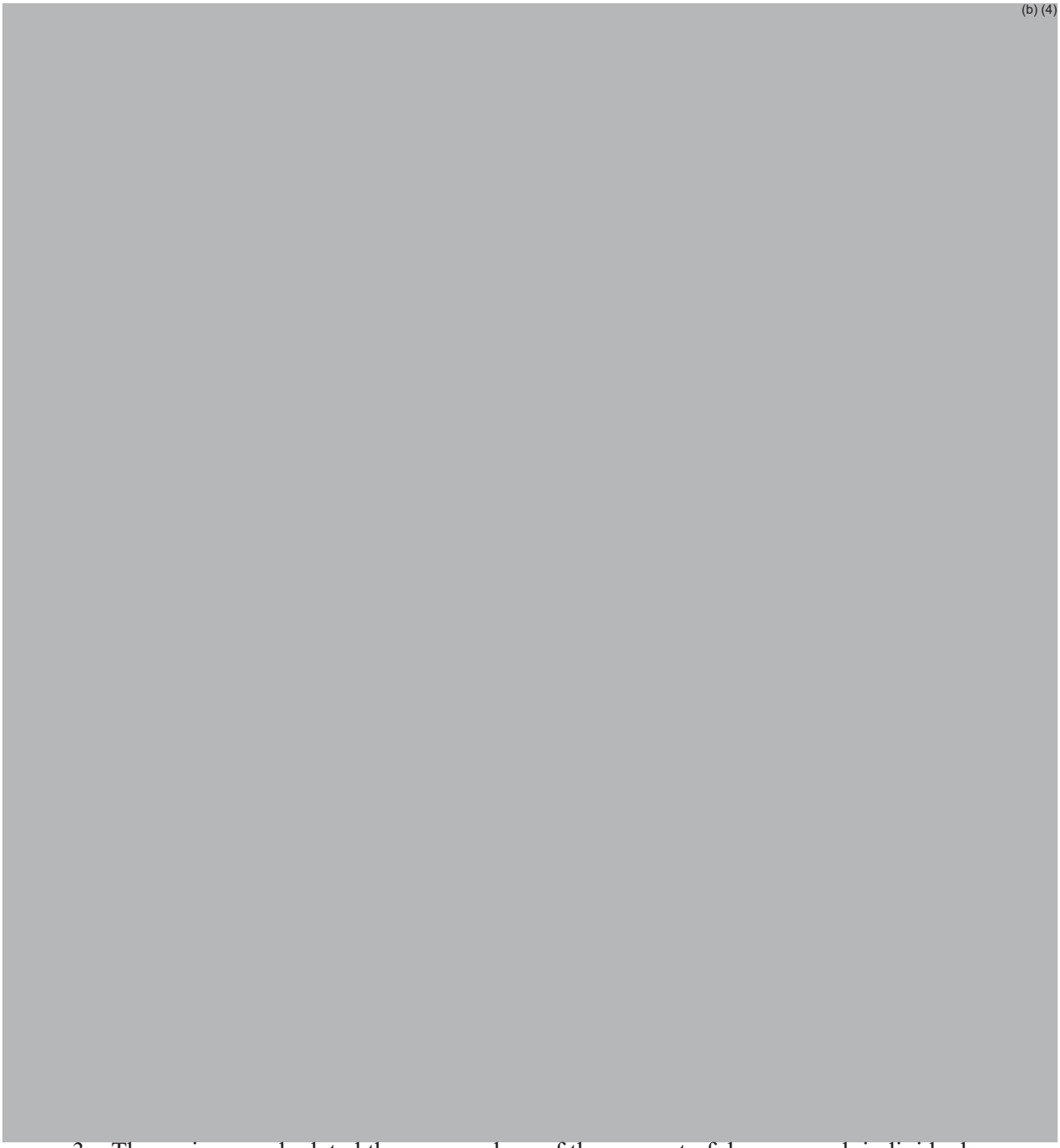
Comments:

1. The firm mentioned that a single quality control sample (b) (4) was used in the analysis of cascade impaction samples. All the in vitro BE studies were conducted according to the direction from the Agency given in a meeting held between the Office of Generic Drugs, the Perrigo Company (ANDA Sponsor), (b) (4) on 05/05/2008 (please refer to appendix section of the current review for the meeting minutes) and in accordance with the FDA Draft Guidance on Albuterol Sulfate published in April 2013 (revised June 2013). The firm mentioned that neither source provided reference to the use of multiple concentrations of quality control samples in the analytical run, nor did the sources indicate that the multiple concentration approach outlined in the nasal guidance was applicable to an inhalation product.

2. (b) (4) (b) (4) Therefore, it is acceptable that the firm used only one quality control sample for the analysis of cascade impaction samples. Please refer to OSIS finding # 2 for the analytical site (b) (4) where the OSIS reviewer was also of the opinion that lack of designated QC samples should not impact the data integrity.

4.1.2.3.3 Results Summary – Aerodynamic Particle Size Distribution by Cascade Impactor (CI)

Comments:



3. The reviewer calculated the mean values of the amount of drug on each individual stage, mass balance (MB), mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD)

[redacted] (b) (4)

4. Per Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI:

   ***"Equivalence based on**: PBE analysis of impactor-sized mass (ISM). The CI profiles representing drug deposition on the individual stages of the CI along with the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) should be submitted as supportive evidence for equivalent APSD".*

5. Currently, the FDA relies on a weight of evidence, including PBE analysis of certain key parameters which characterize the particle size distribution, together with a statistical approach for comparing the distribution profiles, namely modified Chi-square ratio method[12], to determine the equivalence of the test product (as compared with corresponding strengths of the RLD). Currently, the following criteria are considered for APSD equivalence[13]:

   I. PBE on SAC

   II. PBE on Impactor Size Mass [redacted] (b) (4)
   (b) (4)

   III. Modified Chi-square ratio method analysis on Impactor Sized Mass stages [redacted] (b) (4)

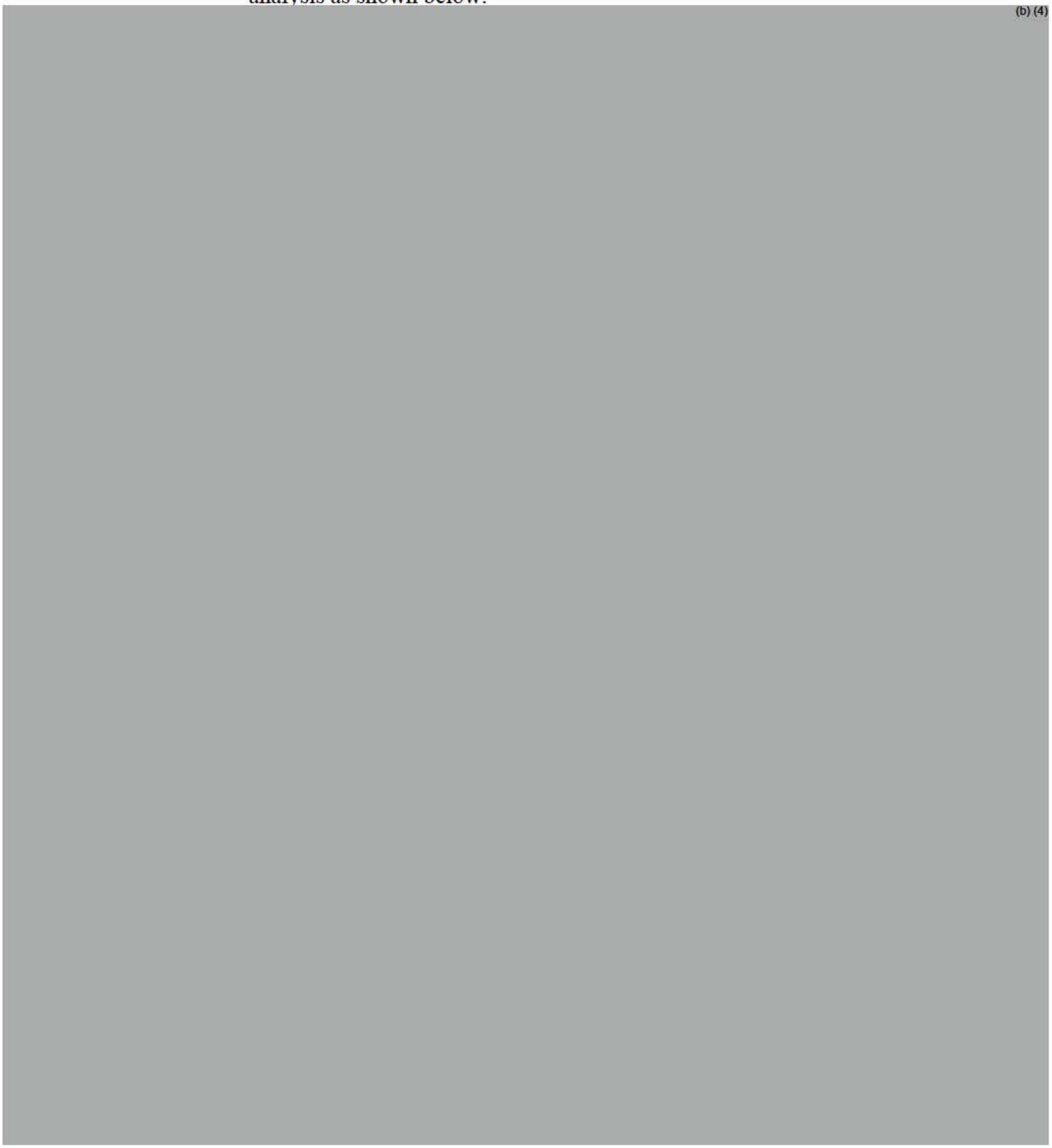
[12] A Stability Analysis of a Modified Version of the Chi-Square Ratio Statistic: Implications for Equivalence Testing of Aerodynamic Particel Size Distribution; Benjamin Weber, Guenther Hochhaus, Wallace Adams, Robert Lionberger, Bing Li, Yi Tsong, and Sau L. Lee; The AAPS Journal, Published online: 25 Sept. 2012.

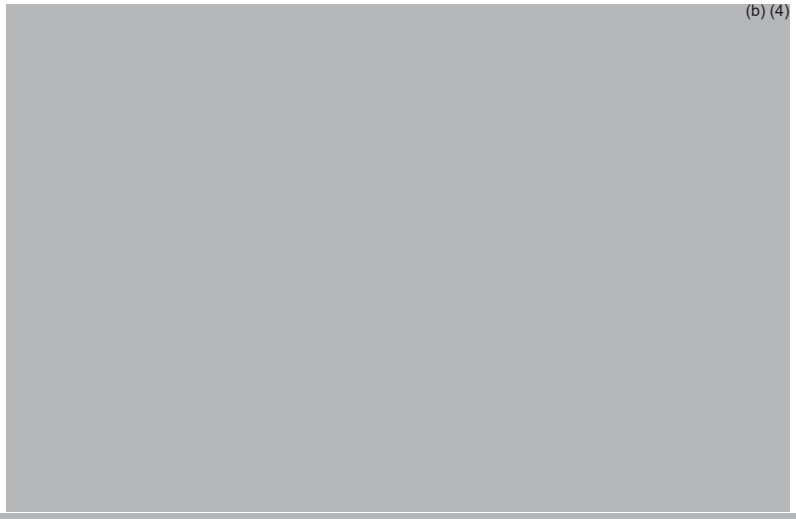
[13] Respiratory Drug Delivery 2012; Webber Et al., Evaluation of Statistical Methods for Determining Equivalence of Aerodynamic Particle Size Distribution.

6. The reviewer employed the above criteria for this application:

   I. PBE on SAC: refer to SAC test section;
   II. PBE on Impactor Size Mass (ISM): result indicated that ISM passed PBE analysis as shown below:

(b) (4)




(b) (4)


(b) (4)

7. In summary, the APSD evaluation for the drug product is currently based on the weight of evidence approach, with the following metrics used to demonstrate equivalence between the two formulations: SAC and ISM, both of which passed PBE. In addition, the paticle size also passed the Modified Chi Square ratio acceptance criteria.

4.1.2.3.4 Conclusions

DRUG IN SMALL PARTICLES / DROPLETS PER ACTUATION	
REVIEW OF TESTING METHODS:	
Is the testing method for CI test validated?	Yes
Is the analytical method (e.g. HPLC) validated?	Yes
Is the analytical method sufficiently sensitive?	Yes
Is testing conducted as per RLD labeling?	Yes
What is the size of the induction port (or expansion chamber) used for testing?	N/A
Are ≤ 10 actuations used for cascade impactor study?	Yes
If >1 actuation, what is the # of actuations used?	Only 1 actuation is used for testing Beginning: Actuation # 4 End: Actuation # 196
Are the testing methods acceptable?	**ACCEPTABLE**

DRUG IN SMALL PARTICLES / DROPLETS PER ACTUATION		
If not, why?		N/A
STUDY RESULTS:		
Is drug deposition reported in mass units?		Yes
Is the mass balance data reported?		Yes
Results	**Does Impactor Size Mass data pass PBE?**	**Yes**
	Does ISM data pass modified chi-square ratio test?	**Yes**
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) pass PBE?	**Yes**
If results not acceptable, why?		N/A

Comments:

1. According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the aerodynamic particle size distribution (APSD) should be performed at **both beginning and end lifestages** of the product. In the current submission, the firm conducted testing at both beginning and end lifestages of the product.

2. The APSD test was performed using a flow rate of 30 ± 0.5 L/min. The USP <601> Apparatus (b) (4) was used in the test. This is according to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI.

3. The firm mentioned that few deviations occurred during the APSD testing and the data mentioned in the following table has been excluded from statistical analysis. The firm only provided the excluded data and did not provide the data with which it was replaced with (the firm only provided the replaced canister numbers). Therefore, the firm will be asked to provide a table with original values and replaced values, so that the reviewer can include the original values and run the statistical analysis.

4. The APSD conducted by the firm is **inadequate**.

4.1.2.3.5 Deficiencies / Recommendations

Please see deficiency comments section.

4.1.2.4 Spray Pattern

Study No.	TTP-CBJ-M0132
Study site	(b) (4)
Principal Investigator	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	(b) (4) Actuation Station (b) (4) Imaging System
Testing Method Description	(b) (4) Evaluation of Spray Pattern for an Albuterol Sulfate HFA Inhalation Aerosol
Study Distances **(distances from actuator orifice)**	3 cm: actuation # 2 – 8 (beginning of use life) 6 cm: actuation # 3 – 5 (beginning of use life)
Testing Equipment Used **(e.g., name, model, etc)**	(b) (4)
Image Analysis Apparatus Used	
Operating Conditions for Testing Equipment Used **(e.g., temperature, humidity, etc.)**	
Analytical Method Description	
Analytical Equipment Used **(e.g., name, model, etc)**	

Comments:

1. The firm confirmed that spray pattern testing was conducted at a distance of 3 cm and 6 cm from the actuator mouthpiece of the reference product. The firm also mentioned that the distance from the spray orifice to the actuator mouthpiece was (b) (4) for both test and reference products. Therefore, based on the information provided by the firm, the spray pattern testing was conducted at a (b) (4) from the actuator orifice for both test and reference products.

2. The distance between the actuator orifice to the point of spray measurements are same for both the test and reference products.

3. The study design is acceptable.

4.1.2.4.1 Validation Summary Table for Spray Pattern

4.1.2.4.1.1 Precision

Table A.5.9 Precision – Spray Pattern

	Area, mm^2		Ovality	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean	174.8	383.6	1.129	1.148
%RSD	3.2%	3.1%	1.7%	3.2%
Range	(b) (4)			

4.1.2.4.1.2 Intermediate Precision (By Date)

Table A.5.10 Intermediate Precision (By Day) – Spray Pattern

Day 1	Area, mm^2		Ovality	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	174.8	383.6	1.129	1.148
%RSD (Precision / Repeatability)	3.2%	3.1%	1.7%	3.2%
Day 2	**Area, mm^2**		**Ovality**	
	Dist 1 30 mm	**Dist 2 60 mm**	**Dist 1 30 mm**	**Dist 2 60 mm**
Mean, n = 10	169.4	383.8	1.147	1.157
%RSD (Precision / Repeatability)	4.1%	5.1%	2.8%	2.8%
% Difference (Day 1 vs. Day 2)	3.1%	0.0%	1.6%	0.7%
Interday %RSD**	3.9%	4.1%	2.4%	2.9%

**RSD of all Day 1 and Day 2 data

4.1.2.4.1.3 Intermediate Precision (By Analyst)

Table A.5.11 Intermediate Precision (By Analyst) – Spray Pattern

Analyst 1	Area, mm^2		Ovality	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	174.8	383.6	1.129	1.148
%RSD	3.2%	3.1%	1.7%	3.2%
Analyst 2	**Area, mm^2**		**Ovality**	
	Dist 1 30 mm	**Dist 2 60 mm**	**Dist 1 30 mm**	**Dist 2 60 mm**
Mean, n = 10	169.4	383.8	1.147	1.157
%RSD	4.1%	5.1%	2.8%	2.8%
% Difference (Analyst 1 vs. Analyst 2)	3.1%	0.0%	1.6%	0.7%
Interday %RSD	3.9%	4.1%	2.4%	2.9%

4.1.2.4.1.4 Robustness

Table A.5.12 Robustness: End of Stroke Force on Spray Pattern Measured 30 mm and 60 mm from the End of Actuator Mouthpiece

	Ovality 30 mm			Area (mm^2) 30 mm		
	(b) (4)					
Mean, n = 5	1.131	1.110	1.117	171.8	166.1	167.4
%RSD	2.3%	1.6%	1.8%	5.8%	3.7%	2.4%

	Ovality 60 mm			Area (mm^2) 60 mm		
	(b) (4)					
Mean, n = 5	1.127	1.158	1.161	380.8	390.3	386.1
%RSD	4.7%	3.0%	4.6%	4.9%	5.6%	5.7%

Table A.5.13 Robustness: Actuation Velocity on Spray Pattern Measured 30 mm and 60 mm from the End of Actuator Mouthpiece

	Ovality 30 mm			Area (mm^2) 30 mm		
	(b) (4)					
Mean, n = 5	1.110	1.110	1.129	164.8	166.1	168.9
%RSD	3.4%	1.6%	1.3%	5.8%	3.7%	3.6%

	Ovality 60 mm			Area (mm^2) 60 mm		
	(b) (4)					
Mean, n = 5	1.129	1.158	1.163	393.4	390.3	393.4
%RSD	1.1%	3.0%	2.6%	6.5%	5.6%	2.8%

Table A.5.14 Robustness: Camera Distance on Spray Pattern Measured 30 mm and 60 mm from the End of Actuator Mouthpiece

	Ovality 30 mm			Area (mm^2) 30 mm		
	(b) (4)					
Mean, n = 5	1.108	1.110	1.118	163.0	166.1	164.6
%RSD	3.1%	1.6%	3.2%	3.0%	3.7%	3.5%

	Ovality 60 mm			Area (mm^2) 60 mm		
	(b) (4)					
Mean, n = 5	1.156	1.158	1.146	384.0	390.3	392.5
%RSD	2.9%	3.0%	2.2%	6.4%	5.6%	1.8%

Number of Bottles and/or Lots Used in the Validation Study	Reference lots #AEA13B and PAEF75A
Does Firm's SOP include validation criteria? (Y/N) **Is so, list the criteria**	The method validation report includes the validation criteria. Acceptance Criteria: **Method Precision and Intermediate Precision** For each spray pattern characteristic measured, the %RSD for each analyst's data set were required to meet the following limits:

Characteristic	RSD Limit
Area	NMT (b)(4)%
Dmax	NMT
Dmin	NMT
Ovality	NMT %

Method Repeatability
The RSD for each spray pattern characteristic must be no greater than (b)(4)%

Method Robustness
For each spray pattern characteristic measured, the %RSD for each data set was required to meet the following limits:

Characteristic	RSD Limit
Area	NMT (b)(4)%
Dmax	NMT
Dmin	NMT
Ovality	NMT

Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)

Acceptable

Comments:

The method validation conducted by the firm is acceptable.

4.1.2.4.2 Results Summary – Spray Pattern

Reviewer Calculated Results

Area – Spray Pattern Summary										
	Dist (cm)	Mean		Variability (%CV)					Mean Ratio (T/R)	
				Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arithm	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	3	160.38	160.20	5.55	4.09	4.21	NP	4.81	0.88	0.88
	6	400.22	399.76	4.82	6.08	3.81	NP	4.82	0.98	0.98
Ref	3	182.07	181.93	3.73	4.15	3.82	NP	4.03		
	6	407.44	406.50	5.57	6.99	5.78	NP	6.92		

OVALITY RATIO – Spray Pattern Summary										
	Dist (cm)	Mean		Variability (%CV)					Mean Ratio (T/R)	
				Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arithm	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	3	1.13	1.13	2.63	2.46	2.60	NP	2.55	1.00	1.00

	6	1.16	1.16	3.02	4.44	3.44	NP	3.72	0.99	0.99
Ref	3	1.13	1.13	4.31	3.03	1.86	NP	3.37		
	6	1.17	1.17	6.72	4.00	4.33	NP	5.07		

NP – Not Provided

The firm did not provide the Spray Pattern results summary table. The reviewer calculated the results from the Spray Pattern data provided by the firm. Since the within lot and total variability is less, it is acceptable that the firm did not provide the between lot variability and therefore the firm will not be asked to provide the same.

(b) (4)

[redacted]

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REVIEW OF TESTING METHODS:				
Is the testing method validated?				Yes
Is testing based upon the *true shape* of the spray pattern?				Yes
Is testing conducted as per RLD labeling?				Yes
Is testing a single actuation per determination?				Yes
If yes, what is the actuation number tested?				3 cm - # 2 – 8 6 cm - # 3 – 5 NOTE: The firm conducted the spray pattern testing only on single actuation
Data measured at two distances from actuator orifice?				Yes
If yes, distances 3 – 7 cm?				3 cm and 6 cm
If yes, distances separated by 3 cm or more?				Yes
Does the firm submit representative spray pattern images?				Yes
Was the analysis based upon the *true shape* of the spray pattern?				Yes
Do Dmax and Dmin pass through the COG or COM as appropriate in extent to the parameter of the true shape?				Yes
Are the testing methods acceptable?				Yes
If not, why?				N/A
STUDY RESULTS:				
Similar qualitative visual shapes?				Yes
Equivalence is based upon acceptable PBE results from **EITHER** Automated **OR** Manual Analysis				
Are PBE results acceptable?	**Automated**	**Ovality Ratio**	**Distance 3**	**ACCEPTABLE**
			Distance 6	**ACCEPTABLE**
		AREA	**Distance3**	**UNCCEPTABLE**
			Distance 6	**ACCEPTABLE**
	Manual	**Ovality Ratio**	**Distance 3**	**N/A**
			Distance 6	**N/A**
		Dmax	**Distance 3**	**N/A**
			Distance 6	**N/A**
If not, why?				Area at 3 cm fails the PBE analysis

Comments:

1. The COG was determined automatically and the Dmax, Dmin, Ovality ratio and Area were determined from the true shape of the spray.

2. The firm provided the spray pattern images and accompanying raw data for 20% samples at both 3 cm and 6 cm distances.

3. As per the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, for automated analysis of spray pattern, the PBE analyses are to be performed on area and ovality ratio. Thus the reviewer performed PBE analysis on spray pattern; Except for the area at 3 cm all the other criteria passed the PBE analysis. The reviewer's results correspond with the firm's results where the area at 3 cm fails the PBE analysis.

4. The firm provided the following explanation for the area at 3 cm failing the PBE analysis:

"An investigation into the 30mm spray pattern area (PR #406727 did not identify any assignable laboratory cause for the atypical results for this parameter. (b) (4) (b) (4) (b) (4) *Further, when evaluating the primary measures of Dmax and Dmin at 30mm, the T/R ratios were both 0.94. Statistical analysis of the Dmax and Dmin data at 30mm indicate bioequivalence of both parameters".*

5. The firm's explanation is not acceptable and the firm will be asked to repeat the spray pattern test on area measured at 3 cm.

6. The firm mentioned that few deviations occurred during the Spray Pattern testing and the data mentioned in the following table has been excluded from statistical analysis. The firm only provided the excluded data and did not provide the data with which it was replaced with (the firm only provided the replaced canister numbers). However, since the firm will be repeating the spray pattern test, the firm will not be asked to provide a table with original values and replaced values.

7. The spray pattern testing conducted by the firm is **inadequate**.

4.1.2.4.4 Deficiencies / Recommendations

Please see deficiency comments section.

4.1.2.5 Plume Geometry

4.1.2.5.1 Study Information

Study No.	TTP-CBJ-M0132
Study site	(b) (4)
Principal Investigator	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	(b) (4) Actuation Station (b) (4) Imaging System
Testing Method Description	(b) (4) Plume Geometry for Albuterol Sulfate HFA MDIs
Criteria for defining plume angle, width, & height borders	(b) (4)
Testing Equipment Used **(e.g., name, model, etc)**	
Image Analysis Apparatus Used	
Operating Conditions for Testing Equipment Used **(e.g., temperature, humidity, etc..)**	
Analytical Method Description	
Analytical Equipment Used **(e.g., name, model, etc)**	

Comments:

1. The firm confirmed that plume geometry testing was conducted at a distance of 6 cm from the actuator mouthpiece of the reference product. The firm also mentioned that the distance from the spray orifice to the actuator mouthpiece was

(b) (4) for both test and reference products. Therefore, based on the information provided by the firm, the plume geometry testing was conducted at a distance of (b) (4) from the actuator orifice for both test and reference products.

2. The study design is acceptable.

4.1.2.5.2 Validation Summary Table for Plume Geometry

4.1.2.5.2.1 Precision

Table A.5.15 Precision – Plume Geometry

	Plume Angle	Plume Width
Mean	18.7°	23.1 mm
%RSD	8.2%	8.5%
Range	(b) (4)	

4.1.2.5.2.2 Intermediate Precision (By Date)

Table A.5.16. Intermediate Precision (By Date) – Plume Geometry

Day 1	**Plume Angle**	**Plume Width**
Mean, mm	18.7°	23.1 mm
%RSD (Precision / Repeatability)	8.2%	8.5%
Range, mm	(b) (4)	
Day 2	**Plume Angle**	**Plume Width**
Mean, mm	20.2°	25.0 mm
%RSD (Precision / Repeatability)	17.6%	17.9%
Range, mm	(b) (4)	
% Difference (Day 1 vs. Day 2)	8%	7%
Inter Day %RSD**	14.0%	14.2%

**RSD of all Day 1 and Day 2 data

4.1.2.5.2.3 Intermediate Precision (By Analyst)

Table A.5.17. Intermediate Precision (By Analyst) – Plume Geometry

Analyst 1	**Plume Angle (degrees)**	**Plume Width (mm)**
Mean, mm	18.7	23.1
%RSD	8.2%	8.5%
Range, mm	(b) (4)	
Analyst 2	**Plume Angle (degrees)**	**Plume Width (mm)**
Mean, mm	20.2	25.0
%RSD	17.6%	17.9%
Range, mm	(b) (4)	
% Difference (Analyst 1 vs. Analyst 2)	8%	7%
Inter Analyst %RSD	14.0%	14.2%

4.1.2.5.2.4 Robustness

Table A.5.18: Robustness: Actuation Force at 60 mm from the End of Actuator Mouthpiece – Plume Geometry

MDI Number	Plume Angle (degrees)			Plume Width (mm)		
	(b) (4)					
Mean, mm	15.2	16.4	18.4	18.8	20.2	19.0
%RSD	15.6%	14.2%	1.6%	15.8%	14.4%	1.9%

Table A.5.19: Robustness: Actuation Velocity at 60 mm from the End of Actuator Mouthpiece – Plume Geometry

MDI Number	Plume Angle (degrees)			Plume Width (mm)		
	(b) (4)					
Mean, mm	14.8	16.4	17.1	18.3	20.2	21.1
%RSD	10.0%	14.2%	11.7%	10.4%	14.4%	12.2%

Number of Bottles and/or Lots Used in the Validation Study	Reference lots #AEA13B and PAEF75A
Does Firm's SOP include validation criteria? (Y/N) **Is so, list the criteria**	The method validation report includes the validation criteria. Acceptance Criteria: (b) (4)
Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	Acceptable

Comments:

The method validation conducted by the firm is acceptable.

4.1.2.5.3 Results – Plume Geometry

Reviewer Calculated Results

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

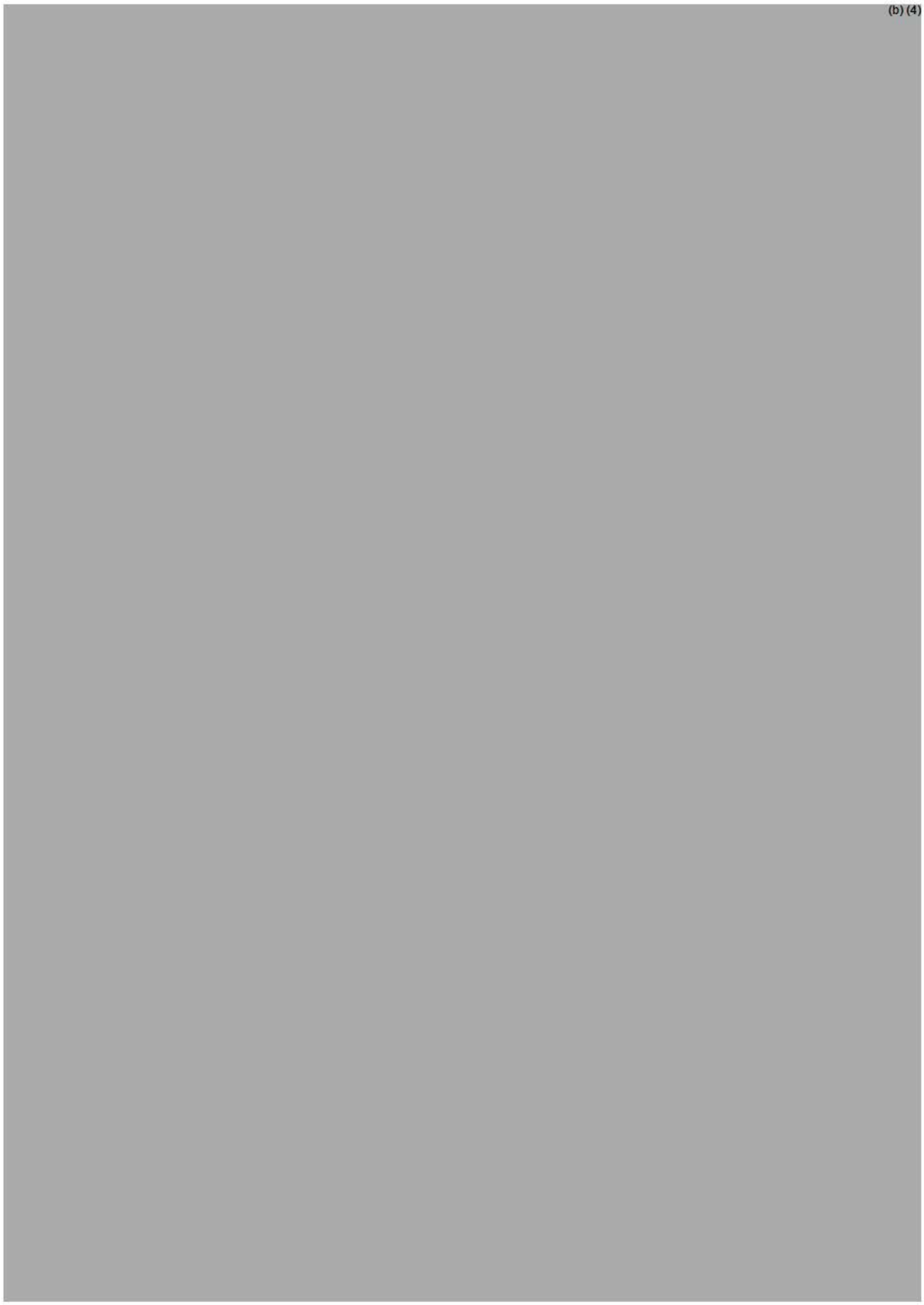
Test	17.69	17.58	8.61	12.40	12.24	NP	10.91	0.98	0.98
Ref	18.03	17.94	9.98	9.29	12.54	NP	10.34		
Plume Width									
Test	21.91	21.77	8.8	12.7	12.6	NP	11.21	0.98	0.98
Ref	22.32	22.20	10.27	9.80	12.97	NP	10.73		

NP – Not Provided

The firm did not provide the Plume Geometry results summary table. The reviewer calculated the results from the plume Geometry data provided by the firm. Since the within lot and total variability is less, it is acceptable that the firm did not provide the between lot variability and therefore the firm will not be asked to provide the same.

(b) (4)

[redacted]


(b) (4)

(b) (4)

4.1.2.5.4 Conclusions

PLUME GEOMETRY	
REVIEW OF TESTING METHODS:	
Is the testing method validated?	**Yes**
Is testing conducted as per RLD labeling?	**Yes**
Is the image a snapshot?	**Yes**
If not, why?	**N/A**
Are representative photographs/digital images provided?	**Yes**
Is plume geometry measured at a single delay time while the fully-developed phase of the plume is still in contact with actuator tip?	**Yes**
Are plume width measures made at a single, fully-developed delay time while plume is still in contact with actuator tip?	**Yes** The firm provided the plume geometry images. Based on the images, the plume width measures were made while the plume is still in contact with the actuator tip. In addition, plume width and angle measurements were assessed from the same side of the plume.
Are plume width measurements made at a distance equal to the greater of the two distances selected for characterization of the spray pattern? (e.g., is plume width measured at 6 cm if spray pattern were measured at 3cm and 6 cm)	**Yes (6 cm)**
Is plume height measured at a distance from the actuator orifice to the leading edge of the plume?	**Yes**
Is plume geometry measured at:	
1) beginning lifestage	**Yes**
2) one side view only	**Yes**
Are plume angle, width, & height all quantitated using same method?	**Yes for angle and width parameters.**
Are the testing methods acceptable?	**Yes**
If not, why?	**N/A**
STUDY RESULTS:	
Is the Plume Angle T/R geo mean ratio between 0.90-1.11%?	**Yes**
Is the Width T/R geo mean ratio between 0.90-1.11%?	**Yes**
Are the (point estimate) results acceptable?	**ACCEPTABLE**
If not, why?	**N/A**

Comments:

- The ratio of the T/R geometric means for plume width and angle in the beginning are within the limits of 0.90-1.11. According to the FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (draft, April 2003), the point estimates would not be applicable for the plume height due to subjectivity.

- In addition, the test product passes the PBE statistical criteria for both width and angle.

- The firm mentioned that few deviations occurred during the Plume Geometry testing and the data mentioned in the following table has been excluded from statistical analysis. The firm only provided the excluded data and did not provide the data with which it was replaced with (the firm only provided the replaced canister numbers). Therefore, the firm will be asked to provide a table with original values and replaced values, so that the reviewer can include the original values and run the statistical analysis.

(b) (4)

The study is **incomplete** with deficiencies.

4.1.2.5.5 Deficiencies / Recommendations – Plume Geometry

Please see deficiency comments section.

5 DEFICIENCY COMMENTS

1. The firm mentioned that few deviations occurred during the conduct of Single actuation content (SAC), aerodynamic particle size distribution (APSD) by cascade impaction and plume geometry (study # TTP-CBJ-M0132) studies comparing the test product with dose counter with reference product with dose counter and the data has been excluded from statistical analysis. The firm only provided the excluded data and did not provide the data with which it was replaced with. Therefore, the firm will be asked to provide a table with original excluded values and replaced values for these tests.

2. The spray pattern testing (study # TTP-CBJ-M0132) comparing the test product with dose counter with the reference product with dose counter fails the PBE analysis for spray area at 3 cm distance. The firm will be asked to repeat this test.

3. According to the following Office of Pharmaceutical Quality (OPQ) deficiency, test product batch # 08MM-050 is not representative of the commercial batch. Therefore, the pharmacokinetic (PK) (study # 10825302) and pharmacodynamic (PD) (study # PRG-723) BE studies conducted using batch # 08MM-050 are not acceptable. In addition, the Office of Study Integrity and Surveillance (OSIS) recommends that the data from PD study (# PRG-723) are not acceptable for further Agency review (please refer to deficiencies based on the inspection findings by the OSIS). Therefore, the firm will be asked to repeat the pharmacokinetic (PK) and pharmacodynamic (PD) BE studies.

   It should be noted that batch # 08MM-050 was not used for the in vitro BE studies comparing the test product with dose counter with the reference product with dose counter.

<u>Deficiencies Based on Inspection Findings by the Office of Study Integrity and Surveillance (OSIS):</u>

4. Following the inspection of the analytical site [redacted] (b) (4) between [redacted] (b) (4) by the Office of Study Integrity and Surveillance (OSIS) for the current ANDA, Form FDA-483 was issued. Subsequently, the analytical site provided its responses to Form 483 and those responses were included in the final evaluation by the OSIS.

   The DBI reviewed the above OSIS inspection report and found that the following objectionable findings by the OSIS at the analytical site could potentially compromise the integrity of the study of the current application:

   Finding # 1: *Not all original data were reported following reanalysis or retest. Specifically, Protocol TTP-CBJ-M0050 required any reanalysis or retest data to be reported along with the original data in the study report. However, the following tests were repeated and the original data were not reported with the retest data:*

1) *Aerodynamic Particle Size Distribution (APSD) by Cascade Impactor (CI) for Study TTP-CBJ-M0050, Part 1, conducted from 4/13/2009 to 4/17/2009.*
2) *Spray Pattern for Study TTP-CBJ-M0050, Part 1, conducted from 3/31/2009 to 4/3/2009.*
3) *Plume Geometry for Study TTP-CBJ-M0050, Part 1, conducted from 4/1/2009 to 4/2/2009.*

Finding # 2: *Out-of-specification (OOS) results were not reported in the study report for Protocols TTP-CBJ-M0050 and TTP-CBJ-M0132. Examples include, but are not limited to, canisters retested/replaced and tests rejected due to assignable causes (e.g., instrument failure, sample collection, or processing errors). Specifically,*

1) *APSD by CI for Study TTP-CBJ-M0132,* (b) (4) (b) (4).
2) *APSD by CI for Study TTP-CBJ-M0132,* (b) (4) (b) (4).
3) *APSD by CI for Study TTP-CBJ-M0132,* (b) (4) (b) (4).
4) *Spray Pattern for Study TTP-CBJ-M0050 Part 1,* (b) (4) (b) (4).
5) *Plume Geometry for Study TTP-CBJ-M0050,* (b) (4) (b) (4)

In addition, a number of canisters were replaced during the study due to other reasons.

Based on the above findings, the firm should submit the following information:

a. The firm should submit all the in vitro BE study data including original and reanalysis or retest and a detailed study summary report which includes all the tests conducted and the details of the investigations for retesting or reanalysis for study # TTP-CBJ-M0132. The firm should also provide the SAS data (original and retested/ reanalyzed) in xpt format.

b. The firm should submit all the in vitro BE study data including original data obtained with original canisters and retested data obtained with replaced canisters and a detailed study summary report which includes justification for the replacement of canisters for study # TTP-CBJ-M0132.

5. Following the inspection of the clinical sites (University of Florida, Gainesville; University of Iowa, Iowa City; California Allergy & Asthma Medical Group, Los Angeles) between 11/03/2014 – 01/09/2015 by the Office of Study Integrity and Surveillance (OSIS) for the current ANDA, Form FDA-483 was issued.

Subsequently, the clinical sites provided its responses to Form 483 and those responses were included in the final evaluation by the OSIS.

The DBI reviewed the above OSIS inspection reports and found that the pharmacodynamic study (PRG-723) conducted is not acceptable based on the following OSIS findings. The firm should repeat the pharmacodynamic study.

a) *There was a discrepancy in the assigned treatments between the randomization schedule in the study report and the protocol.*
b) *The original code-blinding scratch-off stickers were not maintained at the clinical site prior to subject enrollment and until the FDA inspection and their integrity cannot be assured.*
c) *Without the code-blinding scratch-off stickers, we are unable to confirm which treatments subjects received.*

6. The firm will also be informed that the case report forms for all the subjects in the pharmacodynamic study (PRG-723) were not submitted based on the following OSIS finding for the California Allergy & Asthma Medical Group:

Investigational records were not retained. Specifically, three randomized subjects' and ten screen-failed subjects' bioequivalence study Source Records, Informed Consent Forms and Case Report Form Files were missing and could not be located during the inspection. The following subjects' entire study records were missing:

Screening Number / Randomization Number

(b) (6)

6 COMMENTS FOR OTHER OGD DISCIPLINES

Discipline	Comment
None	None

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

This OSIS finding is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ **Isolated**	☒ **Systemic**

7.2 Clinical Sites (Pharmacodynamic Study)

The University of Iowa Hospitals & Clinic
200 Hawkins Drive
Iowa City, Iowa 52242
Principal Investigator: Richard C Ahrens, MD

University of Florida
Asthma Research Lab
1600 SW Archer Road
Gainesville, FL 32610
Principal Investigator: Leslie Hendeles, Pharm D

California Allergy & Asthma Medical Group (CAAMG)
11645 Wilshire Blvd, Suite 1155
Los Angeles, CA 90025
Principal Investigator: Sheldon L Spector, MD

7.2.1 Executive Summary

This is a review of the OSIS Inspection Report dated 05/18/2015[15].

The inspection report references the Pharmacodynamic Study (PRG-723, Study Dates: 02/24/2011 – 03/31/2011) in the current ANDA that was submitted in the original application dated 12/16/2011. The Reference drug product is NDA 021457, ProAir® HFA (albuterol sulfate) Inhalation Aerosol, Metered, 0.09 mg Base/Inhalation from Teva.

The Division of Bioequivalence I (DBI) requested a new site inspection of the above mentioned three clinical sites (The University of Iowa, The University of Florida and California Allergy & Asthma Medical Group). The OSIS conducted an inspection of the clinical sites from:

11/03/2014 – 11/06/2014: The University of Iowa
12/08/2014 – 12/17/2014: The University of Florida
01/05/2015 – 01/09/2015: California Allergy & Asthma Medical Group

Form 483 was issued for The University of Iowa and California Allergy & Asthma Medical Group. The inspection included the study report for pharmacodynamic study (PRG-723).

The firm's response to Form 483 was received on 11/24/2014 and 02/02/2015 for University of Iowa and California Allergy & Asthma Medical Group respectively.

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[15] Panorama Database, ANDA 203760, Project # ANDA-203760-ORIG-1-RESUB-2, Clinical PK/PD Sites, Document # 203760 Alb Per.pdf, Version 01, Modified Date: 05/19/2015, Author: Hansong Chen

The OSIS outcome was voluntary action indicated (VAI), VAI and official action indicated (OAI) for The University of Iowa, The University of Florida and California Allergy & Asthma Medical Group respectively.

In a Memo dated 05/18/2015, the OSIS provided the Division of Bioequivalence I (DBI) with its findings. Based on the inspection and firm's response, the OSIS provided the following conclusion:

Following the above inspections, this reviewer recommends that data from study PRG-723 are NOT acceptable for further Agency review based on the following reasons:

1. *There was a discrepancy in the assigned treatments between the randomization schedule in the study report and the protocol.*
2. *The original code-blinding scratch-off stickers were not maintained at the clinical site prior to subject enrollment and until the FDA inspection and their integrity cannot be assured.*
3. *Without the code-blinding scratch-off stickers, we are unable to confirm which treatments subjects received.*

The DBI has reviewed the inspection report and concurs with the OSIS's evaluation.

For the OSIS Inspection Report Review of the Parent ANDA (203760):

The DBI recommendations for the OSIS report review are inadequate for the current ANDA, and the issues identified in OSIS's report are systemic and may affect other studies conducted at the clinical sites (The University of Iowa, The University of Florida and California Allergy & Asthma Medical Group). The Project Manager should assign all related ANDAs for review to determine the acceptability of other studies conducted at the same clinical facilities.

7.2.2 Inspectional Observations

The OSIS provided the DBI with the following findings:

The University of Iowa

Finding # 1: Failure to permit an authorized officer or employee of FDA to verify records or reports. Specifically, I was notified on 11/04/2014 that the blinding code (scratch-off stickers affixed to investigational drug product box labels) was removed by the study monitor during the course of the study. The firm did not maintain the sealed code on site; therefore, I was unable to establish with certainty the identity of the test and reference drugs used for the dosing of subjects as well as to confirm if the subjects received the correct study treatment (i.e., test or reference product) as per the treatment randomization schedule.

The sponsor did not use a sealed envelope containing the study randomization schedule and blinding codes for the study as indicated in the study protocol. Instead, the study

medication kits contained the code-breaking scratch-off stickers. As a kit was assigned to a subject, the site removed the sticker from the kit and placed it onto a study drug dispensation record for the subject.

Later, a study monitor collected the original study drug dispensation record – MDI labels containing the code-breaking scratch-off stickers from the site. The site only maintained photocopies of the records, which were provided to Mr. Campos during the inspection. However, the copies for seven subjects (Subjects (b) (6) were missing, which the firm did not present to Mr. Campos. It should be noted that the study was still in progress when the monitor took the original study drug dispensation record – MDI labels from the site. (b) (6) subjects completed the study and (b) (6) subjects were terminated early after the date when the monitor removed the original MDI labels from the site.

During the inspection, Dr. Ahrens contacted the sponsor and arranged the original study drug dispensation record – MDI labels containing the code-breaking scratch-off stickers to be sent back to the site. Mr. Campos confirmed their presence at the site.

The site provided Mr. Campos with copies of the original drug dispensation record – MDI labels containing the scratch-off stickers (that were returned to the site) and the copies maintained at the site (made before collection by the study monitor). However, the obscure parts of the copies of the study drug dispensation record – MDI labels returned to the site did not show a description stating "Drug Information Inside in Case of Emergency Scratch off the Surface of Blinded Area", while it was visible on the copy of the copies maintained at the site.

Dr. Ahrens stated in his response to Form FDA 483 that the study drug dispensation record – MDI labels containing the original scratch-off stickers are identical to the copies left at the site. However, his statement could not be substantiated because for Kit Number (b) (4), for example, there were additional hole punches on the upper right and left corners on the copy made from the original MDI labels maintained at the site that were not present on the original documents. Due to the additional punch holes, some telephone numbers were missing on the copy. Similar discrepancies were noted on all other records' copies, despite Dr. Ahrens' statement that the copies maintained at the site were exact copies of the originals.

Firm's Response to Finding # 1: We must respectfully disagree with Inspector Campos' characterization of what occurred during his inspection. Rather than failing to permit the Inspector access to the labels containing the scratch-off stickers, we acted promptly to facilitate his access to this code for both test product used in the study and for retention samples maintained at the site. These labels were provided to him on Tuesday, November 4, 2014 for the retention samples and on the morning of November 5, 2014 for the test products.

We maintained at our site the labels containing the scratch-off stickers for test products assigned to each subject until that subject had completed study. During a monitoring

visit, [redacted] Retention samples of test product, including their associated intact original labels containing the scratch-off sticker, remained at the site.

On Monday, November 3, 2014, the first day of the FDA inspection, we made the Pharmacy records we had on site available to Inspector Campos and showed him our fifteen (15) retention samples with the intact original scratch-off blinding stickers attached. On Tuesday, November 4, 2014, Inspector Campos asked to see the original labels containing the scratch off blinding stickers for the test products used in the study. We informed him that we had exact copies of the labels on site, but not the originals, as we had been directed to provide those to the [redacted] as described above. We showed Inspector Campos [redacted] documentation of the collection of the test products and original scratch-off blinding labels made by the [redacted] and the exact copies of the original labels that remained in our site files. When the Inspector indicated that he needed to review the original labels, we contacted the Sponsor, Perrigo Pharmaceuticals, and requested the originals be sent back to us immediately. The Sponsor over-night expressed the originals to us and the labels containing the scratch-off sticker pages arrived before 10 A.M. the next morning, November 5, 2014. The blinding stickers were then promptly given to Inspector Campos. Thus, the 483 observation that we "fail[ed] to permit" review of these records is inaccurate.

Although we provided the records to Inspector Campos, he informed us later in the day of November 5, 2014 that he had been instructed by FDA reviewers not to examine the labels we had provided to him. This included both original scratch-off stickers for the test products used in the study as well as the retention samples. It is unclear to us why this occurred, since a comparison of the original labels containing the scratch-off stickers with the copies left at our site by [redacted] reveals conclusively that the originals are identical to the retained copies. There is no question on this point. The originals, including the study documents to which they are affixed, are identical to the copies in every detail, including handwritten study subject number, subject initials, kit number, principal investigator name, and error corrections; the position of the blinding label on the documents; and 3-hole punch marks, smudges, and defects present on both the originals and the copies. We understand from the Sponsor that the [redacted] placed the original scratch-off sticker labels in the Sponsor's retained study master file and that treatment assignments were not visible to the Sponsor until after the data analysis was complete, the results were known, and the final report was issued.

