

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-949

CHEMISTRY REVIEW(S)

PULMICORT TURBUHALER
(BUDESONIDE INHALATION POWDER)
NDA 21-949

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: AstraZeneca LP
1800 Concord Pike
Wilmington, DE 19803

Indication: "PULMICORT TURBUHALER is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age or older. It is also indicated for patients requiring oral corticosteroid therapy for asthma."

Presentation: 2 strengths

90 mcg metered per actuation (60 doses, corresponding emitted dose of 80 mcg budesonide); assay of mg budesonide per gram of formulation; mcg of lactose emitted per dose;

180 mcg metered per actuation (120 doses, corresponding emitted dose of 160 mcg budesonide); assay of mg budesonide per gram of formulation; mcg of lactose emitted per dose;

b(4)

EER Status: Pending.

Consults: EA – categorical exclusion provided
Biometrics – No consult requested. Expiry period of 30 months is acceptable.
Methods Validation – Forwarded to Agency laboratory on 31-MAY-2006.

Original Submission: 12-SEP-2005

Post-Approval Agreements:
None

Drug Substances:

Budesonide, a corticosteroid, has the chemical name (R,S)-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17 acetal with butyraldehyde. Budesonide is a white to off-white powder with a molecular weight of 430.55 g/mol and a molecular formula of C₂₅H₃₄O₆. CMC information for budesonide is referenced to NDA 20-441 (Pulmicort Turbuhaler) and associated supplements

Conclusion: Drug substance is acceptable.

Drug Product:

The Pulmicort Turbuhaler M3 drug product (DP) is a multi-dose dry powder inhaler that is provided in two strengths of budesonide. The formulation includes _____% lactose _____ and _____

b(4)

The low strength of the drug product meters 90 mcg budesonide per actuation with a target emitted dose of 80 mcg budesonide per actuation. The powder of _____mg budesonide per gram of formulation gave _____ mcg of lactose _____ emitted per dose;

b(4)

The high strength of the drug product meters 180 mcg budesonide per actuation with a target emitted dose of 160 mcg budesonide per actuation. The powder of _____mg budesonide per gram of formulation gave _____mcg of lactose _____ emitted per dose;

b(4)

The design of the M3 device is basically the same as the M0 device (used for M0-ESP variant as well) with some improvements. The dose indicator enumerates every 20th dose and marks every 10th dose. At 10 doses prior to the end of unit life, the red background color appears as a warning to the patient. The device does not lock out and contains a substantial overfill due to a gradual tail-off in terms of the dose delivery. Other improvements include a better seal of the cover to the device base as well as the permanent fixture of the mouthpiece to the device to prevent patient tampering.

This new M3 device includes a modification to the mouthpiece. The underside of the mouthpiece now contacts a wiper that continually removes dose build-up from the underside of the mouthpiece. Mitigation of dose buildup diminishes potential for occasional superpotent dosing.

The *in vitro* dose delivery data are relatively insensitive to the testing flow rate over a range of 30 – 80 L/min, however, the *in vitro* aerodynamic particle size distribution (APSD) of the delivered dose from the device is quite sensitive to flow rates below 60 L/min. Whereas a flow rate of 80 L/min does not appreciably alter the APSD of the delivered dose, a flow rate of 30 L/min results in less than half of the fine particles of drug substance retained at 60 L/min. Flow resistance of the new M3 device is about 6% greater than the older M0-ESP device.

It is noted that the applicant has also provided data to support the use of two manufacturers for the device.

Conclusion: Drug product is satisfactory.

Additional Items:

The applicant adequately responded to all deficiencies and information requests in the discipline review letter of 25-JAN-2006.

Adequate stability data were provided to support a **30 month expiration date**.

With one exception, all associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

The exception, DMF ~~holder~~ holder, did not respond to the deficiency letter regarding details of the formulation of ~~_____~~ but did agree in writing to continue ~~_____~~

b(4)

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval**, pending an acceptable recommendation from the Office of Compliance.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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CHEMISTRY NDA FILEABILITY CHECK

NDA: 21-949

Applicant: AstraZeneca LP

Letter Date: 12-SEP-2005

FILING REVIEW

DATE: 12-OCT-2005

TO: N21-949 File

THROUGH: Richard T. Lostritto, Ph.D.
Chemistry Team Leader
Division of Pulmonary Drug Products (HFD-570)

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
Division of Pulmonary Drug Products (HFD-570)

SUBJECT: Filing Review for N21-949 Pulmicort® Turbuhaler® (M3 version)
(budesonide inhalation powder) 90 and 180 mcg ..

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		Follows CTD format.
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?		X	No CFNs provided but the two pertinent sites are found in the EES database.
5	Is a statement provided that all facilities are ready for GMP inspection?		X	Since the main manufacturing facility in Södertälje, SW is currently preparing the approved M0 version of the drug product from N20-441, it can be assumed that the site is ready for inspection.
6	Has an environmental assessment report or categorical exclusion been provided?	X		Request exclusion.
7	Does the section contain controls for the drug substance?	X		Specifications are included and methods are referenced

- For the most part the applicant has referred to sections of the approved N20-441 for information on the drug substance, as agreed. See 12-SEP-2002, meeting minutes. Note that as per the agreement at the 08-SEP-2004, pre-NDA CMC meeting, once the M3 version is approved the applicant will withdraw N20-441 and the DS information will be placed in a DMF. A letter of authorization for our reference to this file will then be included in N21-949.
- As agreed at the pre-NDA CMC meeting, the hold period for the [REDACTED] product (spheronized formulation) is no more than [REDACTED]. Also, the applicant has undertaken stability studies to justify the hold period and have prepared and compared the stability of DP prepared with both “fresh” and [REDACTED] old [REDACTED] DP (i.e., the formulation) (see 3.2.P.