Based on the foregoing, we object the decision to issue a 483 in this case. We were informed by the TKL study monitor during a study visit that she would collect the test products and the labels containing the scratch-off stickers; we retained exact copies of those records at our site. When inspector Campos asked to see the original labels, we promptly produced the records for the retained samples, which were always at our

site, and obtained from the Sponsor he original records for the test products used in the study, verified that they were identical to the copies we had retained, and made them available to him for his review. Instead of "fail[ing] to permit" his review of the records, we made every effort to facilitate that review. To the best of our knowledge, all of our actions on this study were entirely consistent with the study protocol as wells as FDA regulations and we respectfully request that the 483 be withdrawn.

OSIS Conclusion for Finding # 1: This reviewer is of the opinion that the data integrity is significantly compromised because the blinded codes were not kept at the site prior to subject enrollment and until the inspection. Thus, this reviewer is unable to authenticate the copies maintained at the site and cannot assure that there were no changes or substitutions made to the blinding codes while they were outside the control of the clinical site.

DB Reviewer Comment # 1 for Current ANDA: The reviewer agrees with the OSIS conclusion that the data integrity of the pharmacodynamics study might have been compromised since the identity of the test and reference products could not be established with certainty and also could not confirm if the subjects received the correct study treatment (i.e., test or reference product) as per the treatment randomization schedule.

This OSIS finding is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ **Isolated**	☒ **Systemic**

The University of Florida

ORA investigator Valerie Grecek-trinh audited the University of Florida, Asthma Research Lab from December 8-17, 2014. Ms. Grecek-trinh did not issue Form FDA 483 at the conclusion of the inspection. However, she determined that the study drug dispensation record – MDI labels containing blind scratch-off stickers were removed from the site by the study monitor after the study was complete. Similar to the case of the University of Iowa described above, the site made photocopies of the drug dispensation records with blinded scratch-off stickers and only the copies remained on site. The originals were returned to the site by the sponsor on 11/04/14, when the inspection at the University of Iowa was ongoing.

During the inspection, Ms. Grecek-trinh removed the obscured sections of the scratch-off stickers on the original study drug dispensation record - MDI labels to un-blind the codes and to verify that subjects received their assigned treatment specified in the randomization sequence in the study report. However, upon review, she noticed that the treatment codes in the study report represented by a single-letter alphabet (A through E) were not consistent with those in the study protocol. The table below shows the treatment codes used in data analysis presented in the study report, compared to those in the study

protocol. The treatment codes in the un-blinded scratch-off stickers matched those in the study report.

Treatment Code	Assigned treatment in the study report used for data analysis	Assigned treatment in the study protocol
A	Vehicle (Placebo)	Vehicle (Placebo)
B	90 mcg of Test	90 mcg of Reference
C	90 mcg of Reference	180 mcg of Reference
D	180 mcg of Test	90 mcg of Test
E	180 mcg of Reference	180 mcg of Test

California Allergy & Asthma Medical Group

Finding # 1: The Biopharmaceutical Clinical Facility failed to appropriately retain bioequivalence samples as required. A blinded key code was not provided to the site for verification of the randomization scheme of bioequivalence test versus reference drug kits. In addition, the "scratchoff" blinded labels were removed from the all of the drug kits and applied to "STUDY DRUG DISPENSATION – MDI LABEL" forms. The monitor had removed all of the forms bearing the obscured blinded labels for all subjects that were randomized and later returned the obscured labels back to the clinical facility. There is no assurance of the integrity of the blinded labels when the facility lost custody of the labels causing a lack of assurance that the labels came from the same kits used in the study. Ten reserve sample kits were retained; however, five kits had the blinded labels removed from drug kits carton.

The FDA 483 was issued to (b) (4) because Dr. Sheldon L. Spector, Principal Investigator, was out of country during the inspection. The site had the same issue of not maintaining the original study drug dispense record – MDI labels, as the other two sites described above.

In addition, the exhibit collected by (b) (4) shows that the other four sites did not maintain the original study drug dispense record – MDI labels containing scratch-off stickers onsite.

a. Allergy & Asthma Diagnostic Treatment center
   2300 Centerville Road
   Tallahassee, FL 32308
   PI: Ronald H Saff, MD

b. Clinical Research Atlanta
   175 Country Club drive, Suite 100A
   Stockbridge, GA 30281
   PI: Nathan Segall, MD, CPI

c. Spartanburg Medical Research

485 Simuel Road
Spartanburg, SC 29303
Lung& Chest Medical Associates
2030 North Church Place
Spartanburg, SC 29303
PI: Charles M Fogarty, MD, CPI

d. AARA Research Center
9900 N Central Expy, Suite 555
Dallas, TX 75231
PI: William R. Lumry, MD

Firm's Response to Finding # 1:

Observation 1) "Ten reserve sample kits were retained however, 5 kits had the blinded labels removed from the drug kits carton. In addition, the "scratch-off" blinded labels were removed from all of the drug kits and applied to "STUDY DRUG DISPENSATION –MDI LABEL" forms. The monitor had removed all of the forms bearing the obscured blinded labels for all subjects that were randomized and later returned the obscured forms back to the clinical facility. There is no assurance of the integrity of the blinded labels when the facility lost custody of the labels causing a lack of assurance that the labels came from the same kits used in the study. The Biopharmaceutical Clinical Facility failed to retain bioequivalence samples as required. A blinded key was not provided to the site for verification of the randomization scheme of bioequivalence test versus reference drug kits."

At the time of conducting the study the site was not aware of our obligation to maintain the original labels on-site in order to demonstrate good custody and ensure the integrity of the samples and their dispensation to the subjects. With this said, the monitor at the time completed the Close-Out Visit notes that summarized the events that occurred, [redacted] (b) (4) and it specifically notes that the "Test Materials Dispensing Logs" which contain the removed labels, were copied and then the copies were taken from the site. This however, is not what happened and the originals were taken and copies left on site. We understand this issue in hindsight and realize its significance in the scheme of bioequivalence versus non-bioequivalence studies. When conducting a side-by-side of the original label forms with the copy of the forms left at the site, it is verifiable that these were not substituted, tampered with or falsified in any way prior to being returned to the site, however, we are aware of the severity of the core issue which is removal of these labels and the consequential integrity issue that arises from it.

In light of this communication from FDA we have created an SOP that is attached, that clarifies our rights and responsibilities and directs staff in the future for selecting studies and the necessary procedures to be followed when implementing and initiating these studies specific to bioequivalence testing. This procedural plan was devised after researching section 7348.001: In Vivo Bioequivalence, on the FDA website as well as discussing with various sponsors, including the one for which the review was conducted.

Implementation & corrections for these findings;

Part 1 of Observation 1)

"The Biopharmaceutical Clinical Facility failed to retain bioequivalence samples as required. A blinded key was not provided to the site for verification of the randomization scheme of bioequivalence test versus reference drug kits."

As stated above, we were not aware of the specific rule indicating a physical code was to be provided by sponsor and kept on site to maintain the integrity randomization scheme and to verify sample to subject to code.

We contacted sponsors from current studies that are bioequivalent in order to confirm or initiate the execution of any outstanding criteria to meet this finding.

Going forward, when selecting studies to participate in we will exercise our right of selection by following our SOP and decide whether the study design is in our best interests to be a part of if this provision is not met in the design of the protocol.

Part 2 Observation 1)

"In addition, the "scratch-off" blinded labels were removed from all of the drug kits and applied to "STUDY DRUG DISPENSATION –MDI LABEL" forms. The monitor had removed all of the forms bearing the obscured blinded labels for all subjects that were randomized and later returned the obscured forms back to the clinical facility. There is no assurance of the integrity of the blinded labels when the facility lost custody of the labels causing a lack of assurance that the labels came from the same kits used in the study."

While the first sentence in itself is not a deviation from the rules set forth in the FDA guidance; being the removal of the labels from the kits to the forms, once those forms left the site custody, is where the deviation and lack of integrity is met.

As an immediate action we have again devised a very specific SOP that has been included here, that will guide our site in the future with its responsibilities to the drug and any corresponding documentation including labels, forms etc.

Part 3 Observation 1)

"Ten reserve sample kits were retained however, 5 kits had the blinded labels removed from the drug kits carton."

These labels were removed from the 5 retention sample kits, however the labels were kept with samples at all times. We have included a memo that was created by the study coordinator for that at the time of the study explaining what happened with the removal of the labels from the retention samples and clearly stating that they were kept with the medication at all times.

In summary of observation 1) our site has been educated to the necessary changes that are required to produce study data that that is valid, verifiable and founded with integrity. We are committed to following our new standards set forth in the SOP and again, welcome any review of the Corrective Action plan we have for any additions, clarifications or alterations that might be necessary to make this effective.

OSIS Conclusion for Finding # 1: The scratch-off labels were removed from five kits of reserve samples. Therefore, OSIS cannot assure which label come from which kit, and these kits could no longer serve to verify the identity of drugs used in the study. Dr. Spector acknowledged the finding and has created a SOP to address the issue for future studies.

DB Reviewer Comment # 1 for Current ANDA: The reviewer agrees with the OSIS conclusion. There is no assurance of the integrity of the blinded labels since the facility lost custody of the labels causing a lack of assurance that the labels came from the same kits used in the study.

This OSIS finding is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ **Isolated**	☒ **Systemic**

Finding # 2: Investigational records were not retained. Specifically, three randomized subjects' and ten screen-failed subjects' bioequivalence study Source Records, Informed Consent Forms and Case Report Form Files were missing and could not be located during the inspection. The following subjects' entire study records were missing:

Screening Number / Randomization Number

(b) (6)

Firm's Response to Finding # 2:

Implementation & corrections for these findings:

Our site has a large storage facility (b) (4) of the building that is utilized for (b) (4) (b) (4) once a study is closed out. This storage facility has been used since the opening of the site in the (b) (4) (b) (4)

With regards to this finding specifically, once the missing documents were noted by the auditor we put in place search teams to organize and find the files in order to produce them during the inspection. Once the inspection concluded and the documents were not recovered, we extended our search further utilizing the site staff over the weekends for the duration of the 15 day period for letter submission in hopes of discovering the items. At this point, we have not recovered the records; subsequently some site wide applications have been imposed:

1) The storage has been re-organized which is characterized by: a) full cataloguing of each study in the storage facility, they are being boxed and stacked and labeled to identify the study name, the year conducted & the contents of the boxes (ex. the regulatory documents, patient source or screen fails etc.) b) the elimination of any non-study related stored documents from the front office that may confound or confuse the research study documents c) access to storage unit will also be regulated through documentation of a log that has been created (and attached) that will document any incoming study documents, the dates they were entered, the personnel that handled the storing, or any other reasons for entering the unit. It also contains a section for "checking documents out and back in" for functional use of the data if so is needed after the documents stored. This includes the date documents were taken out, the reason they were taken, the personnel utilizing the documents and again the date they were returned to the storage.

As an additional precaution the site inspected the Investigator's personal storage units to exclude any possibility that the documents in question were misfiled with the clinic office medical records, billing and or patient records.

Research site staff is currently still in progress of discarding all non-research related material in the storage unit but will continue to monitor and actively re-locate any non-research related documents necessary. Until this is completed, site staff will consider the status of the missing documents as still in progress. Periodic written updates will be sent to FDA on a monthly basis until this task has been completed and/or the documents located or deemed officially outstanding. Should any evidence of the missing records be recovered, site staff will immediately contact and send appropriate copies of the informed consent forms where necessary.

In support and verification of the existence of these subjects and in support of the review of all consents, source documents and case report forms by the sponsor during the study, I have attached the monitoring follow-up communications from the time the study was conducted.

In summary of Observation 2; the site has done a complete restructuring of the storage department and completed a thorough inspection of all documents in order to discover the missing records. At this point this observation status is considered open. Under the following conditions will the site change the status of this finding to "complete" if:

1) the documents are recovered and the restructuring of storage is fully executed and functioning
2) the restructuring has been completed and the storage functional yet the documents are not recovered

Again, monthly updates will be sent highlighting the progress of this Corrective Action until it is Complete.

In conclusion, attached to this document you will find:

1) An SOP in support of our commitment to implementing the site changes necessary to conduct effective studies in Bioequivalence
2) A memo written at the time the study was conducted discussing the retention sample label removals
3) 3 monitor formal monitor letters from the time the study was conducted verifying the existence and review of missing patient data as well as documenting the Close-Out Visit activities
   Note 1: January 22, 2011-informed consent and source data review
   Note 2: April 2, 2011-informed consent and source data review
   Note 3: May 21, 2011-COV notes indicating intentions to remove copies of IP label logs
4) The "Storage Accountability Log" for reference

We have also included a letter written for the Auditor, [redacted] (b) (4) that reiterates the absence of the Investigator and company president at the time of inspection and also our thanks for the thorough review.

OSIS Conclusion for Finding # 2: CAAMG failed to retain the above subjects' investigational records. This reviewer is of the opinion that the lack of subjects' study records compromises the integrity of the data and raises concerns on the safety of the subjects enrolled in the study.

For the University of Iowa and CAAMG sites, the ORA investigators did not un-blind the original scratch-off labels (blind codes). Therefore, we are unable to confirm if those subjects received their assigned treatment as designated in the study protocol.

DB Reviewer Comment # 2 for Current ANDA: The reviewer agrees with the OSIS conclusion, that failure of retaining the subjects' investigational records compromises the data integrity as well as raises concerns on the safety of the subjects enrolled in the study. The pharmacodynamic study (PRG-723) conducted by the firm is not acceptable and the firm will be asked to repeat the study.

This OSI finding is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ **Isolated**	☒ **Systemic**

Meeting Minutes

MEETING MINUTES

Perrigo Industry meeting

Meeting Date: May 5th, 2008 **Time:** 10:00 AM-12:20 PM

Location: MPN 4 - Conference Room "A"

Firm Name: Perrigo

Drug Name: Albuterol Sulfate HFA Inhalation Aerosol (RLD: ProAir HFA, Ivax)

Meeting Type: Industry meeting

Meeting Chair: Gary Buehler, R.Ph., Director, OGD

Meeting Recorder: Doan Nguyen, Pharm.D., Project Manager

FDA Office of Generic Drug Attendees, Titles and Offices:

Gary Buehler, R.Ph.	Director, OGD
Wallace Adams, Ph.D	Team Leader, Science Staff
Angela Payne	DLPS/LRB
Lawrence Yu, Ph.D	Director for Science
Dale Conner, Pharm.D.	Director, DBE I
Michael Smela Jr	Team Leader, Chemistry I
Bing Li, Ph.D	Acting Team Leader, DBE I
Hoainhon Nguyen, M.S.	Acting Deputy Director, DBE I
Sau Lee, Ph.D	Reviewer, Science Staff
Rashmikant Patel, Ph.D	Director, Chemistry I
Paul Schwartz, Ph.D	Deputy Director, Chemistry I
David Read, JD	Regulatory Counsel, OGD
Doan Nguyen, Pharm.D.	Project Manager, Science Staff

Industry Representatives, Titles and Offices:

From Perrigo Research and Development Company (*Applicant*):

Jatin Shah, Ph.D. - Chief Scientific Officer

Mushtaq Fruitwala, Ph.D. - Director, Research and Development

Herbert Luther, Ph.D. - Vice President, Global Regulatory Affairs.

Brian Schuster - Associate Director, Regulatory Affairs

Beatriz North - MPH, CCRA, Director, Clinical Affairs

Jonathan Schwartz - Project Manager, Clinical Affairs

(b) (4)

[redacted]

MEETING MINUTES

Perrigo Industry meeting

(b) (4)

Meeting Objectives:

Meeting request from Perrigo.

To discuss:

- Regulatory Issues
- Bioequivalence Studies Program
- Chemistry

Background:

- (b) (4)
- ProAir lacks a dose counter
- (b) (4)

Discussion Points:

8.1 REGULATORY ISSUES

A. Appropriate Filing as ANDA

Confirm test product qualifies for filing as an ANDA, differing as follows from ProAir HFA

- (b) (4)
  a. Necessitates a label change - 21 CFR 314.94(a)(iv) permits this change
- (b) (4)
  a. Acceptable as long as they meet OGD CMC expectations
- (b) (4)
  a. Acceptable providing in vitro and in vivo equivalence are acceptable

B. Retention Samples

Confirm that the number of retains (maximum 50) will apply to the test product

a. The draft Nasal BA/BE Guidance specifies a minimum of 50 units of each T and R batch for nasal aerosols. The same expectation applies to orally inhaled aerosols for each batch used for both in vitro and in vivo studies. If placebo product is used in either in vitro or in vivo studies, the minimum 50 units also applies.

8.2 Bioequivalence Studies Program

A. In Vitro Studies

1. Dose Content Uniformity Through Container Life (B,M,E)

a. Dose Content Through Container Life (not Dose Content Uniformity. Note that Delivered-Dose Uniformity is a USP <601> test which is noncomparative). The firm should provide Single Actuation Content Through Container Life, not Dose Content Uniformity Through Container Life. The distinction is that the studies should be conducted using one actuation, not two actuations, since PROAIR HFA labeling allows one inhalation every 4 fours in certain instances.

2. Aerodynamic Particle Size Distribution (APSD)

Comparative data for drug deposition on individual deposition site, and mass balance data based on drug deposition on all sites, should be provided.

3. (b) (4)

3. (b) (4)

4.

5. Spray Pattern and Plume Geometry

   a. Should be conducted
   b. Please confer the draft Guidance: MDI and DPI Drug Products - CMC Documentation (Section F.1.m: Spray Pattern and Plume Geometry)
   c. Draft CMC Guidance states that these tests are important for evaluating the performance of valve and actuator.

5. Priming and repriming data (last bullet, Perrigo package, p. 5 - 6)

   Firm needs to be clear in its text as to comparative testing for BE and noncomparative testing for CMC.

6. Comparative in vitro testing will be conducted on three batches of T and three batches of R

(b) (4)

B. Pharmacokinetic Study

1. Statistical methodology

   a. Agree

2. (b) (4)

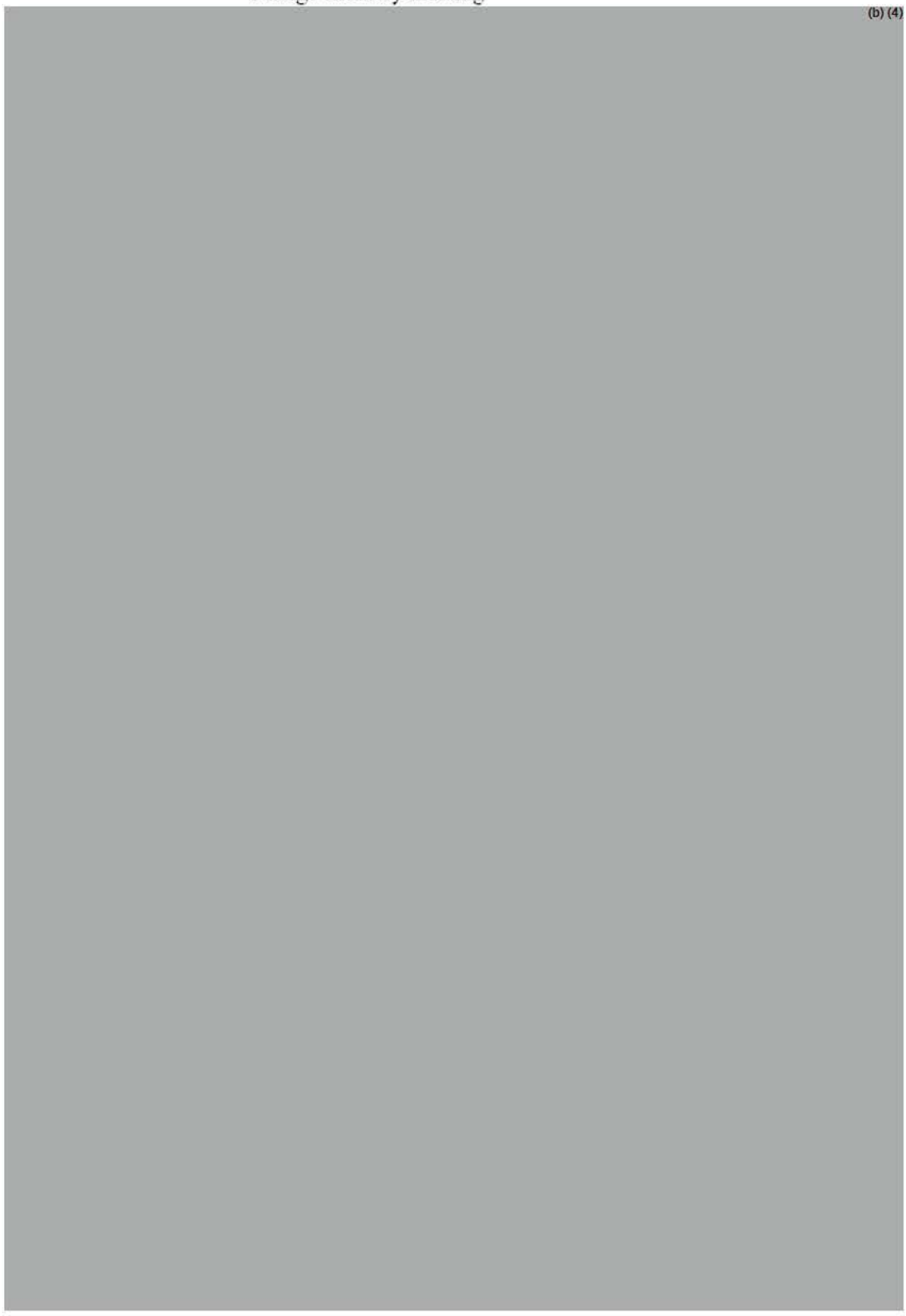
C.

MEETING MINUTES

Perrigo Industry meeting

(b) (4)

D.



MEETING MINUTES

Perrigo Industry meeting

8.3 (b) (4) [redacted]

Unresolved issues or issues requiring further discussion:

None

Action items:

None

Teleconference meeting minutes with the Office of Generic Drugs (OGD) on August 26, 2011

FDA MEETING MINUTES
Teleconference
(Prepared by FDA)

FDA/Perrigo
Albuterol Sulfate HFA Inhalation Aerosol

Meeting Date:	August 26, 2011	**Time:**	10:00 - 11:30 AM
Location:	7519 Standish Place, MPN4, C/R A, Rockville MD 20855		
Meeting Chair:	Sau (Larry) Lee, Ph.D., OGD Science Staff		

FDA representatives, titles and offices:

Dale P. Conner, Pharm.D., Director	OGD/DB1
Bing Li, Ph.D., Team Leader	OGD/DB1
John Peters, M.D., Medical Officer	OGD/DCR
Bita Mirzai Azarm, MS, Team Leader	OGD/DC1
David T Read, JD	OGD/IO
William P. Rickman, Director	OGD/DLPS
Wallace P. Adams, Ph.D	OGD Science Staff
Bhawana Saluja, Ph.D.	OGD Science Staff
Feiyan Jin, Ph.D.	OGD Science Staff

Perrigo representatives, titles and company:

Jatin Shah, Ph.D.	Chief Scientific Officer
Mushtaq Fruitwala, Ph.D.	Director, Research and Development
Richard Stec, Ph.D.	VP, Global Regulatory Affairs
Brian Schuster	Associate Director, Regulatory Affairs
Beatriz North, MPH	CCRA, Director, Clinical Affairs
Jonathan Schwartz	Project Manager, Clinical Affairs

(b) (4)

[redacted]

[redacted] (b) (4)

The agency's minutes are the official minutes of the meeting.

BACKGROUND:
On October 5, 2010 (by hard copy with a cover letter), Perrigo submitted a meeting request package to the Office of Generic Drugs (OGD). In this package, Perrigo requested a meeting (either in person or teleconference) with OGD to discuss the ANDA submission and approval requirements for the addition of a dose counter to the proposed generic Albuterol Sulfate Inhalation Aerosol (eq 0.09 mg base/Inhalation) (Attachment 1). The reference listed drug (RLD) is ProAir HFA (albuterol sulfate) Inhalation Aerosol developed and marketed by Teva Respiratory, LLC (NDA 021457). The RLD currently does not have a dose counter.

In addition, Perrigo, in the October 5, 2010 meeting request package, made reference to the OGD-Perrigo meeting on May 5, 2008. During that meeting, several issues related to the initial ANDA filing requirements, including regulatory issues, bioequivalence (BE) studies program, dose counter and chemistry issues were discussed (Attachment 2). Based on that meeting, Perrigo and Catalent stated that they have proceeded with their product development process.

The purpose of the August 26, 2011, telecon was to seek OGD's inputs on the firm's questions listed in the October 5, 2010 meeting request package.

RESPONSES TO PERRIGO QUESTIONS

OGD sent a list of numbered Perrigo questions (Q1-Q19) to the firm prior to the August 26, 2011 telecon to facilitate the discussion (Attachment 3).

At the beginning of the telecon, the firm summarized its progress in developing a generic version of Albuterol Sulfate HFA MDI product. Then OGD discussed with Perrigo the Agency's responses to questions Q1-Q19.

[redacted] (b) (4)

9 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

OGD's response

Please send OGD a follow-up email with the firm's questions on the statistical analysis of the PD BE data.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 203760

APPLICANT: Perrigo Pharmaceuticals Company

DRUG PRODUCT: Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiencies:

1. You mentioned that few deviations occurred during the conduct of Single actuation content (SAC), aerodynamic particle size distribution (APSD) by cascade impaction and plume geometry (study # TTP-CBJ-M0132) studies comparing the test product with dose counter with reference product with dose counter and the data has been excluded from statistical analysis. You only provided the excluded data and did not provide the data with which it was replaced with. Therefore, please provide a table with original excluded values and replaced values.

2. The spray pattern testing (study # TTP-CBJ-M0132) comparing the test product with dose counter with the reference product with dose counter fails to meet the Population Bioequivalence (PBE) criteria for spray area at 3 cm distance. Please repeat this test.

3. According to the following Office of Pharmaceutical Quality (OPQ) review comments, your test product batch # 08MM-050 is not considered as representative of the commercial batch:

   (b) (4)

   Therefore, the pharmacokinetic (PK) (study # 10825302) and pharmacodynamic (PD) (study # PRG-723) BE studies conducted using batch # 08MM-050 are not acceptable. In addition, the Office of Study Integrity and Surveillance (OSIS) recommends that the data from PD study (# PRG-723) are not acceptable for further Agency review (please refer to deficiencies based on the inspection findings by the OSIS). Therefore, please repeat the pharmacokinetic (PK) and pharmacodynamic (PD) BE studies.

<u>Deficiencies Based on Inspection Findings by the Office of Study Integrity and Surveillance (OSIS):</u>

4. Following the inspection of the analytical site (b) (4) between (b) (4) by the Office of Study Integrity and

Surveillance (OSIS) for the current ANDA, Form FDA-483 was issued. Subsequently, the analytical site provided its responses to Form 483 and those responses were included in the final evaluation by the OSIS.

The DBI reviewed the above OSIS inspection report and found that the following objectionable findings by the OSIS at the analytical site could potentially compromise the integrity of the study of the current application:

Finding # 1: *Not all original data were reported following reanalysis or retest. Specifically, Protocol TTP-CBJ-M0050 required any reanalysis or retest data to be reported along with the original data in the study report. However, the following tests were repeated and the original data were not reported with the retest data:*

1) *Aerodynamic Particle Size Distribution (APSD) by Cascade Impactor (CI) for Study TTP-CBJ-M0050, Part 1, conducted from 4/13/2009 to 4/17/2009.*
2) *Spray Pattern for Study TTP-CBJ-M0050, Part 1, conducted from 3/31/2009 to 4/3/2009.*
3) *Plume Geometry for Study TTP-CBJ-M0050, Part 1, conducted from 4/1/2009 to 4/2/2009.*

Finding # 2: *Out-of-specification (OOS) results were not reported in the study report for Protocols TTP-CBJ-M0050 and TTP-CBJ-M0132. Examples include, but are not limited to, canisters retested/replaced and tests rejected due to assignable causes (e.g., instrument failure, sample collection, or processing errors). Specifically,*

1) *APSD by CI for Study TTP-CBJ-M0132,* (b) (4) (b) (4)
2) *APSD by CI for Study TTP-CBJ-M0132,* (b) (4) (b) (4)
3) *APSD by CI for Study TTP-CBJ-M0132,* (b) (4) (b) (4).
4) *Spray Pattern for Study TTP-CBJ-M0050* (b) (4) (b) (4)
5) *Plume Geometry for Study TTP-CBJ-M0050,* (b) (4) (b) (4).

In addition, a number of canisters were replaced during the study due to other reasons.

Based on the above findings, the firm should submit the following information:

a. Please submit all the in vitro BE study data including original and reanalysis or retest and a detailed study summary report which includes all the tests conducted and the details of the investigations for retesting or

reanalysis for study # TTP-CBJ-M0132 (comparing the test product with dose counter with the reference product with dose counter). Please provide the sas data (original and retested/ reanalyzed) in xpt format. Please note that you do not need to submit such data for the in vitro study Study # TTP-CBJ-M0050, since this study was conducted with the product without dose counter and the product is not intended to be the final commercial use.

b. Please submit all the in vitro BE study data including original data obtained with original canisters and retested data obtained with replaced canisters and a detailed study summary report which includes justification for the replacement of canisters study # TTP-CBJ-M0132 (comparing the test product with dose counter with the reference product with dose counter). Please provide the SAS data (data from original and replaced canisters) in xpt format. Please note that you do not need to submit such data for the in vitro study Study # TTP-CBJ-M0050, since this study was conducted with the product without dose counter and the product is not intended to be the final commercial use.

5. Following the inspection of the clinical sites (University of Florida, Gainesville; University of Iowa, Iowa City; California Allergy & Asthma Medical Group, Los Angeles) between 11/03/2014 – 01/09/2015 by the Office of Study Integrity and Surveillance (OSIS) for the current ANDA, Form FDA-483 was issued. Subsequently, the clinical sites provided its responses to Form 483 and those responses were included in the final evaluation by the OSIS.

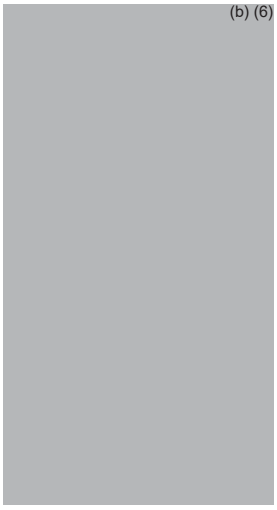
   The DBI reviewed the above OSIS inspection reports and found that the pharmacodynamic study (PRG-723) conducted is not acceptable based on the following OSIS findings. Please repeat the pharmacodynamic study.

   1. *There was a discrepancy in the assigned treatments between the randomization schedule in the study report and the protocol.*
   2. *The original code-blinding scratch-off stickers were not maintained at the clinical site prior to subject enrollment and until the FDA inspection and their integrity cannot be assured.*
   3. *Without the code-blinding scratch-off stickers, we are unable to confirm which treatments subjects received.*

6. Please be informed that the case report forms for all the subjects in the pharmacodynamic study (PRG-723) were not retained based on the following OSIS finding for the California Allergy & Asthma Medical Group:

   Investigational records were not retained. Specifically, three randomized subjects' and ten screen-failed subjects' bioequivalence study Source Records, Informed Consent Forms and Case Report Form Files were missing and could not be located during the inspection. The following subjects' entire study records were missing:

Screening Number / Randomization Number



The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Bing V. Li, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203760
Drug Product Name	Albuterol Sulfate Inhalation Aerosol
Strength(s)	0.09 mg Base/Inhalation
Applicant Name	Perrigo Pharmaceuticals Company
Applicant Address	515 Eastern Ave., Allegan, MI 49010
Contact's Name and the mailing address	Diane L. Morgan, ANDA/NDA Regulatory Affairs Project Manager
Contact's Telephone Number	269-686-1729
Contact's Fax Number	269-673-7655
Original Submission Date(s)	December 16, 2011
Submission Date(s) of Amendment(s) Under Review	April 24, 2015
Reviewer	Vipra Kundoor, Ph.D.
Overall Review Result	**ADEQUATE**

REVIEW OF A POST-CR MEETING REQUEST

This is a review of a post-CR (Complete Response) meeting request.

This is the *first generic drug application.* This application references NDA 021457, ProAir® HFA (albuterol sulfate) Inhalation Aerosol, Metered, 0.09 mg Base/Inhalation from Teva.

In the original submission dated 12/06/2011, the firm Perrigo Pharmaceuticals Company submitted the results of the following studies comparing the Test and Reference products: one single-dose fasting pharmacokinetic bioequivalence (BE) study (#10825302), one clinical pharmacodynamics study (#PRG-723), and five types of in vitro bioequivalence studies (single actuation content, aerodynamic particle size distribution by cascade impactor, spray pattern, plume geometry and priming/re-priming). In addition, the firm also submitted the particle size distribution by laser diffraction, which is not required per Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI[1]. None of studies were acceptable due to deficiencies. A complete response letter was sent to the firm on 04/13/2015[2].

In the current post-CR meeting request dated 04/24/2015, the firm is requesting a teleconference to clarify the following specific bioequivalence deficiency (Bioequivalence deficiency # 5) received in the complete response letter dated 04/13/2015:

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[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf

[2] DARRTS, ANDA 203760, COR-ANDAACTION-09 (Complete Response), 04/13/2015

Deficiency # 5: *For Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study you did not provide 100% raw numerical data (analyst's printouts) for all analytical runs (accepted and rejected) conducted during the HPLC sample analysis of these studies. The raw numerical data should include the data of peak area/height for the drug, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard concentration samples, and quality control samples.*

Firm's Comment:
Submission of 100% of the data specified would entail providing a volume of over (b) (4) pages of raw source data. Bioequivalence deficiency #6 specifies to provide 20% of the chromatograms from the Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study. The 100% raw numerical data (analyst's printouts) were previously reviewed by an FDA inspector during the IVBE audit. In addition, a full report with all of the worked up data will be provided in the complete response amendment to satisfy bioequivalence deficiency #3.

Perrigo is requesting confirmation whether the agency wants to review the same raw numerical data that was reviewed during the IVBE audit, and clarification on the distinction between bioequivalence deficiencies #5 and #6 with regard to the number of chromatograms to be submitted.

Reviewer's Comment:
Since there are no current issues for which the 100% raw numerical data needs to be looked at, the firm will be informed that the Division of Bioequivalence I (DBI) will not request the 100% raw numerical data at this time, but suggests the firm to keep the raw data available should that be needed in the future review processes.

DBI would like to clarify the firm that bioequivalence deficiency # 5 is related to submission of 100% raw numerical data and bioequivalence deficiency # 6 is related to submission of 20% of chromatograms. While it is not necessary at this time to submit the 100% raw numerical data, the firm is requested to submit 20% chromatograms from Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	203760
APPLICANT:	Perrigo Pharmaceuticals Company
DRUG PRODUCT:	Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation

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

Comment #1:
Submission of 100% of the data specified would entail providing a volume of over (b) (4) *pages of raw source data. Bioequivalence deficiency #6 specifies to provide 20% of the chromatograms from the Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study. The 100% raw numerical data (analyst's printouts) were previously reviewed by an FDA inspector during the IVBE audit. In addition, a full report with all of the worked up data will be provided in the complete response amendment to satisfy bioequivalence deficiency #3.*

Perrigo is requesting confirmation whether the agency wants to review the same raw numerical data that was reviewed during the IVBE audit, and clarification on the distinction between bioequivalence deficiencies #5 and #6 with regard to the number of chromatograms to be submitted.

DBI's Response:

Please be advised that DBI is not requesting the 100% raw numerical data at this time, but suggests that you keep the raw data available should that be needed in the future review processes.

We also would like to clarify that bioequivalence deficiency # 5 is related to submission of 100% raw numerical data and bioequivalence deficiency # 6 is related to submission of 20% of chromatograms. While it is not necessary at this time to submit the 100% raw numerical data, please submit 20% chromatograms from Single Actuation Content Study, Priming and Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Wayne I. DeHaven, Ph.D.
Acting Director, Division of Bioequivalence 1
Office of Generic Drugs
Center for Drug Evaluation and Research

1.1 Outcome Page

ANDA: 203760

DIVISION OF BIOEQUIVALENCE REVIEW ADDENDUM

ANDA No.	203760
Drug Product Name	Albuterol Sulfate Inhalation Aerosol
Strength(s)	0.09 mg Base/Inhalation
Applicant Name	Perrigo Pharmaceuticals Company
Applicant Address	515 Eastern Ave., Allegan, MI 49010
Applicant's Point of Contact	Diane L. Morgan, ANDA/NDA Regulatory Affairs Project Manager
Contact's Telephone Number	(b) (6)
Contact's Fax Number	269-673-7655
Original Submission Date(s)	Date of application: December 16, 2011
Submission Date(s) of Amendment(s) Under Review	Date of acceptable for filling: March 8, 2012 (SAS data and SOPs) May 18, 2012 (Formulation Table)
First Generic (Yes or No)	Yes
Reviewer	Vipra Kundoor, Ph.D.
Study Number (s)	10825302
Study Type (s)	Fasting
Strength (s)	2 x 90 mcg actuations (total dose = 180 mcg)
Clinical Site	Novum Pharmaceutical Research Services
Clinical Site Address	Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712
Analytical Site	(b) (4)
Analytical Site Address	
Study Number (s)	TTP-CBJ-M0050
Study Type (s)	In Vitro Bioequivalence
Strength (s)	90 mcg/ actuation
Analytical Site (In Vitro Studies)	(b) (4)
Analytical Site Address (In Vitro Studies)	
Study Number (s)	PRG-723
Study Type (s)	Pharmacodynamic Bioequivalence Study
Strength (s)	90 mcg/ actuation
Clinical Sites	**Site 1** University of Florida Asthma Research Lab **Site 2** Roy J and Lucille A Carver College of Medicine

	Department of Pediatrics, Allergy/Pulmonary **Site 3** Allergy & Asthma Diagnostic Treatment Center **Site 4** California Allergy & Asthma Medical Group **Site 5** Clinical Research Atlanta **Site 6** Spartanburg Medical Research **Site 7** AARA Research Center
Clinical Site Address	**Site 1** 1600 SW Archer Road Gainesville, FL 32610-0486 **Site 2** The University of Iowa 200 Hawkins Drive Iowa City, Iowa 52242-1083 **Site 3** 2300 Centerville Road Tallahassee, FL 32308 **Site 4** 11645 Wilshire Blvd, Suite 1155 Los Angeles, CA 90025 **Site 5** 175 Country Club Drive, Suite 100A Stockbridge, GA 30281 **Site 6** 485 Simuel Road Spartanburg, SC 29303 **Site 7** 9900 N Central Expy, Suite 555 Dallas, TX 75231
Analytical Site	N/A
Analytical Site Address	N/A
OSI Status	Clinical Site for Pharmacokinetic Study: ADEQUATE Analytical Site for Pharmacokinetic Study: INADEQUATE

	Analytical Site for In Vitro BE Studies: INADEQUATE (pending) Clinical Site for Pharmacodynamics Study: INADEQUATE (pending)		
OVERALL REVIEW RESULT	**INADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2, 6	**FASTING STUDY**	**0.09 mg Base/Inhalation**	**INADEQUATE**
1, 2, 6	**IN VITRO BIOEQUIVALENCE STUDIES**	**0.09 mg Base/Inhalation**	**INADEQUATE**
1, 2, 6	**PHARMACODYNAMIC STUDY**	**0.09 mg Base/Inhalation**	**INADEQUATE**

1 EXECUTIVE SUMMARY

This is an addendum to the bioequivalence review of ANDA 203760 finalized on 08/04/2014[1].

On 03/23/2015, the Office of Pharmaceutical Quality (OPQ) contacted Division of Bioequivalence I (DBI) with regards to concerns on the bio batch (batch # 08MM-050) used to conduct pharmacokinetic (PK), pharmacodynamic (PD) and *in vitro* BE studies. OPQ indicated that the (b) (4) in batch # 08MM-050 were not representative of the whole batch as (b) (4)

On 03/30/2015, the OPQ finalized their review[3]. As per their review, the following deficiencies relating to batch # 08MM-050 are listed:

Deficiency # 8: *Please provide release and stability data of the* (b) (4) *canisters in Batch 08MM-50,* (b) (4) *used for clinical supplies. The release and stability data of canisters* (b) (4) (b) (4) *should be included.*

Deficiency # 34: *We have significant concerns of the exhibit batches and regulatory batches you have provided.* (b) (4) (b) (4) (b) (4) (b) (4) *Please include detail information of these commercial batches including drug substance COAs, executed batch record, drug product release tests, and accelerated and long term stability data. The stability data should include both valve up and valve down positions.*

Based on the above mentioned deficiencies from OPQ, DBI revises the letter attached to the 08/04/2014 DBI review of the application. The revised letter is attached to this addendum review and supersedes the original letter. The revised letter, added deficiency #24, to advise the applicant to provide justification to address OPQ's concerns that the bio batch (# 08MM-50) used for clinical study was not representative of the whole batch. The firm is also noticed that

[1] DARRTS, ANDA 203760 REV-BIOEQ-21 (Primary Review), 08/04/2014
[2] DARRTS, ANDA 203760 FRM-MINUTES-01 (Internal Meeting Minutes), 03/26/2015
[3] Panorama Database, ANDA 203760, Drug Product Primary Review, Document Name: 203760CR01_03192015.doc, Finalized Date: 03/30/2015

additional bioequivalence studies may be needed if OPQ determines the firm's response is inadequate to address this issue.

The application remains **inadequate**.

2 ATTACHMENT

ANDA 203760 Meeting Minutes

OLDP/DMRP & DBE Meeting Minutes

March 23th, 2015

Attendees: Xihao Li, Bhagwant Rege, Bing Li, Vipra Kundoor, Ke Ren, Wayne Dehaven, Dhaval Gaglani

(b) (4)

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10. DBE will follow up on the additional comments to firm with regards to the BE studies (PK/PD/In Vitro).

NOTE TO REGULATORY PROJECT MANAGER (RPM): Currently there are OSI inspections pending for the clinical and analytical sites.

NOTE TO REGULATORY PROJECT MANAGER (RPM): This deficiency letter supersedes that attached to the review of ANDA 203760 dated 08/04/2014.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 203760

APPLICANT: Perrigo Pharmaceuticals Company

DRUG PRODUCT: Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

Deficiencies Related to Fasting Bioequivalence (BE) Study (# 10825302)

1. Please provide the Certificate of Analysis (CoA) of the reference product lot # AEA13B.

2. Per your analytical report for the fasting study (# 10825302), there were seven rejected batch runs for albuterol (Run ID #s 1AFGI, 4AFGI, 7AFGI, 8AFGI, 9AFGI, 13AFGI and 14AFGI). You provided the specific reasons for rejection of the batch runs in the analytical report. However, you did not include the original data to support the reasons for batch rejections. Therefore, please submit the raw data for calibration standards, quality control (QC) samples and study samples, such as peak area of analyte and internal standard, calculated concentration, etc. of the failed batches.

   In addition, you did not include those rejected batches in the calculation of repeat percentage in the "Reanalysis of Study Samples" Table. For the future submissions, please include all analytical repeats, including failed repeat runs, in the "Reanalysis of Study Samples" Table.

Deficiencies Common to ALL In Vitro Equivalence Studies

3. Please provide detailed study reports for all the in vitro equivalence studies.

4. Manual actuation was used for conducting Single Actuation Content Test, Priming/Re-Priming, Aerodynamic Particle Size Distribution by Cascade Impaction and Particle Size Distribution by Laser Diffraction. You only indicated that both test and reference products were tested under the same instrumental conditions. Please provide the information regarding whether the test was conducted under blinded conditions to avoid the operator's bias.

5. For Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study you did not provide 100% raw numerical data (analyst's printouts) for all analytical runs (accepted and rejected) conducted during the HPLC sample analysis of these studies. The raw numerical data should include the data of peak area/height for the drug, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard concentration samples, and quality control samples.

6. Please submit 20% of the chromatograms from Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study.

Deficiencies Related to Single Actuation Content (SAC) through Container Life Test

7. You did not provide the validation data for the manual spray pump actuator for the SAC testing. Please submit the data using formatted summary tables. You may reference the CTD tables designed for nasal spray drug products (where applicable) from the FDA's website at the following location: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf

8. Please indicate if stock solutions and working standards underwent freeze-thaw cycles prior to use. If so, please submit the appropriate data to demonstrate stability.

9. Please provide working standards refrigerator stability data.

Deficiencies Related to Priming/Re-Priming Tests

10. As per the in vitro summary tables you submitted, the Priming and Re-priming study was conducted between February – April 2009. However, your SOP (b) (4) for Priming and Re-priming testing was effective from (b) (4). Please justify how you objectively conducted the study without a pre-established SOP.

Deficiencies Related to Aerodynamic Particle Size Distribution (APSD) by Cascade Impactor (CI) Test

11. You did not provide number of actuations (i.e., how many actuations were employed in the CI test) and the sequential number of actuation (e.g. the 6th-11th sprays/actuations) used in the Cascade Impaction test. Please provide this information.

12. According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the APSD test should be performed at both beginning and end lifestages of the product. However, you only conducted the test at the beginning lifestage, indicated in your SAS

dataset as "B". Please conduct the test at both beginning and end lifestages of the product as recommended by Albuterol Sulfate MDI guidance.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf

13. Please specify how many quality control samples were used in each analytical run and at what concentrations. According to the Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Actions (April 2003): *"analytical runs include at least three or more concentrations of quality control samples that represent the entire range of the standard curve or the expected concentration range of samples from the various stages of the CI."* This is also applicable to the same test of inhalation drug product.

Deficiencies Related to Spray Pattern Test

14. According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the Spray Pattern should be performed at the beginning lifestage of the product at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm **from the reference product mouthpiece**. It should also be noted that the **distance between the actuator orifice and the point of spray pattern measurement should be the same for test and reference products.**

    In the current ANDA, you conducted spray pattern test at 3 cm and 6 cm from the actuator mouthpiece. However, it is not clear from your submission whether the selected 3 cm and 6 cm distances are from the actuator mouthpiece of **the reference product.** Therefore, please clarify whether the 3 cm and 6 cm distances are from the reference product actuator mouthpiece. In addition, please confirm whether the distances between the actuator orifice to the point of spray pattern measurements are the same for the test and reference products.

15. According to the in vitro summary table provided in Module 5.2, the effective date of both SOP (b) (4). However, according to the SOP (b) (4), the effective date of both the SOPs was (b) (4) (b) (4). Please clarify this discrepancy.

16. Please provide the Intermediate Precision (By Date) data for the validation of the spray pattern test.

17. You provided the spray pattern images and the accompanying raw data for 20% samples at both 3 cm and 6 cm distances. However, it is not clear from your submission whether the images are of the test or reference product. Please clarify.

Deficiencies Related to Plume Geometry Test

18. Please clarify whether the 6 cm distance selected for the Plume Geometry test is from **the reference product actuator mouthpiece**. In addition, please confirm whether the distances between the actuator orifice to the point of spray pattern measurements are the same for the test and reference products.

19. Please provide the Intermediate Precision (By Date) data for the validation of the plume geometry test.

Deficiencies Related to Pharmacodynamic (PD) Study (# PRG-723)

20. Please provide the certificate of analysis of the reference product lot # PAEF75A.

21. You only provided the case report forms of subject (b) (6). Please provide the case report forms of all subjects included in the pharmacodynamic study.

22. In your submission (Module 5.3.4.1) for the study design of PD study (# PRG-723), you indicated that "*placebo MDI*" was used in treatments 1 through 5. However, you did not specify whether the "*placebo MDI*" is the test or reference product placebo. Please clarify which placebo, test or reference placebo, were used in each treatment in your PD study. In addition, please provide the formulation of the placebo product.

Deficiency Related to Inspection Findings by the Office of Scientific Investigations (OSI):

23. Following the inspection of the analytical site (b) (4) (b) (4) by the Office of Scientific Investigation (OSI) (for the BE studies from other applications), Form FDA-483 was issued. Subsequently, the analytical site provided its responses to Form 483 and those responses were included in the final evaluation by the OSI.

    For considering the impact of similar study conduct and site practices by the same analytical facility on the BE study of the current ANDA, the DBI reviewed the above OSI inspection report and found that the following objectionable finding by the OSI at the analytical site could potentially compromise the integrity of the study of the current application as well:

    (b) (4)

    Please address the above systemic finding by the OSI with respect to its impact on the fasting BE study (# 10825302) of the current ANDA.

Deficiency Related to Office of Pharmaceutical Quality (OPQ)'s concern on the bio batch (batch # 08-MM-050)

24. Based on the following deficiency issued by Office of Pharmaceutical Quality (deficiency #34 in Product Quality Section), the Office of Pharmaceutical Quality (OPQ) concerns that the bio batch (08MM-50) used for clinical study was not representative of the whole batch.

> *"We have significant concerns of the exhibit batches and regulatory batches you have provided.* (b) (4) (b) (4) (b) (4) (b) (4) *Please include detail information of these commercial batches including drug substance COAs, executed batch record, drug product release tests, and accelerated and long term stability data. The stability data should include both valve up and valve down positions".*

Please provide justifications to OPQ to address their concerns. Please note that additional bioequivalence studies may be needed if OPQ determines your response is inadequate to address this issue.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. These comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Wayne DeHaven, Ph.D
Acting Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203760
Drug Product Name	Albuterol Sulfate Inhalation Aerosol
Strength(s)	0.09 mg Base/Inhalation
Applicant Name	Perrigo Pharmaceuticals Company
Applicant Address	515 Eastern Ave., Allegan, MI 49010
Applicant's Point of Contact	Diane L. Morgan, ANDA/NDA Regulatory Affairs Project Manager
Contact's Telephone Number	(b) (6)
Contact's Fax Number	269-673-7655
Original Submission Date(s)	Date of application: December 16, 2011
Submission Date(s) of Amendment(s) Under Review	Date of acceptable for filling: March 8, 2012 (SAS data and SOPs) May 18, 2012 (Formulation Table)
First Generic (Yes or No)	Yes
Reviewer	Vipra Kundoor, Ph.D
Study Number (s)	10825302
Study Type (s)	Fasting
Strength (s)	2 x 90 mcg actuations (total dose = 180 mcg)
Clinical Site	Novum Pharmaceutical Research Services
Clinical Site Address	Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712
Analytical Site	(b) (4)
Analytical Site Address	
Study Number (s)	TTP-CBJ-M0050
Study Type (s)	In Vitro Bioequivalence
Strength (s)	90 mcg/ actuation
Analytical Site (In Vitro Studies)	(b) (4)
Analytical Site Address (In Vitro Studies)	
Study Number (s)	PRG-723
Study Type (s)	Pharmacodynamic Bioequivalence Study
Strength (s)	90 mcg/ actuation
Clinical Sites	**Site 1** University of Florida Asthma Research Lab **Site 2** Roy J and Lucille A Carver College of Medicine Department of Pediatrics, Allergy/Pulmonary **Site 3**

	Allergy & Asthma Diagnostic Treatment Center **Site 4** California Allergy & Asthma Medical Group **Site 5** Clinical Research Atlanta **Site 6** Spartanburg Medical Research **Site 7** AARA Research Center
Clinical Site Address	**Site 1** 1600 SW Archer Road Gainesville, FL 32610-0486 **Site 2** The University of Iowa 200 Hawkins Drive Iowa City, Iowa 52242-1083 **Site 3** 2300 Centerville Road Tallahassee, FL 32308 **Site 4** 11645 Wilshire Blvd, Suite 1155 Los Angeles, CA 90025 **Site 5** 175 Country Club Drive, Suite 100A Stockbridge, GA 30281 **Site 6** 485 Simuel Road Spartanburg, SC 29303 **Site 7** 9900 N Central Expy, Suite 555 Dallas, TX 75231
Analytical Site	N/A
Analytical Site Address	N/A
OSI Status	Clinical Site for Pharmacokinetic Study: ADEQUATE Analytical Site for Pharmacokinetic Study: INADEQUATE Analytical Site for In Vitro BE Studies: INADEQUATE (pending) Clinical Site for Pharmacodynamics Study: INADEQUATE (pending)
OVERALL REVIEW RESULT	**INADEQUATE**
REVISED/NEW DRAFT	**NO**

GUIDANCE INCLUDED			
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2, 6	**FASTING STUDY**	**0.09 mg Base/Inhalation**	**INADEQUATE**
1, 2, 6	**IN VITRO BIOEQUIVALENCE STUDIES**	**0.09 mg Base/Inhalation**	**INADEQUATE**
1, 2, 6	**PHARMACODYNAMIC STUDY**	**0.09 mg Base/Inhalation**	**INADEQUATE**

1 EXECUTIVE SUMMARY

This is the *first generic drug application.*

This application references NDA 021457, ProAir® HFA (albuterol sulfate) Inhalation Aerosol, Metered, 0.09 mg Base/Inhalation from Teva.

Consistent with current Division of Bioequivalence I (DBI) recommendations, the firm submitted the results of the following studies comparing the Test and Reference products: one single-dose fasting pharmacokinetic bioequivalence (BE) study (#10825302), one clinical pharmacodynamics study (#PRG-723), and five types of in vitro bioequivalence studies (single actuation content, aerodynamic particle size distribution by cascade impactor, spray pattern, plume geometry and priming/re-priming). In addition, the firm also submitted the particle size distribution by laser diffraction, which is not required per Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI[1]. The findings and outcome of the studies are summarized as follows:

Fasting study: The fasting BE study was designed as a single-dose, two-way crossover study on healthy subjects. The firm's fasting BE study is **inadequate** due to bioanalytical deficiencies. The results of the BE study are summarized in the table below:

Albuterol Sulfate Inhalation Aerosol
Dose: 2 x 90 mcg/Inhalation
Fasting Bioequivalence Study No. 10825302, N=24 (Male=17 and Female=7)
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *pg/ml)	3777.60	24	3883.57	24	0.97	91.67	103.21
AUC∞ (hr *pg/ml)	4027.62	24	4146.43	24	0.97	91.81	102.77
Cmax (pg/ml)	562.71	24	603.18	24	0.93	84.74	102.70

Five types of in vitro bioequivalence studies: All of the *in vitro* BE studies are **inadequate** due to the multiple deficiencies.

Pharmacodynamics BE study: A bronchoprovocation pharmacodynamics study was conducted. The study was designed as a multi-center, randomized, double-blind, five-way crossover study comparing the test and reference products using a methacholine challenge design in asthmatic subjects. The 90% confidence interval for the relative bioavailability (F) falls within the 67.00 – 150.00% BE criteria. However, the firm's pharmacodynamics study is **inadequate** due to clinical deficiencies. The results of the pharmacodynamics study (reviewer calculated) are summarized in the table below:

1 http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf

Method	N	F (Test/Reference)	90% CI
Using both Doses (0.09 mg and 0.18 mg to calculate F)	93	1.17	102.68% – 132.85%

The formulation of firm's test product which is quantitatively (Q1) and qualitatively (Q2) the same as that of the reference product is acceptable.

Office of Scientific Investigation (OSI): No OSI inspection is pending or necessary for the clinical and analytical sites used in the fasting BE study. There is no OSI inspection history for the analytical site used in the In Vitro BE studies and clinical sites (site #1, #2 and #4) used in the pharmacodynamics BE study (please refer to section 4.7 for the details). Therefore, OSI inspection for the analytical site used in the In Vitro BE studies and clinical sites (site #1, #2 and #4) were requested for current ANDA on June 26, 2014[2].

The application is **inadequate** with deficiencies.

NOTE TO REGULATORY PROJECT MANAGER (RPM): Currently, there are OSI inspections pending for the analytical (in vitro BE studies) and clinical (pharmacodynamics BE study) sites.

[2] DARRTS ANDA 203760 Wong, Jennie Z 06/26/2014 N/A 06/26/2014 FRM-CONSULT-09(Biopharmaceutical Inspections Request) Rachive

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[3]

Test Product	Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation
Reference Product	ProAir® HFA (albuterol sulfate) Inhalation Aerosol, 0.09 mg Base/Inhalation
RLD Manufacturer	Teva Global
NDA No.	021457
RLD Approval Date	October 29, 2004
Indication[4]	PROAIR HFA® Inhalation Aerosol is a beta$_2$-adrenergic agonist indicated for: • Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease. • Prevention of exercise-induced bronchospasm in patients 4 years of age and older.

3.2 PK/PD Information[5,6]

Bioavailability	The systemic levels of albuterol are low after inhalation of recommended doses. In a crossover study conducted in healthy male and female volunteers, high cumulative doses of PROAIR HFA Inhalation Aerosol (1,080 mcg of albuterol base administered over one hour) yielded mean peak plasma concentrations (Cmax) and systemic exposure (AUCinf) of approximately 4,100 pg/mL and 28,426 pg/mL*hr, respectively compared to approximately 3,900 pg/mL and 28,395 pg/mL*hr, respectively following the same dose of an active HFA-134a albuterol inhaler comparator. The pharmacokinetic profile of PROAIR HFA Inhalation Aerosol was evaluated in a two-way cross-over study in 11 healthy pediatric volunteers, 4 to 11 years of age. A single dose administration of PROAIR HFA Inhalation Aerosol (180 mcg albuterol base) yielded a least square mean (SE) Cmax and AUC0-∞ of 1,100 (1.18) pg/mL and 5,120 (1.15) pg/mL*hr, respectively.
Food Effect	Not indicated in the labeling
Tmax	0.5 – 2 hours Onset of bronchodilation occurs within 5- 15 minutes and lasts 2 - 6 hrs.
Metabolism	Information available in the published literature suggests that the

[3] Electronic Orange Book, last accessed date: 01/06/2013
[4] Drugs@FDA, Keyword Search: Proair, RLD Label approved on 08/17/2010, last accessed date: 01/06/2013.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021457s021lbl.pdf
[5] Drugs@FDA, Keyword Search: Proair, RLD Label approved on 08/17/2010, last accessed date: 01/06/2013.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021457s021lbl.pdf
[6] Clinical Pharmacology, Keyword Search: Albuterol, last accessed date: 01/06/2013
http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=11&aprid=3403

	primary enzyme responsible for the metabolism of albuterol in humans is SULTIA3 (sulfotransferase). When racemic albuterol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)- albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULTIA3.
Excretion	The primary route of elimination of albuterol is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R) albuterol in the urine.
Half-life	6 hours
Dosage and Administration	• Treatment or prevention of bronchospasm in adults and children 4 years of age and older: 2 inhalations every 4 to 6 hours. In some patients, one inhalation every 4 hours may be sufficient. • Prevention of exercise-induced bronchospasm in adults and children 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise. • Priming information: Prime PROAIR HFA before using for the first time, or when the inhaler has not been used for more than 2 weeks. To prime PROAIR HFA, release 3 sprays into the air away from the face. Shake well before each spray.
Maximum Daily Dose	Adults, Elderly and Adolescents: 32 mg/day Children: 6-12 years = 24 mg/day < 6 years = 12 mg/day
Drug Specific Issues	PROAIR® HFA (albuterol sulfate) is contraindicated in patients with a history of hypersensitivity to albuterol and any other PROAIR HFA inhalation aerosol components **How Supplied**: PROAIR HFA Inhalation Aerosol is supplied as a pressurized aluminum canister with a red plastic actuator with a dose counter and white dust cap each in boxes of one. Each canister contains 8.5 g of the formulation and provides 200 actuations. Each actuation delivers 120 mcg of albuterol sulfate from the canister valve and **108 mcg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base).** **Priming**: Priming is essential to ensure appropriate albuterol content in each actuation. Instruct patients to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing **three sprays** into the air, away from the face. **Cleaning:** To ensure proper dosing and prevent actuator orifice blockage, instruct patients to wash the red plastic actuator mouthpiece and dry thoroughly at least once a week.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	5 in vitro bioequivalence studies, 1 in vivo fasting bioequivalence study and 1 clinical pharmacodynamic (PD) study

In Vitro Studies

1.	**Type of study:**	Single actuation content (SAC) – *in vitro*
	Design:	The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages of the product using a flow rate of 28.3 L/min. The USP <601> Apparatus A or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one.
	Equivalence based on:	Population bioequivalence (PBE) analysis of SAC. Please refer to the draft Budesonide Inhalation Suspension BE Guidance for additional information regarding PBE

2.	**Type of study:**	Aerodynamic particle size distribution (APSD) – *in vitro*
	Design:	The APSD test should be performed at the B and E life stages of the product using a flow rate of 28.3 L/min or 30 L/min. The USP <601> Apparatus 1, Apparatus 6, or another appropriate method may be used to determine APSD using a validated assay. The APSD determination of each unit should be performed with a minimum number of inhalations justified by the sensitivity of the validated assay.
	Equivalence based on:	PBE analysis of impactor-sized mass (ISM). The CI profiles representing drug deposition on the individual stages of the CI along with the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) should be submitted as supportive evidence for equivalent APSD.
	Additional Comments:	Drug deposition on individual sites, including the mouthpiece adapter, the induction port, each stage of the cascade Impactor (CI) and the filter, is requested. Mass balance accountability should be reported based on the sum of all deposition sites. For electronic submission of the individual CI data for the T and R products, please provide a table using the format in the appendix, and send them as part of the abbreviated new drug application (ANDA) submission for BE evaluation.

3.	**Type of study:**	Spray Pattern
	Design:	The spray pattern test should be performed at the B lifestage of the product and at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the R actuator mouthpiece. Impaction (thin-layer chromatography plate impaction), non-impaction (laser light sheet technology), or other suitable method may be used to determine the spray pattern.
	Equivalence based on:	At two selected distances, (i) qualitative comparison of spray shape, and (ii) PBE analysis of ovality ratio and area within the perimeter of the true shape or ovality ratio and Dmax.

	Additional Comments:	Spray pattern should be measured quantitatively in terms of ovality ratio and area within the perimeter of the true shape (to include a high proportion, e.g., 95 % of the total pattern) for the automated analysis or ovality ratio and Dmax for the manual analysis. Ovality ratio is defined as the ratio of Dmax to Dmin. Dmax and Dmin are the longest and shortest diameters, respectively, that pass through the center of mass or the center of gravity, as appropriate. The number of sprays per spray pattern would preferably be one.

4.	**Type of study:**	Plume Geometry
	Design:	The plume geometry test should be performed at B lifestage of the product. The time sequence sound-triggered flash photography method, laser light sheet technology, or other suitable method may be used to determine the plume geometry at the appropriate post-actuation delay time.
	Equivalence based on:	Ratio of the geometric mean of the three batches of T to that of the three batches of R (based on log transformed data) for both plume angle and width, which should fall within 90 – 111%.
	Additional Comments:	Plume geometry measurements should be reported at a single delay time while the fully developed plume is still in contact with the actuator tip. Plume geometry should be measured quantitatively in terms of plume angle and width. The plume angle is based on the conical region of the plume extending from a vertex that occurs at or near the actuator tip. The plume width is measured at a distance equal to the greater of the two distances selected for characterization of the spray pattern.

5.	**Type of study:**	Priming and repriming
	Design:	Priming and repriming tests should be based on the emitted dose (ex-actuator) of a single actuation immediately following the specified number of priming or repriming actuations specified in the R product labeling. The repriming test should be performed following storage for the specified period of non-use after initial use and/or other conditions (e.g., dropping), if the R product labeling provides such repriming information.
	Equivalence based on:	PBE analysis of the emitted dose of a single actuation immediately following the specified number of priming or repriming actuations specified in the R product labeling.
	Additional Comments:	For BE evaluation, the priming and repriming tests should be based on products stored in the valve upright position, with the exception of MDIs for which the R labeling recommends storage in the valve down position. The priming data can be based on the SAC data at the B lifestage.

Pharmacokinetic (PK) BE Study

6.	**Type of study:**	Fasting
	Design:	Single-dose, two-way crossover in-vivo
	Dose:	0.18 mg (two inhalations)
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	The subjects enrolled for in vivo studies should be trained in the use of the inhalation aerosols in a standard fashion prior to each treatment session to assure a relatively consistent inspiratory flow rate and inspiratory duration.

Analytes to measure (in plasma/serum/blood):	Albuterol in plasma
Equivalence based on:	AUC and Cmax for albuterol. The 90% confidence intervals (CIs) for the geometric mean T/R ratios of AUC and Cmax should fall within the limits of 80.00–125.00%

Pharmacodynamic (PD) BE Study

A method using either bronchoprovocation (7a) or bronchodilation (7b) study is recommended for this part of in vivo requirements.

7a.	**Type of study:**	Bronchoprovocation study
	Design:	Single-dose, double-blind, double dummy, randomized, crossover study that is recommended at minimum to consist of: • Zero Dose: One actuation each from two different placebo R inhalation aerosols and one actuation each from two different placebo T inhalation aerosols • 0.09 mg of R: One actuation each from the R inhalation aerosol and the placebo R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols • 0.18 mg of R: One actuation each from two different R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols • 0.09 mg of T: One actuation each from the T inhalation aerosol and the placebo T inhalation aerosol and one actuation each from two different placebo R inhalation aerosols No less than a 24 hour washout period should be allotted between treatments.
	Subjects	Male and non-pregnant females with asthma
	Additional Comments	• Inclusion criteria should, at minimum, include: a. Male and non-pregnant female subjects (18-65 years of age). b. Stable mild asthmatics based on National Asthma Education and Prevention Program (NAEPP)

guidelines.

c. $FEV_1 \geq 80\%$ of predicted.
d. Airway responsiveness to methacholine demonstrated by a pre-albuterol-dose (baseline) $PC20 \leq 8$ mg/ml.
e. Nonsmokers for at least six months prior to the study and a maximum smoking history of five pack-years (the equivalent of one pack per day for five years).
f. Written informed consent.

- Exclusion criteria should, at minimum, include:
  a. Conditions which could alter airway reactivity to methacholine (e.g., pneumonia, upper respiratory tract infection, viral bronchitis and/or sinobronchitis) within past six weeks.
  b. History of seasonal asthma exacerbations, in which case the subject should be studied outside of the relevant allergen season.
  c. History of cystic fibrosis, bronchiectasis or other respiratory diseases.
  d. History of cardiovascular, renal, neurologic, liver or endocrine dysfunction, including ECG with evidence of ischemic heart disease.
  e. Treatment in an emergency room or hospitalization for acute asthmatic symptoms or need for daily oral corticosteroids within past three months.
  f. Known intolerance or hypersensitivity to any component of the albuterol MDI.
- The study day evaluation should take into consideration the following:
  a. Drug administration should begin within two weeks following screening for admission to the study.
  b. Baseline FEV_1 should not be less than 70% of predicted normal value and within 88-112% of qualifying day FEV_1 value. If either occurs, the study should be rescheduled.
  c. FEV_1 due to the saline control should fall no more than 10 % from the baseline FEV_1, or the study should be postponed. This limits the drop in FEV_1 shown by some subjects due to the saline control vehicle in which the challenge agent is dissolved.
  d. Baseline PC_{20} or PD_{20} on each study day should be within a two-fold dilution (i.e., within 50-200 %) of the value measured on the qualifying day.
  e. A subject failing three consecutive visits should be dropped from the study.
- A **bio-IND is required** prior to conduct of the PD study as the concentration of methacholine chloride solution may exceed the labeled 25.0 mg/ml concentration, particularly at the higher albuterol dose (e.g., 0.18 mg) where 25.0 mg/ml methacholine chloride may not lead to a 20% reduction in FEV_1.
- Firms are encouraged to consider the conduct of a pilot study to refine the study design (e.g., inclusion and exclusion criteria) and estimate the study power based on intra- and inter-subject variability and slope of the E_{max} dose-response curve. The method for blinding should be

		described.
	PD endpoint(s):	Post-dose PC20 or PD20, which are the provocative concentration or dose, respectively, of the methacholine challenge agent required to reduce the forced expiratory volume in one second (FEV1) by 20% following administration of differing doses of albuterol (or placebo) by inhalation. The 20 % reduction in FEV1 is determined relative to the saline FEV1 measured before the placebo or albuterol administration.
	Equivalence based on:	Dose-scale analysis of the PD data. For details regarding the dose-scale analysis, please refer to the draft Orlistat Capsule BE Guidance. The 90% CI for the relative bioavailability (F) should fall within 67.00-150.00 % to establish equivalence in the PD study

7b.	**Type of study:**	Bronchodilatation study
	Design:	Single-dose, double-blind, double-dummy, randomized, crossover study that is recommended at minimum to consist of: • Zero dose: One actuation each from two different placebo R inhalation aerosols and one actuation each from two different placebo T inhalation aerosols • 0.09 mg of R: One actuation each from the R inhalation aerosol and the placebo R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols • 0.18 mg of R: One actuation each from two different R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols • 0.09 mg of T: One actuation each from the T inhalation aerosol and the placebo T inhalation aerosol and one actuation each from two different placebo R inhalation aerosols No less than a 24 hour washout period should be allotted between treatments.
	Subjects	Males and non-pregnant females with asthma
	Additional comments	• Inclusion criteria should, at minimum , include: a. Male and non-pregnant female subjects (18-65 years of age). b. Moderate-to-severe asthmatics based on NAEPP guidelines. c. FEV_1 within 40-70% of predicted. d. Reversible airway obstruction as demonstrated by an improvement of 15 % or more in FEV_1 30 minutes after inhalation of two puffs (0.18 mg) of R inhalation aerosol. e. Nonsmokers for at least six months prior to the study and a maximum smoking history of five pack-years). f. Written informed consent. • Exclusion criteria should, at minimum, include: a. History of cardiovascular, renal, neurologic, liver or endocrine dysfunction. b. Evidence of respiratory tract infection within six weeks

		prior to the study. c. Intolerance to aerosolized β2-adrenergic agonists. d. Inability to tolerate temporary withdrawal of current asthma medication. e. Other co-morbid respiratory and sinus diseases. f. History of status asthmaticus, cystic fibrosis or bronchiectasis. g. History of frequent exacerbations in the previous year. h. Asthmatics who are taking oral corticosteroids. i. Known intolerance or hypersensitivity to any component of the albuterol MDI. • The study day evaluation should take into consideration the following: a. Randomized treatment should begin within two weeks of the screening visit. b. Baseline FEV_1 should not be less than 45% of predicted or vary by more than ±12% from screening visit FEV_1 value. If either occurs, the study should be rescheduled. If the subject fails to meet these criteria on three separate study days (consecutive or not), they should be dropped from the study. • Firms are encouraged to consider the conduct of a pilot study to refine the study design (e.g., inclusion and exclusion criteria) and estimate the study power based on intra- and inter-subject variability and slope of the Emax dose-response curve. The method for blinding should be described. • FEV_1 should be measured at 0, 10, 15, 30, 60, 90, 120, 180, 240, 300 and 360 minutes (6 hours) post-dose. FEV1 should be defined as the highest of the three values obtained at each pulmonary function evaluation period. • For each treatment group, time to peak bronchodilator response (Tmax) and FEV1 values at all measurement times within each evaluation period should be included in the final study report.
	PD endpoint(s):	Areas under the effect curve calculated from the zero time to four hours (AUEC0-4h) and from zero time to six hours (AUEC0-6h) and maximum FEV1 (FEV1max). These endpoints should be baseline-adjusted using the pre-dose FEV1.
	Equivalence based on:	Dose-scale analysis of the PD data. The 90% CIs for Fs should fall within 67.00-150.00% to establish equivalence in the PD study.

Source of most recent recommendations:	The current BE recommendations for the drug product are listed in the Draft Guidance for Industry: Bioequivalence Recommendations for Specific Products. Recommended April 2013; Revised June 2013. FDA Guidance for Industry: Draft Guidance on Albuterol Sulfate Aerosol Inhalation: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf (Recommended April 2013; Revised June 2013)

Summary of OGD or DB History	This is the first generic drug. According to the orange book (last accessed date: 06/13/2014), there are no approved generic products for Albuterol Sulfate Metered Aerosol Inhalation. There are several control correspondences received by the OGD for Albuterol Sulfate Metered Dose Inhaler[7]. There are few protocols received by the OGD for Albuterol Sulfate Metered Dose Inhaler[8]. The Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI recommends for the submission of a Bio-IND prior to the conduct of the PD study as the concentration of methacholine chloride solution may exceed the labeled 25.0 mg/mL concentration, particularly at the higher 0.18 mg Albuterol Sulfate dose where 25.0 mg/mL methacholine chloride will not lead to a 20% reduction in FEV_1. On November 23, 2009, Perrigo submitted Bio-IND 105337 (Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation) because of the high proposed dose limits for methacholine. The protocol was found acceptable by Division of Pulmonary and Allergy Products in OND[9] (please refer to 4.6.3 for the details).

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	--
In vitro equivalence testing	Yes	6
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	Yes	1
Failed Studies	No	--
Amendments	Yes	1 (resubmission after refuse to receive)

[7] Control Correspondence Database, last accessed date: 06/24/2014
[8] Protocols Database, last accessed date: 06/24/2014
[9] DARRTS IND 105337 Chang, Nancy S 12/22/2009 N/A 12/22/2009 REV-CLINICAL-03 (General Review) Archive

3.5 Pre-Study Bioanalytical Method Validation (For Fasting BE Study)

Information Requested	Albuterol
Bioanalytical method validation report location	(b) (4)
Study Report Number	
Analyte	
Internal standard (IS)	
Method description	
Limit of quantitation	
Anticoagulant Used	
LLOQ Intraday precision (%)	
LLOQ Intraday accuracy (%)	
LLOQ Interday precision (%)	
LLOQ Interday accuracy (%)	
% recovery (and %CV) at each concentration tested	
Average recovery of IS (%)	
Standard curve concentrations (pg/mL)	
QC concentrations (pg/mL)	
QC Intraday precision range (%)	
QC Intraday accuracy range (%)	
QC Interday precision range (%)	
QC Interday accuracy range (%)	
Bench-top stability (hrs)	
Stock stability (days)	
Processed stability (hrs)	
Freeze-thaw stability (cycles)	
Long-term storage stability (days)	
Dilution integrity (concentration, percent CV) dilution factor, accuracy	
Selectivity	
For combination products: Did the matrix include all analytes?	

Was the % recovery consistent across QC concentrations?	**No**
Is the same anticoagulant used in the pre-method validation study used in the sample assay?	Yes
If not, was cross validation study conducted?	N/A
Was the dilution factor adequate for the current study sample analysis?	Yes
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	Yes
Does the duration of the each of the stability parameters support the sample preparation and assay dates	Yes
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	**Adequate**

SOPs submitted	SOP # (b) (4), Data Acceptance Criteria for Chromatographic Assays; effective date: (b) (4) SOP # (b) (4), Defining Assignable Cause for Sample Reanalysis and Excluding Results from Bioanalytical Data Sets; effective date: (b) (4) SOP # (b) (4) Validation of Chromatographic Bioanalytical Methods; effective date (b) (4) SOP # L (b) (4) Conduct of an Analytical Study; effective date: (b) (4) SOP # (b) (4) Calibration Standards: Preparation and Acceptance Criteria for Chromatographic Assays; effective date: (b) (4)

Comments on the Pre-Study Method Validation:

1. (b) (4)

2.

3. The pre-study validation data for albuterol are **adequate**.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD) Cmax (pg/ml)	Tmax[1] (hr)	AUC0-t (pg·hr/ml)	AUC∞ (pg·hr/ml)	T½ (hr)	Kel (hr-1)	Study Report Location
Study No. 10825302	A Study to Investigate the Relative Pharmacokinetics of a Test Formulation of albuterol sulfate inhalation aerosol 90 mcg/actuation (manufactured by Catalent Pharma Solutions) Compared to ProAir® HFA (albuterol sulfate) Inhalation Aerosol 90 mcg/actuation (marketed by Teva Specialty Pharmaceuticals LLC, manufactured by IVAX Pharmaceuticals Ireland) in Healthy Subjects Under Fasting Conditions	Single-Dose, Two-Period, Randomized Crossover Study (Fasting)	**Test product** Albuterol Sulfate Inhalation Aerosol 90 mcg/actuation Dose:2 x 90 mcg actuations (total dose = 180 mcg), Route: Inhalation Lot No.: 08MM-050	24 completing (17 M/7 F) Healthy subjects 30.96 ± 12.11 (18 - 58)	586.3333 ± 181.1271 (30.8915)	1.2500 (0.4170 – 3.0167)	3875.5656 ± 960.4646 (24.7826)	4123.0914 ± 976.9080 (23.6936)	6.1779 ± 0.8891 (14.3921)	0.1146 ± 0.0176 (15.3906)	report-body.p28
			Ref. product ProAir® HFA (albuterol sulfate) Inhalation Aerosol 90 mcg/actuation Dose:2 x 90 mcg actuations (total dose = 180 mcg), Route: Inhalation Lot No.: AEA13B		630.4167 ± 195.8668 (31.0694)	1.3800 (0.5000 – 6.0000)	3978.5067 ± 879.4522 (22.1051)	4246.7645 ± 929.4915 (21.8871)	6.2789 ± 0.9802 (15.6112)	0.1129 ± 0.0175 (15.4978)	

[1]Median Tmax (range)

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer using CALCKE

Albuterol Sulfate 2 x 90 mcg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 10825302							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	3777.60	24	3883.57	24	0.97	91.67	103.21
AUC∞ (hr *pg/ml)	4027.62	24	4146.43	24	0.97	91.81	102.77
Cmax (pg/ml)	562.71	24	603.18	24	0.93	84.74	102.70

Are the PK parameters within the acceptance limits for the 90% CI and meeting BE? Yes

Table 3. Reanalysis of Study Samples

Reason why assay was repeated	Study No. 10825302							
	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	Sequence 1	Sequence 2	Sequence 1	Sequence 2	Sequence 1	Sequence 2	Sequence 1	Sequence 2
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Analytical - No internal standard detected	1	0.0	0.22	0.0	0.0	0.0	0.0	0.0
Unacceptable internal standard response	3	5	0.66	1.10	0.0	0.0	0.0	0.0
Confirmatory reanalysis performed in conjunction with ISR investigation	0	2	0	0.44	0.0	0.0	0.0	0.0
Total	4	7	0.88	1.54	0.0	0.0	0.0	0.0

Notes: Sequence 1- Test; Sequence 2- Reference

Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	(b) (4)	Defining assignable cause for sample reanalysis and excluding results from bioanalytical data sets
(b) (4)	(b) (4)	Conduct of an analytical study

Reanalysis SOPs submitted?	Yes
Do you agree that the reassay criteria**: analytical and pharmacokinetic**	Yes
If not, list the criteria that you don't agree and provide additional comment below	N/A
Are the data in the summary table consistent with the data in the full analytical report?	No
If not, provide comment below	A total of seven rejected batches in the fasting BE study was not included in the "Reanalysis

	of Study Samples" Table.
Did reviewer reanalyze study results?	Yes
Was the study outcome changed based on reviewer reanalysis?	No
Did the firm provide a comprehensive table of repeat samples in the format recommended by the DB?	Yes
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)?	Yes, except the **original** raw numerical data for seven rejected bathes in the fasting BE study.

Comments from the Reviewer:

- There was one repeat due to no internal standard response (Subject (b) (6) Period II at 40 minute post-dose). The reviewer checked the raw analytical data and verified that this repeat was due to no internal standard response.

- There were eight samples repeated due to unacceptable internal standard response. The firm's SOP (b) (4) (Defining assignable cause for sample reanalysis and excluding results from bioanalytical data sets; effective date: (b) (4)) defines the unacceptable internal standard response as following : *failure to meet internal standard response criteria applied consistently to all study sample data.* (b) (4) (b) (4)

  Therefore, the reviewer used the original values in the statistical analysis and the study still passed BE criterion. The 90% confidence intervals of Ln AUC and Ln Cmax are provided below:

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	3768.87	3832.34	0.98	92.47	104.59
LAUCI	4018.79	4095.66	0.98	92.52	104.06
LCMAX	562.52	603.18	0.93	84.69	102.70

- There were two samples repeated due to confirmatory reanalysis performed in conjunction with ISR investigation. These samples were repeated only for confirmation of the ISR and the original values were used in the statistical analysis. Those repeats should not affect the study outcome.

Rejected Batches

- Per the analytical report for the fasting study, there were seven rejected batch runs (Run ID#s 1AFGI, 7AFGI, 8AFGI, 9AFGI, 14 AFGI, 4AFGI and 13AFGI). The firm provided the specific reasons for rejection of the batch runs in the analytical report. However, the firm did not include the original data to support the reasons for batch rejections. Therefore, the firm will be asked to submit the raw data for calibration standards, QC samples and study samples, such as peak area of analyte and internal standard, calculated concentration, etc. of the failed batches. In addition, the firm did not include those rejected batches in the calculation of repeat percentage. The firm will be informed that in future submissions, the firm

should include all analytical repeats, including failed repeat runs, in the "Reanalysis of Study Samples" Table.

3.7 Formulation

Location in appendix	Section 4.2
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biostudy/exhibit batch scored	N/A
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

N/A

3.9 Waiver Request(s) For Immediate Release Dosage Forms

N/A

3.10 Deficiency Comments

Deficiencies Related to Fasting BE Study (# 10825302)

1. The firm did not provide the Certificate of Analysis (CoA) of the reference product (lot # AEA13B). The firm will be asked to provide this information.

2. Per the analytical report for the fasting study (# 10825302), there were seven rejected batch runs for albuterol (Run ID #s 1AFGI, 4AFGI, 7AFGI, 8AFGI, 9AFGI, 13AFGI and 14AFGI). The firm provided the specific reasons for rejection of the batch runs in the analytical report. However, the firm did not include the original data to support the reasons for batch rejections. Therefore, the firm will be asked to submit the raw data for calibration standards, QC samples and study samples, such as peak area of analyte and internal standard, calculated concentration, etc. of the failed batches. In addition, the firm did not include those rejected batches in the calculation of repeat percentage. The firm will be informed that in future submissions, the firm should include all analytical repeats, including failed repeat runs, in the "Reanalysis of Study Samples" Table.

Deficiencies Common to ALL In Vitro Equivalence Studies

3. The firm did not provide detailed study reports for all the in vitro equivalence studies. The firm should provide these reports for each in vitro equivalence study.

4. Manual actuation was used for conducting single actuation content test, priming/re-Priming, aerodynamic particle size distribution by cascade impaction and particle size distribution by laser diffraction. The firm only indicated that both test and reference products were tested under the same instrumental conditions. In addition, the firm's testing procedures does not confirm blinding of the samples during analysis. Therefore, the firm will be asked to confirm, if the samples were blinded during analysis.

5. For Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study, the firm did not provide 100% raw numerical data (analyst's printouts) for all analytical runs (accepted and rejected) conducted during the HPLC sample analysis of these studies. The raw numerical data should include the data of peak area/height for the drug, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard concentration samples, and quality control samples.

6. The firm did not submit 20% of the chromatograms from Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study and will be requested to submit the information.

Deficiencies Related to Single Actuation Content (SAC) through Container Life

7. The firm did not provide the validation data for the manual spray pump actuator for the SAC testing. The firm should submit the formatted summary data tables. Please note that the firm can reference the formatted summary data tables designed for nasal drug products for the same in vitro test. The tables for nasal drug product can be found on the FDA's website at the following location: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf

8. The firm should indicate if stock solutions and working standards underwent freeze-thaw cycles prior to use. If so, the firm will be asked to submit the appropriate data to demonstrate stability.

9. The firm will be asked to provide working standards refrigerator stability data.

Deficiencies Related to Priming/Re-Priming Tests

10. As per the in vitro summary tables submitted by the firm, the priming and re-priming study was conducted between February – April 2009. However, the firm's SOP (# (b) (4)) for priming and re-priming testing was effective on (b) (4). The firm will be asked provide explanation.

Deficiencies Related to Aerodynamic Particle Size Distribution (APSD) by Cascade Impactor

11. The firm did not provide the number of actuations and actuation numbers used in the cascade impaction testing. The firm will be asked to provide this information.

12. According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the APSD test should be performed at both beginning and end lifestages of the product. However, the firm conducted testing only at the beginning lifestage. Therefore, the firm will be asked to conduct APSD testing at the end lifestage of the product.

13. The firm did not specify how many quality control samples were used in each analytical run and at what concentrations. According to the Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal sprays for Local Actions (April 2003): *"analytical runs include at least three or more concentrations of quality control samples that represent the entire range of the standard curve or the expected concentration range of samples from the various stages of the CI."* This is also applicable to the same test of inhalation drug product. Therefore, the firm will be asked to clarify this issue.

Deficiencies Related to Spray Pattern Testing

14. According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the spray pattern should be performed at the beginning lifestage of the product at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm **from the reference product mouthpiece**. It should also be noted that the distance between the actuator orifice and point of spray pattern measurement should be same for the test and reference products. In the current ANDA, the firm conducted the spray pattern testing at 3 cm and 6 cm from the actuator mouthpiece. However, it is not clear from the firm's submission whether the selected 3 cm and 6 cm distances are from the actuator mouthpiece of the reference product. Therefore, the firm will be asked to clarify whether the 3 cm and 6 cm distances selected for the spray pattern testing are from the reference product actuator mouth piece. In addition, the firm will also be asked to confirm whether the distance between the actuator orifice and point of spray pattern measurement is same for the test and reference products.

15. According to the in vitro summary table provided by the firm, the effective date of both SOP #s (b) (4) and (b) (4). However, according to the SOP #s (b) (4), the effective date of both the SOPs was (b) (4). The firm will be asked to clarify this discrepancy.

16. The firm will be asked to provide the Intermediate Precision (By Date) for the validation of the spray pattern testing.

17. The firm provided the spray pattern images and accompanying raw data for 20% samples at both 3 cm and 6 cm distances. However, it is not clear from the firm's

submission, whether the images are of the test product or reference product. The firm will be asked to clarify.

Deficiencies Related to Plume Geometry Testing

18. The firm will be asked to clarify whether the 6 cm distance selected for the plume geometry testing is from the reference product actuator mouth piece. In addition, the firm will also be asked to confirm whether the distance between the actuator orifice and point of plume geometry measurement is same for the test and reference products.

19. The firm will be asked to provide the Intermediate Precision (By Date) for the validation of the plume geomerty testing.

Deficiencies Related to Pharmacodynamic Study (# PRG-723)

20. The firm will be asked to provide the certificate of analysis of the reference product lot # PAEF75A.

21. The firm only provided the case report forms of subject #s (b) (6) and (b) (6). The firm will be asked to provide the case report forms of all subjects included in the pharmacodynamic study.

22. In its submission (Module 5.3.4.1) for the study design of Pharmacodynamic Study (# PRG-723), the firm indicated that "placebo MDI" is used in treatments 1 through 5. However, the firm did not specify whether the "placebo MDI" is the test or reference product placebo. The firm should clarify which placebo, Test or Reference placebo, were used in each treatment of its PD study. In addition, the firm will be asked to provide the formulation of the placebo drug product.

Deficiency Related to Inspection Findings by the Office of Scientific Investigations (OSI):

23. Following the inspection of the analytical site (b) (4), (b) (4) by the Office of Scientific Investigation (OSI) (for the BE studies from other applications), Form FDA-483 was issued. Subsequently, the analytical site provided its responses to Form 483 and those responses were included in the final evaluation by the OSI.

    For considering the impact of similar study conduct and site practices by the same analytical facility on the BE study of the current ANDA, the DBI reviewed the above OSI inspection report and found that the following objectionable finding by the OSI at the analytical site could potentially compromise the integrity of the study of the current application as well:

(b) (4)

The firm will be asked to explain the relevance of this finding to its current application.

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (10825302) **inadequate** due to the reasons cited in the deficiency comments. The Perrigo Pharmaceuticals Company conducted the fasting study on its Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation, lot #08MM-050, comparing it to Proair® HFA (albuterol sulfate) Inhaltion Aerosol, 0.09 mg Base/Inhalation, lot #AEA13B, manufactured by Teva.

2. The Division of Bioequivalence finds the in vitro BE studies **inadequate** due to the reasons cited in the deficiency comments. The Perrigo Pharmaceuticals Company conducted the in vitro BE studies on its Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation, lot #08MM-050, 08MM-034 and 08MM-039, comparing it to Proair® HFA (albuterol sulfate) Inhaltion Aerosol, 0.09 mg Base/Inhalation, lot #AEA13B, AEA12C and AEA14A, manufactured by Teva.

3. The Division of Bioequivalence finds the pharmacodynamics BE study conducted **inadequate** due to the reasons cited in the deficiency comments. The Perrigo Pharmaceuticals Company conducted the pharmacodynamics BE study on its Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation, lot #08MM-050, comparing it to Proair® HFA (albuterol sulfate) Inhaltion Aerosol, 0.09 mg Base/Inhalation, lot #AEA13B and PAEF75A, manufactured by Teva.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
N/A	N/A

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 5 Study Information

Study Number	10825302
Study Title	A Study to Investigate the Relative Pharmacokinetics of a Test Formulation of albuterol sulfate inhalation aerosol 90 mcg/actuation (manufactured by Catalent Pharma Solutions) Compared to ProAir® HFA (albuterol sulfate) Inhalation Aerosol 90 mcg/actuation (marketed by Teva Specialty Pharmaceuticals LLC, manufactured by IVAX Pharmaceuticals Ireland) in Healthy Subjects Under Fasting Conditions
Clinical Site (Name & Address)	Novum Pharmaceutical Research Services 3320 Walnut Bend Lane Houston, TX 77042-4712
Principal Investigator	Soran Hong, M.D.
Dosing Dates	Period I: March 17, 2009 Period II: March 24, 2009
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	
Analytical Director	
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	42 days

Table 6. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Albuterol sulfate inhalation aerosol	PROAIR® HFA INHALATION AEROSOL
Manufacturer	Catalent Pharma Solutions	Teva Respiratory, LLC
Batch/Lot No.	08MM-050	AEA13B
Manufacture Date	December 11, 2008	
Expiration Date		June 2010
Strength	90 mcg/actuation	90 mcg/actuation

Dosage Form	Metered Dose Inhaler	Metered Dose Inhaler
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)		(b) (4)
Content Uniformity (expressed as mean, %CV or per USP)		
Dose Administered	180 mcg (2 x 90 mcg)	180 mcg (2 x 90 mcg)
Route of Administration	Inhalation	Inhalation

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	Yes
Is the bio-batch size at least the recommended minimum of 100K for oral solid dosage form?	N/A

Reviewer's Notes: The reviewer cannot find the Certificates of Analysis for the Reference product (lot # AEA13B). The firm will be asked to identify the location of this document in the submission, or to submit the document in an amendment, as appropriate.

Table 7. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled: 24** **Dosed: 24** **Completed: 24** **Samples Analyzed: 24** **Data Analyzed: 24**
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme (Sequence of T and R)	**TR:** **RT:** (b) (6)
Blood Sampling Times	Pre-dose and at 5, 10, 15, 20, 25, 30, 40, 50 minutes and 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 6.0, 12.0, 16.0 and 24 hours post dose
Blood Volume Collected/Sample	10 mL per sample in sodium heparin vacutainers
Anticoagulant Used	Sodium Heparin

Blood Sample Processing & Storage (include storage temperature)	After collection, the whole blood samples were inverted 5-10 times to ensure proper mixing with the anticoagulant. After mixing, the samples were placed in the centrifuge and spun at approximately (b) (4). The resulting plasma was separated into two approximately equal aliquots in appropriately labeled (b) (4) tubes and placed in the freezer until analysis. During the processing, blood tubes and plasma aliquots were kept in an ice water bath. The time from blood collection to centrifugation did not exceed 60 minutes and the time from blood collection until the plasma was placed in the freezer did not exceed 2 hours. All blood samples were stored frozen to at least –21°C.
IRB Approval	Yes, 03/10/2009
Informed Consent	Yes, 03/10/2009
Length of Fasting	All subjects received the test and reference product as 2 x inhalation of 90 mcg albuterol aerosol following an overnight fast of at least 10 hours. Within 24 hours prior to dosing, the device was "primed" according to the package label instructions and then weighed with the mouthpiece cover on. Following the second dose in each period the subject was required to drink 240 ml of water. During the confinement periods of the study, fluid was restricted from one hour before dosing until one hour after dosing with the exception of water (240 ml) administered with the dose.
Length of Confinement	In each period, the subjects reported for check-in (Day -1) the evening prior to dosing. The subjects were released from the clinical facility approximately 24 hours after dosing in each study period.
Safety Monitoring	Temperature, respiratory rate, pulse rate, and blood pressure (sitting) were measured prior to dosing. The pre-dose vital sign measurements were found to be clinically acceptable for dosing in each period. Blood pressure and pulse rate (sitting) were measured approximately 2 hours (±30 minutes) after dosing and prior to release in each study period.

Was the study design used for the fasting BE study acceptable?	YES

Comments on Study Design:

- As part of the screening procedures the subjects must have demonstrated an acceptable and reproducible inhalation technique of a consistent inhalation flow rate of 25 - 60 L/min on three consecutive tests. The results of these inspiratory flow rate tests were documented and reviewed by an Investigator prior to the subject being considered acceptable for the study. On the evening prior to dosing in each study period the subjects were retrained on the inhalation technique and must have demonstrated a flow rate of 25-60 L/min.

- In addition, on the evening prior to dosing all subjects had a training session using a placebo inhaler provided by the Sponsor. Only those subjects who were able to

demonstrate that they could dose according to the instructions were dosed in the study.

- Doses were administered under direct observation of the study staff following the procedures as detailed in the package labeling.

- The study design is acceptable.

4.1.1.2 Clinical Results

Table 8. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. 10825302		N =24
Age (years)	Mean ± SD	30.96 ± 12.11
	Range	18 – 58
Age Groups	< 18	0 (0%)
	18 – 40	20 (83.3%)
	41 – 64	4 (16.7%)
	65 – 75	0 (0%)
	> 75	0 (0%)
Sex	Male	17 (70.8%)
	Female	7 (29.2%)
Race	Asian	1 (4.1%)
	Black	15 (62.5%)
	Caucasian	3 (12.5%)
	Hispanic	0 (%)
	Other	5 (20.9%)
Ethnicity	Hispanic/Latino	5 (20.8%)
	Not Hispanic/Latino	19 (79.2%)
Weight (lbs)	Mean ± SD	162.4 ± 23.9
	Range	120.0 – 220.0
BMI (Kg/m^2)	Mean ± SD	24.56 ± 3.04
	Range	20.4 – 30.0
Tobacco User[1]	Yes	0 (0%)
	No	113 (100.0%)

[1] Defined as current tobacco user (having used tobacco within 90 days of first dose).

Table 9. Dropout Information, Fasting Bioequivalence Study

Study No. 10825302				
Subject No	**Reason for dropout/replacement***	**Period**	**Replaced?**	**Replaced with**
N/A	No dropouts	N/A	N/A	N/A

Table 10. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Bioequivalence Study Study No. 10825302	
	Test A	Reference B
Investigations		
Blood glucose increased	0 (0.0%)	1 (4.1%)
Blood pressure increased	1 (4.1%)	3 (12.5%)
Blood pressure decreased	1 (4.1%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	1 (4.1%)	1 (4.1%)
Total	3 (12.5%)	4 (16.6%)

N% = (Number of subjects reporting AE / number of subjects dosed with respective study drug) × 100
Total N%= (Number of subjects that reported at least one AE / number of subjects dosed with respective study drug) × 100
Test Product A =24 subjects dosed and Reference Product B =24 subjects dosed

Do any of the adverse events require statistical analysis consideration (e.g. emesis)?

No

If yes, does the time exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products) according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*?

N/A

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product?

Comparable. There is no strong evidence suggesting that the test drug caused substantially more serious adverse events compared to the reference drug.

Are there any safety concerns based on the adverse event profile? No

Table 11. Protocol Deviations, Fasting Bioequivalence Study

Study No. 10825302		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
No Protocol Deviations	N/A	N/A

Did dropouts/adverse events/protocol deviations affect the study outcome? No

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were no dropouts in the fasting BE study.
- No serious adverse events (SAEs) were reported during the fasting BE study. All the adverse events were described as "mild" by the physician.
- No emesis was experienced by any of the subjects.
- There were no protocol deviations in the fasting BE study.
- No concomitant medications were administered in the fasting BE study.
- There were few sampling time point deviations. The overall time deviations are minor (within 12 minutes, most of the deviations being within 5 minutes). Thus are considered to be insignificant by the reviewer. The firm used actual sampling times for its pharmacokinetic (PK) calculations while this reviewer used nominal times for its PK calculations. Based on the results (which are similar for both), time deviations do not have an impact on the overall statistical outcome of the study.
- The clinical results are acceptable.

4.1.1.3 Bioanalytical Results

Table 12. Sample Analysis Calibration and Quality Control – Within the Fasting Bioequivalence Study

Albuterol								
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	2.00	4.00	10.0	40.0	200	800	3200	4000
Inter day Precision (%CV)	9.51	7.04	6.40	6.96	6.11	6.04	5.69	5.22
Inter day Accuracy (%Actual)	100	99.3	98.5	102	101	101	99.2	98.6
Linearity	0.9927 to 0.9990							
Linearity Range (pg/mL)	2.00 to 4000							
Sensitivity/LOQ (pg/mL)	2.00							

Parameter	**Quality Control Samples**				
Concentration (pg/mL)	6.00	20.0	90.0	400	3000
Inter day Precision (%CV)	10.2	7.39	5.57	5.82	5.24
Inter day Accuracy (%Actual)	100	102	102	102	98.5
Number of Acceptable Runs	16 runs				
Number of Rejected Runs (Run ID, volume/page location)	7 Rejected runs, Run ID # 1AFGI, 4AFGI, 7AFGI, 8AFGI, 9AFGI, 13AFGI and 14AFGI, Module: 5.3.1.2, Page: 45 The following are the reasons provided by the firm for rejected runs: Run ID #s 1AFGI, 7AFGI, 8AFGI, 9AFGI, 14 AFGI – Run rejected due to unacceptable quality control samples Run ID # 4AFGI – Run rejected due to extraction error Run ID # 13AFGI – Run rejected due to unacceptable calibration standards The firm did not provide the analytical raw data for the rejection batches. The firm will be asked to provide this information				
If sample and QC diluted during study, specify all dilution factors	No samples were diluted.				
Was 100% of raw numerical data submitted?	Yes, except the **original** raw numerical data for the seven rejected runs.				

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Yes

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially, sub #s (b) (6)

Were the chromatograms submitted by the firm acceptable?	Yes

Table 13. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Defining assignable cause for sample reanalysis and excluding results from bioanalytical data sets
		Conduct of an Analytical Study

Reviewer's Comments:

- There were seven rejected batch runs in the fasting study (Run ID # 1AFGI, 4AFGI, 7AFGI, 8AFGI, 9AFGI, 13AFGI and 14AFGI). The firm provided the specific reasons for those rejections. However, the firm did not include the original data to support the reasons for batch rejections. Therefore, the firm will be asked to submit these data for the rejected batches.

- The total number of samples collected from the clinical study was 912. The firm used 86 samples for incurred samples reanalysis (ISR) testing. A total of 76 out of 86 (88.37%) were found to be within 20% difference.

Table 14. Additional Comments on Repeat Assays

Were all SOPs followed?	Pending firm's submission of raw data for its rejected analytical runs
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Pending firm's submission of raw data for its rejected analytical runs
If no, reason for disagreement	Please see deficiency comments

Summary/Conclusions, Study Assays:

- At this time, the reviewer is unable to assess the acceptability of the reanalysis of study samples. The reviewer will be able to properly evaluate the reanalysis study samples once the firm provides all information requested in the Deficiency Comments Section of this review.

- The study assay is **incomplete.**

4.1.1.4 Pharmacokinetic Results

Table 15. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 19 and Figure 1

		Test				Reference				Ratio
Parameter	Unit	Mean	CV %	Min	Max	Mean	CV %	Min	Max	(T/R)
AUCT	pg hr/mL	3876.553	24.75		(b) (4)	3978.782	22.11		(b) (4)	0.97
AUCI	pg hr/mL	4124.660	23.66			4247.587	21.90			0.97
CMAX	pg/mL	586.333	30.89			630.417	31.07			0.93
TMAX	hr	1.250	.			1.375	.			0.91
KE	hr-1	0.114	15.50			0.112	14.88			1.02
THALF	hr	6.192	14.44			6.297	15.19			0.98

* Tmax values are presented as median, range

Table 16. Geometric Means and 90% Confidence Intervals - Firm Calculated

Albuterol Sulfate Inhalation Aerosol 2 x 90 mcg/inhalation Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study, Study No. 10825302						
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUC0-t (hr *pg/ml)	3776.29	24	3883.37	24	0.97	91.63 – 103.20
AUC∞ (hr *pg/ml)	4025.73	24	4145.78	24	0.97	91.77 – 102.75
Cmax (pg/ml)	562.71	24	603.18	24	0.93	84.74 – 102.70

Table 17. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Albuterol Sulfate Inhalation Aerosol 2 x 90 mcg/Inhalation Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 10825302							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	3777.60	24	3883.57	24	0.97	91.67	103.21
AUC∞ (hr *pg/ml)	4027.62	24	4146.43	24	0.97	91.81	102.77
Cmax (pg/ml)	562.71	24	603.18	24	0.93	84.74	102.70

Table 18. Additional Study Information, Fasting Study No.10825302

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE	
Reason(s) for Selecting Above SAS Program Macro	Please see below	
Root mean square error, AUC0-t	0.1195	
Root mean square error, AUC∞	0.1138	
Root mean square error, Cmax	0.1939	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	24	24
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Cmax at the first time point	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	24	0.94	0.89	0.97
Reference	24	0.94	0.87	0.97
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

- The reviewer used the SAS code, CALCKE, for statistical analysis of the data. This particular SAS code allows the reviewer to select the values which are used as the time points to calculate the elimination rate constant, Kel (Note: AUCI and THALF are dependent variables), along with other PK parameters. The elimination rate constant (Kel) of the drug was calculated by individually selecting the last four to five non-zero data points for each subject. The selection of the time points for calculating the Kel was based on the terminal loglinear phase of the drug for the subjects.

- The arithmetic mean and 90% CI of Cmax calculated by the reviewer agree with the firm's calculations.

- The AUCt values calculated by the reviewer are slightly different from those by the firm. This is more than likely due to the fact that the current reviewer used scheduled sampling times for PK calculation while the firm used actual sampling times for its PK calculation.

- The 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC∞ and LnCmax calculated by the reviewer is consistent with the firm's calculations and meet the criteria for BE.

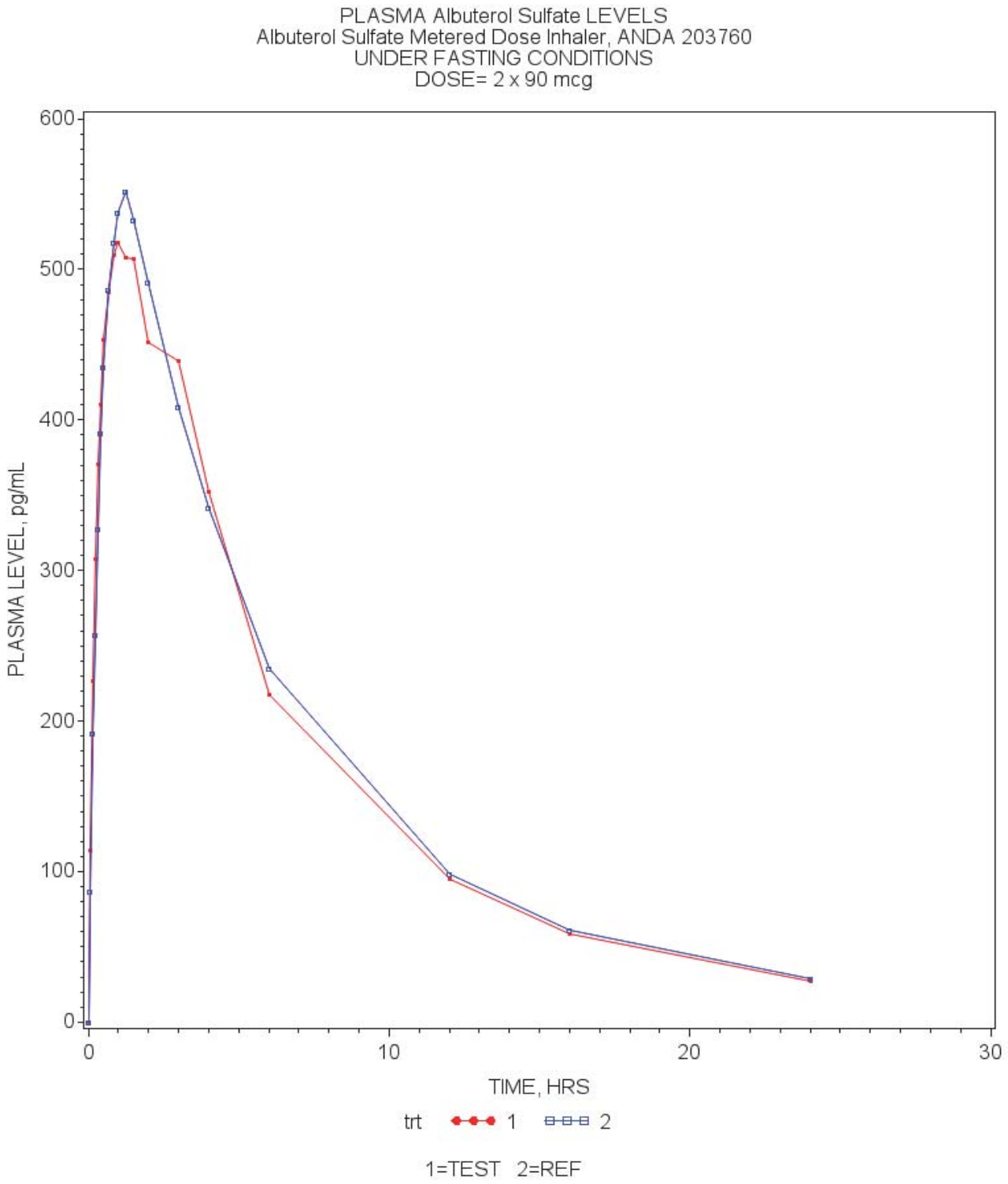
Was the fasting bioequivalence study acceptable?

The firm's *in vivo* BE study under fasted conditions is **inadequate** due to the deficiencies specified in Section 3.10.

Table 19. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=24)		Reference (n=24)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.08	114.03	69.51	86.30	103.37	1.32
0.17	226.31	63.96	191.89	84.07	1.18
0.25	307.87	55.78	256.94	74.16	1.20
0.33	370.45	53.88	327.40	65.84	1.13
0.42	410.48	49.26	390.96	64.59	1.05
0.50	453.55	46.27	434.76	59.33	1.04
0.67	484.36	43.01	486.36	48.57	1.00
0.83	509.33	40.67	518.04	41.60	0.98
1.00	517.62	40.24	537.75	37.10	0.96
1.25	507.46	35.71	551.42	35.84	0.92
1.50	507.33	34.27	532.54	31.67	0.95
2.00	451.29	30.99	491.13	30.96	0.92
3.00	438.88	30.06	408.67	28.95	1.07
4.00	352.29	24.62	341.50	24.62	1.03
6.00	217.25	29.10	235.08	29.83	0.92
12.00	94.96	25.94	98.23	24.07	0.97
16.00	58.64	25.34	61.22	27.93	0.96
24.00	27.15	27.68	28.69	32.98	0.95

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.2 Formulation Data

Test Formulation (amendment submission date May 18, 2012)

Component	Unit Quantity			Function	Reference to Standards
	% w/w	Per canister (g)	Per actuation (mg)		
Active Ingredient:					
Albuterol sulfate (b) (4)	(b) (4)			Active	USP
Excipients:					
(b) (4) alcohol (ethanol)					(b) (4)
Propellant 134a (b) (4)					
Total weight:	100	(b) (4)			

RLD Formulation[10]

Component	Function	Supplier	Qty Actuation	Qty Can	Qty/Batch[2] 120000 Cans
Albuterol sulfate[1]	Active				(b) (4)
(b) (4) Alcohol USP	(b) (4)				
Total Suspension Weight					
Propellant HFA-134a (b) (4)					
Total Weight					
(b) (4)					
(b) (4)					

[10] DARRTS, NDA 021457, Rev-QUALITY-03 (General Review), 11/28/2003, last accessed date: 01/15/2014

RLD Formulation

Ingredients	Amount per Actuation	Amount per Canister	% (w/w)[11]
Albuterol Sulfate USP	(b) (4)	(b) (4)	(b) (4)
(b) (4) Alcohol USP			
Propellant HFA 134a			
Total theoretical Weight			100

Comparison of Test and RLD Formulation

Ingredients	Test Formulation (%w/w)	Reference Formulation (%w/w)	Difference (%)
Albuterol Sulfate USP			(b) (4)
(b) (4) Alcohol USP			
Propellant HFA 134a			

Reviewer's Comments:

- The test product contains (b) (4) of Albuterol Sulfate, and (b) (4) per actuation; the reference product contains (b) (4) of Albuterol Sulfate, and (b) (4) per actuation. (b) (4) the reviewer considers the amount of the active ingredient in the test formulation, as compared with the RLD formulation, is acceptable[12].

- The Agency recommends that the formulations of the generic metered dose inhalers (MDIs) should be qualitatively (Q1) and quantitatively (Q2) the same as the innovator products based on concentration. Q_1 (Qualitative sameness) means that the generic product contains the same inactive ingredients as the RLD. Q_2 (Quantitative sameness) means that the generic product contains all inactive ingredients at concentrations within ± 5% of the concentrations in the RLD.

- The test and RLD products are Q1 and Q2 essentially the same with respect to the inactive ingredients. The amounts of the inactive ingredient(s) in the test product differ within **± 5 percent** of those in the reference listed drug.

- The test formulation is acceptable.

[11] Calculated by Reviewer
[12] DARRTS, ANDA 203760, REV-BIOEQ-07 (Filing Review), 05/24/2012, last accessed date: 01/15/2014

Is the formulation of the Test product Q_1 and Q_2 same as the Reference product?	Yes
Is the formulation acceptable?	**ACCEPTABLE**
If not, why?	N/A

4.3 In Vitro Equivalence Testing

4.3.1 Information Common to ALL *In Vitro* Equivalence Tests

4.3.1.1 Batch Information

Study Type	TEST					REFERENCE		
	Lot No.	Potency (%w/w)	Lot Size		Manufacture Date	Lot No.	Potency (%w/w)	Expiration Date
			Theoretical Quantity	Actual Quantity Used				
Bioequivalence study (PK and PD Study)	08MM-050	[redacted] (b) (4)			12/11/2008	AEA13B	[redacted] (b) (4)	6/2010
In-Vitro equivalence studies	08MM-034				11/11/2008	AEA13B		6/2010
	08MM-039				11/20/2008	AEA12C		7/2010
	08MM-050				12/11/2008	AEA14A		6/2010

Comments:

1. Per the current ANDA Filing Requirements for Nasal Products[13] , the lot size (# of bottles) [redacted] (b) (4) The current reviewer applied the same criterion for Inhalation Products. Since the firm's theoretical lot size is [redacted] (b) (4) the test product lot size is acceptable.

2. For each in vitro test, ten (10) units from each of the three lots of the test product and each of the three lots of the reference product were tested for each. Therefore, for each test a total of 30 units of the test product and 30 units of the reference product were tested.

3. All the in vitro tests were performed on unexpired lots of reference products.

4. The batch information provided by the firm is **adequate**.

[13] 2010 GPhA Annual Meeting, Title "The Orange Book, and ANDA Filing Requirements" presented by Martin Shimer

4.3.1.2 Device Comparability

Comments:

- The firm submitted the comparative data for three device components: can, valve and actuator**.** The dimensions of the critical components such as actuator orifice diameter and metering volume are the same for the test and reference product.

- According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the test product should have a dose counter if the reference product has a dose counter. Both the test and reference products have a dose counter. On November 15, 2013, the labeling reviewer requested a consult to the DCR regarding the dose counter system[14].

- There are two differences on the display of the dose counter system between test and reference products: 1) display of beginning number on the dose counter is different; and 2) refill dose reminder is different. Per DCR consult response, *the Perrigo's proposed dose counter system manufactured by* (b) (4) *acceptable and not considered a safety concern*[15].

[14] DARRTS ANDA 203760 Vu, Thuyanh 11/15/2013 N/A 11/15/2013 FRM-CONSULT-01(General Consult Request)
[15] DARRTS ANDA 203760 Kim, Carol Y 01/13/2014 N/A 01/13/2014 CONSULT REV-CLINICAL-01(General Consult Review) Archive

- The devices used for the test and reference products were comparable.
- The information provided by the firm is **adequate**.

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

3. The actuation methods used by the firm are **incomplete**.

4.3.2 Individual In Vitro Test reviews

4.3.2.1 Single Actuation Content through Container Life

4.3.2.1.1 Study Information

Study No.	TTP-CBJ-M0050
Study Site	(b) (4)
Principal Investigator	
Study Dates	
SOP No.	
SOP Effective Date	
SOP Title	Determination of Dose Content Uniformity, shot weight, and number of actuations from Albuterol Sulfate HFA Inhalation Aerosol Product
Test Method Description	(b) (4)
Testing Equipment Used (e.g., name, model, etc)	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc.)	
Analytical Method Description	
Analytical Equipment Used (e.g., name, model, etc.)	

Comments:

- This is a metered dose inhaler, therefore, the single actuation content (SAC) at beginning, middle and end of the unit life are requested according to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI (recommended April 2003; Revised June 2013). The firm performed the test at the beginning, middle and end lifestages using flow rate 30.0± 1.0 L/min. The USP <601> Apparatus A was used in the SAC testing.

- The firm did not submit a detailed study report for SAC testing.

4.3.2.1.1 Analytical Method Validation for HPLC

Information Requested	
Analytical method validation report location	(b) (4)
Study Report Number	
Analyte	
Internal Standard (IS)	
Method description	
Selectivity or Specificity	
Limit of quantitation	
Detection Limit	
Linearity Range (µg/mL)	
Linearity (R^2)	
Accuracy (% recovery at the high and low concentrations)	
Precision -- Repeatability	
Precision --Intermediate Precision	
Bench-top stability (hrs(CV%)) (working std solution)	
Refrigerator stability (hrs(CV%)) (working std solution)	
Stock solution stability (days (CV %))	
Freeze-thaw stability (cycles (CV %))	
Robustness	

	(b) (4)
Dilution integrity	Not Provided

Does Firm's SOP include validation criteria? (Y/N) **If so, list the criteria.**	(b) (4)
Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	Acceptable

Comments:

- The firm should indicate if stock solutions and working standards underwent freeze-thaw cycles prior to use. If so, the firm will be asked to submit the appropriate data to demonstrate stability.
- The firm did not provide working standards refrigerator stability data.
- Therefore, the HPLC method validation is incomplete.

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

4.3.2.1.2 Precision

Not Provided.

4.3.2.1.3 Ruggedness (by Date)

Not Provided.

4.3.2.1.4 Ruggedness (by Analyst)

Not Provided.

4.3.2.1.5 Ruggedness (Unit to Unit if more than one unit is used)

Not Provided.

Comments on Method Validation:

Did the firm provide a table of pump specific parameters of each actuator used for each in vitro test? (Y/N) **If yes, please include the table(s) above.**	No
Number of Bottles and/or Lots Used in the Validation Study	The reference lots# used in the validation report are AEA13B and AEF75A.
Does Firm's SOP include validation criteria? (Y/N) **If so, list the criteria.**	**No**
Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	INCOMPLETE

Comments: The firm did not submit the precision and ruggedness individual and summary data for the calibration of manual spray pump actuator used in its SAC studies. The firm should conduct the ruggedness studies before conducting the pivotal SAC test and submit the study results using CTD tables. Please note that the format validation summary tables for nasal spray products can be referenced (where appropriate) from FDA's website at the following location:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf

4.3.2.1.1 Results Summary

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Spray #	Mean				Variability (%CV)					Mean Ratio (T/R)	
			Drug Mass		% label claim		Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
BEG	Test	1	114	113	105	105	4.9	6.3	3.6	1.1	5.0	1.03	1.03
	Ref	1	110	110	102	102	4.2	4.4	3.7	1.5	4.1		
MID	Test	124	118	118	109	109	3.8	4.3	4.2	2.5	5.3	1.05	1.05
	Ref	124	113	113	104	104	4.1	3.1	3.7	0.4	4.0		
END	Test	200	117	117	108	108	4.4	3.9	5.1	2.0	4.7	1.03	1.03
	Ref	200	113	113	105	105	3.8	5.0	6.1	2.1	5.2		

NOTE: The drug mass is expressed as Albuterol Sulfate and not the base.

(b) (4)

[redacted]

4.3.2.1.1 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE		
REVIEW OF TESTING METHODS:		
Is the testing method validated?		No, the firm did not submit the validation data for manual actuation
Is the Quantitative Analytical Method Validated? (e.g., HPLC)		Yes
Is the method sufficiently sensitive?		Yes
Is testing performed as per RLD labeling?		Yes
Are data measured at both beginning, middle & end lifestages?		Data are measured at beginning, middle and end stages. This is according to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI.
Is testing a single actuation per determination?		Yes
If yes, what is the actuation number tested?		**# 1 (beginning) after priming # 124 (middle) # 200 (end)**
Are the testing methods acceptable?		**INCOMPLETE**
If not, why?		Due to deficiencies in the method validation
STUDY RESULTS:		
Are data expressed as actual amount and % of label claim?		Yes
Is the geo-mean of the test product (% of label claim) within 95-105%?	**Beginning**	Yes
	Middle	No
	End	No

Are the PBE results acceptable?	Acceptable (pass PBE)
If not, why?	N/A

Reviewer Comments on SAC:

1. The RLD labeling of Albuterol Sulfate Metered Dose Inhaler states the following regarding the priming of the inhaler[16]:
   "You must prime the inhaler to get the right amount of medicine. Prime the inhaler before you use it for the first time or if you have not used it for more than 14 days. To prime the inhaler, take the cap off the mouthpiece of the actuator. Then shake the inhaler well, and spray it into the air away from your face. Shake and spray the inhaler like this 2 more times to finish priming it".

2. In the current ANDA, both the test and reference products were primed three actuations and then performed the SAC testing. This is according to the RLD labeling. Actuation #1 actually is actuation #3. Actuation #124 actually is actuation #126. Actuation #200 actually is actuation #202.

3. After priming, the firm assayed actuation #1, actuation #124 and actuation #200 of the test product and reference products to represent the beginning, middle and end life stages respectively.

4. According to Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, recommended June 2013, SAC testing should be conducted using a flow rate of 28.3 L/min. In the current ANDA, the firm used a flow rate of 30.0 ± 1.0 L/min. The SAC testing in the current ANDA is conducted prior to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI. In addition, the difference is minor. Therefore, the use of 30.0 ± 1.0 L/min flow rate is acceptable.

5. The test product passes the PBE analysis. The firm also provided the PBE analysis results for 95% upper bound. The 95% upper bound of drug mass calculated by the reviewer is slightly different from the firm's calculations. But the firm did not provide detail calculation procedure. The reviewer could not able to evaluate the firm's PBE analysis. However, this difference does not have impact on the outcome of the study (95% upper bounds from both calculations are less than 0). Please see the summary results of 95% upper bounds.

[16] Drugs@FDA, Keyword Search: Proair, RLD Label approved on 08/17/2010, last accessed date: 01/06/2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021457s021lbl.pdf

Parameters	Firm's Calculation		Reviewer's Calculation	
	Reference-Scaled	Constant-Scaled	Reference-Scaled	Constant-Scaled
Drug Mass	-0.00105	-0.00805	-0.0005	-0.0176
Final BE Conclusion Based on	**Constant-Scaled**		**Constant-Scaled**	

6. The geo-mean of the test product (% of label claim) for the beginning unit life is within 95-105%. However, the geo-means of the test product (% of label claim) for the middle (109%) and end (108%) of unit life are not within 95-105%. However, the T/R raio of the geometric means are close to 1 (1.05 and 1.03 for mid and end stages respectively). In addition, according to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the test product should pass PBE analysis only. Therefore, it is acceptable that the geo-means of the test product (% of label claim) for the middle and end of unit life are slightly off 95-105%.

7. The firm did not submit 20% of the HPLC chromatograms from the SAC testing and will be requested to submit this information.

8. The firm did not provide 100% raw numerical data (Analyst's printouts) for all analytical runs (accepted and rejected) conducted during the HPLC sample analysis of the SAC and Priming & Re-Priming studies. The raw numerical data should include the data of peak area/height for the drug, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard samples, and quality control samples.

This study is **incomplete** with deficiencies.

4.3.2.1.2 Deficiencies / Recommendations

Please see Section 3.10.

4.3.2.2 Priming & Re-priming

4.3.2.2.1 Study Information

Study No.	TTP-CBJ-M0050
Study site	(b) (4)
Principal Investigator	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	Determination of Dose Content Uniformity, shot Weight, and Number of actuations from an Albuterol Sulfate HFA Inhalation Aerosol Product.
Test Method Description	(b) (4)
Testing Equipment Used (e.g., name, model, etc)	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	
Analytical Method Description	
Analytical Equipment Used (e.g., name, model, etc)	

Comments:

1. The firm's labeled actuation #1 is actual actuation #4 (following 3 priming actuations as specified in the drug product label).

2. The RLD labeling of Albuterol Sulfate Inhalation Aerosol states that when 14 or more days have elapsed since the last use, the pump should be reprimed with 2 actuations.

Therefore, a repriming study is necessary for the current application. The firm stored the products and then tested the repriming on Day 15.

3. The firm stored the containers in valve down position without being actuated before priming and repriming. The bottles were shaken as per the RLD labeling prior to use.

4. The firm did not submit a detailed study report for priming and re-priming testing. The firm will be asked to submit this information.

5. As per the in vitro summary tables submitted by the firm, the priming and re-priming study was conducted between February – April 2009. However, the firm's SOP (b) (4) (b) (4) for priming and re-priming testing was effective on 06/17/2011. The firm will be asked to provide explanation.

4.3.2.2.2 Analytical Method Validation for HPLC

Please refer to the method validation for SAC test.

4.3.2.2.3 Results Summary – Priming & Re-Priming

PRIMING												
Number of actuations used to **prime** each product = 3												
Actuation number used for testing each product = # 1												
	Spray #	**Mean**				**Variability (%CV)**					**Mean Ratio (T/R)**	
		Drug Mass		**% label claim**		Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	1	114	113	105	105	4.9	6.3	3.6	1.1	5.0	1.03	1.03
Ref	1	110	110	102	102	4.2	4.4	3.7	1.5	4.1		

RE-PRIMING												
Period of time each product was stored in the vertical position following priming (nasal sprays only) = 14 days												
Number of actuations used to **re-prime** each product = 3												
Actuation number used for testing each product = # 5												
	Spray #	**Mean**				**Variability (%CV)**					**Mean Ratio (T/R)**	
		Drug Mass		**% label claim**		Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	5	114	114	105	105	5.5	4.0	3.8	0.1	4.4	1.06	1.06
Ref	5	108	107	100	99	8.7	6.0	3.7	2.0	6.4		

4.3.2.2.4 Conclusions

PRIMING & RE–PRIMING		
REVIEW OF TESTING METHODS:		
Is the testing method validated?		**No**
PRIMING	**Number of actuations required**	3 priming actuations
	Is priming conducted as per RLD label?	Yes
RE – PRIMING	**Number of actuations required**	3 repriming actuations
	Is re-priming conducted as per RLD label?	Yes
Is testing a single actuation per determination?		Yes
If yes, what is the actuation number tested?		# 1 (after 3 priming actuations) for priming and # 5 (after 3 repriming actuations) for repriming
Are studies performed on products stored in the valve-upright position? (nasal spray only)		No, valve down position
Are the testing methods acceptable?		**INCOMPLETE**
If not, why?		See deficiency section for details
STUDY RESULTS:		
PRIMING	**Is the geo-mean of the test product (% of label claim) within 95-105%?**	Yes
RE – PRIMING	**Is the geo-mean of the test product (% of label claim) within 95-105%?**	Yes
Are the PBE results acceptable?		**ACCEPTABLE (pass PBE)**
If not, why?		N/A

Reviewer Comments on Priming:

1. The RLD label states that *"You must prime the inhaler to get the right amount of medicine. Prime the inhaler before you use it for the first time or if you have not used it for more than 14 days. To prime the inhaler, take the cap off the mouthpiece of the actuator. Then shake the inhaler well, and spray it into the air away from your face. Shake and spray the inhaler like this 2 more times to finish priming it".*

2. For priming, the inhaler was primed by wasting the first 3 actuations for both the test and reference products and actuation # 4 (or actuation # 1 after priming) was used for testing.

3. For re-priming, the firm mentioned that the inhaler was stored for at least two weeks (14 days) valve down, without being actuated, prior to re-prime data collection. After 14 days, the inhaler was primed 3 times and actuation # 5 was used for re-priming testing.

4. The test product passes the PBE analysis for both priming and re-priming. The firm also provided the PBE analysis results for 95% upper bound. The 95% upper bound of drug mass calculated by the reviewer is slightly different from the firm's calculations. But the firm did not provide detail calculation procedure. The reviewer could not able to evaluate the firm's PBE analysis. However, this difference does not have impact on the outcome of the study (95% upper bound from both calculations are less than 0). Please see the summary results of 95% upper bounds.

Parameters	Firm's Calculation		Reviewer's Calculation	
	Reference-Scaled	Constant-Scaled	Reference-Scaled	Constant-Scaled
Prime	0.00234	-0.00710	-0.0005	-0.0176
Prime: Final BE Conclusion Based on	Constant-Scaled		Constant-Scaled	
Reprime	0.00005	-0.00666	-0.0031	-0.0162
Reprime: Final BE Conclusion Based on	Constant-Scaled		Constant-Scaled	

5. The firm did not submit 20% of the chromatograms from the priming and re-priming testing and will be requested to submit this information.

6. The firm did not provide 100% raw numerical data.

4.3.2.2.5 Deficiencies / Recommendations – Priming & Re-Priming

Please see deficiency comments in section 3.10.

4.3.2.3 Droplet Size Distribution by Laser Diffraction (For Information Only)

4.3.2.3.1 Study Information

Study No.	TTP-CBJ-M0050 Part 1
Study site	(b) (4)
Principal Investigator	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	Particle Size Distribution (PSD) of an Albuterol Sulfate HFA Inhalation Aerosol by Laser Diffraction
Testing Method Description (including DSD measurement over entire life of spray, fully developed phase, etc)	(b) (4)
Study Distances (distances from actuator orifice)	
Testing Equipment Used (e.g., name, model, etc)	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	
Analytical Method Description	
Analytical Equipment Used (e.g., name, model, etc)	

Comments:

- According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI (recommended April 2013; Revised June 2013), the Agency does not recommend laser diffraction for particle size distribution test. Therefore, the reviewer did not review this study.

- The firm did not submit the detailed study report.

Please note that the following summary tables as provided by the firm are listed here for information purposes only. The reviewer did not perform statistical analysis for the firm's particle size distribution by laser diffraction.

(b) (4)

4.3.2.3.2.4 Intermediate Precision (By Unit)

Not Provided

Number of Bottles and/or Lots Used in the Validation Study	Not Provided
Does Firm's SOP include validation criteria? (Y/N) **If so, list the criteria.**	Not Provided
Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	Not Provided

Comments: The firm only provided the validation summary information. The firm did not provide method validation SOP and method validation report. Since, this study is not required according to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the firm will not be asked to provide any information.

4.3.2.3.3 Results Summary – Droplet Size Distribution by Laser Diffraction (Calculated by the firm)

4.3.2.3.4 Conclusions

DROPLET SIZE DISTRIBUTION BY LASER DIFFRACTION	
REVIEW OF TESTING METHODS:	
Are ~20% of the time-history plots provided by the firm?	Yes
Are data measured at the fully-developed phase only?	Not Reviewed
Is the testing method validated?	Not Reviewed
Is testing conducted as per RLD labeling?	Not Reviewed
Is testing a single actuation per determination?	Not Reviewed
If yes, what is the actuation number tested?	Not Reviewed
Is an example of instrument setup/operating conditions included?	Not Reviewed
Are data reported per volume (mass) & not droplet counts?	Not Reviewed
Are data measured at both beginning & end lifestages?	Not Reviewed

DROPLET SIZE DISTRIBUTION BY LASER DIFFRACTION				
Are data measured at two distances from actuator orifice?				Not Reviewed
Which two distances are tested?				Not Reviewed
Are the two testing distances between 2 – 7 cm?				Not Reviewed
Are the two testing distances separated by ≥ 3 cm?				Not Reviewed
Are the testing methods acceptable?				**N/A**
If not, why?				N/A
STUDY RESULTS:				
Are the PBE results acceptable?		**D_{50}**	**Distance 1** (3 cm)	N/A
			Distance 2 (6 cm)	N/A
		SPAN	**Distance 1** (3 cm)	N/A
			Distance 2 (6 cm)	N/A
If not, why?				N/A

4.3.2.3.5 Deficiencies / Recommendations – Laser Diffraction

N/A

4.3.2.4 Aerodynamic Particle Size Distribution (APSD) by [redacted] Cascade

4.3.2.4.1 Study Information

Study No.	TTP-CBJ-M0050 Part 1
Study site	[redacted]
Principal Investigator	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	Standard Operating Procedure for Next Generation Pharmaceutical Impactor
Testing Method Description	[redacted]
Testing Equipment Used (e.g., name, model, etc)	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	
Analytical Method Description	
Analytical Equipment Used (e.g., name, model, etc)	

Comments:

1. The firm should clarify whether the testing was conducted per the RLD labeling (e.g. the units were primed 2 times when tested at the beginning of lifestage) and what were the sequential number of the actuation tested for each product.

2. As per the in vitro summary table submitted by the firm, SOP [redacted] was used for cascade impaction testing. However, the firm submitted SOP [redacted] The firm mentioned the significant changes between the two versions and there are no major differences between the two versions. Therefore, the firm will not be asked to submit [redacted] of the SOP.

3. The firm did not provide the study report for the cascade impaction testing. The firm will be asked to provide this information.

4.3.2.4.2 Validation Summary Table for Particle Size Distribution by Cascade Impactor

4.3.2.4.2.1 Analytical Method Validation for HPLC

Information Requested	(b) (4)
Analytical method validation report location	
Study Report Number	
Analyte	
Internal Standard (IS)	
Method description	
Selectivity or Specificity	
Limit of quantitation	
Detection Limit	
Linearity Range (mcg/mL)	
Linearity (R^2)	
Accuracy (% recovery at the high and low concentrations)	
Precision -- Repeatability	
Precision --Intermediate Precision	

	(b) (4)
Bench-top stability (hrs) (working std solution)	
Refrigerator stability (hrs) (working std solution)	
Stock solution stability (days)	
Freeze-thaw stability (cycles)	
Robustness	
Dilution integrity	

Does Firm's SOP include validation criteria? (Y/N)	The firm's method validation report includes the validation criteria
Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	Acceptable

Comments:

- The firm should indicate if stock solutions and working standards underwent freeze-thaw cycles prior to use. If so, the firm will be asked to submit the appropriate data to demonstrate stability.

- The firm did not provide working standards refrigerator stability data.

4.3.2.4.2.2 Validation Table for Cascade Impaction

(b) (4)

(b) (4)

Number of Bottles and/or Lots Used in the Validation Study	Reference lot #AEA13B Reference lot #PAEF75A
Does Firm's SOP include validation criteria? (Y/N)	Yes
Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	Acceptable

Comments:

1. The firm did not specify how many quality control samples were used in the analytical runs. According to the Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal sprays for Local Actions (April 2003): *"analytical runs include at least three or more concentrations of quality control samples that represent the entire range of the standard curve or the expected concentration range of samples from the various stages of the CI."* The firm will be asked to address the above issue.

2. The firm did not provide chromatograms respective of sample analysis. The firm will be asked to provide at least 20% of the chromatograms selected sequentially of the analytical study and summary table include the follows: sample ID, acquisition date and time, analyte peak area, analyte concentration, calculated concentration, analyte retention time, etc.

3. The firm did not provide 100% raw numerical data (Analyst's printouts) for all analytical runs (accepted and rejected) conducted during the HPLC sample analysis of the APSD by Cascade Imapctor study.

4.3.2.4.3 Results Summary – Aerodynamic Particle Size Distribution by Cascade Impactor (CI)

Comments:

1. The aerodynamic particle size distribution was determined using (b) (4) (b) (4) HPLC was used for sample analysis. Cascade impaction performed on the product has been done by analyzing the amount of drug deposited on various stages of the impactor. This study was evaluated on three batches of reference product and three batches of test product. Ten replicate samples for each batch of the test and reference products were measured.

2. (b) (4)

(b) (4)

3. The reviewer calculated the mean values of the amount of drug on each individual stage, mass balance (MB), mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD)

4. Per Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI:

   "Equivalence based on*: PBE analysis of impactor-sized mass (ISM). The CI profiles representing drug deposition on the individual stages of the CI along with the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) should be submitted as supportive evidence for equivalent APSD*".

5. Currently, FDA does not have a well-defined criterion for evaluating the data for this test. The FDA has relied on a weight of evidence, including PBE analysis of certain key parameters which characterize the particle size distribution, together with a statistical approach for comparing the distribution profiles, namely modified Chi-square ratio

method[17], to determine the equivalence of the test product (as compared with corresponding strengths of the RLD). Currently, the following criteria are considered for APSD equivalence[18]:

I. PBE on SAC

II. PBE on Impactor Size Mass (b) (4)
(b) (4)

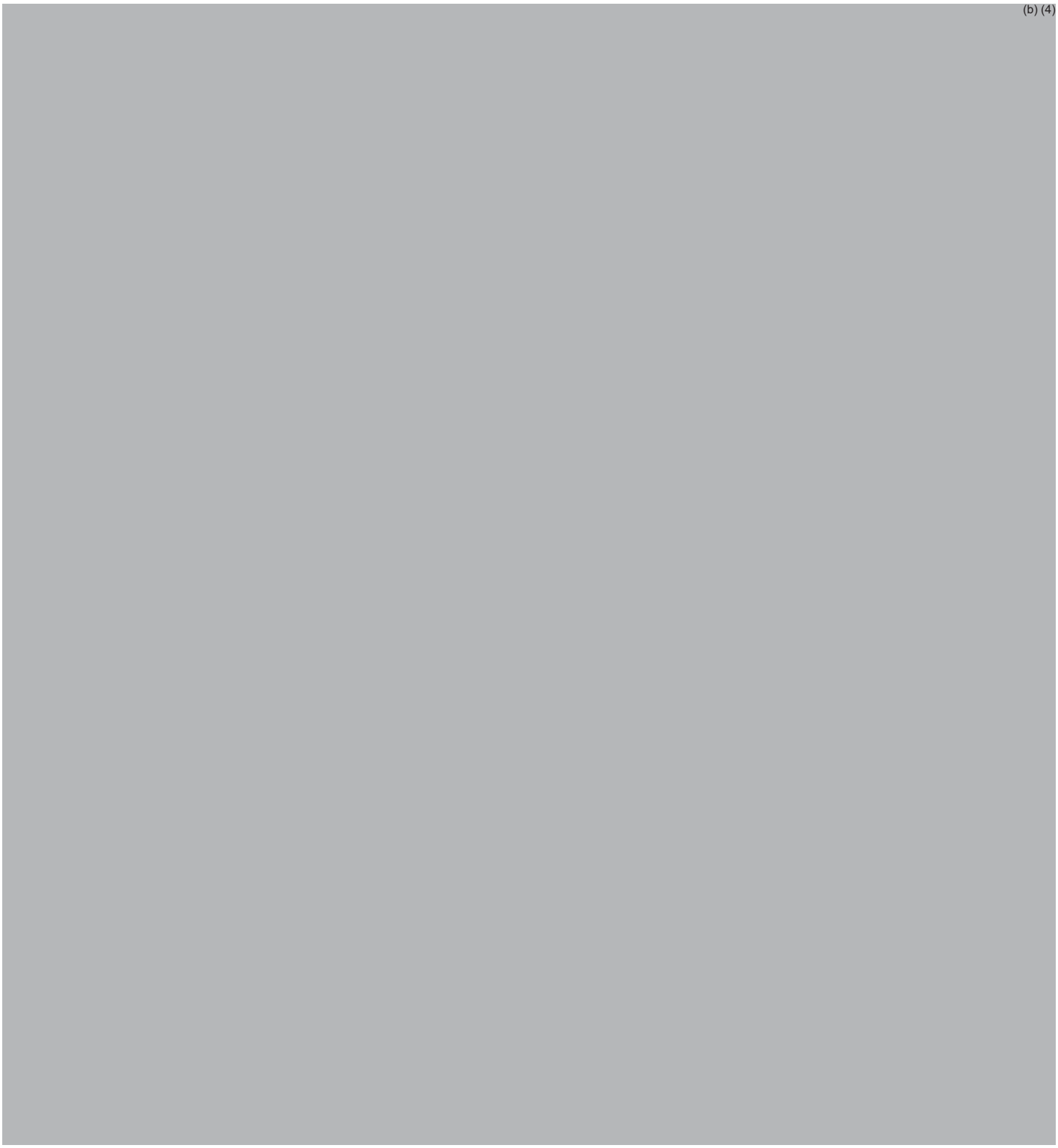
III. Modified Chi-square ratio method analysis on Impactor Sized Mass stages (b) (4)
(b) (4)

6. The reviewer employeed the above criteria for this application:

I. PBE on SAC: refer to SAC test section;
II. PBE on Impactor Size Mass (ISM): result indicated that ISM passed PBE analysis

(b) (4)

[17] A Stability Analysis of a Modified Version of the Chi-Square Ratio Statistic: Implications for Equivalence Testing of Aerodynamic Particel Size Distribution; Benjamin Weber, Guenther Hochhaus, Wallace Adams, Robert Lionberger, Bing Li, Yi Tsong, and Sau L. Lee; The AAPS Journal, Published online: 25 Sept. 2012.
[18] Respiratory Drug Delivery 2012; Webber Et al., Evaluation of Statistical Methods for Determining Equivalence of Aerodynamic Particle Size Distribution.



7. As supporting evidence, the reviewer also run PBE Analysis and Geometric Mean Ratio for other critical parameters, the results are showing below:

- The PBE analysis results for each individual deposition site (S1 to S7, MOC and throat), as well as for MB, MMAD, FPD (sum of stages 3-7, filter and MOC) and GSD. Based on the PBE analysis, all of these parameters passed PBE analysis except for stage 1, 2 and 3. The results are summarized in the table below (refer to the end of section for detailed PBE analysis).

- According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the ISM is the sum of the drug mass on all stages of the CI plus the terminal filter, but excluding the top CI stage (S1). The ISM data provided by the firm included the drug mass from stage 1 as well. Therefore, the reviewer calculated the ISM excluding the data from the top stage and this value was used in the statistical analysis.

(b) (4)

- The reviewer calculated the ratio of the geometric mean of T/R for each individual deposition site (S1 to S7 and throat), as well as MB, MMAD, FPD, GSD and ISM. All those parameters fell within 90-111% except S1, S2, S3, S6, S7 and MOC. The results are summarized in the table below.

(b) (4)

(b) (4)

4.3.2.4.4 Conclusions

DRUG IN SMALL PARTICLES / DROPLETS PER ACTUATION		
REVIEW OF TESTING METHODS:		
Is the testing method for CI test validated?		Incomplete
Is the analytical method (e.g. HPLC) validated?		Incomplete
Is the analytical method sufficiently sensitive?		Yes
Is testing conducted as per RLD labeling?		Not Provided
What is the size of the induction port (or expansion chamber) used for testing?		N/A
Are ≤ 10 actuations used for cascade impactor study?		Not Provided
If >1 actuation, what is the # of actuations used?		Not Provided
Are the testing methods acceptable?		**INCOMPLETE**
If not, why?		The firm should provide the missing validation data for HPLC and quality control samples used in the analytical runs.
STUDY RESULTS:		
Is drug deposition reported in mass units?		Yes
Is the mass balance data reported?		Yes
Results	**Does Impactor Size Mass data pass PBE?**	**Yes**
	Does ISM data pass modified chi-square ratio test?	**Yes**
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) pass PBE?	**Yes**
If results not acceptable, why?		see comments below

Comments:

1. According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the aerodynamic particle size distribution (APSD) should be performed at **both beginning and end lifestages** of the product. However, in the current submission, the firm conducted the testing only at the beginning lifestage. Therefore, the firm will be asked to conduct APSD testing at the end lifestage of the product.

2. The APSD test was performed using a flow rate of 30 ± 0.5 L/min. The USP <601> Apparatus A was used in the test. This is according to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI.

3. The firm did not provide the number of actuations and actuation numbers used in the cascade impaction testing. The firm will be asked to provide this information.

4. The APSD conducted by the firm is **inadequate**.

4.3.2.4.5 Deficiencies / Recommendations

Please see Section 3.10 for deficiency comments.

4.3.2.5 Spray Pattern

Study Information Study No.	TTP-CBJ-M0062 MV
Study site	(b) (4)
Principal Investigator	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	(b) (4) Actuation Station (b) (4) Imaging System
Testing Method Description	(b) (4)
Study Distances (distances from actuator orifice)	3 cm: actuation # 2 – 8 (beginning of use life) 6 cm: actuation # 3 – 5 (beginning of use life) NOTE: The firm used only one actuation for spray pattern analysis.
Testing Equipment Used (e.g., name, model, etc)	(b) (4)
Image Analysis Apparatus Used	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc.)	
Analytical Method Description	N/A
Analytical Equipment Used (e.g., name, model, etc)	N/A

Comments:

1. According to the in vitro summary table provided by the firm, the effective date of both SOP #s (b) (4) was January 8, 2009. However, according to the SOP #s (b) (4), the effective date of both the SOPs was July 21, 2011. The firm will be asked to clarify this discrepancy.

2. The firm did not provide the study report for the spray pattern study. The firm will be asked to provide this information.

4.3.2.5.1 Validation Summary Table for Spray Pattern

4.3.2.5.1.1 Precision

Table 9.2.1 Precision

	Area (mm^2)		Ovality Ratio	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean	174.8	383.6	1.129	1.148
%RSD	3	3	2	3
Range	(b) (4)			

30 mm Distance

Analyst	Sample #	D_{min} (mm)	D_{max} (mm)
Analyst 1	1	(b) (4)	
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
Mean Analyst 1 (n = 10)		14.0	15.8
%RSD (n = 10)		2%	1%

Analyst	Sample #	D_{min} (mm)	D_{max} (mm)
Analyst 2	1	(b) (4)	
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
Mean Analyst 2 (n = 10)		13.6	15.6
%RSD (n = 10)		3%	2%

Overall Mean (n = 20)	**13.8**	**15.7**
% RSD (n = 20)	**3%**	**2%**

Analyst 1 to Analyst 2 Comparison

Acceptance Criterion	D_{min} (mm)	D_{max} (mm)
ANOVA (a > 0.05)	**Fail (0.01)**	**Pass (0.12)**
% Difference in Mean	**2.9%**	**1.4%**

60 mm Distance

Analyst	Sample #	D_{min} (mm)	D_{max} (mm)
Analyst 1	1	(b) (4)	
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
Mean Analyst 1 (n = 10)		20.7	23.7
%RSD (n = 10)		2%	2%

Analyst	Sample #	D_{min} (mm)	D_{max} (mm)
Analyst 2	1	(b) (4)	
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
Mean Analyst 2 (n = 10)		20.5	23.7
%RSD (n = 10)		2%	4%

Overall Mean (n = 20)	20.6	23.7
% RSD (n = 20)	2%	3%

Analyst 1 to Analyst 2 Comparison

Acceptance Criterion	D_{min} (mm)	D_{max} (mm)
ANOVA (a > 0.05)	**PASS (0.48)**	**PASS (0.98)**
% Difference in Mean	**0.7%**	**0.0%**

4.3.2.5.1.2 Intermediate Precision (By Date)

Not Provided

4.3.2.5.1.3 Intermediate Precision (By Analyst)

Table 9.2.2 Intermediate Precision (By Analyst)

Analyst 1	Area (mm^2)		Ovality Ratio	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	174.8	383.6	1.129	1.148
%RSD	3	3	2	3
Analyst 2	**Area (mm^2)**		**Ovality Ratio**	
	Dist 1 30 mm	Dist 2 60 mm	Dist 1 30 mm	Dist 2 60 mm
Mean, n = 10	169.4	383.8	1.147	1.157
%RSD	4	5	3	3
% Difference (Analyst 1 vs. Analyst 2)	3.1	0.0	1.6	0.7
Interday %RSD	4	4	2	3

4.3.2.5.1.4 Robustness

Table 9.3.1 Robustness: End of Stroke Force on Spray Pattern Measured 30 mm and 60 mm from the End of Actuator Mouthpiece

	Ovality 30 mm			Area (mm^2) 30 mm		
	(b) (4)					
Mean, n = 5	1.131	1.110	1.117	171.8	166.1	167.4
%RSD	2	2	2	6	4	2

	Ovality 60 mm			Area (mm^2) 60 mm		
	(b) (4)					
Mean, n = 5	1.127	1.158	1.161	380.8	390.3	386.1
%RSD	5	3	5	5	6	6

30 mm Distance

MDI Number	D_{min} (mm)			D_{max} (mm)		
1	[redacted] (b) (4)					
2						
3						
4						
5						
Mean	13.9	13.8	13.7	15.7	15.3	15.3
%RSD	2%	2%	1%	4%	2%	2%
ANOVA $\alpha > 0.05$	PASS (0.40)			PASS (0.26)		
Ratio (Max/Min)	1.01			1.03		

60 mm Distance

MDI Number	D_{min} (mm)			D_{max} (mm)		
1	[redacted] (b) (4)					
2						
3						
4						
5						
Mean	20.8	20.7	20.5	23.4	23.9	23.8
%RSD	2%	4%	2%	5%	3%	4%
ANOVA $\alpha > 0.05$	PASS (0.70)			PASS (0.74)		
Ratio (Max/Min)	1.02			1.02		

Table 9.3.2 Robustness: Actuation Velocity on Spray Pattern Measured 30 mm and 60 mm from the End of Actuator Mouthpiece

	Ovality 30 mm			Area (mm^2) 30 mm		
	(b) (4)					
Mean, n = 5	1.110	1.110	1.129	164.8	166.1	168.9
%RSD	3	2	1	6	4	4

	Ovality 60 mm			Area (mm^2) 60 mm		
	(b) (4)					
Mean, n = 5	1.129	1.158	1.163	393.4	390.3	393.4
%RSD	1	3	3	7	6	3

30 mm Distance

MDI Number	D_{min} (mm)			D_{max} (mm)		
	(b) (4)					
1	(D) (4)					
2						
3						
4						
5						
Mean	13.7	13.8	13.8	15.2	15.3	15.6
%RSD	5%	2%	1%	2%	2%	2%
ANOVA $\alpha > 0.05$	Pass (0.92)			Pass (0.21)		
Ratio (Max/Min)	1.01			1.03		

60 mm Distance

MDI Number	D_{min} (mm)			D_{max} (mm)		
	(b) (4)					
1						
2						
3						
4						
5						
Mean	21.1	20.7	20.8	23.8	23.9	24.2
%RSD	3%	4%	1%	4%	3%	2%
ANOVA $\alpha > 0.05$	PASS (0.63)			PASS (0.65)		
Ratio (Max/Min)	1.02			1.02		

Table 9.3.3 Robustness: Camera Distance on Spray Pattern Measured 30 mm and 60 mm from the End of Actuator Mouthpiece

	Ovality 30 mm			Area (mm^2) 30 mm		
	(b) (4)					
Mean, n = 5	1.108	1.110	1.118	163.0	166.1	164.6
%RSD	3	2	3	3	4	4

	Ovality 60 mm			Area (mm^2) 60 mm		
	(b) (4)					
Mean, n = 5	1.156	1.158	1.146	384.0	390.3	392.5
%RSD	3	3	2	6	6	2

30 mm Distance

MDI Number	D_{min} (mm)			D_{max} (mm)		
1	(b) (4)			(b) (4)		
2						
3						
4						
5						
Mean	13.8	13.8	13.7	15.3	15.3	15.3
%RSD	2%	2%	2%	3%	2%	3%
ANOVA $\alpha > 0.05$	Pass (0.71)			Pass (1.00)		
Ratio (Max/Min)	1.01			1.00		

60 mm Distance

MDI Number	D_{min} (mm)			D_{max} (mm)		
1	(b) (4)			(b) (4)		
2						
3						
4						
5						
Mean	20.5	20.7	20.9	23.7	23.9	23.9
%RSD	3%	4%	1%	4%	3%	2%
ANOVA $\alpha > 0.05$	PASS (0.66)			PASS (0.87)		
Ratio (Max/Min)	1.02			1.01		

Number of Bottles and/or Lots Used in the Validation Study	Reference lots #AEA13B and PAEF75A
Does Firm's SOP include validation criteria? (Y/N) Is so, list the criteria	The method validation report includes the validation criteria. Acceptance Criteria:

	Method Precision and Intermediate Precision For each spray pattern characteristic measured, the %RSD for each analyst's data set were required to meet the following limits: Characteristic / RSD Limit Area / NMT (b) (4)% Dmax / NMT Dmin / NMT Ovality / NMT **Method Repeatability** The RSD for each spray pattern characteristic must be no greater than (b) (4) **Method Robustness** For each spray pattern characteristic measured, the %RSD for each data set was required to meet the following limits: Characteristic / RSD Limit Area / NMT (b) (4)% Dmax / NMT % Dmin / NMT % Ovality / NMT %
Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	**Incomplete**. The firm did not provide the validation data on intermediate precision by date.

Comments:

The study dates are August 21 – September 2, 2009 for the spray pattern test. The test was not conducted on the same day. The firm did not provide the Intermediate Precision (By Date). The firm will be asked to provide this information.

4.3.2.5.2 Results Summary – Spray Pattern

Area* – Spray Pattern Summary										
	Dist (cm)	Mean		Variability (%CV)					Mean Ratio (T/R)	
				Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arithm	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	3	173.5	173.4	3.1	4.7	3.7	0.8	3.8	0.96	0.97
	6	371.2	370.7	5.4	6.8	3.8	1.1	5.3	0.96	0.96
Ref	3	179.9	179.6	6.1	6.0	3.8	1.1	5.3		
	6	386.9	386.3	7.3	4.9	4.4	2.6	5.9		

OVALITY RATIO – Spray Pattern Summary										
	Dist (cm)	Mean		Variability (%CV)					Mean Ratio (T/R)	
				Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
		Arithm	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=30)	Geo (n=30)
Test	3	1.120	1.119	2.1	1.1	3.5	0.6	2.4	1.00	1.00
	6	1.144	1.144	3.6	3.7	3.3	0.5	3.4	0.98	0.98
Ref	3	1.120	1.120	2.0	1.2	3.3	0.3	2.3		
	6	1.162	1.161	4.1	2.9	3.4	1.5	3.6		

(b) (4)

4.3.2.5.3 Conclusions

SPRAY PATTERN				
REVIEW OF TESTING METHODS:				
Is the testing method validated?				Incomplete
Is testing based upon the *true shape* of the spray pattern?				Yes
Is testing conducted as per RLD labeling?				Yes
Is testing a single actuation per determination?				Yes
If yes, what is the actuation number tested?				3 cm - # 2 – 8 6 cm - # 3 – 5 NOTE: The firm conducted the spray pattern testing only on single actuation
Data measured at two distances from actuator orifice?				Yes
If yes, distances 3 – 7 cm?				3 cm and 6 cm
If yes, distances separated by 3 cm or more?				Yes
Does the firm submit representative spray pattern images?				Yes
Was the analysis based upon the *true shape* of the spray pattern?				Yes
Do Dmax and Dmin pass through the COG or COM as appropriate in extent to the parameter of the true shape?				Yes
Are the testing methods acceptable?				Yes
If not, why?				N/A
STUDY RESULTS:				
Similar qualitative visual shapes?				Yes
Equivalence is based upon acceptable PBE results from **EITHER** Automated **OR** Manual Analysis				
Are PBE results acceptable?	**Automated**	**Ovality Ratio**	**Distance 3**	**ACCEPTABLE**
			Distance 6	**ACCEPTABLE**
		AREA	**Distance3**	**ACCEPTABLE**
			Distance 6	**ACCEPTABLE**
	Manual	**Ovality Ratio**	**Distance 3**	**N/A**
			Distance 6	**N/A**
		Dmax	**Distance 3**	**N/A**
			Distance 6	**N/A**
If not, why?				N/A

Comments:

1. The COG was determined automatically and the Dmax, Dmin, Ovality ratio and Area were determined from the true shape of the spray.

2. The firm provided the spray pattern images and accompanying raw data for 20% samples at both 3 cm and 6 cm distances. However, it is not clear from the firm's submission, whether the images are of the test product or reference product. Therefore, the reviewer is not able to qualitatively compare the spray shapes of the test and reference products. The firm will be asked to clarify.

3. According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the spray pattern should be performed at the beginning lifestage of the product at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm **from the reference product mouthpiece**. **It should also be noted that the distance between the actuator orifice and point of spray pattern measurement should be same for the test and reference products.** In the current ANDA, the firm conducted the spray pattern testing at 3 cm and 6 cm from the actuator mouthpiece. However, it is not clear from the firm's submission whether the selected 3 cm and 6 cm distances are from the actuator mouthpiece of the **Test** or from the **Reference** product. Therefore, the firm will be asked to clarify whether the 3 cm and 6 cm distances selected for the spray pattern testing are from the reference product actuator mouth piece. In addition, the firm will also be asked to confirm whether the distance between the actuator orifice and point of spray pattern measurement is same for the test and reference products.

4. As per the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, for automated analysis of spray pattern, the PBE analyses are to be performed on area and ovality ratio. Thus the reviewer performed PBE analysis on spray pattern; both the area and ovality ratio passed the PBE criteria.

The study is incomplete with deficiencies.

4.3.2.5.4 Deficiencies / Recommendations

Please see Section 3.10 for deficiency comments.

4.3.2.6 Plume Geometry

4.3.2.6.1 Study Information

Study No.	TTP-CBJ-M0062 MV
Study site	(b) (4)
Principal Investigator	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	(b) (4) Actuation Station (b) (4) Imaging System
Testing Method Description	(b) (4)
Criteria for defining plume angle, width, & height borders	
Testing Equipment Used (e.g., name, model, etc)	
Image Analysis Apparatus Used	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	
Analytical Method Description	
Analytical Equipment Used (e.g., name, model, etc)	

Comments:

1. According to the in vitro summary table provided by the firm, the effective date of both SOP (b) (4) was January 8, 2009. However, according to the SOP #s (b) (4), the effective date of both the SOPs was July 21, 2011. The firm will be asked to clarify this discrepancy.

2. The firm did not provide the study report for the plume geometry study. The firm will be asked to provide this information.

4.3.2.6.1 Validation Summary Table for Plume Geometry

4.3.2.6.1.1 Precision

Table 10.2.1 Precision

	Plume Width (mm)	Plume Angle (°)
Mean	25.5	20.6
%RSD	6	6
Range	(b) (4)	

4.3.2.6.1.2 Intermediate Precision (By Date)

Not Provided

4.3.2.6.1.3 Intermediate Precision (By Analyst)

Table 10.2.2. Intermediate Precision (By Analyst)

Analyst 1	Plume Width (mm)	Plume Angle (°)
Mean	25.5	20.6
%RSD	6	6
Range	(b) (4)	
Analyst 2	**Plume Width (mm)**	**Plume Angle (°)**
Mean	23.6	19.1
%RSD	10	9
Range	(b) (4)	
% Difference (Analyst 1 vs. Analyst 2)	7.6	7.5
Inter Analyst %RSD	9	8

4.3.2.6.1.4 Robustness

Table 10.2.3.1: End of Stroke Force at 60 mm from the End of Actuator Mouthpiece

MDI Number	Plume Angle (°)			Plume Width (mm)		
	(b) (4)					
Mean	20.7	20.1	19.4	25.6	24.9	24.0
%RSD	11	12	13	11	12	13

Table 10.2.3.2: Actuation Velocity at 60 mm from the End of Actuator Mouthpiece

MDI Number	Plume Angle (°)			Plume Width (mm)		
	(b) (4)					
Mean	20.3	20.1	19.9	25.0	24.9	24.6
%RSD	5	12	15	5	12	15

Table 10.2.3.3: Measurement Time at 60 mm from the End of Actuator Mouthpiece

MDI Number	Plume Angle (°)			Plume Width (mm)		
	(b) (4)					
Mean	17.6	20.1	21.9	21.7	24.9	27.1
%RSD	5	12	14	5	12	14

Number of Bottles and/or Lots Used in the Validation Study	Reference lots #AEA13B and PAEF75A
Does Firm's SOP include validation criteria? (Y/N) **Is so, list the criteria**	The method validation report includes the validation criteria. Acceptance Criteria: **Method Precision and Intermediate Precision** For each plume characteristic (width and angle), the %RSD for each data set must be less than (b) (4) **Method Repeatability** The RSD for each plume characteristic must be no greater than (b) (4) **Method Robustness** The %RSD for the three replicates for each parameter evaluated should be not more than (b) (4).
Comments on Firm' s SOPs and Criteria (Acceptable/ or Explain)	**Incomplete**. The firm did not provide validation data of intermediate precision by date.

Comments:

The firm also did not provide the Intermediate Precision (By Date). The firm will be asked to provide this information.

4.3.2.6.1 Results – Plume Geometry

	Mean		Variability (%CV)					Mean Ratio (T/R)	
			Within Lot (n=10)			Between Lot (n=3)	Total (n=30)		
	Arith	Geo	Lot 1	Lot 2	Lot 3			Arith	Geo
Plume Angle (°)									
Test	19.0	18.8	12.7	12.4	15.7	3.0	13.5	0.95	0.95
Ref	20.0	19.9	9.2	11.6	15.5	0.8	11.9		
Plume Width									
Test	23.5	23.3	12.9	12.7	16.0	3.2	13.8	0.95	0.95
Ref	24.7	24.6	9.4	11.7	15.8	0.8	12.2		

4.3.2.6.2 Conclusions

PLUME GEOMETRY	
REVIEW OF TESTING METHODS:	
Is the testing method validated?	**Yes**
Is testing conducted as per RLD labeling?	**Yes**
Is the image a snapshot?	**Yes**
If not, why?	**N/A**
Are representative photographs/digital images provided?	**Yes**
Is plume geometry measured at a single delay time while the fully-developed phase of the plume is still in contact with actuator tip?	**Yes**
Are plume width measures made at a single, fully-developed delay time while plume is still in contact with actuator tip?	**Yes** The firm provided the plume geometry images. Based on the images, the plume width measures were made while the plume is still in contact with the actuator tip. In addition, plume width and angle measurements were assessed from the same side of the plume.
Are plume width measurements made at a distance equal to the greater of the two distances selected for characterization of the spray pattern? (e.g., is plume width measured at 6 cm if spray pattern were measured at 3cm and 6 cm)	**Yes (6 cm)**
Is plume height measured at a distance from the actuator orifice to the leading edge of the plume?	**Yes**
Is plume geometry measured at:	
1) beginning lifestage	**Yes**
2) one side view only	**Yes**
Are plume angle, width, & height all quantitated using same method?	**Yes for angle and width parameters.**
Are the testing methods acceptable?	**Yes**
If not, why?	**N/A**
STUDY RESULTS:	
Is the Plume Angle T/R geo mean ratio between 0.90-1.11%?	**Yes**
Is the Width T/R geo mean ratio between 0.90-1.11%?	**Yes**
Are the (point estimate) results acceptable?	**ACCEPTABLE**
If not, why?	**N/A**

Comments: INCOMPLETE

- The ratio of the T/R geometric means for plume width and angle in the beginning are within the limits of 0.90-1.11. According to the FDA Guidance for Industry:

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (draft, April 2003), the point estimates would not be applicable for the plume height due to subjectivity.

- As mentioned earlier in the spray pattern testing, the selected 6 cm distance in the plume geometry testing should be from the reference product actuator mouth piece and also the distance between the actuator orifice and point of spray pattern measurement should be same for the test and reference products. In the current ANDA, the firm conducted the plume geometry testing at 6 cm from the actuator mouthpiece. However, it is not clear from the firm's submission whether the selected 6 cm distance is from the actuator mouthpiece of the reference product. Therefore, the firm will be asked to clarify whether the 6 cm distance selected for the plume geometry testing is from the reference product actuator mouth piece. In addition, the firm will also be asked to confirm whether the distance between the actuator orifice and point of plume geometry measurement is same for the test and reference products.

- In addition, the test product passes the PBE statistical criteria for both width and angle.

The study is **incomplete** with deficiencies.

4.3.2.6.3 Deficiencies / Recommendations – Plume Geometry

Please see Section 3.10 for deficiency comments.

4.4 Pharmacodynamic Study

4.4.1 Study Information

Study Number	PRG-723
Study Title	A multi-center, randomized, double-blind, five-way crossover, pharmacodynamic study comparing perrigo's albuterol inhalation aerosol to Teva's Proair® HFA inhalation aerosol using a methacholine challenge design in asthmatic subjects
Clinical Site (Name & Address)	The pharmacodynamic study was conducted at the following 7 sites: **Site 1 (enrolled 25 subjects)** University of Florida Asthma Research Lab 1600 SW Archer Road Gainesville, FL 32610-0486 **Site 2 (enrolled 21 subjects)** Roy J and Lucille A Carver College of Medicine Department of Pediatrics, Allergy/Pulmonary The University of Iowa 200 Hawkins Drive Iowa City, Iowa 52242-1083 **Site 3 (enrolled 14 subjects)** Allergy & Asthma Diagnostic Treatment Center 2300 Centerville Road Tallahassee, FL 32308 **Site 4 (enrolled 31 subjects)** California Allergy & Asthma Medical Group 11645 Wilshire Blvd, Suite 1155 Los Angeles, CA 90025 **Site 5 (enrolled 6 subjects)** Clinical Research Atlanta 175 Country Club Drive, Suite 100A Stockbridge, GA 30281 **Site 6 (enrolled 10 subjects)** Spartanburg Medical Research 485 Simuel Road Spartanburg, SC 29303 **Site 7 (enerolled 6 subjects)** AARA Research Center 9900 N Central Expy, Suite 555 Dallas, TX 75231
Principal Investigator	Site 1: Leslie Hendeles, Pharm D Site 2: Richard C Ahrens, MD Site 3: Ronald H Saff, MD Site 4: Sheldon L Spector, MD

	Site 5: Nathan Segall, MD, CPI Site 6: Charles M Fogarty, MD, CPI Site 7: William R Lumry, MD
Dosing Dates	Date of First Enrollment: February 24, 2010 Date of Last Completed: March 31, 2011

4.4.2 Product Information

Product	Test	Reference	Placebo
Product Name	Albuterol sulfate inhalation aerosol	Proair® HFA Inhalation Aerosol	Vehicle inhalation aerosol
Manufacturer	Catalent Pharma Solutions	Teva Pharmaceuticals	Catalent Pharma Solutions
Batch/Lot No.	08MM-050	AEA13B PAEF75A	08MM-020
Manufacture Date	December 2008	N/A	June 2008
Expiration Date	N/A	June 2010 October 2011	N/A
Strength	90 mcg/actuation	90 mcg/actuation	N/A
Bio-batch Size	(b) (4)	N/A	N/A
Production Batch Size		N/A	N/A
Dosage Form	Metered Dose Inhaler	Metered Dose Inhaler	Metered Dose Inhaler
Potency, %	(b) (4)		
Content Uniformity (Mean, %CV)			
Dose Administered	90 mcg and180 mcg	90 mcg and 180 mcg	N/A
Route of Administration	Inhalation	Inhalation	Inhalation

(b) (4)

Reviewer's Notes:

- The firm did not provide the certificate of analysis (CoA) of the reference product lot #s AEA13B and PAEF75A. The firm will be asked to provide this information.

- The firm did not provide formulation of the placebo product. The firm will be asked to provide this information.

4.4.3 Study Design

Number of Subjects	Enrolled:	113
	Dosed:	113
	Completed:	101
	Analyzed:	93
No. of Periods	5 periods	
No. of Treatments	5 treatments **Treatment 1 (A):** Vehicle (Placebo): two actuations of placebo MDI **Treatment 2 (B):** 90 mcg of Test: One actuation each from a Test product and placebo MDI **Treatment 3 (C):** 90 mcg of Reference: One actuation each from a reference product and placebo MDI **Treatment 4 (D):** 180 mcg of Test: two actuations of the Test product **Treatment 5 (E):** 180 mcg of Reference: two actuations of the Reference product	
No. of Sites	7	

Randomization Scheme

There are 5 sequences.
ABECD
BCADE
CDBEA
DECAB
EADBC

Site	In Population	Screening Number	Randomization Number	Sequence [a]
01	PP	(b) (6)	001	DECAB
01	PP		002	CDBEA
01	PP		003	BCADE
01	PP		004	EADBC
01	PP		005	ABECD
01	PP		006	BCADE
01	ITT		007	DECAB
01	PP		008	EADBC
01	PP		009	ABECD
01	PP		010	CDBEA
01	PP		011	CDBEA
01	ITT		012	EADBC
01	PP		013	BCADE
01	PP		014	DECAB
01	PP		015	ABECD
01	PP		106	DECAB
01	PP		107	CDBEA
01	ITT		108	ABECD

Site	In Population	Screening Number	Randomization Number	Sequence [a]
01	PP	(b) (6)	109	BCADE
01	PP		110	EADBC
01	PP		111	BCADE
01	PP		112	EADBC
01	PP		113	ABECD
01	PP		114	CDBEA
01	PP		115	DECAB
02	PP		046	DECAB
02	PP		047	CDBEA
02	PP		048	ABECD
02	PP		049	EADBC
02	PP		050	BCADE
02	ITT		051	EADBC
02	PP		052	DECAB
02	PP		053	CDBEA
02	PP		054	BCADE
02	ITT		055	ABECD
02	PP		056	EADBC

Site	In Population	Screening Number	Randomization Number	Sequence [a]
02	PP	(b) (6)	057	BCADE
02	PP		071	EADBC
02	PP		073	ABECD
02	ITT		116	BCADE
02	PP		117	DECAB
02	PP		118	EADBC
02	PP		119	CDBEA
02	ITT		120	ABECD
02	PP		126	CDBEA
02	ITT		128	BCADE
03	PP		271	ABECD
03	PP		272	DECAB
03	PP		273	CDBEA
03	PP		274	EADBC
03	ITT		275	BCADE
03	PP		276	ABECD
03	PP		277	DECAB
03	PP		278	BCADE

Site	In Population	Screening Number	Randomization Number	Sequence [a]
03	PP	(b) (6)	279	CDBEA
03	ITT		280	EADBC
03	ITT		281	BCADE
03	PP		282	EADBC
03	ITT		283	CDBEA
03	ITT		284	ABECD
04	PP		166	ABECD
04	PP		167	CDBEA
04	PP		168	DECAB
04	PP		169	BCADE
04	ITT		170	EADBC
04	PP		171	CDBEA
04	PP		172	DECAB
04	PP		173	ABECD
04	PP		174	BCADE
04	PP		175	EADBC
04	PP		176	DECAB
04	PP		177	BCADE

Site	In Population	Screening Number	Randomization Number	Sequence [a]
04	PP	(b) (6)	178	EADBC
04	PP		179	CDBEA
04	PP		180	ABECD
04	PP		181	CDBEA
04	PP		182	BCADE
04	PP		183	ABECD
04	PP		184	EADBC
04	PP		185	DECAB
04	PP		186	ABECD
04	PP		187	DECAB
04	PP		188	BCADE
04	PP		189	CDBEA
04	ITT		190	EADBC
04	PP		191	CDBEA
04	ITT		192	DECAB
04	PP		193	EADBC
04	PP		194	ABECD
04	ITT		195	BCADE

Site	In Population	Screening Number	Randomization Number	Sequence [a]
04	PP	(b) (6)	263	EADBC
05	PP		201	ABECD
05	PP		202	BCADE
05	PP		203	CDBEA
05	PP		204	EADBC
05	PP		205	DECAB
05	PP		206	DECAB
06	PP		131	ABECD
06	PP		132	DECAB
06	PP		133	CDBEA
06	PP		134	BCADE
06	PP		135	EADBC
06	PP		136	ABECD
06	PP		137	DECAB
06	PP		138	EADBC
06	PP		139	CDBEA
06	ITT		140	BCADE
07	PP		241	EADBC

Site	In Population	Screening Number	Randomization Number	Sequence [a]
07	PP	(b) (6)	242	DECAB
07	ITT		243	ABECD
07	ITT		244	BCADE
07	PP		245	CDBEA
07	PP		246	EADBC

A: Vehicle (Placebo): Two actuations of placebo MDI
B: 90 mcg of Test: One actuation each from a Test product and placebo MDI
C: 90 mcg of Reference: One actuation each from a Reference product and placebo MDI
D: 180 mcg of Test: Two actuations of the Test product
E: 180 mcg of Reference: Two actuations of the Reference product

Inclusion Criteria

1. Male and female subjects between the ages of 18 and 65 years inclusive that had been previously diagnosed with asthma by a physician.
2. Non-smokers for at least 12 months before the baseline visit, with a maximum smoking history of 10 pack years.
3. Screening FEV_1 of $\geq$ 70% of predicted normal value for age, height, and sex.
4. PC_{20} FEV_1 after methacholine challenge of less than 8 mg/mL during the first screening visit.
5. Fourfold increase of PC_{20} FEV_1 after 2 puffs of Reference Product during the second screening visit.
6. Ability to discontinue albuterol for at least 6 hours before study visits.
7. Ability to discontinue inhaled corticosteroids (ICS) starting two (2) hours prior to their visit. Subjects were permitted to begin use again after all visit-related procedures had been completed.
8. Ability to discontinue long-acting beta agonists (LABA) for 3 weeks prior to study visit.
9. Had the ability to perform spirometry reproducibly.
10. ECG with normal QT and QTc intervals.
11. Subjects taking monotherapy with inhaled corticosteroids were to be on a stable low dose for at least 30 days (see Appendix 16.1.1).
12. Otherwise healthy individuals as determined by the Principal Investigator with a clinically acceptable medical history, physical examination, vital signs, and 12-lead ECG.
13. Understood English and provided written informed consent.

Exclusion Criteria	1. Could not demonstrate proper coordination of the inhalation and actuation following training with a placebo MDI. 2. Were allergic or sensitive to albuterol, or to other components of the formulations used in the clinical trial materials. 3. Exhibited any of the following findings in a 12-lead ECG: conduction defects, rhythm disturbances (except sinus arrhythmia or isolated PAC/PVC), biphasic T waves, U waves that are > 0.3 of the preceding T waves, PR > 210, QRS > 120 and QT_c > 430. 4. Had been exposed to investigational drugs or devices within 30 days before screening / enrollment. 5. Required continuous treatment with beta-blockers (administered by any route), monoamine oxidase inhibitors, tricyclic antidepressants, and/or systemic corticosteroids after study admission. 6. Had been treated with oral or injectable corticosteroids in last 30 days or with theophylline-SR within 36 hours before the screening visit. 7. Were unable to tolerate or unwilling to comply with required washout periods for all applicable medications and foods in Section 9.4.7. 8. Had been hospitalized for acute exacerbation of asthma more than once in the past year. 9. Had been treated in an emergency room for asthmatic symptoms or hospitalization for asthmatic symptoms within 3 months before the screening visit. 10. Had shown evidence of life-threatening asthma within the previous 5 years (usually defined as a loss of consciousness from asthma or admission to an intensive care unit for asthma). 11. Were a known substance abuser or were suspected of substance abuse (eg, alcohol, marijuana, etc) and/or any other medical or psychological condition(s) that in the investigator's opinion precluded study enrollment. 12. Had been diagnosed with any illness that could have interfered with the assessments of the study or altered the airway reactivity to methacholine within 4 weeks of screening visit (eg, viral respiratory tract infection). 13. Was either a lactating or pregnant female subject or a female of childbearing capability who was sexually active and unwilling to use an acceptable method of contraception. 14. Had a current or past medical condition that would affect the pharmacodynamic response to albuterol other than asthma. 15. Had a history of seasonal allergies. (see section 4.20 of the Protocol, in Appendix 16.1.1, for further clarification) 16. Required Short-Acting Beta Agonist therapy more frequently than 3 times a week.

IRB Approval	Yes IRB Contact Information **Site 1:** University of Florida Institutional Review Board Broad Building 1853 Mowry Road, Room 130 Gainesville, FL 32610 **Site 2:** University of Iowa – Institutional Review Board Human Subjects Office 340 College of Medicine Administration Building The Uniersity of Iowa Iowa City, IA 52242 **Site 3 – 7:** Quorum Review 1601 Fifth Ave, Suite 1000 Seattle, WA 98101 University of Florida IRB: 12/16/2009, 05/04/2010, 06/18/2010 University of Iowa IRB: 02/10/2010, 05/14/2010, 09/29/2010 Quorum IRB: 05/19/2010
Informed Consent	Yes University of Florida IRB: 12/16/2009, 05/04/2010, 06/18/2010 University of Iowa IRB: 02/10/2010, 05/14/2010, 09/29/2010 Quorum IRB: 05/19/2010
Subject Screening	One-hundred thirteen (113) adult subjects 18 to 65 years of age who had been previously diagnosed with asthma by a physician were enrolled into the study. Subjects' eligibility for the study was determined at 2 screening visits. At the first screening visit, subjects provided demographic information and medical and medication history, and were administered a baseline methacholine challenge, underwent a physical examination and electrocardiogram (ECG), and provided blood and urine samples for laboratory tests. At the second screening visit (at least 48 hours but not more than 7 days after the first screening visit), subjects were administered a methacholine challenge after receiving 2 actuations of open-label PROAIR HFA® INHALATION AEROSOL (albuterol sulfate).
Methacholine Challenge Design	• Calibrated wright nebulizers will be used to generate the aerosols to be inhaled during the methacholine bronchoprovocation tests. The nebulizer output was regulated at 0.12 – 0.14 mL/min and the duration of nebulization was 2 minutes. • Methacholine chloride for inhalation (Provocholine®) was used to prepare dilutions. The following are the methacholine concentrations used during the challenge: 0.0625, 0.125, 0.25, 0.50, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, 64.0 and 128 mg/mL The 128 mg/mL was administered as 64 mg/mL nebulized over 4 minutes. • Sequential steps in the methacholine challenge procedure: **a. Stabilized baseline Forced Expiratory Volume in 1 second (FEV_1):** Spirometric efforts will start approximately 8 minutes before saline administration. A minimum of 3 efforts which meet the American Thorasic Society (ATS) acceptability criteria are needed. Stabilized baseline reproducibility criteria:

1. The final ATS-acceptable FEV_1 values must differ by $\leq 0.10L$. Spirometry maneuvers are repeated at approximately 1 minute intervals, until this criterion is met. The higher of these 2 efforts is the stabilized baseline FEV_1
2. Stabilized baseline reproducibility criterion must be met to proceed with the challenge.

b. Timing of challenge stages (saline and methacholine):

1. Each stage should last 5 minutes
2. 2 minutes for administration of saline or methacholine
3. Spirometric maneuvers will be performed 30 and 90 seconds after completion of nebulization
4. If needed, additional spirometric maneuvers are performed as soon as possible to obtain at least one ATS acceptable effort. Once this has been accomplished, efforts should continue until either the 5-minute cycle is complete or the reproducibility criterion is met (highest ATS-acceptable FEV_1 – second highest ATS-acceptable $FEV_1 \leq 0.10L$).
5. If the 5 minute cycle is exceeded in order to obtain one ATS-acceptable effort, begin the next stage as soon as possible.
6. If ATS acceptability and reproducibility criteria are met before the 5-minute cycle is complete, DO NOT begin administration of the next stage until the full 5 minutes have passed
7. Never compromise the 2-minute duration of inhalation of methacholine or the timing of the 30 and 90 second spirometric efforts while attempting to make up time lost during a previous stage.

c. Performing the saline control:

1. The purpose of the saline control is to identify and exclude subjects who have severe airway hyper-responsiveness as manifested by > 10% decreases in FEV_1 in response to inhaling saline diluent
2. The saline diluent (0.9% NaCl) is nebulized for 2 minutes
3. Spirometric maneuvers are done at 30 and 90 seconds following the completion of the nebulization.
4. If needed, repeated spirometric maneuvers are performed as soon as possible to obtain at least one ATS-acceptable effort. Efforts should continue until either the 5-minute cycle is done or the reproducibility criterion is met (highest ATS-acceptable FEV_1 – second highest ATS-acceptable $FEV_1 \leq 0.10L$).
5. At least 1 ATS-acceptable effort must be obtained, even if this occasionally takes longer than the 2.5 minutes allotted for spirometry during each 5-minute cycle.
6. The goal is to obtain two spirometric efforts which meet the methacholine challenge reproducibility criterion. Although this will not always be possible, it is usually possible to meet this criterion at least 75% of the time.
7. The saline control FEV_1 is taken as the highest ATS-acceptable FEV_1 obtained at this challenge stage.
8. If the saline control FEV_1 is more than 10% below the stabilized baseline FEV_1, the study will be rescheduled
9. Determine and record the ATS Quality Control Grade (QCG), defined in the 1999 ATS Methacholine guidelines as follows:
   A = 2 ATS-acceptable FEV_1 values that match within 0.10L
   B = 2 ATS-acceptable FEV_1 values that match within 0.20L
   C = 2 ATS-acceptable FEV_1 values that do not match within 0.20L

D = only 1 ATS-acceptable FEV_1 maneuver
F = no ATS-acceptable FEV_1 maneuvers

d. Methacholine dosing stages:

1. The starting concentration of methacholine is predetermined in accordance with the specific protocol. The lowest possible starting concentration is 0.0625 mg/mL. The methacholione concentration is doubled at each subsequent 5-minute cycle, i.e. if the first concentration is 0.0625 mg/mL, the next concentration would be 0.125 mg/mL and so on until there is a 20% drop in FEV_1 from saline control FEV_1 or the highest concentration of methacholine has been given per study protocol.
2. Each methacholine dilution is nebulized for 2 minutes with the exception of 128 mg/mL – this concentration is accomplished by nebulizing 64 mg/mL for 4 minutes rather than 2 minutes.
3. Spirometric maneuvers are done at 30 and 90 seconds after the completion of a methacholine nebulization
4. If additional spirometric maneuvers are needed to obtain at least 1 ATS-acceptable effort, they should be done as soon as possible. Efforts should continue until either the 5-minute cycle is reached or the reproducibility criterion is met (highest ATS-acceptable FEV_1 – second highest ATS-acceptable FEV_1 $\leq$ 0.10L).
5. At least 1 ATS-acceptable effort must be obtained even if this occasionally takes longer than the 2.5 minutes allotted for spirometry during each 5-minute cycle.
6. Determine and record QCG

e. Stopping a methacholine challenge:

During all challenges, the procedure should be discontinued if any of the following occur:

1. The highest ATS-acceptable FEV_1 for a given stage decreases by >20% below saline control
2. The subject requests to stop the challenge
3. The status of the subject warrants stopping the challenge
4. The challenge procedure is interrupted for more than 15 minutes

f. Reversing methacholine-induced bronchospasm/subject recovery:

Once a methacholine challenge is complete:

1. Have the subject take 2-4 actuations of albuterol MDI or Combivent MDI; an anti-static valved holding chamber with mouthpiece may be used
2. Perform spirometry at approximately 5-10 minute intervals after the last bronchodilator dose
3. If the FEV1 has returned to $\geq$ 90% of the stabilized baseline FEV_1, the subject may be discharged
4. If the subject's FEV_1 is < 40% of predicted or subject is dyspneic:
    a) Administer albuterol MDI or Combivent MDI at a rate of 1 puff per minute for 4 doses; an anti-static valved holding chamber with mouthpiece may be used.
    b) Repeat every 10 minutes until FEV_1 is $\geq$ 90% of the stabilized baseline FEV_1.
    c) Although symptoms of severe bronchospasm are very unlikely, notify study physician if they occur, and follow procedures outlined in "Safety of the subject

	during bronchoprovocation challenge SOP". d) Consider intramuscular (IM) epinephrine and/or oxygen if the subject is severely dyspneic **g. Accidental overdose of methacholine:** 1. Administer ipratropium or Combivent MDI 2-4 puffs; an anti-static valved holding chamber with mouthpiece may be used. 2. Repeat as clinically warranted, but at least every 30 minutes until FEV_1 is $\geq$ 90% of the stabilized baseline FEV_1 3. Consider IM epinephrine and/or oxygen if the subject is severely dyspneic.
Safety Monitoring	The following safety labs were performed at the first screening visit only: complete blood count (CBC), urinalysis, metabolic panel (including liver and kidney function tests). This was done in conjunction with other visit 1 procedures to assess the subject's overall health. As subjects with clinically significant laboratory results were not enrolled in the study and laboratory data were not collected for safety purposes. The investigator periodically assessed subjects for the occurrence of AEs. In order to avoid bias in eliciting AEs, the subject was asked a nonspecific question (eg, "How have you been feeling since your last visit?") to assess whether any AE has been experienced since the last visit. All AEs that had been either observed by the Investigator or one of his/her medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, were reported and documented in the source and the study reporting forms. When reporting an AE, the Investigator was to assign a severity grade to each event and declare an opinion on the relatedness of the event to the study medication or procedure. Serious or unexpected AEs were to be reported to the sponsor within 24 hours of when the Investigator first learned of the occurrence of the event. Adverse events were documented in source documents and recorded in a timely manner on CRFs. Adverse events that were identified at the last assessment visit (or the early termination visit) were recorded on the AE CRF with the status of the AE noted. All events that were ongoing at the time they were recorded were to be recorded as ongoing on the CRF. Adverse events were to be followed until resolved or until 30 days after the final study treatment (whichever came first). In any case, SAEs that were not resolved or considered to be chronic within 30 days of the final study treatment were to be followed by the investigator until they resolved or were considered to be chronic (stabilized for at least 30 days). All events that were ongoing at that time were recorded as ongoing on the CRF. For any serious or unexpected adverse event occurring in a subject receiving study medication or during the 30 days following discontinuation of study medication, the sponsor was to be notified within 24 hours of when the Investigator first learned of the occurrence of the event. Expedited reporting requirements for serious adverse events are described in the Protocol. Adequate information was to be collected with supporting documentation to complete a standard report for submission to the sponsor. The AE term on the AE CRF and the SAE report was to agree exactly. Special attention was to be given to recording hospitalizations and concomitant medications.

Comments on Study Design:

- For establishing bioequivalence, the Agency considers a method using either a bronchoprovocation or a bronchodilataion study to be satisfactory for establishment of equivalence in pharmacodynamic (PD) for albuterol MDIs. The decision to use either approach is left to the judgment of the sponsor/applicant. In the current ANDA, the firm conducted a bronchoprovocation PD study.

- The Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI recommends for the submission of a Bio-IND prior to the conduct of the PD study as the concentration of methacholine chloride solution may exceed the labeled 25.0 mg/mL concentration, particularly at the higher 0.18 mg Albuterol Sulfate dose where 25.0 mg/mL methacholine chloride will not lead to a 20% reduction in FEV_1. In the current ANDA, the firm submitted an Investigational New Drug Application (IND) # 105337 on November 23, 2009 for Albuterol Sulfate Inhalation Aerosol (Eq 0.09 mg base/inhalation). The firm proposed the following methacholine solution strengths in the study: 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32 and 64 mg/mL. The highest (128 mg/mL) methacholine dose will be administrated as 64 mg/mL nebulized over 4 minutes. The study protocol was found acceptable by the Division of Pulmonary and Allergy Products in OND[19].

- The Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI recommends a minimum of four way cross-over study, with placebo, one actuation of the 0.09 mg Reference, two actuations of 0.09 mg Reference and one actuation of 0.09 mg Test. In the current ANDA, the firm conducted a five way cross-over study which included 0.18 mg of the Test product.

- According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, stable mild asthmatics based on the National Asthma Education and Prevention Program (NAEPP) guidelines are recommended for the bronchoprovocation study because the bronchial smooth muscle stimulation induced by methacholine inhalation can result in airway narrowing and airway closure and may pose an increasing risk for patients with moderate and severe asthma. In the inclusion criteria of the current ANDA, inclusion of mild asthmatics is not included. However, no life threating adverse effects or deaths were reported. Therefore, it is acceptable.

- The Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI recommends the use of subjects with $FEV_1 \geq 80\%$ of predicted. However, the firm included subjects with $FEV_1 \geq 70\%$ of predicted. This revision was found acceptable in an earlier IND review[20].

[19] DARRTS IND 105337 Chang, Nancy S 12/22/2009 N/A 12/22/2009 REV-CLINIAL-03 (General Review) Archive
[20] DARRTS IND 105337 NGUYEN, DOAN T 11/04/2010 REV-NONCLINICAL-03(General Review) Archive

- All the other inclusion/exclusion criteria of the firm are according to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI.

- The firm indicated that "placebo MDI" is used in treatments 1 through 5. However, the firm did not specify whether the "placebo MDI" is the test or reference product placebo. The firm should clarify which placebo, Test or Reference placebo, were used in each treatment of its PD study. In addition, the firm will be asked to provide the formulation of the placebo drug product.

- The study design is **inadequate**.

4.4.4 Demographic Profile of Subjects

Study No. PRG-723		
		N =113
Age (years)	Mean ± SD	34.4 ± 12.7
	Range	18.7 – 63.5
Age Groups	< 18	0 (0%)
	18 – 40	78 (69.1%)
	40 – 64	35 (30.9%)
	65 – 75	0 (0%)
	> 75	0 (0%)
Sex	Male	44 (38.9%)
	Female	69 (61.1%)
Race	Asian	1 (0.9%)
	Black	18 (15.9%)
	Caucasian	92 (81.4%)
	Hispanic	0(%)
	Other	2 (1.8%)
Ethnicity	Hispanic/Latino	14 (12.4%)
	Not Hispanic/Latino	99 (87.6%)
FEV_1 Percent Predicted	Mean ± SD	85.8 ± 11.5
	Range	70.0 – 118.4
Tobacco User[2]	Yes	0 (0%)
	No	113 (100.0%)

[2] Defined as current tobacco user (having used tobacco within 12 months of first dose)

Reviewer comments:

- In the Pharmacodynamic study, 44 subjects in this study were male (38.9%) and 69 subjects (61.1%) were female. A total of 14 subjects were Hispanic or Latino (12.4%). A total of 92 subjects (81.4%) were White or Caucasian, 18 subjects (15.9%) were Black or African American, and 1 subject (0.9%) was Asian, and

2 subjects (1.8%) were reported as "others." Subjects ranged in age from 18 to 63 years.

- The Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI recommends male and non-pregnant female subjects of 18-65 years of age. The, study was conducted according to the guidance.

4.4.5 Dropout Information

Number of subjects randomized	113
Number of subjects completing study, n (%)	101 (89.4)
Number of subjects discontinued, n (%)	12 (10.6)
Reason for discontinuation, n (%)	
Subject's request	1 (0.9)
Subject failed to use correct technique during 2 consecutive visits	4 (3.5)
Adverse event	5 (4.4)
Protocol violation	1 (0.9)
Concomitant therapy	0 (0.0)
Lost to follow-up	1 (0.9)
Subject became pregnant	0 (0.0)
Subject had an asthma exacerbation requiring oral corticosteroids	0 (0.0)

4.4.6 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups				
	Test		Reference		Placebo
	90 mcg (N = 113)	180 mcg (N = 113)	90 mcg (N = 113)	180 mcg (N = 113)	0 mcg (N = 113)
Subjects with Any AE, n (%)	4 (3.7)	3 (2.8)	4 (3.7)	5 (4.7)	6 (5.4)
Infections and infestations	2 (1.9)	2 (1.9)	2 (1.9)	2 (1.9)	0
Upper respiratory tract infection	1 (0.9)	2 (1.9)	2 (1.9)	0	0
Nasopharyngitis	1 (0.9)	0	0	1 (0.9)	0
Acute sinusitis	0	0	0	1 (0.9)	0
Respiratory, thoracic and mediastinal disorders	1 (0.9)	0	2 (1.9)	1 (0.9)	1 (0.9)
Asthma	0	0	1 (0.9)	0	1 (0.9)
Rhinorrhea	1 (0.9)	0	1 (0.9)	0	0
Cough	0	0	1 (0.9)	0	0
Rhinitis allergic	0	0	0	1 (0.9)	0
Musculoskeletal and connective tissue disorders	1 (0.9)	0	1 (0.9)	1 (0.9)	1 (0.9)
Back pain	1 (0.9)	0	0	0	0
Costochondritis	0	0	0	1 (0.9)	0
Musculoskeletal chest pain	0	0	1 (0.9)	0	0
Myalgia	0	0	0	0	1 (0.9)
Gastrointestinal disorders	0	0	0	1 (0.9)	2 (1.8)
Abdominal discomfort	0	0	0	0	1 (0.9)
Abdominal pain upper	0	0	0	1 (0.9)	0
Vomiting	0	0	0	0	1 (0.9)
General disorders and administration site conditions	0	1 (0.9)	1 (0.9)	1 (0.9)	0
Fatigue	0	1 (0.9)	0	0	0
Pain	0	0	0	1 (0.9)	0
Pyrexia	0	0	1 (0.9)	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	2 (1.8)
Dermatitis contact	0	0	0	0	1 (0.9)
Rash	0	0	0	0	1 (0.9)
Vascular disorders	0	0	1 (0.9)	0	1 (0.9)
Deep vein thrombosis	0	0	1 (0.9)	0	0
Epistaxis	0	0	0	0	1 (0.9)
Immune system disorders	0	0	0	0	1 (0.9)
Hypersensitivity	0	0	0	0	1 (0.9)
Nervous system disorders	0	1 (0.9)	0	0	0
Headache	0	1 (0.9)	0	0	0

4.4.7 Protocol Deviations

Protocol Violation/Deviation	Site number/Subject number(s)[a]
Protocol Violations	
Inclusion/exclusion error[b]	06/ (b) (6)
Improper technique at 2 consecutive visits[b]	01/ (b) (6)
Methacholine challenge stopped too early	03/
Pre-drug FEV_1 >20% of Baseline at one or more visits	01/
Percent decrease in FEV_1 miscalculated	04/ (b) (6)
Protocol Deviations	
Methacholine challenge done incorrectly	01/ (b) (6)
Subject did not sign most updated or correct version of ICF	01/
UPT not performed according to schedule	02/
Changed nebulizer and rotameter setting	02/
Screening procedures incomplete or incorrectly performed	02/
Error in dispensing investigational product	01/ (b) (6)
Incorrect visit scheduling	06/

a: A subject could have more than one violation or deviation.
b: These categories were counted separately from "Protocol Violation" in Appendix 16.2.3, Data Listing 16.2.3.2.Source: Appendix 16.2.2, Data Listing 16.2.2.

Comments on Dropouts/Adverse events/Protocol Deviations:

- Out of the 113 Intent to Treat (ITT) subjects, adverse events were reported in 19 subjects following treatment with test or reference product or placebo. The frequency of adverse events (AE) reports ranged from a minimum value 2.8% following treatment with 180 mcg Test Drug to a maximum of 5.4% following treatment with placebo. One serious and severe adverse event was reported. Subject (b) (6) experienced deep vein thrombosis and pulmonary embolism with the reference product, 90 mcg. Subject was discontinued from the study. An AE reported following treatment with 180 mcg Reference Drug was considered to be severe, but not serious. Subject (b) (6) experienced costochondritis (musculoskeletal and connective tissue disorders). In 4 subjects AEs resulted in study product discontinuation (subject (b) (6)); these AEs occurred in one subject who received 90 mcg Test Drug, in 2 subjects who received 180 mcg Test Drug, and in one subject who received 90 mcg Reference Drug. No deaths were reported. No subjects became pregnant during the study and were discontinued.The adverse event profile observed during the study was comparable for the test and reference product. There is no strong evidence suggesting that the test drug caused substantially more serious adverse events compared to the reference drug.

- There were 12 dropouts in the pharmacodynamics study. Out of the 12 subjects, 5 subjects experienced adverse events. Subject #s (b) (6) were discontinued from the study because of adverse events. The following is the

summary of adverse events experienced by the subjects discontinued from the study:

Subject #	Drug Product	Adverse Event
(b) (6)	Test, 180 mcg	Upper Respiratory Tract Infection
	Reference, 90 mcg	Worsening Allergic Rhinitis Symptoms Epistaxis Upper Respiratory Tract Infection
	Test, 180 mcg	Upper Respiratory Tract Infection
	Test, 90 mcg	Upper Respiratory Tract Infection
	Reference, 180 mcg	Deep Vein Thrombosis Pulmonary Embolism Rhinorrhea Low Grade Fever Lower Rib Pain in Back Increased Nasal Secretions

- The firm only provided the case report forms of subject #s (b) (6) (b) (6). The firm will be asked to provide the case report forms of all subjects included in the PD study.

- Total of 113 subjects were enrolled in the Pharmacodynamic study and 101 subjects complete the study. The following 12 subjects were discontinued from the study:

Discontinued Subject #	Reason for Discontinued
(b) (6)	Adverse events
	Subject failed to use correct technique during 2 consecutive visits
	Lost to follow up
	Personal reason (due to conflict with new work schedule)
	Unsatisfactory spirometry tests

- The following 8 subjects had protocol deviations and were not included in the statistical analysis. The reviewer also agrees with the firm's decision to not include the data of these subjects in the data analysis. Please see the summary for the reasons of exclusion.

Subject #s Excluded from the Statistical Analysis	Reason for Exclusion
(b) (6)	Subject's FEV1 was within 20.5% of all other initial FEV1S.
	1) Methacholine challenge test was stopped at 32.0 mg/mL. FEV1 had not dropped below > 20% of control. 2) Upper respiratory infection
	The FEV2 at visit 7 was not within 20% of the FEV1 at visiy 2 (21.5%) and visit 5 (27.4%). The visit should have been rescheduled.
	Percent drop was miscalculated for SKG/008 at visit 3. Therefore, the PC20 can not be determined. Additionally, other procedure; errors were noted.
	The methacholine challenge was stopped in error by

(b) (6)	the coordinator prior to the subject reaching the 20% drop from the post salive FEV1.
	Subject failed to use correct technique at two consecutive study visits. Subject should have been discontinued.
	Upper respiratory infection

- The exclusion of eight (8) subjects with protocol deviations from the statistical analysis was according to the firm's pre-established protocol (#PRG-723).

- The rest of the protocol deviations were minor and should not have an impact on the outcome of the current study.

- The clinical results are **inadequate**.

4.4.8 Statistical Results

Summary of Bioavailability Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	PC20 Geometric Mean Parameters (+/-SD)					Study Report Location
					Vehicle (Placebo)	90 µg Reference product	180 µg Reference product	90 µg Test product	180 µg Test product	
Study No. PRG-723	The objectives of the study were to establish a dose response curve for the Reference Product, and use the established dose-response curve to determine the relative bioavailability (F) of the Test Product to the Reference Product	Multicenter, double-blind, randomized, five-way crossover methacholine challenge study	**Test product** Albuterol Sulfate Inhalation Aerosol 90 mcg/actuation Dose:1x90 and 2x90 mcg actuations, Route: Inhalation Lot No.: 08MM-050 **Ref. product** ProAir® HFA (albuterol sulfate) Inhalation Aerosol 90 mcg/actuation Dose:1x90 and 2x90 mcg actuations, Route: Inhalation Lot No.: AEA13B and PAEF75A **Placebo product** Dose:1 and 2 actuations, Route: Inhalation Lot No.: 08MM-020	113 randomized (44 M/69F) Asthmatic subjects 34.4 ± 12.7 (18 - 63)	2.495 (206.423)	13.409 (204.405)	22.057 (154.758)	14.239 (227.004)	26.699 (163.259)	report-body.p28

Bronchoprovocation study involves administration of differing doses of the albuterol MDI on separate days in a cross-over study design coupled with subsequent challenge with a bronchoprovocation agent, such as methacholine, to provide a bronchoprotection dose-response curve. The provocative dose or concentration of methacholine challenge agent required to reduce the FEV_1 by 20% following administration of differing doses of albuterol (or placebo) by inhalation aerosol (PD_{20} or PC_{20}) is used to support BE. The 20% reduction in FEV_1 is determined relative to the saline FEV_1 measured before the placebo or albuterol administration.

Calculation of PC_{20} Data

Individual FEV_1 values were used to derive PC_{20} parameters. The response of FEV_1 to each methacholine concentration was calculated using the following formula:

$$\% \text{ decrease } FEV_1 = 100 \times \frac{(\text{Baseline } FEV_1 - \text{Lowest } FEV_1 \text{ postmethacholine})}{\text{Baseline } FEV_1}$$

The percent decrease in FEV_1 was then plotted against the logarithim of the methacholine concentration (from stock solutions) on a logarithmic scale and the PC_{20} was determined based on data interpolation for each subject and treatment. Linear interpolation of the PC_{20} values (on a semilog scale) based on methacholine concentrations (from stock solutions) was used. When interpolation was not possible, a single point extrapolation was used. Individual FEV_1 and PC_{20} parameters were summarized with descriptive statistics (eg, N, mean, standard deviation, coefficient of variation [CV%], median, minimum, maximum, geometric mean, and geometric CV%)

Dose-Scale Analysis of PC_{20} Data and Bioequivalence Assessment

In the first step, relative bioavailability "F" of the Test Product was determined by simultaneously fitting the within-study dose response data of both the Test and Reference Products to the following model:

$$E = E_0 + \frac{E_{max} * Dose * F^i}{ED_{50} + Dose * F^i}$$

where

i = treatment indicator (0 = Ref, 1 = Test) with the understanding that $F^0 = 1$

E = predicted response (ie, PC_{20})

E_0 = Baseline response (PC_{20}) in the absence of drug (ie, placebo value)

E_{max} = Fitted maximum drug effect response

Dose = Albuterol dose (ie, either 90 or 180 mcg)

F^i = Relative bioavailability at the site of efficacy (where F^0=1 for the Reference Product and F^1 was to be estimated for the Test Product)

ED_{50} = Estimated albuterol dose required to achieve 50% of fitted maximal value of the pharmacodynamic effect above baseline

In the second step, a 90% confidence interval (CI) for the relative bioavailability (F) of the test to reference formulation of albuterol was established using a bootstrap resampling procedure. Each bootstrap estimation included calculation of "F" by fitting the above model to a resampled dose-response data set, which was generated by random repetitive sampling with replacement of individual subject's data. Confidence intervals (90% CI) of F were constructed using Efron's bias corrected and accelerated (BCA) method.9 Dose-scale modeling was performed using R software.

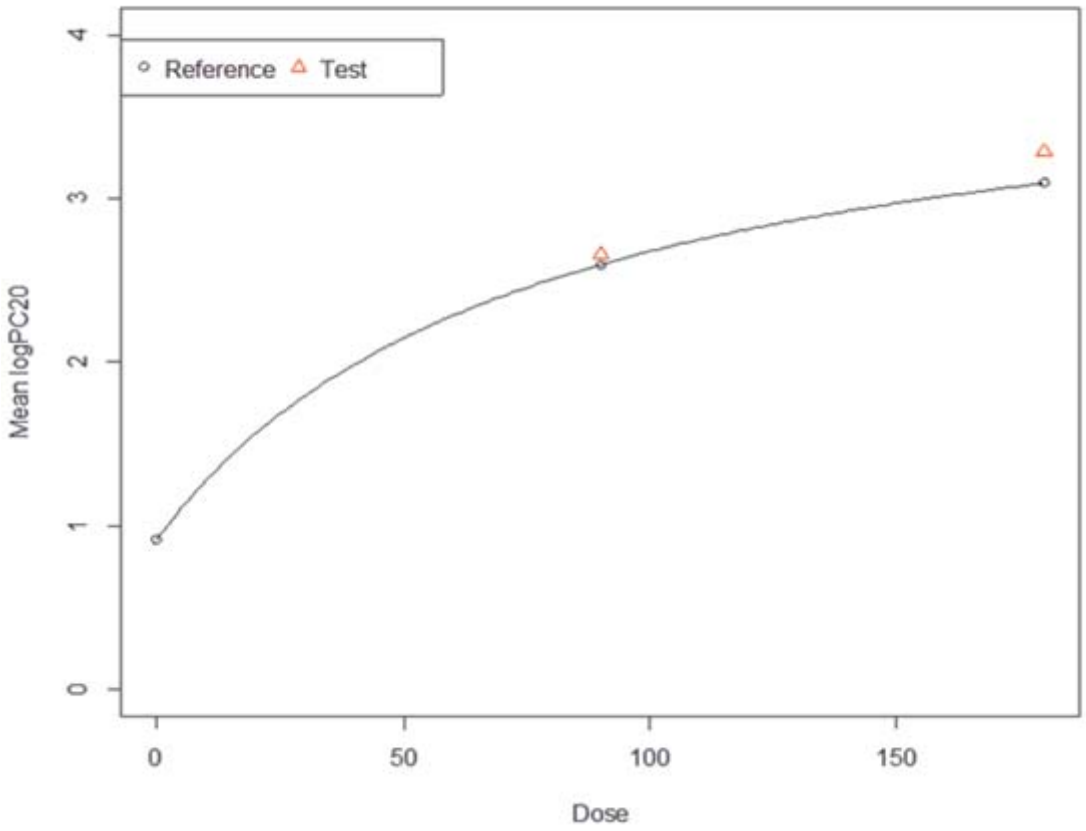
The following are the firm's results:

Population Defined by T/S Ratio	N	F (TEST/REF)	90% CI
All PP subjects	93	115.9%	102.3 - 133.0%
0.40 – 2.50	80	109.4%	95.8 – 123.4%
0.50 – 2.00	65	102.2%	90.4 – 115.3%

Source: Appendix 16.5.2
T/S ratio = ratio of treatment to screen PC20 values for Reference 180 mcg; F (TEST/REF)= relative bioequivalency of Test Product and Reference Product; CI = confidence interval

The following are the reviewer calculated results:

Method	N	F (Test/Reference)	90% CI
Using both Doses (0.09 mg and 0.18 mg to calculate F)	93	1.17	102.68% – 132.85%



Reviewer's Comments:

- The point estimate of the bioavailability (F) value calculated by the reviewer is similar with the firm's calculation when included 93 subjects in the statistical analysis.

- Per firm's study report (#PRG-723), the firm also conducted further statistical analysis on the subgroups. T/S ratio (ratio of treatment to screen PC20 values for reference 180 mcg) was used as an objective indicator for selection of the subjects in the statistical analysis. Two T/S ratios were applied for subject selection. 1) T/S ratio range 0.4- 2.5: 80 subjects were included in the data analsysis; and 2) T/S ratio range 0.5- 2.0: 65 subjects were included in the data analsysis. In both cases, the 90% confidence intervals for F are within the acceptable range of 67.00-150.00%. Per Drug Specifc Bioequivalence guidance for Albuterol Sulfate MDI, the agency does not recommend any statistical analysis based on the subgroups. Therefore, the firm's subgroups analysis results are used as the supporting data.

- Nevertheless, the firm's statistical analysis was consistent with the FDA's requirements and the 90% CI of bioavailability (F) is within the 67.00 – 150.00% BE criteria when included 93 subjects in the data analysis.

Pharmacodynamic Study Output (reviewer calculated)

```
> require(SASxport)
Loading required package: SASxport
Warning message:
In library(package, lib.loc = lib.loc, character.only = TRUE, logical return = TRUE,  :
  there is no package called 'SASxport'
> mysas<-"C:\\Users\\RENKE\\Desktop\\Team15\\Dosescale\\ANDA203760\\ANDA203760.csv"
>
> try<-read.csv(mysas)
> head(try)
  row.names          ID   VISIT    PC20 TRT DOSE    FORM     LPC20    PC20QC
1         1 PRG-723-01 (b) (6) VISIT 3 51.4062   D  180    TEST 3.9397590 51.406220
2         2 PRG-723-01         VISIT 4 50.2133   E  180     REF 3.9162800 50.213380
3         3 PRG-723-01         VISIT 5 21.8715   C   90     REF 3.0851840 21.871500
4         4 PRG-723-01         VISIT 6  1.7296   A    0 PLACEBO 0.5478902  1.729645
5         5 PRG-723-01         VISIT 7 22.6988   B   90    TEST 3.1223120 22.698820
6         6 PRG-723-01         VISIT 3 17.5339   C   90     REF 2.8641360 17.533910
    LPC20QC
1 3.9397590
2 3.9162820
3 3.0851850
4 0.5479163
5 3.1223130
6 2.8641360
> try[1:20,]
   row names          ID   VISIT    PC20 TRT DOSE    FORM      LPC20
1         1 PRG-723-01 (b) (6) ISIT 3 51.4062   D  180    TEST  3.9397590
2         2 PRG-723-01         ISIT 4 50.2133   E  180     REF  3.9162800
3         3 PRG-723-01         ISIT 5 21.8715   C   90     REF  3.0851840
4         4 PRG-723-01         ISIT 6  1.7296   A    0 PLACEBO  0.5478902
5         5 PRG-723-01         ISIT 7 22.6988   B   90    TEST  3.1223120
6         6 PRG-723-01         ISIT 3 17.5339   C   90     REF  2.8641360
7         7 PRG-723-01         ISIT 4 34.4060   D  180    TEST  3.5382310
8         8 PRG-723-01         ISIT 5 20.3179   B   90    TEST  3.0115020
9         9 PRG-723-01         ISIT 6 33.7205   E  180     REF  3.5181060
10       10 PRG-723-0          VISIT 7  5.1443   A    0 PLACEBO  1.6378890
11       11 PRG-723-0          VISIT 3  0.5863   B   90    TEST -0.5339237
12       12 PRG-723-0          VISIT 4  1.5070   C   90     REF  0.4101209
13       13 PRG-723-0          VISIT 5  0.3458   A    0 PLACEBO -1.0618950
14       14 PRG-723-0          VISIT 6 10.7034   D  180    TEST  2.3705610
15       15 PRG-723-0          VISIT 7  7.4246   E  180     REF  2.0047990
16       16 PRG-723-0          VISIT 3  7.9447   E  180     REF  2.0725050
17       17 PRG-723-0          VISIT 4  2.4868   A    0 PLACEBO  0.9109967
18       18 PRG-723-0          VISIT 5  7.3708   D  180    TEST  1.9975260
19       19 PRG-723-0          VISIT 6  2.9113   B   90    TEST  1.0686000
20       20 PRG-723-0          VISIT 7  3.1431   C   90     REF  1.1452100
      PC20QC    LPC20QC
1  51.4062200  3.9397590
2  50.2133800  3.9162820
3  21.8715000  3.0851850
4   1.7296450  0.5479163
5  22.6988200  3.1223130
6  17.5339100  2.8641360
7  34.4059700  3.5382300
```

```
8  20.3179200  3.0115030
9  33.7205400  3.5181070
10  5.1442580  1.6378810
11  0.5862669 -0.5339801
12  1.5069870  0.4101121
13  0.3458181 -1.0618420
14 10.7034200  2.3705630
15  7.4245710  2.0047950
16  7.9447400  2.0725100
17  2.4867920  0.9109934
18  7.3707850  1.9975240
19  2.9113060  1.0686020
20  3.1430690  1.1452000
> dim(try)
[1] 465  10
> try$TRMNTGRP=paste(try$FORM,try$DOSE,sep='')
>
> wide <- reshape(try, v names = "LPC20", idvar = "ID",
+                 timevar = "TRMNTGRP", direction = "wide")
Warning message:
In reshapeWide(data, idvar = idvar, timevar = timevar, varying = varying,  :
  some constant variables (row names,VISIT,PC20,TRT,DOSE,FORM,PC20QC,LPC20QC) are really
varying
> test=try[try$TRMNTGRP=="W90",]
> test2=test[duplicated(test$SUBNUMB),]
> test[test$SUBNUMB==180112,]
 [1] row.names ID       VISIT    PC20     TRT      DOSE     FORM
 [8] LPC20    PC20QC   LPC20QC  TRMNTGRP
<0 rows> (or 0-length row.names)
> dim(wide)
[1] 93 14
> head(wide)
  row names          ID   VISIT    PC20 TRT DOSE    FORM     PC20QC
1         1 PRG-723-01-[redacted]ISIT 3 51.4062   D  180    TEST 51.4062200
6         6 PRG-723-01-[redacted]ISIT 3 17.5339   C   90     REF 17.5339100
11       11 PRG-723-01[redacted]VISIT 3  0.5863   B   90    TEST  0.5862669
16       16 PRG-723-01[redacted]VISIT 3  7.9447   E  180     REF  7.9447400
21       21 PRG-723-01[redacted]VISIT 3  0.4368   A    0 PLACEBO  0.4368253
26       26 PRG-723-01[redacted]VISIT 3 49.9072   B   90    TEST 49.9072100
     LPC20QC LPC20.TEST180 LPC20.REF180 LPC20.REF90 LPC20.PLACEBO0
1   3.9397590     3.939759    3.916280   3.0851840      0.5478902
6   2.8641360     3.538231    3.518106   2.8641360      1.6378890
11 -0.5339801     2.370561    2.004799   0.4101209     -1.0618950
16  2.0725100     1.997526    2.072505   1.1452100      0.9109967
21 -0.8282220     1.237156    1.867423   0.6238507     -0.8282799
26  3.9101660     3.511945    3.810486   3.5018990      0.4902351
  LPC20.TEST90
1   3.12231200
6   3.01150200
11 -0.53392370
16  1.06860000
21  0.02858746
26  3.91016500
> wide[1:20,]
  row names          ID   VISIT     PC20 TRT DOSE    FORM      PC20QC
1         1 PRG-723-01[redacted]VISIT 3  51.4062   D  180    TEST  51.4062200
6         6 PRG-723-01[redacted]VISIT 3  17.5339   C   90     REF  17.5339100
```

11	11	PRG-723-01	[redacted]	VISIT 3	0.5863	B	90	TEST	0.5862669
16	16	PRG-723-01		VISIT 3	7.9447	E	180	REF	7.9447400
21	21	PRG-723-01		VISIT 3	0.4368	A	0	PLACEBO	0.4368253
26	26	PRG-723-01		VISIT 3	49.9072	B	90	TEST	49.9072100
31	31	PRG-723-01		VISIT 3	15.8423	E	180	REF	15.8423500
36	36	PRG-723-01		VISIT 3	14.8200	A	0	PLACEBO	14.8200000
41	41	PRG-723-01		VISIT 3	23.0297	C	90	REF	23.0297000
46	46	PRG-723-01		VISIT 3	9.3378	C	90	REF	9.3377630
51	51	PRG-723-01		VISIT 3	9.6122	B	90	TEST	9.6121880
56	56	PRG-723-01		VISIT 3	147.5504	D	180	TEST	147.5368000
61	61	PRG-723-01		VISIT 3	0.9473	A	0	PLACEBO	0.9473380
66	66	PRG-723-01		VISIT 3	99.6268	D	180	TEST	99.6267700
71	71	PRG-723-01		VISIT 3	74.5177	C	90	REF	74.5177500
76	76	PRG-723-01		VISIT 3	8.4431	B	90	TEST	8.4431290
81	81	PRG-723-01		VISIT 3	23.1878	E	180	REF	23.1878000
86	86	PRG-723-01		VISIT 3	100.1594	B	90	TEST	100.1594000
91	91	PRG-723-01		VISIT 3	32.7480	E	180	REF	32.7479600
96	96	PRG-723-01		VISIT 3	1.1855	A	0	PLACEBO	1.1854660

	LPC20QC	LPC20.TEST180	LPC20.REF180	LPC20.REF90	LPC20.PLACEBO0
1	3.93975900	3.939759	3.916280	3.0851840	0.54789020
6	2.86413600	3.538231	3.518106	2.8641360	1.63788900
11	-0.53398010	2.370561	2.004799	0.4101209	-1.06189500
16	2.07251000	1.997526	2.072505	1.1452100	0.91099670
21	-0.82822200	1.237156	1.867423	0.6238507	-0.82827990
26	3.91016600	3.511945	3.810486	3.5018990	0.49023510
31	2.76268700	2.426014	2.762684	1.8047910	1.45175400
36	2.69597800	4.622302	3.319405	3.8816240	2.69597800
41	3.13678500	3.148535	3.304422	3.1367850	2.49532700
46	2.23406700	2.556940	2.463938	2.2340710	0.42846520
51	2.26303200	3.068332	2.721243	2.8173770	0.41995960
56	4.99407800	4.994170	5.375435	4.7932180	2.07187500
61	-0.05409929	3.125136	2.822586	2.7247830	-0.05413945
66	4.60143100	4.601431	4.879645	4.3437220	1.16365100
71	4.31103700	4.701346	4.849510	4.3110370	1.62843600
76	2.13335300	2.729022	1.832613	1.3425250	0.38301500
81	3.14362600	3.206560	3.143626	2.1348880	-0.49906180
86	4.60676300	5.449867	5.075174	4.8228450	1.97546900
91	3.48884100	3.289562	3.488842	2.7456350	-0.38949330
96	0.17013610	2.466522	1.873109	2.2841670	0.17016460

	LPC20.TEST90
1	3.12231200
6	3.01150200
11	-0.53392370
16	1.06860000
21	0.02858746
26	3.91016500
31	0.84496660
36	4.08052800
41	2.90512400
46	3.09765200
51	2.26303300
56	4.22964100
61	2.80314800
66	3.93443600
71	4.42154900
76	2.13335000
81	2.24579200

```
86   4.60676300
91   2.52656800
96   0.53003980
>
raw1=wide[,c('LPC20.TEST90','LPC20.TEST180','LPC20.PLACEBO0','LPC20.REF90','LPC20.REF180')
]
> Pmean=mean(wide[,'LPC20.PLACEBO0'],na rm=T)
> T1mean=mean(wide[,'LPC20.TEST90'],na.rm=T)
> T2mean=mean(wide[,'LPC20.TEST180'],na.rm=T)
> R1mean=mean(wide[,'LPC20.REF90'],na.rm=T)
> R2mean=mean(wide[,'LPC20.REF180'],na.rm=T)
> T1mean
[1] 2.656005
> T2mean
[1] 3.284634
> R1mean
[1] 2.595943
> R2mean
[1] 3.09364
> T1mean/R1mean
[1] 1.023137
> T2mean/R2mean
[1] 1.061738
> plot(x=c(0,90,180),y=c(Pmean,R1mean, R2mean),ylim=c(0,3.5))
> points(x=c(90,180),y=c(T1mean, T2mean),pch=2,col="red")
>
> boot.sample.int=1000# number of simulation to calculated 90% CI using BCA
>
#########################################################################################
#######
> # Define doses
>
#########################################################################################
#######
> Test1<-90
> Test2<-180
> Placebo<-0
> Ref1<-90
> Ref2<-180
> sample.size<-dim(raw1)[1] # sample size
>
#########################################################################################
#######
> #Load required R Packages
>
#########################################################################################
#######
> library(psych)
Error in library(psych) : there is no package called ‘psych’
> library(mvtnorm)
Error in library(mvtnorm) : there is no package called ‘mvtnorm’
> library(boot)
> library(MASS)
> library(caTools)
Error in library(caTools) : there is no package called ‘caTools’
Error in library(DoseFinding) : there is no package called ‘DoseFinding’
>
```

```
> head(wide)
  row names           ID   VISIT    PC20 TRT DOSE    FORM     PC20QC
1         1 PRG-723-01-  (b) (6)  ISIT 3 51.4062   D  180    TEST 51.4062200
6         6 PRG-723-01-           ISIT 3 17.5339   C   90     REF 17.5339100
11       11 PRG-723-01            VISIT 3  0.5863   B   90    TEST  0.5862669
16       16 PRG-723-01            VISIT 3  7.9447   E  180     REF  7.9447400
21       21 PRG-723-01            VISIT 3  0.4368   A    0 PLACEBO  0.4368253
26       26 PRG-723-01            VISIT 3 49.9072   B   90    TEST 49.9072100
     LPC20QC LPC20.TEST180 LPC20.REF180 LPC20.REF90 LPC20.PLACEBO0
1   3.9397590     3.939759    3.916280   3.0851840      0.5478902
6   2.8641360     3.538231    3.518106   2.8641360      1.6378890
11 -0.5339801     2.370561    2.004799   0.4101209     -1.0618950
16  2.0725100     1.997526    2.072505   1.1452100      0.9109967
21 -0.8282220     1.237156    1.867423   0.6238507     -0.8282799
26  3.9101660     3.511945    3.810486   3.5018990      0.4902351
  LPC20.TEST90
1   3.12231200
6   3.01150200
11  -0.53392370
16   1.06860000
21   0.02858746
26   3.91016500
> head(try)
  row.names           ID   VISIT    PC20 TRT DOSE    FORM     LPC20    PC20QC
1         1 PRG-723-01   (b) (6) VISIT 3 51.4062   D  180    TEST 3.9397590 51.406220
2         2 PRG-723-01           VISIT 4 50.2133   E  180     REF 3.9162800 50.213380
3         3 PRG-723-01           VISIT 5 21.8715   C   90     REF 3.0851840 21.871500
4         4 PRG-723-01           VISIT 6  1.7296   A    0 PLACEBO 0.5478902  1.729645
5         5 PRG-723-01           VISIT 7 22.6988   B   90    TEST 3.1223120 22.698820
6         6 PRG-723-01           VISIT 3 17.5339   C   90     REF 2.8641360 17.533910
   LPC20QC TRMNTGRP
1 3.9397590  TEST180
2 3.9162820   REF180
3 3.0851850    REF90
4 0.5479163 PLACEBO0
5 3.1223130   TEST90
6 2.8641360    REF90
> long=reshape(wide,direction="long")
> long$TRMNTGRP
  [1] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
  [7] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [13] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [19] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [25] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [31] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [37] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [43] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [49] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [55] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [61] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [67] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [73] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [79] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [85] "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"  "TEST180"
 [91] "TEST180"  "TEST180"  "TEST180"  "REF180"   "REF180"   "REF180"
 [97] "REF180"   "REF180"   "REF180"   "REF180"   "REF180"   "REF180"
[103] "REF180"   "REF180"   "REF180"   "REF180"   "REF180"   "REF180"
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[109] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[115] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[121] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[127] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[133] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[139] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[145] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[151] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[157] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[163] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[169] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[175] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[181] "REF180"  "REF180"  "REF180"  "REF180"  "REF180"  "REF180"
[187] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[193] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[199] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[205] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[211] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[217] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[223] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[229] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[235] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[241] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[247] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[253] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[259] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[265] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[271] "REF90"   "REF90"   "REF90"   "REF90"   "REF90"   "REF90"
[277] "REF90"   "REF90"   "REF90"   "PLACEBO0" "PLACEBO0" "PLACEBO0"
[283] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[289] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[295] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[301] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[307] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[313] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[319] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[325] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[331] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[337] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[343] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[349] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[355] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[361] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[367] "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0" "PLACEBO0"
[373] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[379] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[385] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[391] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[397] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[403] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[409] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[415] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[421] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[427] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[433] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[439] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
[445] "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"  "TEST90"
```

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[451] "TEST90"   "TEST90"   "TEST90"   "TEST90"   "TEST90"   "TEST90"
[457] "TEST90"   "TEST90"   "TEST90"   "TEST90"   "TEST90"   "TEST90"
[463] "TEST90"   "TEST90"   "TEST90"
> dose=rep(c(Test2, Ref2, Ref1, Placebo,  Test1),each=sample.size)
> ind=rep(c(1, 0,  0, 0, 1),each=sample.size)
>
>
> #fix(long)
> #fix(wide)
>
> head(long)
                row names           ID   VISIT    PC20 TRT DOSE
PRG-723-01-(b)(6) TEST180        1 PRG-723-01 (b) (6) VISIT 3 51.4062   D  180
PRG-723-01-       TEST180        6 PRG-723-01       VISIT 3 17.5339   C   90
PRG-723-01-       TEST180       11 PRG-723-01       VISIT 3  0.5863   B   90
PRG-723-01-       TEST180       16 PRG-723-01       VISIT 3  7.9447   E  180
PRG-723-01-       TEST180       21 PRG-723-01       VISIT 3  0.4368   A    0
PRG-723-01-       TEST180       26 PRG-723-01       VISIT 3 49.9072   B   90
                  FORM     PC20QC    LPC20QC TRMNTGRP    LPC20
PRG-723-01-(b)(6) TEST180    TEST 51.4062200  3.9397590  TEST180 3.939759
PRG-723-01-       TEST180     REF 17.5339100  2.8641360  TEST180 3.538231
PRG-723-01-       TEST180    TEST  0.5862669 -0.5339801  TEST180 2.370561
PRG-723-01-       TEST180     REF  7.9447400  2.0725100  TEST180 1.997526
PRG-723-01-       TEST180 PLACEBO  0.4368253 -0.8282220  TEST180 1.237156
PRG-723-01-       TEST180    TEST 49.9072100  3.9101660  TEST180 3.511945
> dim(long)
[1] 465  11
> long$DOSE=dose
> long$IND=ind
> long$IND1=rep(c(0, 0,  0, 0, 1),each=sample.size)
> long$IND2=rep(c(1, 0,  0, 0, 0),each=sample.size)
> emaxfit.R=nls(LPC20~E0+EMAX*DOSE*(F^IND)/(ED50+DOSE*F^IND), data=long,
start=list(EMAX=R2mean, ED50=Ref1,E0=Pmean,F=1),control=list(tol=1e-10,minFactor=1e-
10,warnOnly=TRUE))
Warning message:
In nls(LPC20 ~ E0 + EMAX * DOSE * (F^IND)/(ED50 + DOSE * F^IND),  :
  number of iterations exceeded maximum of 50
> t=coef(emaxfit.R)
> t
     EMAX      ED50        E0         F
 3.4115543 96.8204961  0.9156725  1.1626362
> summary(emaxfit.R)
Formula: LPC20 ~ E0 + EMAX * DOSE * (F^IND)/(ED50 + DOSE * F^IND)
Parameters:
    Estimate Std. Error t value Pr(>|t|)
EMAX   3.4116     0.5470   6.237 1.01e-09 ***
ED50  96.8205    39.3430   2.461   0.0142 *
E0     0.9157     0.1281   7.149 3.46e-12 ***
F      1.1626     0.1883   6.174 1.46e-09 ***
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Residual standard error: 1.235 on 461 degrees of freedom
Number of iterations till stop: 50
Achieved convergence tolerance: 9.393e-10
Reason stopped: number of iterations exceeded maximum of 50
>
emaxfit.R2=nls(LPC20~E0+EMAX*DOSE*(F1^IND1)*(F2^IND2)/(ED50+DOSE*F1^IND1*F2^IND2),
```

```
data=long, start=list(EMAX=R2mean, ED50=Ref1,E0=Pmean,F1=1,F2=1),control=list(tol=1e-
10,minFactor=1e-10,warnOnly=TRUE))
> t2=coef(emaxfit.R2)
> t2
      EMAX       ED50         E0         F1         F2
 3.0954148 75.6723649  0.9143876  1.0816672  1.3741030
> summary(emaxfit.R2)
Formula: LPC20 ~ E0 + EMAX * DOSE * (F1^IND1) * (F2^IND2)/(ED50 + DOSE *
    F1^IND1 * F2^IND2)
Parameters:
     Estimate Std. Error t value Pr(>|t|)
EMAX   3.0954     0.6806   4.548 6.93e-06 ***
ED50  75.6724    46.0579   1.643   0.1011
E0     0.9144     0.1282   7.132 3.86e-12 ***
F1     1.0817     0.2469   4.381 1.46e-05 ***
F2     1.3741     0.5985   2.296   0.0221 *
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
Residual standard error: 1.236 on 460 degrees of freedom
Number of iterations to convergence: 4
Achieved convergence tolerance: 1.985e-12

> anova(emaxfit.R, emaxfit.R2)
Analysis of Variance Table
Model 1: LPC20 ~ E0 + EMAX * DOSE * (F^IND)/(ED50 + DOSE * F^IND)
Model 2: LPC20 ~ E0 + EMAX * DOSE * (F1^IND1) * (F2^IND2)/(ED50 + DOSE * F1^IND1 *
F2^IND2)
  Res.Df Res.Sum Sq Df  Sum Sq F value Pr(>F)
1    461     703.65
2    460     703.15  1 0.49443  0.3235 0.5698
> T1mean=mean(raw1[,1],na rm=T)
> T2mean=mean(raw1[,2],na rm=T)
> Pmean=mean(raw1[,3],na.rm=T)
> R1mean=mean(raw1[,4],na.rm=T)
> R2mean=mean(raw1[,5],na.rm=T)
> meandata=data frame(lnPC20=c(T1mean,T2mean, Pmean,R1mean,R2mean), DOSE=c(Test1, Test2,
Placebo, Ref1, Ref2),  IND=c(1,1,0,0,0))
> emaxfit.R=nls(lnPC20~E0+EMAX*DOSE*(F^IND)/(ED50+DOSE*F^IND), data=meandata,
start=list(EMAX=R2mean, ED50=Ref1,E0=Pmean,F=1),control=list(tol=1e-10,minFactor=1e-
10,warnOnly=TRUE))
Warning message:
In nls(lnPC20 ~ E0 + EMAX * DOSE * (F^IND)/(ED50 + DOSE * F^IND),  :
  number of iterations exceeded maximum of 50
> t=coef(emaxfit.R)
> t
      EMAX       ED50         E0          F
 3.4115543 96.8204981  0.9156725  1.1626362
##########################################################################################
##########
> F ratio={}
> F1 ratio={}
##########################################################################################
##########
> #calculation of 90% CI using boot strapping approch
##########################################################################################
##########
> for (v in 1:boot.sample.int){
+ boot.data<-raw1[sample(nrow(raw1), size=sample.size, replace=T), ]
```

```
+ boot.data=as.data.frame(boot.data)
+ T1data=as.data.frame(boot.data[,1])
+ colnames(T1data)[1]="lnPC20"
+ T1data$DOSE=Test1
+ T1data$IND=1
+ T1mean=mean(T1data[,1],na.rm=T)
+ T2data=as.data.frame(boot.data[,2])
+ colnames(T2data)[1]="lnPC20"
+ T2data$DOSE=Test2
+ T2data$IND=1
+ #T2mean=mean(T2data[1])
+ T2mean=mean(T2data[,1],na.rm=T)
+ Pdata=as.data frame(boot.data[,3])
+ colnames(Pdata)[1]="lnPC20"
+ Pdata$DOSE=Placebo
+ Pdata$IND=0
+ #Pmean=mean(Pdata[1])
+ Pmean=mean(Pdata[,1],na.rm=T)
+ R1data=as.data frame(boot.data[,4])
+ colnames(R1data)[1]="lnPC20"
+ R1data$DOSE=Ref1
+ R1data$IND=0
+ #R1mean=mean(R1data[1])
+ R1mean=mean(R1data[,1],na.rm=T)
+ R2data=as.data frame(boot.data[,5])
+ colnames(R2data)[1]="lnPC20"
+ R2data$DOSE=Ref2
+ R2data$IND=0
+ #R2mean=mean(R2data[1])
+ R2mean=mean(R2data[,1],na.rm=T)
+ meandata=data frame(lnPC20=c(T1mean,T2mean, Pmean,R1mean,R2mean), DOSE=c(Test1, Test2,
Placebo, Ref1, Ref2),  IND=c(1,1,0,0,0))
+ emaxfit.R=nls(lnPC20~E0+EMAX*DOSE*(F^IND)/(ED50+DOSE*F^IND), data=meandata,
start=list(EMAX=R2mean, ED50=Ref1,E0=Pmean,F=1),control=list(tol=1e-10,minFactor=1e-
10,warnOnly=TRUE))
+ t=coef(emaxfit.R)
+ F ratio[v]=t[4]
+ }
There were 50 or more warnings (use warnings() to see the first 50)
> LowerCI=c(sort(F ratio)[c(v*0.05)])
> UpperCI=c(sort(F.ratio)[c(v*0.95)])
> point.est=mean(F.ratio)
> LowerCI
[1] 1.028122
> UpperCI
[1] 1.330993
> point.est
[1] 1.171861
> ############################BCA Method###################################
>
> Fsim={}
> F1sim={}
> diff1={}
> diff2={}
> for (n in 1:sample.size)
+ {
+ accdata=raw1[-n,]
```

```
+ accdata=as.data.frame(accdata)
+ T1data=as.data.frame(accdata[,1])
+ colnames(T1data)[1]="lnPC20"
+ T1data$DOSE=Test1
+ T1data$IND=1
+ #T1mean=mean(T1data[1])
+ T1mean=mean(T1data[,1], na rm=T)
+ T2data=as.data.frame(accdata[,2])
+ colnames(T2data)[1]="lnPC20"
+ T2data$DOSE=Test2
+ T2data$IND=1
+ #T2mean=mean(T2data[1])
+ T2mean=mean(T2data[,1], na rm=T)
+ Pdata=as.data frame(accdata[,3])
+ colnames(Pdata)[1]="lnPC20"
+ Pdata$DOSE=Placebo
+ Pdata$IND=0
+ #Pmean=mean(Pdata[1])
+ Pmean=mean(Pdata[,1], na rm=T)
+
+ R1data=as.data frame(accdata[,4])
+ colnames(R1data)[1]="lnPC20"
+ R1data$DOSE=Ref1
+ R1data$IND=0
+ #R1mean=mean(R1data[1])
+ R1mean=mean(R1data[,1], na.rm=T)
+ R2data=as.data frame(accdata[,5])
+ colnames(R2data)[1]="PC20"
+ R2data$DOSE=Ref2
+ R2data$IND=0
+ #R2mean=mean(R2data[1])
+ R2mean=mean(R2data[,1], na.rm=T)
+ meandata=data frame(lnPC20=c(T1mean,T2mean, Pmean,R1mean,R2mean), DOSE=c(Test1, Test2,
Placebo, Ref1, Ref2),  IND=c(1,1,0,0,0))
+ emaxfit.R=nls(lnPC20~E0+EMAX*DOSE*(F^IND)/(ED50+DOSE*F^IND), data=meandata,
start=list(EMAX=R2mean, ED50=Ref1,E0=Pmean,F=1),control=list(tol=1e-10,minFactor=1e-
10,warnOnly=TRUE))
+ t=coef(emaxfit.R)
+ Fsim[n]=t[4]
+ }
There were 50 or more warnings (use warnings() to see the first 50)
> T1data=as.data.frame(raw1[,1])
> colnames(T1data)[1]="lnPC20"
> T1data$DOSE=Test1
> T1data$IND=1
> T1mean=mean(T1data[1])
Warning message:
mean(<data.frame>) is deprecated.
 Use colMeans() or sapply(*, mean) instead.
> T2data=as.data.frame(raw1[,2])
> colnames(T2data)[1]="lnPC20"
> T2data$DOSE=Test2
> T2data$IND=1
> T2mean=mean(T2data[1])
Warning message:
mean(<data.frame>) is deprecated.
 Use colMeans() or sapply(*, mean) instead.
```

```
> Pdata=as.data frame(raw1[,3])
> colnames(Pdata)[1]="PC20"
> Pdata$DOSE=Placebo
> Pdata$IND=0
> Pmean=mean(Pdata[1])
Warning message:
mean(<data.frame>) is deprecated.
 Use colMeans() or sapply(*, mean) instead.
> R1data=as.data frame(raw1[,4])
> colnames(R1data)[1]="PC20"
> R1data$DOSE=Ref1
> R1data$IND=0
> R1mean=mean(R1data[1])
Warning message:
mean(<data.frame>) is deprecated.
 Use colMeans() or sapply(*, mean) instead.
> R2data=as.data frame(raw1[,5])
> colnames(R2data)[1]="lnPC20"
> R2data$DOSE=Ref2
> R2data$IND=0
> R2mean=mean(R2data[1])
Warning message:
mean(<data.frame>) is deprecated.
 Use colMeans() or sapply(*, mean) instead.
> meandata=data frame(lnPC20=c(T1mean,T2mean, Pmean,R1mean,R2mean), DOSE=c(Test1, Test2,
Placebo, Ref1, Ref2),  IND=c(1,1,0,0,0))
> emaxfit.R=nls(lnPC20~E0+EMAX*DOSE*(F^IND)/(ED50+DOSE*F^IND), data=meandata,
start=list(EMAX=R2mean, ED50=Ref1,E0=Pmean,F=1),control=list(tol=1e-10,minFactor=1e-
10,warnOnly=TRUE))
Warning message:
In nls(lnPC20 ~ E0 + EMAX * DOSE * (F^IND)/(ED50 + DOSE * F^IND),  :
  number of iterations exceeded maximum of 50
> t=coef(emaxfit.R)
> Fraw1=t[4]
> for (n in 1:sample.size)
+ {
+ diff1[n]=(Fsim[n]-Fraw1)^3
+ diff2[n]=(Fsim[n]-Fraw1)^2
+ }
> accel=sum(diff1)/(6*(sum(diff2)^1.5))
> ct<-sum(F ratio<Fraw1)
> z=qnorm(ct/v)
> alpha1=(v-1)*pnorm(z+(z+qnorm(0.05))/(1-accel*(z+qnorm(0.05))))
> alpha2=(v-1)*pnorm(z+(z+qnorm(0.95))/(1-accel*(z+qnorm(0.95)))) #upperbound
>
> bcaLowerCI=c(sort(F.ratio)[c(floor(alpha1))])
> bcaUpperCI=c(sort(F.ratio)[c(ceiling(alpha2))])
> point.est
[1] 1.171861
> bcaLowerCI
[1] 1.026379
> bcaUpperCI
[1] 1.327635
> ############
> #plot DR
> meandata=data frame(lnPC20=c( Pmean,R1mean,R2mean), DOSE=c(Placebo, Ref1, Ref2))
> mfitsum=fitMod(DOSE, lnPC20, data=meandata, model="emax",bnds = c(0,50000))
```

```
> parai=coef(mfitsum)
> e0i=parai[1]
Error: object 'parai' not found
> emaxi=parai[2]
Error: object 'parai' not found
> ed50i=parai[3]
> Pmean=mean(wide[,'LPC20.PLACEBO0'],na rm=T)
> T1mean=mean(wide[,'LPC20.TEST90'],na.rm=T)
> T2mean=mean(wide[,'LPC20.TEST180'],na.rm=T)
> R1mean=mean(wide[,'LPC20.REF90'],na.rm=T)
> R2mean=mean(wide[,'LPC20.REF180'],na.rm=T)
> doserange=seq(0,180,1)
> doserange
  [1]   0   1   2   3   4   5   6   7   8   9  10  11  12  13  14  15  16  17  18  19  20  21  22  23  24  25  26  27  28
29  30  31  32  33  34  35  36  37  38  39
 [41]  40  41  42  43  44  45  46  47  48  49  50  51  52  53  54  55  56  57  58  59  60  61  62  63  64  65  66
67  68  69  70  71  72  73  74  75  76  77  78  79
 [81]  80  81  82  83  84  85  86  87  88  89  90  91  92  93  94  95  96  97  98  99 100 101 102 103 104 105
106 107 108 109 110 111 112 113 114 115 116 117 118 119
[121] 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142
143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159
[161] 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180
> pred=e0i+emaxi*doserange/(ed50i+doserange)
> plot(x=c(0,90,180),y=c(Pmean,R1mean, R2mean),ylab="Mean logPC20", xlab="Dose", ylim=c(0,4))
> points(x=c(90,180),y=c(T1mean, T2mean),pch=2,col="red")
> lines(x=doserange,y=pred)
Error in xy.coords(x, y) : object 'pred' not found
> legend( par()$usr[1],3.8, legend=c("Reference", "Test"),
+ pch=c(1,2), col=c(1,"red"), xpd=TRUE, xjust=0, yjust=0.5,ncol=1,horiz=T)
```

Consult with Ke Ren and Devvrat Patel regarding the statistical analysis of the pharmacodynamic study

From: Patel, Devvrat
Sent: Wednesday, June 25, 2014 11:51 AM
To: Ren, Ke
Subject: Dose scaling results

```
> point.est
[1] 1.172082
> bcaLowerCI
[1] 1.008603
> bcaUpperCI
[1] 1.314282
```

From: Ren, Ke
Sent: Friday, June 20, 2014 6:59 AM
To: Patel, Devvrat
Subject: Dose-sacle analysis (ANDA 203760)

Good Morning Dev:

Please see the attached R code for 5-way crossover dose scale analysis. I got code from Science Team. Could you confirm my calculation for ANDA 203760? The table below includes the results from my calculation and firm's calculation.

Method	F (Test/Reference)	90% CI
Reviewer's Calculation	1.171	1.02681 – 1.328477
Firm's Calculation	1.159	1.023- 1.33

Thanks,

Ke

From: Ren, Ke
Sent: Tue 5/20/2014 10:54 AM
To: Kundoor, Vipra
Cc: Tampal, Nilufer; Li, Bing; Nguyen, Hoainhon T
Subject: PD endpoint BE study for ANDA 203760 (Albuterol Sulfate Metered/Inhalation)

Good Morning Vipra:

Please see the background and study results of the PD BE(bronchoprovocation) study for ANDA 203760 (Albuterol Sulfate Metered/Inhalation) by using the dose-scaled approach.

Background: We issued a drug Specific BE recommendation for Albuterol Sulfate Metered/Inhalation at the following web site: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf We recommend five in vitro tests, one in vivo PK BE study and one in vivo PD BE study. For the in vivo BE study based on a PD endpoint, we recommend a bronchoprovocation study or bronchodilation study. For a bronchoprovocation study, the recommended PD endpoint is PC20, which is the provocation concentration or dose of the methacholine challenge agent required to reduce the forced expiratory volume in one second (FEV1) by 20% following administration of differing doses of albuterol (or placebo) by inhalation. The 20% reduction in FEV1 is determined relative to saline FEV1 measured before the placebo or albuterol administration. These values were used to construct the albuterol-PC20 dose-response curve (Emax model) from which the bioavailability of the test product was determined relative to that of the reference product. The 90% CI for the relative bioavailability (F) should be within 67.00- 150.00% to establish equivalence in the PD study.

To conduct a dose scaled analysis for bioequivalence assessment based on PC20 data, we generally follow the following two steps:

1) First step: determining the relative bioavailability (F) of the test product versus the reference product by simultaneously fitting the within-study dose-response data of both the test and reference products to the following model:

$$E = E_0 + \frac{E_{max} * Dose * F^i}{ED_{50} + Dose * F^i}$$

where i= treatment indicator (0= ref, 1= test) ; E= PC20; E0= baseline response (PC20) in the absence of drug; Emax= maximum drug effect response; Dose= albuterol dose (ie,

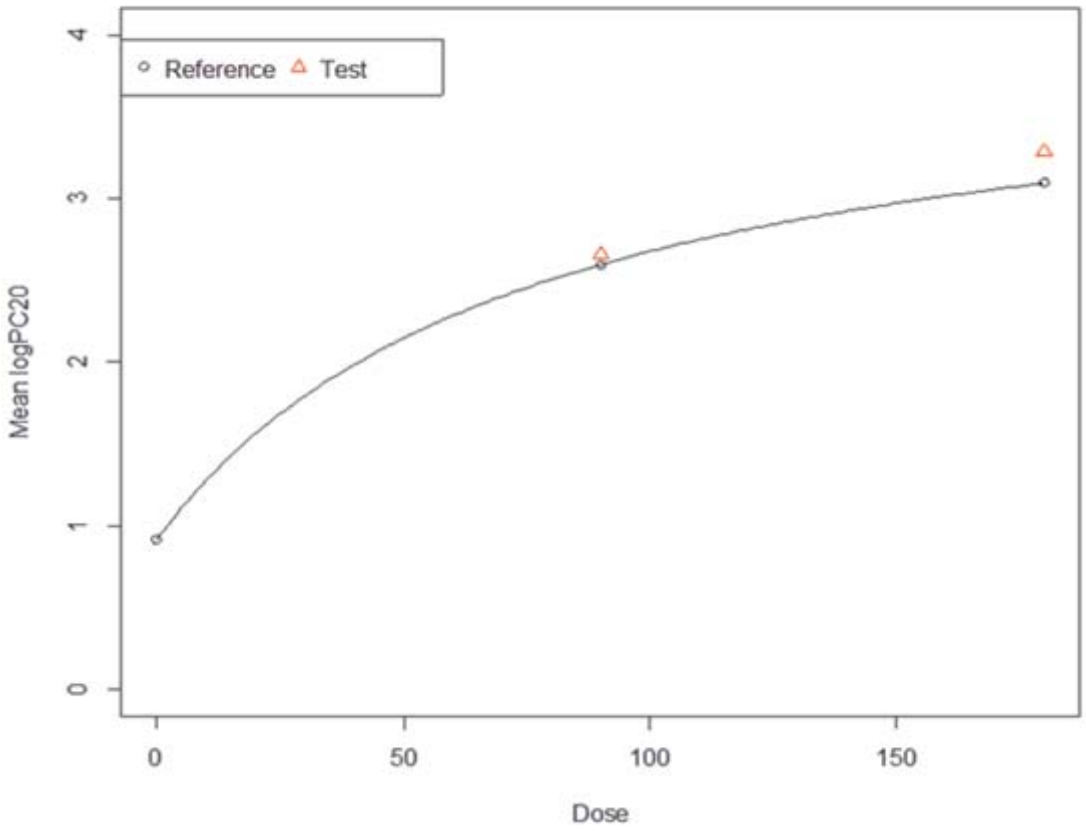
either 0.09 mg or 0.18 mg); F^i = relative bioavailability at the site of efficacy; ED50= estimated albuterol dose required to achieve 50% of fitted maximal value of the PD effect above baseline.

2) Second step: establishing the 90% CI for the relative bioavailability of the test to reference products by using a bootstrap procedure. Each bootstrap estimation included calculation of F by fitting the above model to a resampled dose-response data set, which was generated by random repetitive sampling with replacement of individual subject data. CI of F was constructed using Efron's bias corrected and accelerated (BCA) method.

Study design and results: In the ANDA 203760 submission, the firm conducted bronchoprovocation study (#PRG-723). The study was designed as multi-center (7 sites), randomized, five-way crossover PD study comparing the test product to Teva's ProAir® HFA Inhalation aerosol using a methacholine challenge in asthmatic subjects. The study enrolled 113 asthmatic subjects and 93 subjects were used in the statistical analysis. Each subject received two actuations per period. The dosing per period was based on the following: 1) Placebo: two actuations of placebo MDI; 2) 0.09 mg of reference product: one actuation each from a reference product MDI and placebo MDI; 3) 0.18 mg of reference product: two actuations of the reference product; 4) 0.09 mg of test product: one actuation each from a test product MDI and placebo MDI; and 5) 0.18 mg of test product: two actuations of the test product.

Based on the 5- way crossover R code provided by the science team, the 90% CI for F is 102.681- 132.8477%, which is within 67.00- 150.00% BE criteria. Therefore, the test and reference products are demonstrated to be bioequivalent in the PD BE study (see the following table and plot for details).

Method	N	F (Test/Reference)	90% CI
Using both Doses (0.09 mg and 0.18 mg) to calculate F	93	1.171	1.02681-1.328477



Please see the attached file for R output.

This is just my personal opinion, you should consult Hoai, Bing and your TL for the decision.

Thanks,

Ke

4.5 Office of Scientific Investigations Inspections of the Clinical and Analytical Site(s)

1) In vivo Fasting BE Study:

Clinical Site

	Summarization of the OSI Inspection of Clinical Site							
Clinical Site Address:		Novum Pharmaceutical Research Services Wilcrest Green Office Park 3320 Walnut Bend Lane Houston, TX 77042-4712						
Application	**Inspected BE Study Type (In Vivo, In Vitro)**	**Inspection Type (Routine or For Cause)**	**OSI Inspection date (EIR date)**	**Inspection Outcome (NAI, VAI, OAI)***	**Current ANDA clinical dates**	**Dates of clinical portion of inspected studies**	**Were the Current ANDA studies conducted within 2 years of the studies under/pending the OSI inspection?**	**Conclusion (Relevant, Irrelevant)**
NDA 022439	In Vivo	Routine	04/14/2011	NAI	3/17/09 – 3/24/09	7/10/10 – 8/29/10	Yes	Relevant
[redacted] (b) (4)								
ANDA 203638	In Vivo	Routine	Pending	Pending	3/17/09 – 3/24/09	7/27/11 – 7/30/11	No	Irrelevant

*NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated

Clinical Site: There is only one NDA #022439 listed in the OSI inspection history status with study dates within ± 2 years from the study dates of the current ANDA. The OSI inspection outcome was NAI (No Action Indicated). [redacted] (b) (4) (b) (4) (b) (4). However, the reviewer does not consider holding the current review for the additional pending OSI inspection and the inspection of NDA 022439 for the clinical site is sufficient.

Analytical Site

	Summarization of the OSI Inspection of Analytical Site
	(b) (4)

4.5.1.1 RELEVANT OSI INSPECTIONS WITH VAI OUTCOMES

NDA 022482[21]

OSI INSPECTION FINDING

Finding 1. Failure to demonstrate analyte stability under the actual conditions of sample handling and storage.

Specifically, for studies M10-535 and M10-662, subject samples were collected and stored up to 62 days at -70° C in (b) (4) tubes. Subject samples were then (b) (4) extraction and analysis. Although the firm demonstrated long term stability (335 days) and freeze/thaw stability (5 cycles) in (b) (4) tubes during pre-study validation, they did not demonstrate stability in glass tubes under these conditions.

2) In vitro Studies:

(b) (4)

There were no inspections for this analytical site. Therefore, the Bio-PM will request a new site OSI inspection for the analytical site.

3) Pharmacodynamics Studies:

Clinical Sites

Site 1
University of Florida
Asthma Research Lab

[21] DARRTS, NDA 022482, CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review), 02/03/2010, last accessed date: 06/05/2014.

1600 SW Archer Road
Gainesville, FL 32610-0486

Site 2
Roy J and Lucille A Carver College of Medicine
Department of Pediatrics, Allergy/Pulmonary
The University of Iowa
200 Hawkins Drive
Iowa City, Iowa 52242-1083

Site 3
Allergy & Asthma Diagnostic Treatment Center
2300 Centerville Road
Tallahassee, FL 32308

Site 4
California Allergy & Asthma Medical Group
11645 Wilshire Blvd, Suite 1155
Los Angeles, CA 90025

Site 5
Clinical Research Atlanta
175 Country Club Drive,
Suite 100A
Stockbridge, GA 30281

Site 6
Spartanburg Medical Research
485 Simuel Road
Spartanburg, SC 29303

Site 7
AARA Research Center
9900 N Central Expy, Suite 555
Dallas, TX 75231

There were no inspections for the above 7 clinical sites. However, the Bio-PM will request a new site OSI inspection only for the following 3 sites, as these 3 sites included more than half of the subjects enrolled in the pharmacodynamics study.

Site 1
University of Florida
Asthma Research Lab
1600 SW Archer Road
Gainesville, FL 32610-0486

Site 2
Roy J and Lucille A Carver College of Medicine
Department of Pediatrics, Allergy/Pulmonary
The University of Iowa
200 Hawkins Drive
Iowa City, Iowa 52242-1083

Site 4
California Allergy & Asthma Medical Group
11645 Wilshire Blvd, Suite 1155
Los Angeles, CA 90025

From: Wong, Jennie
Sent: Wed 6/25/2014 1:59 AM
To: Kundoor, Vipra

Subject: OSI inspection for clinical sited of PD study and analytical site for the in vitro study for ANDA 203760

Hey Vipra,

I wanted to say thank you for your help in providing the information for the OSI request form. As I have mention, I put in an OSI request form for all 3 clinical sites and the (b) (4) analytical site since there was no OSI inspection history available in the 2 databases (OSI search and Contacts).
I have already check-in the form in DARRTS. I have attached the fill out form for your reference.

Thanks!
Jennie

4.6 Detailed Regulatory History (Recommemded April 2013, Revised June 2013)[22]

Active ingredient:	Albuterol Sulfate
Form/Route:	Aerosol, Metered/Inhalation
Strength:	EQ 0.09 mg BASE/INH
Recommended studies:	In Vitro and In Vivo Studies

The following in vitro and in vivo studies are recommended to establish bioequivalence (BE) of the test (T) and reference (R) metered dose inhalers (MDIs) containing albuterol sulfate.

In Vitro Studies

The following in vitro studies are recommended to be conducted using at least three batches each of T and R products with no fewer than 10 units from each batch.

1. Type of study: Single actuation content (SAC)
   Design: The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages[1] of the product using a flow rate of 28.3 L/min. The USP <601> Apparatus A or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one.

   Equivalence based on: Population bioequivalence (PBE) analysis of SAC. Please refer to the draft Budesonide Inhalation Suspension BE Guidance for additional information regarding PBE.[2]

2. Type of study: Aerodynamic particle size distribution (APSD)
   Design: The APSD test should be performed at the B and E lifestages of the product using a flow rate of 28.3 L/min or 30 L/min. The USP <601> Apparatus 1, Apparatus 6, or another appropriate method may be used to determine APSD using a validated assay. The APSD determination of each unit should be performed with a minimum number of inhalations justified by the sensitivity of the validated assay.

[1] Based on the labeled number of actuations, the terms, B lifestage, M lifestage, and E lifestage represent the first actuation(s) following the labeled number of priming actuations, the actuation(s) corresponding to 50 percent of the labeled number of actuations, and the actuation(s) corresponding to the labeled number of actuations, respectively.

[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf

[22] Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, Effective Date: 06/2013

Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the induction port, each stage of the cascade Impactor (CI) and the filter, is requested. Mass balance accountability should be reported based on the sum of all deposition sites. For electronic submission of the individual CI data for the T and R products, please provide a table using the format in the appendix, and send them as part of the abbreviated new drug application (ANDA) submission for BE evaluation.

Equivalence based on: PBE analysis of impactor-sized mass (ISM).[3] The CI profiles representing drug deposition on the individual stages of the CI along with the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) should be submitted as supportive evidence for equivalent APSD.

3. Type of study: Spray pattern
   Design: The spray pattern test should be performed at the B lifestage of the product and at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the R actuator mouthpiece.[4] Impaction (thin-layer chromatography plate impaction), non-impaction (laser light sheet technology), or other suitable method may be used to determine the spray pattern.
   Additional comments: Spray pattern should be measured quantitatively in terms of ovality ratio and area within the perimeter of the true shape (to include a high proportion, e.g., 95 % of the total pattern) for the automated analysis or ovality ratio and D_{max} for the manual analysis. Ovality ratio is defined as the ratio of D_{max} to D_{min}. D_{max} and D_{min} are the longest and shortest diameters, respectively, that pass through the center of mass or the center of gravity, as appropriate. The number of sprays per spray pattern would preferably be one.

   Equivalence based on: At two selected distances, (i) qualitative comparison of spray shape, and (ii) PBE analysis of ovality ratio and area within the perimeter of the true shape or ovality ratio and D_{max}.

4. Type of study: Plume geometry
   Design: The plume geometry test should be performed at B lifestage of the product. The time sequence sound-triggered flash photography method, laser light sheet technology, or other suitable method may be used to determine the plume geometry at the appropriate post-actuation delay time.
   Additional comments: Plume geometry measurements should be reported at a single delay time while the fully developed plume is still in contact with the actuator tip. Plume geometry should be measured quantitatively in terms of plume angle and width. The plume angle is based on the conical region of the plume extending from a vertex that occurs at or near the actuator tip. The plume width is measured at a distance equal to the greater of the two distances selected for characterization of the spray pattern.

[3] ISM is defined as a sum of the drug mass on all stages of the CI plus the terminal filter, but excluding the top CI stage because of its lack of a specified upper cutoff size limit.
[4] The distance between the actuator orifice and point of spray pattern measurement should be same for T and R.

Equivalence based on: Ratio of the geometric mean of the three batches of T to that of the three batches of R (based on log transformed data) for both plume angle and width, which should fall within 90 – 111%.

5. Type of study: Priming and repriming
   Design: Priming and repriming tests should be based on the emitted dose (ex-actuator) of a single actuation immediately following the specified number of priming or repriming actuations specified in the R product labeling. The repriming test should be performed following storage for the specified period of non-use after initial use and/or other conditions (e.g., dropping), if the R product labeling provides such repriming information.
   Additional comments: For BE evaluation, the priming and repriming tests should be based on products stored in the valve upright position, with the exception of MDIs for which the R labeling recommends storage in the valve down position. The priming data can be based on the SAC data at the B lifestage.
   Equivalence based on: PBE analysis of the emitted dose of a single actuation immediately following the specified number of priming or repriming actuations specified in the R product labeling.

Pharmacokinetic (PK) BE Study

6. Type of Study: Fasting
   Design: Single-dose, two-way crossover
   Dose: 0.18 mg (two inhalations)
   Subjects: Normal healthy males and non-pregnant females, general population.
   Additional comments: The subjects enrolled for in vivo studies should be trained in the use of the inhalation aerosols in a standard fashion prior to each treatment session to assure a relatively consistent inspiratory flow rate and inspiratory duration.

   Analyte(s) to measure (in appropriate biological fluid): Albuterol in plasma

   Equivalence based on: AUC and C_{max} for albuterol. The 90% confidence intervals (CIs) for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00–125.00%.

Pharmacodynamic (PD) BE Study

A method using either bronchoprovocation (7a) or bronchodilatation (7b) study is recommended for this part of in vivo requirements.

7a. Type of Study: Bronchoprovocation study
   Design: Single-dose, double-blind, double dummy, randomized, crossover study that is recommended at minimum to consist of:

- Zero dose: One actuation each from two different placebo R inhalation aerosols and one actuation each from two different placebo T inhalation aerosols
- 0.09 mg of R: One actuation each from the R inhalation aerosol and the placebo R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols
- 0.18 mg of R: One actuation each from two different R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols
- 0.09 mg of T: One actuation each from the T inhalation aerosol and the placebo T inhalation aerosol and one actuation each from two different placebo R inhalation aerosols

No less than a 24 hour washout period should be allotted between treatments.

Subjects: Males and non-pregnant females with asthma

Additional comments:

- Inclusion criteria should, at minimum, include:
    a. Male and non-pregnant female subjects (18-65 years of age).
    b. Stable mild asthmatics based on National Asthma Education and Prevention Program (NAEPP) guidelines.
    c. $FEV_1 \geq 80\%$ of predicted.
    d. Airway responsiveness to methacholine demonstrated by a pre-albuterol-dose (baseline) $PC_{20} \leq 8$ mg/ml.
    e. Nonsmokers for at least six months prior to the study and a maximum smoking history of five pack-years (the equivalent of one pack per day for five years).
    f. Written informed consent.
- Exclusion criteria should, at minimum, include:
    a. Conditions which could alter airway reactivity to methacholine (e.g., pneumonia, upper respiratory tract infection, viral bronchitis and/or sinobronchitis) within past six weeks.
    b. History of seasonal asthma exacerbations, in which case the subject should be studied outside of the relevant allergen season.
    c. History of cystic fibrosis, bronchiectasis or other respiratory diseases.
    d. History of cardiovascular, renal, neurologic, liver or endocrine dysfunction, including ECG with evidence of ischemic heart disease.
    e. Treatment in an emergency room or hospitalization for acute asthmatic symptoms or need for daily oral corticosteroids within past three months.
    f. Known intolerance or hypersensitivity to any component of the albuterol MDI.
- The study day evaluation should take into consideration the following:
    a. Drug administration should begin within two weeks following screening for admission to the study.
    b. Baseline FEV_1 should not be less than 70% of predicted normal value and within 88-112% of qualifying day FEV_1 value. If either occurs, the study should be rescheduled.
    c. FEV_1 due to the saline control should fall no more than 10 % from the baseline FEV_1, or the study should be postponed. This limits the drop in

FEV_1 shown by some subjects due to the saline control vehicle in which the challenge agent is dissolved.

d. Baseline PC_{20} or PD_{20} on each study day should be within a two-fold dilution (i.e., within 50-200 %) of the value measured on the qualifying day.
e. A subject failing three consecutive visits should be dropped from the study.

- A Bio-IND is required prior to conduct of the PD study as the concentration of methacholine chloride solution may exceed the labeled 25.0 mg/ml concentration, particularly at the higher albuterol dose (e.g., 0.18 mg) where 25.0 mg/ml methacholine chloride may not lead to a 20% reduction in FEV_1.
- Firms are encouraged to consider the conduct of a pilot study to refine the study design (e.g., inclusion and exclusion criteria) and estimate the study power based on intra- and inter-subject variability and slope of the E_{max} dose-response curve. The method for blinding should be described.

PD endpoint(s): Post-dose PC_{20} or PD_{20}, which are the provocative concentration or dose, respectively, of the methacholine challenge agent required to reduce the forced expiratory volume in one second (FEV_1) by 20% following administration of differing doses of albuterol (or placebo) by inhalation. The 20 % reduction in FEV_1 is determined relative to the saline FEV_1 measured before the placebo or albuterol administration.

Equivalence based on: Dose-scale analysis of the PD data. For details regarding the dose-scale analysis, please refer to the draft Orlistat Capsule BE Guidance.[5] The 90% CI for the relative bioavailability (F) should fall within 67.00-150.00 % to establish equivalence in the PD study.

7b. Type of Study: Bronchodilatation study
Design: Single-dose, double-blind, double-dummy, randomized, crossover study that is recommended at minimum to consist of:

- Zero dose: One actuation each from two different placebo R inhalation aerosols and one actuation each from two different placebo T inhalation aerosols
- 0.09 mg of R: One actuation each from the R inhalation aerosol and the placebo R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols
- 0.18 mg of R: One actuation each from two different R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols
- 0.09 mg of T: One actuation each from the T inhalation aerosol and the placebo T inhalation aerosol and one actuation each from two different placebo R inhalation aerosols

No less than a 24 hour washout period should be allotted between treatments.
Subjects: Males and non-pregnant females with asthma
Additional comments:

- Inclusion criteria should, at minimum, include:

[5] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201268.pdf

a. Male and non-pregnant female subjects (18-65 years of age).
b. Moderate-to-severe asthmatics based on NAEPP guidelines.
c. FEV_1 within 40-70% of predicted.
d. Reversible airway obstruction as demonstrated by an improvement of 15 % or more in FEV_1 30 minutes after inhalation of two puffs (0.18 mg) of R inhalation aerosol.
e. Nonsmokers for at least six months prior to the study and a maximum smoking history of five pack-years).
f. Written informed consent.

- Exclusion criteria should, at minimum, include:
  a. History of cardiovascular, renal, neurologic, liver or endocrine dysfunction.
  b. Evidence of respiratory tract infection within six weeks prior to the study.
  c. Intolerance to aerosolized β_2-adrenergic agonists.
  d. Inability to tolerate temporary withdrawal of current asthma medication.
  e. Other co-morbid respiratory and sinus diseases.
  f. History of status asthmaticus, cystic fibrosis or bronchiectasis.
  g. History of frequent exacerbations in the previous year.
  h. Asthmatics who are taking oral corticosteroids.
  i. Known intolerance or hypersensitivity to any component of the albuterol MDI.
- The study day evaluation should take into consideration the following:
  a. Randomized treatment should begin within two weeks of the screening visit.
  b. Baseline FEV_1 should not be less than 45% of predicted or vary by more than ±12% from screening visit FEV_1 value. If either occurs, the study should be rescheduled. If the subject fails to meet these criteria on three separate study days (consecutive or not), they should be dropped from the study.
- Firms are encouraged to consider the conduct of a pilot study to refine the study design (e.g., inclusion and exclusion criteria) and estimate the study power based on intra- and inter-subject variability and slope of the E_{max} dose-response curve. The method for blinding should be described.
- FEV_1 should be measured at 0, 10, 15, 30, 60, 90, 120, 180, 240, 300 and 360 minutes (6 hours) post-dose. FEV_1 should be defined as the highest of the three values obtained at each pulmonary function evaluation period.
- For each treatment group, time to peak bronchodilator response (T_{max}) and FEV_1 values at all measurement times within each evaluation period should be included in the final study report.

PD endpoint(s): Areas under the effect curve calculated from the zero time to four hours ($AUEC_{0\text{-}4h}$) and from zero time to six hours ($AUEC_{0\text{-}6h}$) and maximum FEV_1 (FEV_{1max}). These endpoints should be baseline-adjusted using the pre-dose FEV_1.

Equivalence based on: Dose-scale analysis of the PD data. The 90% CIs for Fs should fall within 67.00-150.00% to establish equivalence in the PD study.

Additional information

Formulation and Device

The T product is recommended to be qualitatively (Q1)[6] and quantitatively (Q2)[7] the same as the R product, and be similar in shape and size to the R product. The T product should have a dose counter if the R product has a dose counter. In vitro and in-use studies should be conducted to support the functionality, accuracy and robustness of the proposed dose counter of the T product.

A sponsor is encouraged to submit a working model of the MDI to the Office of Generic Drugs prior to the ANDA submission, in order to ensure the eligibility of a T device under the 505(j) pathway.

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[6] Q_1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.
[7] Q_2 (quantitative sameness) means that concentration of the inactive ingredient(s) used in the T product are within ±5% of those used in the R product.

4.7 SAS Output

4.7.1 Fasting Study Data

FASTING CONCENTRATION DATASET

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
1	(b) (6)	2	1	1	B	0	11.0	28.10	47.80	61.3	85.2	114.0	196.0	326.0	369.0	378	413	404	621	458	263	126.0	89.6	47.5	16	19	2
2		2	2	1	A	0	59.3	111.00	147.00	184.0	194.0	208.0	236.0	243.0	291.0	297	343	401	406	291	175	88.0	68.3	35.4	16	19	1
3		1	1	1	A	0	34.2	81.30	136.00	210.0	274.0	324.0	434.0	551.0	633.0	598	748	614	334	254	170	78.8	48.4	23.0	16	19	1
4		1	2	1	B	0	11.4	49.60	112.00	193.0	269.0	333.0	400.0	435.0	420.0	358	386	708	543	341	201	90.5	52.4	27.5	16	19	2
5		1	1	1	A	0	96.3	242.00	346.00	448.0	528.0	565.0	665.0	661.0	636.0	573	522	426	547	427	256	113.0	54.5	27.6	16	19	1
6		1	2	1	B	0	380.0	588.00	645.00	679.0	1040.0	1100.0	1100.0	1020.0	1000.0	930	817	729	456	381	250	98.0	55.0	22.4	16	19	2
7		2	1	1	B	0	138.0	369.00	481.00	566.0	664.0	679.0	757.0	828.0	848.0	836	775	705	650	520	272	126.0	84.8	33.2	16	19	2
8		2	2	1	A	0	197.0	448.00	637.00	723.0	785.0	818.0	822.0	796.0	804.0	833	833	778	895	567	301	146.0	86.0	36.7	16	19	1
9		1	1	1	A	0	273.0	420.00	624.00	716.0	726.0	828.0	916.0	986.0	1020.0	941	988	822	591	468	401	142.0	72.8	25.3	16	19	1
10		1	2	1	B	0	249.0	385.00	458.00	556.0	625.0	699.0	827.0	773.0	711.0	840	798	713	508	427	371	133.0	75.2	26.2	16	19	2
11		2	1	1	B	0	180.0	237.00	276.00	324.0	362.0	393.0	424.0	445.0	437.0	427	355	327	483	403	199	78.9	47.4	20.2	16	19	2
12		2	2	1	A	0	221.0	316.00	398.00	456.0	498.0	490.0	445.0	446.0	373.0	394	441	449	391	294	168	73.5	46.2	23.4	16	19	1
13		1	1	1	A	0	110.0	251.00	291.00	300.0	349.0	342.0	397.0	386.0	379.0	384	454	431	525	461	260	116.0	61.5	27.1	16	19	1
14		1	2	1	B	0	96.9	178.00	247.00	290.0	355.0	347.0	408.0	419.0	379.0	383	406	380	390	330	195	79.7	51.7	23.7	16	19	2
15		2	1	1	B	0	33.8	80.20	116.00	172.0	218.0	277.0	343.0	406.0	419.0	439	428	449	318	222	155	85.1	62.8	36.2	16	19	2
16		2	2	1	A	0	62.8	129.00	190.00	260.0	299.0	372.0	421.0	475.0	479.0	530	497	479	447	311	187	90.0	60.2	27.7	16	19	1
17		2	1	1	B	0	42.1	490.00	566.00	653.0	687.0	744.0	679.0	632.0	585.0	592	566	507	529	440	279	124.0	84.2	42.2	16	19	2
18		2	2	1	A	0	205.0	500.00	557.00	826.0	844.0	899.0	923.0	942.0	894.0	879	795	669	581	427	282	136.0	89.2	40.2	16	19	1
19		1	1	1	A	0	48.7	174.00	267.00	382.0	447.0	544.0	505.0	583.0	602.0	547	498	388	353	330	206	104.0	68.5	40.4	16	19	1
20		1	2	1	B	0	173.0	390.00	615.00	759.0	725.0	784.0	748.0	843.0	812.0	664	616	517	413	341	230	120.0	76.8	46.7	16	19	2
21		1	1	1	A	0	198.0	382.00	446.00	534.0	567.0	622.0	665.0	638.0	794.0	693	663	505	410	275	167	57.6	30.6	12.8	16	19	1

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
22	(b) (6)	1	2	1	B	0	43.7	110.00	176.00	199.0	257.0	337.0	349.0	395.0	406.0	463	445	502	321	256	147	58.3	33.0	13.0	16	19	2
23		2	1	1	B	0	13.4	51.30	129.00	198.0	267.0	327.0	406.0	443.0	517.0	503	590	465	283	217	129	57.1	37.0	17.6	16	19	2
24		2	2	1	A	0	46.2	136.00	248.00	301.0	331.0	434.0	469.0	492.0	447.0	530	431	447	353	272	149	60.8	41.4	18.9	16	19	1
25		2	1	1	B	0	12.5	32.80	47.60	91.4	142.0	237.0	465.0	534.0	688.0	954	860	776	481	358	244	109.0	61.1	26.0	16	19	2
26		2	2	1	A	0	24.9	41.80	67.40	114.0	176.0	237.0	401.0	432.0	496.0	435	374	320	492	327	190	75.5	42.6	16.0	16	19	1
27		1	1	1	A	0	85.5	121.00	191.00	242.0	301.0	328.0	402.0	430.0	484.0	477	489	440	340	337	207	104.0	70.1	34.9	16	19	1
28		1	2	1	B	0	78.7	174.00	223.00	371.0	464.0	537.0	617.0	706.0	698.0	695	678	645	495	371	254	130.0	85.0	39.6	16	19	2
29		1	1	1	A	0	40.0	100.00	177.00	225.0	219.0	227.0	265.0	286.0	337.0	427	391	306	442	276	208	98.3	63.2	32.0	16	19	1
30		1	2	1	B	0	42.9	163.00	249.00	278.0	311.0	303.0	311.0	314.0	385.0	462	503	383	239	198	221	96.4	61.9	28.2	16	19	2
31		2	1	1	B	0	126.0	268.00	307.00	357.0	393.0	419.0	480.0	554.0	637.0	682	595	501	380	327	195	88.4	44.2	19.2	16	19	2
32		2	2	1	A	0	251.0	508.00	638.00	650.0	712.0	714.0	682.0	545.0	508.0	441	438	379	341	378	195	81.2	50.1	20.7	16	19	1
33		1	1	1	A	0	55.7	170.00	276.00	356.0	434.0	433.0	515.0	618.0	617.0	634	548	489	505	404	223	92.4	57.2	25.3	16	19	1
34		1	2	1	B	0	117.0	318.00	470.00	638.0	790.0	824.0	770.0	821.0	847.0	733	668	546	456	340	205	92.0	55.3	25.6	16	19	2
35		2	1	1	B	0	67.0	128.00	215.00	301.0	329.0	364.0	427.0	455.0	484.0	435	434	368	315	419	318	110.0	61.9	25.2	16	19	2
36		2	2	1	A	0	118.0	225.00	292.00	408.0	439.0	485.0	489.0	584.0	553.0	428	461	353	300	418	338	106.0	57.1	21.4	16	19	1
37		2	1	1	B	0	42.8	49.30	89.20	132.0	192.0	237.0	358.0	380.0	334.0	339	281	225	197	269	425	110.0	64.8	29.6	17	19	2
38		2	2	1	A	0	168.0	339.00	333.00	348.0	310.0	367.0	377.0	368.0	324.0	326	318	268	414	393	203	102.0	58.6	31.5	16	19	1
39		1	1	1	A	0	66.8	132.00	215.00	252.0	333.0	394.0	396.0	416.0	427.0	425	425	375	339	348	202	95.4	59.7	31.6	16	19	1
40		1	2	1	B	0	83.3	173.00	216.00	369.0	421.0	465.0	455.0	494.0	513.0	463	421	349	288	330	222	108.0	63.3	33.8	16	19	2
41		2	1	1	B	0	86.4	254.00	332.00	422.0	466.0	520.0	586.0	479.0	507.0	591	603	508	418	430	278	116.0	80.6	38.5	17	19	2
42		2	2	1	A	0	172.0	283.00	393.00	404.0	410.0	457.0	415.0	474.0	463.0	412	432	351	497	441	255	110.0	80.8	31.4	17	19	1
43		1	1	1	A	0	6.2	13.00	21.40	22.8	22.6	21.1	24.6	35.9	87.9	237	342	380	253	202	154	77.9	53.2	29.0	15	19	1
44		1	2	1	B	0	0.0	5.91	9.57	13.2	12.9	13.2	29.7	120.0	313.0	453	475	380	261	294	269	91.2	64.2	28.3	17	19	2
45		2	1	1	B	0	18.8	48.20	86.50	149.0	203.0	234.0	291.0	305.0	285.0	260	276	303	394	235	148	48.9	26.5	13.5	17	19	2
46		2	2	1	A	0	38.0	90.30	258.00	253.0	344.0	437.0	419.0	434.0	390.0	399	391	405	374	251	149	57.1	34.3	16.1	17	19	1
47		1	1	1	A	0	159.0	218.00	240.00	276.0	309.0	339.0	341.0	402.0	384.0	339	354	356	403	303	168	73.6	52.9	23.1	16	19	1

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE_FIRST	KE_LAST	trt
48	(b) (6)	1	2	1	B	0	23.6	35.00	52.80	85.8	105.0	147.0	246.0	306.0	312.0	354	392	397	369	289	172	81.0	50.5	24.7	16	19	2

4.7.2 Fasting Study Codes

```
/*=============================================================================
=====
/ Program   : TWOWAYCALCKE20AUG2009.SAS (Updated: 20 Aug 2009)
/ SubMacros : macrolib.sas, calcke.sas
/ Purpose   : To analyze two-way crossover bioequivalence studies.
/ Notes     :
/
/=============================================================================
====
/ PARAMETERS:
/-------name------- ------------------------description---------------------
----

/=============================================================================
====
/ AMENDMENT HISTORY:
/ Init --Date--  ----------------------Description-------------------------
/ CALCULATION OF KE BASED ON INDIVIDUAL KE_FIRST AND KE_LAST DATA VERIFIED BY
THE REIVEWER
      AND INCLUDED IN CONCENTRATION DATASET
/ CALCULATION BASED ON ACTUAL SAMPLING TIMES INCLUDED IN CONCENTRATION
DATASET
/=============================================================================
====*/
**** NODATE OPTION generates error in word document.. with bodytitle ods
****;

**********FOLLOW THE STEPS 1-15 TO RUN THIS PROGRAM**********;

OPTIONS PS=60;

****** STEP 1:  LOCATION OF MACRO FILE (MACROLIB.SAS). CHANGE LOCATION IF
APPLICABLE ********;
%INCLUDE "V:\DIVISION\BIO\SAS PROGRAMS\MACROS\MACROLIB.SAS";

/*******************************************************
  ASSIGN WHETHER HAVE GROUP EFFECT:
   TRTGROUP = 1      TRT*GROUP INTERACTION IN GLM MODEL
   TRTGROUP = 2      TRT*GROUP INTERACTION NOT IN GLM MODEL
   TRTGROUP =        NO GROUP EFFECT IN STUDY
 NOTE:  group variable has to be named GRP in the dataset.
*******************************************************/;

*****STEP 2:  ASSIGN FLAG FROM ABOVE FOR TREAT*GROUP INTERACTION*****;
%let trtgroup=;

*****STEP 3: ENTER ANDA INFORMATION *****;
%let level = Albuterol Sulfate;
%let drug=Albuterol Sulfate Metered Dose Inhaler;
%let dose= 2 x 90 mcg;
```

```
%let anda=203760;
%let studytype=FASTING;

***** STEP 4: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=M:\ANDAs\MDIs\203760\PK;

*****STEP 5: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = pg hr/mL;
%let cmaxunit = pg/mL;
%let timeunit = hr;


**** DO NOT CHANGE: NAME OF MS WORD STATISTICAL OUTPUT FILE ****;
%LET ODSFILE=&studydir\&anda._&studytype._stat_&level.ACTUAL.doc;

**** DO NOT CHANGE: NAME OF MS WORD REVIEW TABLES OUTPUT FILE ****;
%LET ODSFILE1=&studydir\&anda._&studytype._table_&level.ACTUAL.doc;

**** DO NOT CHANGE: NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC
FILE****;
%LET PLOTFILE=&studydir\&anda._&studytype._plot_&level.ACTUAL.png;

**** DO NOT CHANGE: NAME OF CONC AND PK DATASETS OUTPUT ****;
%LET CONCOUTPUT=&studydir\&anda._&studytype._Datasets_&level..doc;


%LET VARSORT=SUB PER;

%GLOBAL SUB PER SEQ TRT GRP TREAT C T AUCT CMAX TMAX AUCI KE DF NNAME
THALF CLAST KE_FIRST KE_LAST OLDNAME NEWNAME;


*****STEP 6: SELECT TYPE OF ANALYSIS FROM BOTTOM******;

/***NOTE:  THE CURRENT PROGRAM DOES NOT INCLUDE CONTINU OR CONTINU2
OPTIONS********
*******SELECT TWOWAYCALCKE07MAR2009.SAS IF YOU WANT TO CALCULATE KE AND OTHER
PARAMETERS ***/
/***SELECT TWOWAYCONTINU(2)07MAR2009.SAS IF YOU DO NOT WANT TO RECALCULATE
KE.
FOR TWOWAYCONTINU(2)07MAR2009.SAS, SPONSOR'S KE WILL BE USED FOR CALCULATION
OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED PARAMETERS (CONTINU).
OR WITH STATISTICS ON CALCULATED PARAMETERS (CONTINU2) ***/

%LET FNAME=%QUOTE(V:\DIVISION\BIO\SAS Programs\Macros\CALCKE.SAS);
/*** WRITE DATA FILE NAMES  ***/

***** STEP 7:  ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
/*** IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
FILENAME ORGPLASM DDE 'EXCEL|conc!R2C1:R49C26';
```

```
* FILENAME ORGPLASM "&studydir.\&plasmadata";
 *%LET FIRSTOBS=1; /* FIRST OBSERVATION */
 *%LET VARPLASM=SUB SEQ PER TRT c1-c22;  /* VARIABLE LIST FOR THE PLASMA DATA
FILE */
%LET PLASMLS=900;   /* INCREASE LINE SIZE IF NEEDED */
 *%READDATA(ORGPLASM,PLASMA,&FIRSTOBS,&VARPLASM,&PLASMLS)
 *RUN;


***** NOTE:  THE FIRST ROW OF THE EXCEL FILE SHOULD CONTAIN PROPER NAMES OF
THE VARIALBES ***;
***** STANDARD NAMES:  SUB SEQ PER GRP TRT C1 C2 C3... KE_FIRST KE_LAST
******;
***** EXCEL FILE DOES NOT NEED TO BE OPEN WHEN RUNNING THIS PROGRAM *****;
* %let excelfile = &studydir\fed.xls;


***** ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING CONCENTRATION
DATA *****;
* %let sheetname = conc;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
*** STANDARD NAMES:  SUB SEQ PER GRP TRT c1-c23  ****;
/*
proc import datafile="&excelfile"
            out=plasma
            dbms=excel replace;
                  sheet="&sheetname";
                  getnames=yes;
                  mixed=yes;
run;
*/


LIBNAME libdata "&studydir";

** STEP 8:  ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY FORMATTED..CHAR
OR NUMERIC **;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
DATA PLASMA;
  * SET PLASMA;

  infile ORGPLASM;
  input sub seq per GRP treat $ c1-c19 KE_FIRST KE_LAST;

  if treat = "A" then trt=1;
  else trt=2;

RUN;


data plasma;
```

```
  set plasma;

  array conc{*} c1-c19;

  do i=1 to 19;
    if conc{i} < 0 then conc{i} = 0;
  end;
run;

proc print data=plasma;




%SORTDS(PLASMA, &VARSORT)
RUN;



*****ACTIVATE THIS STEP AND STEP 9A BELOW ONLY IF USING CONTINU.SAS OR
CONTINU2.SAS*********
****PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
*****;

***** STEP 9:  ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING PK STUDY
DATA *****;
/***IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
FILENAME ORGPARAM DDE 'EXCEL|pk!R2C1:R49C11';
* FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1; /* FIST OBSERVATION */
*%LET VARPARAM=SUB SEQ PER TRT $ TMAX CMAX AUCT AUCI KE THALF; /* VARIABLE
LIST */
%LET PARAMLS=500;  /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPARAM,PARAME,&FIRSTOBS,&VARPARAM,&PARAMLS)
RUN;

/*
***** ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING PK STUDY DATA
*****;
*%let pksheetname = pk;

proc import datafile="&excelfile"
            out=parame
            dbms=excel replace;
                  sheet="&pksheetname";
                  getnames=yes;
                  mixed=yes;
run;
*/
```

```
** STEP 10:  ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY
FORMATTED..CHAR OR NUMERIC **;
DATA PARAME;
  * set parame;

   infile ORGPARAM ls=&paramls;
   input sub seq per GRP treat $ AUCT AUCI CMAX TMAX KE THALF;

 if treat = "A" then trt=1;
  else trt=2;
RUN;


%SORTDS(PARAME, &VARSORT)
RUN;


*****STEP 11: ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY *****;
%LET CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10,
             C11, C12, C13, C14, C15, C16, C17, C18, C19);


/***STEP 12: USE THIS STEP IF COMMON SAMPLING TIMES ARE USED,
                   ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE
TIME,
                   OR ADD FEW DEVIATED SAMPLING TIME POINTS,
                   ALSO MAKE SURE TO DEACTIVATE "SET TIME" AND ACTIVATE
"&TIME" UNDER STEP 15***/
DATA TIME
%LET TIME=%STR(T1=0.0; T2=0.083; T3=0.166; T4=0.25; T5=0.333;
T6=0.416; T7=0.5; T8=0.666; T9=0.833; T10=1.0; T11=1.25; T12=1.5;
T13=2.0; T14=3.0; T15=4.0; T16=6.0; T17=12.0; T18=16.0; T19=24.0);


/*USE THIS STEP INSTEAD OF STEP 11 IF ACTUAL SAMPLING TIME DATASET INCLUDED
                   IN THE CONCENTRATION DATASET,
                  ALSO, MAKE SURE TO ACTIVATE "SET TIME" AND DEACTIVATE
"&TIME" UNDER STEP 15***/;

*DATA TIME;
*SET PLASMA;
*FILE'DESKTOP\TIME';
*PUT SUB TRT SEQ PER GRP T1-T27;
*KEEP SUB TRT SEQ PER GRP T1-T27;

/*PROC PRINT DATA=TIME;RUN;*/


*****STEP 13: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS *****;
%LET NO_ASSAY=19;


*****INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE ARE NOT
```

```
IN THE DATA SUBMITTED. *****;
** DO NOT CHANGE SINCE KE_FIRST AND KE_LAST VALUES ARE IN CONC DATASET **;
* %LET KE_FIRST=20;
* %LET KE_LAST=27;


*****STEP 14: SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION *****;
/***VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL***/
/***LEAVE AS IT IS IF NO CHANGE IS DESIRED***/
/* %LET REMOVSUB=%STR(IF SUB^=10;IF SUB^=15;IF SUB^=34;IF SUB^=37;IF
SUB^=49); */
*%LET REMOVSUB=%STR(IF SUB^=1);


*****IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR MODIFIED *****;
/***CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC  ***/
/***  IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM
CLOSED ***/
/* %LET ADD_VAR=%STR(KE_FIRST=&KE_FIRST; KE_LAST=&KE_LAST
IF TREAT='A' THEN TRT=1; ELSE TRT=2 );*/



DATA ORIGIN;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
SET PLASMA;
*SET TIME;
* SET PARAME;
*SET MERGED;
&TIME;
*KE_FIRST=0;
*KE_LAST=0;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);


/***DO NOT CHANGE: TITLES FOR TABLES***/
%LET TITLE1=MEAN PLASMA &level LEVELS;
%LET TITLE2=MEAN PLASMA &level LEVELS FOR TEST AND REFERENCE PRODUCTS;

/*** DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH ***/
%LET TITLE3=PLASMA &level LEVELS;
%LET TITLE4= &drug, ANDA &anda;
%LET TITLE5=UNDER &STUDYTYPE CONDITIONS;
%LET TITLE6=DOSE= &dose;
%LET FOOTNOT1=1=TEST   2=REF;
%LET FOOTNOT2=Tmax values are presented as median, range.;
%LET FOOTNOT3=;
%LET FOOTNOT4=;
%LET FOOTNOT5=;
%LET LABEL1=PLASMA LEVEL, &cmaxunit;
%LET LABEL2=TIME, HRS;
```

```
%LET LABEL3=TEST;
%LET LABEL4=REFERENCE;


%COPYDS(ORIGIN, NEW)
RUN;


proc print data=origin;
run;



*****STEP 15: OPEN IF YOU WANT TO REMOVE, ADD OR EDIT*****;
*%REMUVSUB(NEW, NEW)
RUN;



***************DO NOT CHANGE ANY OF THE STATMENTS BELOW THIS LINE
****************;
***************YOU CAN NOW SUBMIT/RUN THE
PROGRAM*********************************;


%*ADDVARIA(NEW, NEW)
RUN;

%RITEDATA(NEW, NEW, SUB TRT KE_FIRST KE_LAST) /****** TO EDIT KE-FIRST AND
KE-LAST**/
RUN;

%COPYDS(NEW, NEWCONC)
RUN;

** CHECK >0 CONC FOR C1 **;
title "PRE-DOSE CONC GREATER THAN 0";

data predose;
  set origin(where=(c1 > 0));
  keep sub per seq trt c1 cmax maxlimit flag;

  maxlimit = 0.05*cmax;

  if c1 > maxlimit then flag = 1;
  else flag=0;
run;

proc print data=predose;
run;

*** dataset for data _null_***;
data updatedconc;
```

```
  set new;
run;*PROC PRINT;*RUN;


DATA NEWCONC;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
       NO_ASSAY=&NO_ASSAY;
SET NEWCONC;
/* TRANSVERSE THE C AND T DATA INTO COLUMNS WITH NEW VARIABLE
NAMES */
DO I=1 TO NO_ASSAY;
TIME=T(I);
CONC=C(I);
I=I;
OUTPUT;
END;


proc template;
  define style mystyle;
  parent = styles.rtf;
    REPLACE fonts /
       'headingFont' = ("Arial", 8pt,Bold)
       'docFont' = ("Arial", 8pt)
     'TitleFont2' = ("Arial",8pt,Bold)
       'TitleFont' = ("Arial",8pt,Bold)
       'StrongFont' = ("Arial",8pt,Bold)
       'EmphasisFont' = ("Arial",8pt)
       'FixedEmphasisFont' = ("Arial",8pt)
       'FixedStrongFont' = ("Arial",8pt,Bold)
       'FixedHeadingFont' = ("Arial",8pt,Bold)
       'BatchFixedFont' = ("Arial",8pt)
       'FixedFont' = ("Arial",8pt)
       'headingEmphasisFont' = ("Arial",8pt,Bold);

    style SysTitleAndFooterContainer from Container /

      cellpadding = 2
      cellspacing = 2
      borderwidth = 0;

      REPLACE Body from Document /
        bottommargin = 1.0in
        topmargin = 1.0in
        rightmargin = 0.25in
        leftmargin = 0.25in;
  END;
run;

proc template;
  define style mystyle1;
  parent = styles.rtf;
```

```
    REPLACE fonts /
       'headingFont' = ("Arial", 8pt,Bold)
       'docFont' = ("Arial", 8pt)
     'TitleFont2' = ("Arial",8pt,Bold)
       'TitleFont' = ("Arial",8pt,Bold)
       'StrongFont' = ("Arial",8pt,Bold)
       'EmphasisFont' = ("Arial",8pt)
       'FixedEmphasisFont' = ("Arial",8pt)
       'FixedStrongFont' = ("Arial",8pt,Bold)
       'FixedHeadingFont' = ("Arial",8pt,Bold)
       'BatchFixedFont' = ("Arial",8pt)
       'FixedFont' = ("Arial",8pt)
       'headingEmphasisFont' = ("Arial",8pt,Bold);

    style SysTitleAndFooterContainer from Container /

      cellpadding = 2
      cellspacing = 2
      borderwidth = 0;

      REPLACE Body from Document /
        bottommargin = 1.0in
        topmargin = 1.0in
        rightmargin = 1in
        leftmargin = 1in;
  END;
run;



options orientation=landscape papersize=letter;

ods rtf file="&concoutput" style=mystyle bodytitle;

TITLE "&STUDYTYPE CONCENTRATION DATASET";
proc print data=plasma;
run;

*TITLE "&STUDYTYPE PHARMACOKINETIC DATASET";
*proc print data=parame;
*run;
ods rtf close;



/* DETERMINE NEWTMAX, KE_FIRST, KE_LAST, NEWAUCT AND AUCLST */
DATA NEW;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
       NO_ASSAY=&NO_ASSAY;
SET NEW;
CLAST=C&NO_ASSAY;
```

```
NEWCMAX=MAX(&CONCENT);



/* CALCULATE THALF IF THALF IS NOT GIVEN */
/* THALF=LOG(2)/KE;  */
/* DETERMINE NEWTMAX */
DO I=1 TO NO_ASSAY;
IF C(I)=NEWCMAX THEN NEWTMAX=T(I);
END;
/* INTERPOLATE MISSING VALUE ON LINEAR SCALE */
IF C(1)=. THEN C(1)=0;  /* MISSING VALUE */
IF C(NO_ASSAY)=. THEN C(NO_ASSAY)=0;  /* MISSING VALUE */
DO I=2 TO (NO_ASSAY-1);
   H=I-1;
   J=I+1;
IF C(I)=. THEN DO;    /* FIRST MISSING VALUE */
IF C(J)=. THEN J=J+1; /* SECOND CONSECUTIVE MISSING VALUE */
IF C(J)=. THEN J=J+1; /* THIRD CONSECUTIVE MISSING VALUE */
C(I)=C(H)+((C(J)-C(H))/(T(J)-T(H)))*(T(I)-T(H));
    END;
    END;
NEWTMAX=NEWTMAX;
/* CALCULATE AUCLST(TO THE LAST SAMPLING TIME POINT) */
AUCLST=0;
DO I=2 TO NO_ASSAY;
K=I-1;
AUCLST=AUCLST+((C(K)+C(I))*(T(I)-T(K))/2);
END;

/* CALCULATE AUCT AND STORE AS NEWAUCT(TO THE LAST DETECTABLE
CONC) */
DO I=NO ASSAY TO 2 BY -1;
IF C(NO_ASSAY)>0 THEN DO;
       NEWAUCT=AUCLST;
       CLAST=C(NO_ASSAY);
       GOTO F;
       END;
   ELSE DO;
        K=I-1;
        IF C(I)=0 AND C(K)>0 THEN DO;
           NEWAUCT=AUCLST-(C(I)+C(K))*(T(I)-T(K))/2;
           CLAST=C(K);
           GOTO F;
           END;
    END;
END;

F: NEWAUCT=NEWAUCT; /* FLAG TO CONTINUE */
NEWAUCI=NEWAUCT+CLAST/KE;
/* TRANSVERSE THE C AND T DATA INTO COLUMNS WITH NEW VARIABLE
NAMES */
DO I=1 TO NO_ASSAY;
```

```
TIME=T(I);
CONC=C(I);

ELSE LOGCONC=LOG(CONC);
NEWAUCT=NEWAUCT;
I=I;
OUTPUT;
END;
/* PROC PRINT;
RUN; */




*******************************************************************************
*****************************;
/*STEP 17: ONLY IF USING CALCKE.SAS: TO CALCULATE THALF AND KEL FOR THE
REVIEWER-CALCULATED PK PARAMETER TABLE*/;

PROC SORT DATA=NEW;
BY SUB TRT PER GRP;

RUN; *PROC PRINT;*RUN;
DATA NEW1;
SET NEW;
IF TIME <=KE_FIRST;
*RUN;*PROC PRINT;RUN;

PROC REG DATA=NEW1 NOPRINT OUTEST=KEOUT;
BY SUB TRT PER GRP;

MODEL LOGCONC=TIME;
RUN;
*PROC PRINT ;
*RUN;


/* NEW KE IS STORED IN NEW4KE */
DATA KEOUT;
SET KEOUT;
KEEP SUB TRT PER GRP TIME;
TIME=ABS(TIME);
KEEP TIME;
RENAME TIME=KEL;

*PROC PRINT DATA=KEOUT;
RUN;
/* CALCULATE THALF FROM REVIEWER'S KEL*/
DATA KEOUT;
SET KEOUT;
THALFR=LOG(2)/KEL;
```

```
*PROC PRINT;RUN;


/* DROP KE AND THALF FROM FIRM'S PK DATASET */
DATA NEW1;
SET NEW;
DROP THALF KE;
PROC SORT DATA=NEW1;
BY SUB TRT PER GRP;

RUN; PROC PRINT;RUN;
/*CREATE NEW PK DATASET WITH REVIEWER'S THALF AND KE*/;

DATA NEW1;
MERGE NEW1 KEOUT;
BY SUB TRT PER GRP;

RUN;PROC PRINT DATA=NEW1;RUN;


DATA NEW1;
ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
       NO_ASSAY=&NO_ASSAY;
SET NEW1;

%LET NO_ASSAY=&NO_ASSAY;
CLAST=C&NO_ASSAY;
/*CLAST AS NON-ZERO*/;

DO J=NO_ASSAY TO 2 BY -1;
IF C(NO_ASSAY)>0 THEN DO;
      CLAST=C(NO_ASSAY);
      NEWAUCI=NEWAUCT+CLAST/KEL;
      END;
   ELSE DO;
        K=J-1;
        IF C(J)=0 AND C(K)>0 THEN DO;
           CLAST=C(K);
               NEWAUCI=NEWAUCT+CLAST/KEL;
           END;
    END;
END;

KEEP I KE_FIRST SUB TRT SEQ PER GRP NEWAUCT NEWAUCI NEWCMAX NEWTMAX THALFR
KEL TIME;

*PROC PRINT DATA=NEW1;

RUN;

*******************************************************************************
*****************************;
```

```
*DATA NEW2;
*SET NEW1;
*PROC SORT;
*BY SUB TRT PER;
*RUN; *PROC PRINT;*RUN;

*DATA CONC;
*SET NEW2;

*BY SUB TRT PER;
/*KEEP SUB SEQ PER TRT C1-C23;OUTPUT;  */

*RUN;*PROC PRINT DATA=CONC;*RUN;

******* DATA SET PK CONTAINS PARAMETERS CALCULATED BY REVIEWER****;
*******  THE USER MAY ENTER AT LINE  8 RAW DATA WITH PK OUTLIERS INCLUDED
          OR EXCLUDED AND COMPARE THOSE AGAINST THE FIRM'S VALUES
ETC********;

DATA PK1;
SET NEW1;
IF I=1;
*IF TIME=0;
* FILE'&studydir\PK';
PUT SUB TRT SEQ PER GRP NEWAUCT NEWAUCI NEWCMAX NEWTMAX THALFR KEL;
KEEP SUB TRT SEQ PER GRP NEWAUCT NEWAUCI NEWCMAX NEWTMAX THALFR KEL;
rename      newauct=auct
            newauci=auci
            NEWCMAX=CMAX
            NEWTMAX=TMAX;
run;

data pkprint;
  set pk1;
run;

title "FDAPK";
PROC PRINT DATA=PK1;RUN;
title;


DATA FDAPK;
SET PK1;
FDAAREA=AUCT;
FDAAUCI=AUCI;
FDACMAX=CMAX;
DROP AUCT AUCI CMAX TMAX KEL THALFR;
PROC PRINT;RUN;

PROC SORT DATA=FDAPK;
BY SUB PER TRT GRP;RUN;*PROC PRINT;*RUN;
```

```
/*
data fdapk;
  set fdapk;
  by sub per trt grp;

  if last.trt then output;
run;

title "DEV";
proc print data=fdapk;
run;
*/

*****READ FIRM'S PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND
VARIABLE LIST *****;

/***IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
*FILENAME ORGPARAM DDE 'EXCEL|pk!R2C1:R121C11';
* FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1; /* FIST OBSERVATION */
*%LET VARPARAM=SUB SEQ PER TRT $ TMAX CMAX AUCT AUCI KE THALF; /* VARIABLE
LIST */
*%LET PARAMLS=256;  /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPARAM,PARAME,&FIRSTOBS,&VARPARAM,&PARAMLS)
RUN;

/*
DATA PARAME;

** IF USING EXCEL FILE ACTIVATE THESE STATEMENTS **;
  infile ORGPARAM;
  input sub seq per GRP TREAT $ TMAX CMAX AUCT AUCI KE THALF;
    if TREAT = "A" then trt=1;
      else trt=2;
      drop TREAT;
** IF SAS DATASET, ACTIVATE THESE STATEMENTS **;


RUN;*PROC PRINT;*RUN;


%SORTDS(PARAME, &VARSORT)
RUN;
*/

DATA FIRMPK;
SET PARAME;
FIRMAREA=AUCT;
FIRMAUCI=AUCI;
FIRMCMAX=CMAX;
DROP AUCT AUCI CMAX;
```

```
DROP TMAX KE THALF;
RUN; *PROC PRINT;*RUN;


PROC SORT DATA=FIRMPK;
BY SUB PER TRT;

title "firmpk";

title;


DATA FIRMREVIEWERRATIO;
SET FDAPK FIRMPK;
MERGE FDAPK FIRMPK;
BY SUB PER TRT GRP;

RAUCT=FIRMAREA/FDAarea;
RAUCI=FIRMAUCI/FDAAUCI;
RCMAX=FIRMCMAX/FDACMAX;
*DROP TMAX KEL KE THALF;


proc print;RUN;

*options orientation=landscape papersize=letter;

*ods rtf file="&concoutput" style=mystyle bodytitle;

*TITLE "&ANDA &STUDYTYPE REVIEWER VERIFIED CONCENTRATION DATASET";
*proc print data=plasma;
*run;


options orientation=landscape papersize=letter;

ods rtf file="&studydir\REVIEWERPK&studytype..RTF" /*style=mystyle
bodytitle*/;
TITLE "&ANDA &STUDYTYPE REVIEWER-CALCULATED PHARMACOKINETIC DATASET";
proc print data=PK1;
VAR SUB TRT SEQ PER GRP AUCT AUCI CMAX TMAX THALFR KEL;
run;

options orientation=landscape papersize=letter;

ods rtf file="&studydir\FIRMREVIEWERRATIO&studytype..RTF" /*style=mystyle
bodytitle*/;
TITLE "&ANDA &STUDYTYPE FIRM TO REVIEWER RATIO";
proc print data=FIRMREVIEWERRATIO;
*VAR RAUCT RAUCI RCMAX;
run;
ods rtf close;
/*****************************************************************/
```

```
/***END OF STEP 17********************/



data _null_;
  set updatedconc(where=(trt=1)) end=last;

  if last then call symput('testsub',trim(left(_N_)));
run;


data _null_;
  set updatedconc(where=(trt=2)) end=last;

  if last then call symput('refsub',trim(left(_N_)));
run;

/* PROC GLM  CALCULATE LSMEANS */
%MACRO GRPANALYSIS(TRTGP=);

      /** TRTGRP INTERACTION **/
      %if &trtgp=1 %then
      %do;
      %PROCGLM(BASE,2,SUB TRT PER SEQ GRP,AUCT,AUCI,CMAX,LAUCT,LAUCI,LCMAX,
      , , , , , ,per GRP SEQ SEQ*GRP SUB(SEQ*GRP) PER(GRP) TRT TRT*GRP,SEQ
GRP,SUB(SEQ*GRP))
      RUN;
      %end;

      /** No TRT*GRP Interaction **/
      %else %if &trtgp=2 %then
      %do;
      %PROCGLM(BASE,2,SUB TRT PER SEQ GRP,AUCT,AUCI,CMAX,LAUCT,LAUCI,LCMAX,
      , , , , , ,per GRP SEQ SEQ*GRP SUB(SEQ*GRP) PER(GRP) TRT,SEQ
GRP,SUB(SEQ*GRP))
      RUN;
      %end;

      /** NO GROUP EFFECT **/
      %else %do;
      %PROCGLM(BASE,2,SUB TRT PER SEQ,AUCT,AUCI,CMAX,LAUCT,LAUCI,LCMAX,
      , , , , , ,SEQ SUB(SEQ) PER TRT,SEQ,SUB(SEQ))
      RUN;
      %end;

%MEND GRPANALYSIS;

/* STATISTICS ON SUBMITTED DATA WITHOUT RECALCULATION */
DATA BASE;
SET NEW;
IF I=NO_ASSAY;

LAUCT=LOG(AUCT);
```

```
LAUCI=LOG(AUCI);
LCMAX=LOG(CMAX);
AUCRATIO=AUCT/AUCI;
OUTPUT;


/* TO RECALCULATE KE  */
%INCLUDE "&FNAME";

/* PRINT SUMMARY OF PARAMETERS */
%LET TITLE=SUMMARY OF PARAMETERS;
%*PRINT(BASE, &TITLE)
RUN;


options orientation=portrait papersize=letter;

TITLE "&STUDYTYPE STATISTICAL OUTPUT";
ods rtf file="&odsfile" style=mystyle1 bodytitle;


ods rtf exclude LSMeans;
ods rtf exclude AUCT.OverallANOVA
                AUCT.FitStatistics
                        AUCT.ModelANOVA
                        AUCT.AltErrTests
                        AUCT.Estimates
                        AUCI.OverallANOVA
                AUCI.FitStatistics
                        AUCI.ModelANOVA
                        AUCI.AltErrTests
                        AUCI.Estimates
                        CMAX.OverallANOVA
                CMAX.FitStatistics
                        CMAX.ModelANOVA
                        CMAX.AltErrTests
                        CMAX.Estimates;

ods listing exclude LSMeans;

ods output "Estimates"=estimates;
ods output "Fit Statistics"=fitstat;

%GRPANALYSIS(TRTGP=&TRTGROUP);


DATA GLMOUT;
SET GLMOUT;
RENAME _NAME_=NNAME;
DATA LSMOUT;
SET LSMOUT;
RENAME _NAME_=NNAME;
/* TRANSFER DF FROM GLMOUT TO LSMOUT3 FOR CI CALCULATIONS */
```

```
DATA GLMOUT1;
SET GLMOUT;
IF _SOURCE_='ERROR';
IF NNAME='AUCT' OR
 NNAME='AUCI' OR
 NNAME='CMAX';
/* KEEP NNAME _SOURCE_ DF; */
%SORTDS(GLMOUT1, NNAME)
RUN;
%*PRINT(GLMOUT1,GLMOUT1)
RUN;
%*LET TITLE=LSMEANS AND STANDARD ERRORS;
%*PRINT(LSMOUT, &TITLE)
RUN;

/* CALCULATE T AND 90% CI FOR NON-TRANSFORMED DATA */
%LSMFILE(LSMOUT,TRT,2,AUCT,AUCI,CMAX,X,X,X,NNAME, OR)
RUN;

%MERGMULT(2,LSMOUT,GLMOUT1, , ,LSMDAT,NNAME)
RUN;
DATA LSMDAT;
SET LSMDAT;
/* FOR 90% CI, P=0.95 */

/* CACULATION OF T BASED ON P AND DF */
%CI(0.95,2);
%*PRINT(LSMDAT,LSMDAT)
RUN;

%LET TITLE=90% CONFIDENCE INTERVALS ON NON-TRANSFORMED DATA;
%*PRINT(LSMDAT, &TITLE)
RUN;

/* TRANSFER DF FROM GLMOUT TO LSMOUT33 FOR CI CALCULATIONS */

DATA GLMOUT11;
SET GLMOUT;
IF _SOURCE_='ERROR';
IF NNAME='LAUCT' OR
 NNAME='LAUCI' OR
 NNAME='LCMAX';
/* KEEP NNAME  SOURCE  DF; */
%SORTDS(GLMOUT11, NNAME)
RUN;

/* CALCULATE T AND 90% CI FOR LOG-TRANSFORMED DATA */
%LSMFILE(LSMOUT,TRT,2,LAUCT,LAUCI,LCMAX, , , ,NNAME,OR)
RUN;

%MERGMULT(2,LSMOUT,GLMOUT11, , ,LLSMDAT,NNAME)
RUN;
```

```
*******************************************;
data estimates;
  set estimates;

  NNAME = dependent;

  keep NNAME estimate stderr;
run;

proc sort data=estimates;
  by nname;
run;

proc sort data=llsmdat;
  by nname;


data llsmdat;
  merge llsmdat(in=a)
        estimates(in=b);
  by nname;
  if a;
run;

*********************************************;



DATA LLSMDAT;
SET LLSMDAT;
/* FOR 90% CI, P=0.95 */
%CILOG(0.95,2);

%LET TITLE=90% CONFIDENCE INTERVALS ON LOG-TRANSFORMED DATA;
%*PRINT(LLSMDAT, &TITLE)
RUN;


/* STATISTICS ON TRT1/TRT2 RATIO */
%SPLITBY(BASE,TRT,2,SUB,AUCT,AUCI,CMAX,TMAX,KE,THALF)
RUN;

%MERGMULT(2,BASE, , , ,RATIODAT,SUB)
RUN;

%RATIOCAL(RATIODAT,2,AUCT,AUCI,CMAX,TMAX,KE,THALF)
RUN;

DATA TCDAT;
SET NEWCONC;
KEEP TRT TIME CONC;
%LET BY=TRT TIME;
```

```
%SORTDS(TCDAT, &BY)
RUN;

/* CALCULATE MEAN BLOOD LEVEL AT EACH TIME POINT */
TITLE "&TITLE2";
%MEANCAL(TCDAT, CONC, TRT TIME, CMEANOUT)
RUN;
%*PRINT(CMEANOUT, CMEANOUT)
RUN;

DATA CMEANOUT;
SET CMEANOUT;
DROP _TYPE_ _FREQ_ ;

%TRANSPOS(CMEANOUT, CMEAN, CONC, TRT TIME)
RUN;
%*PRINT(CMEAN, CMEAN)
RUN;

DATA CMEAN;
SET CMEAN;
RENAME COL4=MEAN
 COL5=SD;
DROP _NAME_ COL1 COL2 COL3;
%*PRINT(CMEAN, &TITLE1)
RUN;


%SPLITBY(CMEAN,TRT,2,TIME,MEAN,SD,X,X,X,X)
RUN;

%MERGMULT(2,CMEAN, , , ,CMEANRAT,TIME)
RUN;
%*PRINT(CMEANRAT,CMEANRAT)
RUN;

%RATIOCAL(CMEANRAT,2,MEAN,X,X,X,X,X)
RUN;
DATA CMEANRAT;
SET CMEANRAT;
DROP TRT;
%*PRINT(CMEANRAT, &TITLE2)
RUN;

%SORTDS(CMEANRAT, TIME)
RUN;

%LET BY=TRT;
%SORTDS(BASE, &BY)
RUN;
```

```
%MACRO MEANCAL(DSN, VARN, BY, MEANOUT);
        PROC MEANS DATA=&DSN NOPRINT;
        VAR &VARN;
        BY &BY;
        OUTPUT OUT=&MEANOUT;
%MEND MEANCAL;


%MACRO univCAL(DSN, VARN, BY, MEANOUT);
        PROC univariate DATA=&DSN NOPRINT;
        VAR &VARN;
        BY &BY;
        OUTPUT OUT=&MEANOUT median=median;
%MEND univCAL;


/* CALCULATE MEAN PHARMACOKINETIC PARAMETERS */
%MEANCAL(BASE,AUCT AUCI CMAX TMAX KE THALF LAUCT LAUCI
LCMAX,TRT,PARMETER)
RUN;


***** TMAX - MEDIAN DP ********;
%univCAL(BASE,TMAX,TRT,PARMETERtmax)
RUN;


data parmeter;
  merge parmeter
        parmetertmax;
  by trt;



data parmeter(drop=median);
  set parmeter;

  if _STAT_ = "MEAN" then tmax = median;
  if _STAT_ = "STD" then tmax = .;  ** for median tmax, no SD or CV **;
run;


%LET TITLE=SUMMARY OF PHARMACOKINETIC PARAMETERS;
%*PRINT(PARMETER, &TITLE)
RUN;

DATA PARM;
SET PARMETER;
DROP _TYPE_ _FREQ_ ;

PROC TRANSPOSE DATA=PARM OUT=TRSPARM;
VAR AUCT AUCI CMAX TMAX KE THALF LAUCT LAUCI LCMAX;
BY TRT;
```

```
RUN;
DATA TRSPARM;
SET TRSPARM;
RENAME _NAME_=NNAME;

%LET BY=NNAME TRT;
%SORTDS(TRSPARM, &BY)
RUN;


***DEV MARCH 23 07**:  COMMENT THIS OUT**;
/*
DATA TRSPARM;
SET TRSPARM;
DROP COL1 COL2 COL3;
RENAME COL4=MEAN
       COL5=SD;
RUN;
*/
*** COL1=N COL2=MIN COL3=MAX COL4=MEAN COL5=STD**;
DATA TRSPARM;
SET TRSPARM;
DROP COL1;
RENAME COL2=MIN COL3=MAX COL4=MEAN
       COL5=SD;
RUN;


%SPLITBY(TRSPARM,TRT,4,NNAME,MEAN,MIN,MAX,SD,X,X)
RUN;


%MERGMULT(2,TRSPARM, , , ,PARMRAT,NNAME)
RUN;


DATA PARMRATS;
SET PARMRAT;
IF %SETLST(NNAME,OR,AUCT,AUCI,CMAX,TMAX,KE,THALF);
%RATIOCAL(PARMRATS,2,MEAN,X,X,X,X,X)
RUN;
DATA PARMRATL;
SET PARMRAT;
IF %SETLST(NNAME,OR,LAUCT,LAUCI,LCMAX,X,X,X);

RUN;
%ANTILOG(PARMRATL,2,MEAN,X,X,X,X,X)
RUN;
DATA PKRATIO;
SET PARMRATS PARMRATL;
DROP TRT;

%LET TITLE=TEST MEAN/REFERENCE MEAN RATIO;
```

```
%*PRINT(PKRATIO, &TITLE)
RUN;

%ANTILOG(LLSMDAT,2,LSMEAN,X,X,X,X,X)
RUN;

DATA CIDAT;
SET LSMDAT LLSMDAT;
KEEP NNAME %LSMENLST(2,LSMEAN)  STDERR %CILST(2);

DATA CIDAT;
SET CIDAT;
%RE_NAME(2,LSMEAN,LSM)
RUN;

%SORTDS(CIDAT, NNAME)
RUN;
%*PRINT(CIDAT, CIDAT)
RUN;


%RATIOCAL(CIDAT,2,LSM,X,X,X,X,X)
RUN;


** DEV **;
** CALCULATE %CV **;
data cmeanrat;
  set cmeanrat;

  CV1 = round((sd1/mean1)*100,.01);
  CV2 = round((sd2/mean2)*100,.01);
run;

data pkratio;
  set pkratio;

  CV1 = round((sd1/mean1)*100,.01);
  CV2 = round((sd2/mean2)*100,.01);
run;



**DEV TEMPORARILY CLOSED ** MARCH 23 07***;
ods listing close;



** sort order of PK parameters **;
data pkratio;
  set pkratio;
```

```
  select(nname);
    when('AUCT') ordervar=1;
      when('AUCI') ordervar=2;
      when('CMAX') ordervar=3;
      when('TMAX') ordervar=4;
      when('KE') ordervar=5;
      when('THALF') ordervar=6;
      when('LAUCT') ordervar=7;
      when('LAUCI') ordervar=8;
      when('LCMAX') ordervar=9;
      otherwise;
  end;
run;

DATA PKRATIO;
  SET PKRATIO;

  IF NNAME IN("LAUCT","LAUCI","LCMAX") THEN DELETE;
RUN;


proc sort
  data=pkratio;
  by ordervar;
run;


data cidat;
  set cidat;

  select(nname);
    when('AUCT') ordervar=1;
      when('AUCI') ordervar=2;
      when('CMAX') ordervar=3;
      when('LAUCT') ordervar=4;
      when('LAUCI') ordervar=5;
      when('LCMAX') ordervar=6;
      otherwise;
  end;
run;

proc sort
  data=cidat;
  by ordervar;


DATA cidat;
  SET cidat;

  IF NNAME IN("AUCT","AUCI","CMAX") THEN DELETE;
RUN;
```

```
data pkratio;
  set pkratio;

  if nname="AUCT" then units="&aucunit";
  if nname="AUCI" then units="&aucunit";
  if nname="CMAX" then units="&cmaxunit";
  if nname="TMAX" then units="&timeunit";
  if nname="KE" then units="&timeunit.-1";
  if nname="THALF" then units="&timeunit";
run;



data rootmse;
  set fitstat(keep=dependent rootmse);

  if dependent = "LAUCT" then ordervar=1;
  else if dependent="LAUCI" then ordervar=2;
  else if dependent="LCMAX" then ordervar=3;

  if dependent in("LAUCT","LAUCI","LCMAX") then output;
run;

proc sort
  data=rootmse;
  by ordervar;
run;



DATA AUCDAT;
SET BASE;
KEEP SUB TRT AUCRATIO;
PROC SORT DATA=AUCDAT;
BY TRT SUB;
RUN;


/* PROC MEANS ON AUCT/AUCI RATIOS */
PROC MEANS DATA=AUCDAT noprint MAXDEC=2 FW=9;
VAR AUCRATIO;
BY TRT;
OUTPUT OUT=AUCRATIO;
TITLE 'STATISTICS ON AUCT/AUCI RATIOS';
RUN;


PROC TRANSPOSE DATA=aucratio OUT=aucratio1;
VAR aucratio;
BY TRT;
RUN;
```

```
data aucratio1;
  length treat $12.;
  set aucratio1;

  rename col1=no col2=mini col3=maxi col4=avg col5=std;
  if trt=1 then treat="TEST";
  else if trt=2 then treat="REFERENCE";
run;



%LET TITLE=AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS;
%PRINT(AUCDAT, &TITLE)
RUN;


PROC PRINT DATA=RATIODAT ROUND noobs;
VAR SUB SEQ %RATLST(2,AUCT,AUCI,CMAX,TMAX,KE,THALF);

TITLE 'TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS';
RUN;


ods listing;

/* PROC MEANS ON TEST/REFERENCE RATIOS */
PROC MEANS DATA=RATIODAT MAXDEC=3 FW=9 noprint;
VAR %RATLST(2,AUCT,AUCI,CMAX,TMAX,KE,THALF);
OUTPUT OUT=MEANOUT;
TITLE 'STATISTICS ON THE TEST/REFERENCE RATIOS';
RUN;


DATA CHECKDAT;
SET BASE;

AUCTO_N=OLDAUCT/NEWAUCT;
AUCIO_N=OLDAUCI/NEWAUCI;
CMAXO_N=OLDCMAX/NEWCMAX;
TMAXO_N=OLDTMAX/NEWTMAX;

OUTPUT;
KEEP SUB TRT PER SEQ AUCTO_N AUCIO_N CMAXO_N TMAXO_N;
LABEL AUCTO_N='AUCT';
LABEL AUCIO_N='AUCI';
LABEL CMAXO_N='CMAX';
LABEL TMAXO_N='TMAX';

*%LET TITLE=RATIO OF SPONSOR/REVIEWER CALCULATED PARAMETERS;
*%PRINT(CHECKDAT, &TITLE)
*RUN;
```

```
%LET TITLE=AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS;
%*PRINT(AUCRATIO, &TITLE)
RUN;

/* GOPTIONS DEVICE=EGAL; */     /* GOPTION #1 */
/* GOPTIONS DEVICE=FX85; */     /* GOPTION #2 */
/* GOPTIONS DEVICE=HPLJS2; */   /* GOPTION #3 */
/* GOPTIONS GACCESS='SASGASTD>LPT2:'; */  /* GOPTION #4 */
* GOPTIONS RESET=ALL DEVICE=WIN TARGETDEVICE=WINPRTM ftext=arial; /* GOPTION
#5 */

ods rtf close;


ods rtf file="&odsfile1" style=mystyle1 bodytitle;

TITLE "MEAN PLASMA CONCENTRATIONS";
proc report data=cmeanrat nowd split='~' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column time ("Test (n=&testsub)" mean1 cv1)
         ("Reference (n=&refsub)" mean2 cv2)
             ("Ratio" rmean12);

  define time /order format=8.2 spacing=2 "Time (hr)";
  define mean1 /format=8.2 spacing=2 "Mean (&cmaxunit)";
  define cv1 /format=8.2 spacing=2 "CV%";
  define mean2 /format=8.2 spacing=2 "Mean (&cmaxunit)";
  define cv2 /format=8.2 spacing=2 "CV%";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;


footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS";
proc report data=pkratio nowd split='\' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column nname units ("Test" mean1 cv1 min1 max1)
         ("Reference" mean2 cv2 min2 max2)
             ("Ratio" rmean12);

  define nname /format=$12. spacing=2 "Parameter";
  define units /format=$12. spacing=2 "Unit";
  define mean1 /format=8.3 spacing=2 "Mean";
  define cv1   /format=8.2 spacing=2 "CV%";
```

```
  define min1  /format=8.2 spacing=2 "Min";
  define max1  /format=8.2 spacing=2 "Max";
  define mean2 /format=8.3 spacing=2 "Mean";
  define cv2   /format=8.2 spacing=2 "CV%";
  define min2  /format=8.2 spacing=2 "Min";
  define max2  /format=8.2 spacing=2 "Max";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

TITLE "LSMEANS AND 90% CONFIDENCE INTERVALS";
proc report data=cidat nowd split='\' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column nname ("Least Squares Geometric Mean" lsm1 lsm2)
         ("Ratio" rlsm12)
             ("90% Confidence Intervals" lowci12 uppci12);

  define nname /format=$12. spacing=2 "Parameter";
  define lsm1  /format=8.2 spacing=2 "Test";
  define lsm2 /format=8.2 spacing=2 "Reference";
  define rlsm12 /format=8.2 spacing=2 "(T/R)";
  define lowci12 /format=8.2 spacing=2 "Lower";
  define uppci12 /format=8.2 spacing=2 "Upper";
run;


TITLE "ROOT MEAN SQUARE ERROR";
proc report data=rootmse nowd split='\' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column dependent rootmse;

  define dependent /format=$12. spacing=2 "Parameter";
  define rootmse /format=8.4 spacing=2 "RMSE";

run;


TITLE "STATISTICS ON AUCT/AUCI RATIOS";

  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column treat no avg mini maxi;
```

```
  define treat /format=$12. spacing=2 "Treatment";
  define no /format=8. spacing=2 "n";
  define avg /format=8.2 spacing=2 "Mean";
  define mini /format=8.2 spacing=2 "Minimum";
  define maxi /format=8.2 spacing=2 "Maximum";
run;

ods rtf close;


filename concplot "&plotfile";

/*
goptions reset=all
         device=cgmof97p
         gsfname=concplot
         gsfmode=replace
         ftext=swiss
         rotate=portrait
           targetdevice=winprtm;
*/
goptions reset=all device=png ftext="Arial" htext=12pt gsfname=concplot
gsfmode=replace



TITLE2 "&TITLE3";
TITLE3 "&TITLE4";
TITLE4 "&TITLE5";
TITLE5 "&TITLE6";
FOOTNOTE1 "&FOOTNOT1";
SYMBOL1 C=RED I=JOIN V=dot  width=0.5 height=0.5;
SYMBOL2 C=BLUE I=JOIN V=SQUARE width=0.5 height=0.5;

AXIS1 label=(a=90 "&label1");

PROC GPLOT DATA=CMEAN UNIFORM;
PLOT MEAN*TIME=TRT / FRAME vaxis=axis1;
LABEL MEAN=("&LABEL1") TIME="&LABEL2";
RUN;
TITLE1;
TITLE2;
TITLE3;
TITLE4;
TITLE5;
TITLE6;

FOOTNOTE1;
FOOTNOTE2;
FOOTNOTE3;
LABEL;
QUIT;
```

4.7.3 Fasting Study Output

FASTING STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	24	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	48
Number of Observations Used	48

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	2.05796838	0.08231874	5.76	<.0001
Error	22	0.31437781	0.01428990		
Corrected Total	47	2.37234619			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.867482	1.448855	0.119540	8.250678

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00008306	0.00008306	0.01	0.9399
sub(seq)	(b) (6)	2.04817127	0.09309869	6.51	<.0001
per	1	0.00052819	0.00052819	0.04	0.8493
trt	1	0.00918587	0.00918587	0.64	0.4313

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00008306	0.00008306	0.01	0.9399
sub(seq)	(b) (6)	2.04817127	0.09309869	6.51	<.0001
per	1	0.00052819	0.00052819	0.04	0.8493

Source	DF	Type III SS	Mean Square	F Value	Pr > F
trt	1	0.00918587	0.00918587	0.64	0.4313

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00008306	0.00008306	0.00	0.9764

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.02766747	0.03450833	-0.80	0.4313

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	2.00075355	0.08003014	6.18	<.0001
Error	22	0.28498305	0.01295377		
Corrected Total	47	2.28573660			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.875321	1.368710	0.113815	8.315466

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00001731	0.00001731	0.00	0.9712
sub(seq)	(b) (6)	1.99054899	0.09047950	6.98	<.0001
per	1	0.00004485	0.00004485	0.00	0.9536
trt	1	0.01014240	0.01014240	0.78	0.3858

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00001731	0.00001731	0.00	0.9712
sub(seq)	(b) (6)	1.99054899	0.09047950	6.98	<.0001
per	1	0.00004485	0.00004485	0.00	0.9536
trt	1	0.01014240	0.01014240	0.78	0.3858

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00001731	0.00001731	0.00	0.9891

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.02907233	0.03285546	-0.88	0.3858

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	3.19400796	0.12776032	3.40	0.0025
Error	22	0.82723270	0.03760149		
Corrected Total	47	4.02124065			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.794284	3.045327	0.193911	6.367494

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.02075204	0.02075204	0.55	0.4654
sub(seq)	22	3.11010724	0.14136851	3.76	0.0015
per	1	0.00525881	0.00525881	0.14	0.7120
trt	1	0.05788986	0.05788986	1.54	0.2278

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.02075204	0.02075204	0.55	0.4654
sub(seq)	22	3.11010724	0.14136851	3.76	0.0015
per	1	0.00525881	0.00525881	0.14	0.7120
trt	1	0.05788986	0.05788986	1.54	0.2278

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.02075204	0.02075204	0.15	0.7053

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.06945614	0.05597729	-1.24	0.2278

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	0.89
2		1	0.94
3		1	0.95
4		1	0.95
5		1	0.97
6		1	0.94
7		1	0.95
8		1	0.93
9		1	0.94
10		1	0.90
11		1	0.97
12		1	0.95
13		1	0.97
14		1	0.91
15		1	0.92
16		1	0.96
17		1	0.95
18		1	0.97
19		1	0.92
20		1	0.92
21		1	0.94
22		1	0.89
23		1	0.95
24		1	0.94
25		2	0.90
26		2	0.94
27		2	0.97
28		2	0.95
29		2	0.97
30		2	0.96
31		2	0.94

Obs	sub	trt	AUCRATIO
32	(b) (6)	2	0.87
33		2	0.92
34		2	0.90
35		2	0.97
36		2	0.94
37		2	0.96
38		2	0.93
39		2	0.93
40		2	0.96
41		2	0.95
42		2	0.96
43		2	0.94
44		2	0.92
45		2	0.92
46		2	0.92
47		2	0.95
48		2	0.93

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	0.73	0.74	0.65	1.00	0.93	1.08
	1	0.91	0.90	1.06	0.75	1.00	1.00
	1	0.89	0.90	0.60	1.00	0.94	1.07
	2	1.12	1.12	1.06	3.00	1.01	0.99
	1	1.11	1.11	1.21	0.80	1.05	0.95
	2	0.93	0.95	1.03	0.14	0.86	1.16
	1	1.27	1.26	1.25	3.60	1.09	0.91
	2	1.16	1.09	1.18	0.63	1.32	0.76
	2	1.13	1.11	1.27	1.67	1.04	0.96
	1	0.83	0.84	0.71	1.20	1.02	0.98
	1	1.23	1.22	1.58	0.50	1.06	0.95
	2	1.10	1.09	0.90	0.83	1.03	0.97
	2	0.72	0.71	0.52	0.80	1.10	0.91
	1	0.77	0.78	0.69	1.80	0.95	1.05
	1	1.04	1.06	0.88	2.00	0.91	1.10
	2	1.00	1.00	1.05	0.40	0.95	1.05
	1	0.97	0.97	0.75	1.25	1.04	0.96
	2	1.02	1.01	1.21	0.83	1.09	0.92
	2	0.90	0.91	0.97	0.50	0.97	1.03
	1	0.96	0.96	0.83	1.00	0.98	1.02
	2	0.93	0.91	0.82	2.00	1.16	0.86
	1	0.74	0.76	0.80	1.33	0.99	1.01
	2	1.16	1.16	1.11	0.17	1.00	1.00
	1	1.04	1.03	1.02	1.50	1.01	0.99

ANDA 203760 Fasting Reviewer-Calculated Pharmacokinetic Dataset

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
1	(b) (6)	1	2	2	1	3262.01	3869.32	406	3.000	11.8913	0.05829
2		2	2	1	1	4467.69	6894.35	621	3.000	35.4112	0.01957
3		1	1	1	1	3459.95	3695.87	748	1.500	7.1099	0.09749
4		2	1	2	1	3822.01	4266.14	708	2.000	11.1944	0.06192
5		1	1	1	1	4435.10	4665.31	665	0.666	5.7814	0.11989
6		2	1	2	1	4999.91	5125.95	1100	0.666	3.9002	0.17772
7		1	2	2	1	6218.61	6505.20	895	3.000	5.4129	0.12806
8		2	2	1	1	5528.83	5801.75	848	1.000	5.6981	0.12165
9		1	1	1	1	6230.48	6410.92	1020	1.000	4.9435	0.14021

Obs	sub (b) (6)	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
10		2	1	2	1	5589.30	5795.93	840	1.250	5.4666	0.12680
11		1	2	2	1	3287.91	3452.63	498	0.416	4.8793	0.14206
12		2	2	1	1	3528.37	3694.86	483	3.000	5.7131	0.12133
13		1	1	1	1	4264.16	4562.42	525	3.000	7.6286	0.09086
14		2	1	2	1	3359.04	3581.41	419	0.833	6.5033	0.10658
15		1	2	2	1	3635.81	3934.02	530	1.250	7.4621	0.09289
16		2	2	1	1	3123.67	3648.42	449	2.000	10.0479	0.06898
17		1	2	2	1	5599.20	5897.24	942	0.833	5.1390	0.13488
18		2	2	1	1	4976.30	5362.56	744	0.500	6.3443	0.10925
19		1	1	1	1	3863.96	4274.74	602	1.000	7.0479	0.09835
20		2	1	2	1	4631.29	4976.41	843	0.833	5.1225	0.13531
21		1	1	1	1	3451.73	3520.50	794	1.000	3.7240	0.18613
22		2	1	2	1	2809.96	2919.81	502	2.000	5.8571	0.11834
23		1	2	2	1	3010.60	3162.59	530	1.250	5.5743	0.12435
24		2	2	1	1	2743.30	2916.96	590	1.500	6.8393	0.10135
25		1	2	2	1	3235.89	3475.95	496	1.000	10.3997	0.06665
26		2	2	1	1	4519.47	5177.75	954	1.250	17.5496	0.03950
27		1	1	1	1	3745.35	4178.77	489	1.500	8.6081	0.08052
28		2	1	2	1	4840.16	5273.74	706	0.833	7.5893	0.09133
29		1	1	1	1	3423.51	3942.26	442	3.000	11.2365	0.06169
30		2	1	2	1	3286.95	3628.26	503	1.500	8.3894	0.08262
31		1	2	2	1	3665.81	3797.17	714	0.500	4.3987	0.15758
32		2	2	1	1	3682.42	3826.68	682	1.250	5.2081	0.13309
33		1	1	1	1	4119.52	4352.27	634	1.250	6.3764	0.10870
34		2	1	2	1	4262.79	4432.81	847	1.000	4.6036	0.15057
35		1	2	2	1	4260.18	4459.49	584	0.833	6.4555	0.10737
36		2	2	1	1	4165.35	4476.37	484	1.000	8.5547	0.08103
37		1	2	2	1	3567.33	3875.89	414	3.000	6.7897	0.10209
38		2	2	1	1	3981.01	4820.50	425	6.000	19.6585	0.03526
39		1	1	1	1	3534.40	3890.24	427	1.000	7.8053	0.08881
40		2	1	2	1	3689.89	4041.56	513	1.000	7.2118	0.09611
41		1	2	2	1	4307.56	4630.03	497	3.000	7.1186	0.09737
42		2	2	1	1	4625.79	5024.00	603	1.500	7.1693	0.09668
43		1	1	1	1	2507.42	2684.73	380	2.000	4.2379	0.16356
44		2	1	2	1	3404.14	3809.87	475	1.500	9.9375	0.06975

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
45	(b) (6)	1	2	2	1	2812.47	2942.98	437	0.500	5.6188	0.12336
46		2	2	1	1	2421.93	2566.60	394	3.000	7.4279	0.09332
47		1	1	1	1	3138.30	3346.63	403	3.000	6.2512	0.11088
48		2	1	2	1	3031.22	3705.17	397	2.000	18.9130	0.03665

ANDA 203760 Fasting Firm to Reviewer Ratio

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	(b) (6)	2	1	1	2	4467.69	6894.35	621	B	4467.54	4974.12	621	0.99997	0.72148	1
2		2	2	1	1	3262.01	3869.32	406	A	3261.50	3668.47	406	0.99984	0.94809	1
3		1	1	1	1	3459.95	3695.87	748	A	3459.73	3667.11	748	0.99994	0.99222	1
4		1	2	1	2	3822.01	4266.14	708	B	3821.84	4070.41	708	0.99996	0.95412	1
5		1	1	1	1	4435.10	4665.31	665	A	4434.87	4655.04	665	0.99995	0.99780	1
6		1	2	1	2	4999.91	5125.95	1100	B	4999.60	5154.07	1100	0.99994	1.00549	1
7		2	1	1	2	5528.83	5801.75	848	B	5528.52	5815.17	848	0.99994	1.00231	1
8		2	2	1	1	6218.61	6505.20	895	A	6218.35	6531.17	895	0.99996	1.00399	1
9		1	1	1	1	6230.48	6410.92	1020	A	6230.42	6395.33	1020	0.99999	0.99757	1
10		1	2	1	2	5589.30	5795.93	840	B	5587.19	5766.33	840	0.99962	0.99489	1
11		2	1	1	2	3528.37	3694.86	483	B	3529.09	3689.22	483	1.00020	0.99847	1
12		2	2	1	1	3287.91	3452.63	498	A	3287.83	3503.00	498	0.99997	1.01459	1
13		1	1	1	1	4264.16	4562.42	525	A	4264.03	4478.32	525	0.99997	0.98157	1
14		1	2	1	2	3359.04	3581.41	419	B	3358.90	3563.84	419	0.99996	0.99510	1
15		2	1	1	2	3123.67	3648.42	449	B	3123.91	3576.70	449	1.00008	0.98034	1
16		2	2	1	1	3635.81	3934.02	530	A	3635.64	3898.59	530	0.99995	0.99099	1
17		2	1	1	2	4976.30	5362.56	744	B	4976.05	5383.44	744	0.99995	1.00389	1
18		2	2	1	1	5599.20	5897.24	942	A	5598.97	5972.36	942	0.99996	1.01274	1
19		1	1	1	1	3863.96	4274.74	602	A	3863.75	4311.80	602	0.99995	1.00867	1
20		1	2	1	2	4631.29	4976.41	843	B	4631.02	5157.61	843	0.99994	1.03641	1
21		1	1	1	1	3451.73	3520.50	794	A	3451.56	3541.68	794	0.99995	1.00602	1
22		1	2	1	2	2809.96	2919.81	502	B	2809.79	2906.57	502	0.99994	0.99547	1
23		2	1	1	2	2743.30	2916.96	590	B	2743.11	2903.55	590	0.99993	0.99540	1

Obs	sub (b) (6)	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
24		2	2	1	1	3010.60	3162.59	530	A	3010.40	3177.89	530	0.99993	1.00484	1
25		2	1	1	2	4519.47	5177.75	954	B	4519.23	4727.63	954	0.99995	0.91307	1
26		2	2	1	1	3235.89	3475.95	496	A	3235.71	3352.42	496	0.99994	0.96446	1
27		1	1	1	1	3745.35	4178.77	489	A	3745.20	4100.11	489	0.99996	0.98118	1
28		1	2	1	2	4840.16	5273.74	706	B	4839.92	5224.16	706	0.99995	0.99060	1
29		1	1	1	1	3423.51	3942.26	442	A	3423.41	3718.82	442	0.99997	0.94332	1
30		1	2	1	2	3286.95	3628.26	503	B	3286.83	3535.47	503	0.99996	0.97443	1
31		2	1	1	2	3682.42	3826.68	682	B	3682.23	3829.66	682	0.99995	1.00078	1
32		2	2	1	1	3665.81	3797.17	714	A	3665.67	3832.99	714	0.99996	1.00943	1
33		1	1	1	1	4119.52	4352.27	634	A	4117.74	4328.64	634	0.99957	0.99457	1
34		1	2	1	2	4262.79	4432.81	847	B	4262.52	4484.44	847	0.99994	1.01165	1
35		2	1	1	2	4165.35	4476.37	484	B	4165.20	4345.61	484	0.99996	0.97079	1
36		2	2	1	1	4260.18	4459.49	584	A	4260.01	4400.83	584	0.99996	0.98685	1
37		2	1	1	2	3981.01	4820.50	425	B	3980.86	4255.56	425	0.99996	0.88280	1
38		2	2	1	1	3567.33	3875.89	414	A	3564.81	3866.68	414	0.99929	0.99762	1
39		1	1	1	1	3534.40	3890.24	427	A	3534.24	3841.68	427	0.99995	0.98752	1
40		1	2	1	2	3689.89	4041.56	513	B	3689.76	4011.55	513	0.99996	0.99257	1
41		2	1	1	2	4625.79	5024.00	603	B	4622.43	5041.02	603	0.99927	1.00339	1
42		2	2	1	1	4307.56	4630.03	497	A	4306.87	4601.91	497	0.99984	0.99393	1
43		1	1	1	1	2507.42	2684.73	380	A	2492.12	2790.39	380	0.99390	1.03936	1
44		1	2	1	2	3404.14	3809.87	475	B	3405.68	3693.83	475	1.00045	0.96954	1
45		2	1	1	2	2421.93	2566.60	394	B	2421.82	2551.66	394	0.99995	0.99418	1
46		2	2	1	1	2812.47	2942.98	437	A	2812.55	2967.46	437	1.00003	1.00832	1
47		1	1	1	1	3138.30	3346.63	403	A	3138.20	3351.49	403	0.99997	1.00145	1
48		1	2	1	2	3031.22	3705.17	397	B	3031.09	3260.74	397	0.99996	0.88005	1

NOTE TO REGULATORY PROJECT MANAGER (RPM): Currently there are OSI inspections pending for the clinical and analytical sites.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 203760

APPLICANT: Perrigo Pharmaceuticals Company

DRUG PRODUCT: Albuterol Sulfate Inhalation Aerosol, 0.09 mg Base/Inhalation

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

Deficiencies Related to Fasting Bioequivalence (BE) Study (# 10825302)

1. Please provide the Certificate of Analysis (CoA) of the reference product lot # AEA13B.

2. Per your analytical report for the fasting study (# 10825302), there were seven rejected batch runs for albuterol (Run ID #s 1AFGI, 4AFGI, 7AFGI, 8AFGI, 9AFGI, 13AFGI and 14AFGI). You provided the specific reasons for rejection of the batch runs in the analytical report. However, you did not include the original data to support the reasons for batch rejections. Therefore, please submit the raw data for calibration standards, quality control (QC) samples and study samples, such as peak area of analyte and internal standard, calculated concentration, etc. of the failed batches.

   In addition, you did not include those rejected batches in the calculation of repeat percentage in the "Reanalysis of Study Samples" Table. For the future submissions, please include all analytical repeats, including failed repeat runs, in the "Reanalysis of Study Samples" Table.

Deficiencies Common to ALL In Vitro Equivalence Studies

3. Please provide detailed study reports for all the in vitro equivalence studies.

4. Manual actuation was used for conducting Single Actuation Content Test, Priming/Re-Priming, Aerodynamic Particle Size Distribution by Cascade Impaction and Particle Size Distribution by Laser Diffraction. You only indicated that both test and reference products were tested under the same instrumental conditions. Please provide the information regarding whether the test was conducted under blinded conditions to avoid the operator's bias.

5. For Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study you did not provide 100% raw numerical data (analyst's printouts) for all analytical runs (accepted and rejected) conducted during the HPLC sample analysis of these studies. The raw numerical data

should include the data of peak area/height for the drug, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard concentration samples, and quality control samples.

6. Please submit 20% of the chromatograms from Single Actuation Content Study, Priming & Re-Priming Study, and Aerodynamic Particle Size Distribution by Cascade Impaction Study.

Deficiencies Related to Single Actuation Content (SAC) through Container Life Test

7. You did not provide the validation data for the manual spray pump actuator for the SAC testing. Please submit the data using formatted summary tables. You may reference the CTD tables designed for nasal spray drug products (where applicable) from the FDA's website at the following location: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf

8. Please indicate if stock solutions and working standards underwent freeze-thaw cycles prior to use. If so, please submit the appropriate data to demonstrate stability.

9. Please provide working standards refrigerator stability data.

Deficiencies Related to Priming/Re-Priming Tests

10. As per the in vitro summary tables you submitted, the Priming and Re-priming study was conducted between February – April 2009. However, your SOP (b) (4) - (b) (4) for Priming and Re-priming testing was effective from 06/17/2011. Please justify how you objectively conducted the study without a pre-established SOP.

Deficiencies Related to Aerodynamic Particle Size Distribution (APSD) by Cascade Impactor (CI) Test

11. You did not provide number of actuations (i.e., how many actuations were employed in the CI test) and the sequential number of actuation (e.g. the 6th-11th sprays/actuations) used in the Cascade Impaction test. Please provide this information.

12. According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the APSD test should be performed at both beginning and end lifestages of the product. However, you only conducted the test at the beginning lifestage, indicated in your SAS dataset as "B". Please conduct the test at both beginning and end lifestages of the product as recommended by Albuterol Sulfate MDI guidance. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf

13. Please specify how many quality control samples were used in each analytical run and at what concentrations. According to the Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Actions (April 2003): *"analytical runs include at least three or more concentrations of quality control samples that represent the entire range of the standard curve or the expected concentration range of samples from the various stages of the CI."* This is also applicable to the same test of inhalation drug product.

Deficiencies Related to Spray Pattern Test

14. According to the Drug Specific Bioequivalence Guidance of Albuterol Sulfate MDI, the Spray Pattern should be performed at the beginning lifestage of the product at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm **from the reference product mouthpiece**. It should also be noted that the **distance between the actuator orifice and the point of spray pattern measurement should be the same for test and reference products.**

    In the current ANDA, you conducted spray pattern test at 3 cm and 6 cm from the actuator mouthpiece. However, it is not clear from your submission whether the selected 3 cm and 6 cm distances are from the actuator mouthpiece of **the reference product.** Therefore, please clarify whether the 3 cm and 6 cm distances are from the reference product actuator mouthpiece. In addition, please confirm whether the distances between the actuator orifice to the point of spray pattern measurements are the same for the test and reference products.

15. According to the in vitro summary table provided in Module 5.2, the effective date of both SOP (b) (4) was January 8, 2009. However, according to the SOP (b) (4), the effective date of both the SOPs was July 21, 2011. Please clarify this discrepancy.

16. Please provide the Intermediate Precision (By Date) data for the validation of the spray pattern test.

17. You provided the spray pattern images and the accompanying raw data for 20% samples at both 3 cm and 6 cm distances. However, it is not clear from your submission whether the images are of the test or reference product. Please clarify.

Deficiencies Related to Plume Geometry Test

18. Please clarify whether the 6 cm distance selected for the Plume Geometry test is from **the reference product actuator mouthpiece**. In addition, please confirm whether the distances between the actuator orifice to the point of spray pattern measurements are the same for the test and reference products.

19. Please provide the Intermediate Precision (By Date) data for the validation of the plume geometry test.

Deficiencies Related to Pharmacodynamic (PD) Study (# PRG-723)

20. Please provide the certificate of analysis of the reference product lot # PAEF75A.

21. You only provided the case report forms of subject #s [redacted (b) (6)]. Please provide the case report forms of all subjects included in the pharmacodynamic study.

22. In your submission (Module 5.3.4.1) for the study design of PD study (# PRG-723), you indicated that "*placebo MDI*" was used in treatments 1 through 5. However, you did not specify whether the "*placebo MDI*" is the test or reference product placebo. Please clarify which placebo, test or reference placebo, were used in each treatment in your PD study. In addition, please provide the formulation of the placebo product.

Deficiency Related to Inspection Findings by the Office of Scientific Investigations (OSI):

23. Following the inspection of the analytical site [redacted (b) (4)], [redacted (b) (4)] by the Office of Scientific Investigation (OSI) (for the BE studies from other applications), Form FDA-483 was issued. Subsequently, the analytical site provided its responses to Form 483 and those responses were included in the final evaluation by the OSI.

    For considering the impact of similar study conduct and site practices by the same analytical facility on the BE study of the current ANDA, the DBI reviewed the above OSI inspection report and found that the following objectionable finding by the OSI at the analytical site could potentially compromise the integrity of the study of the current application as well:

    Failed to demonstrate analyte stability under the actual conditions of sample handling and storage.

    Please address the above systemic finding by the OSI with respect to its impact on the fasting BE study (# 10825302) of the current ANDA.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. These comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Wayne DeHaven, Ph.D
Acting Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

ANDA: 203760

COMPLETED ASSIGNMENT FOR 203760 ID: 22803

Reviewer: Kundoor, Vipra **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***
22803	12/16/2011	Bioequivalence Study (REGULAR)	Fasting Study	1	1
22803	12/16/2011	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1
22803	12/16/2011	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1
22803	12/16/2011	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1
22803	12/16/2011	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1
22803	12/16/2011	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1
22803	12/16/2011	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1
22803	12/16/2011	Bioequivalence Study (REGULAR)	Pharmacodynamic Pivotal Study	1	1
				Total:	8

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIPRA R KUNDOOR
08/04/2014

KE REN
08/04/2014

WAYNE I DEHAVEN
08/04/2014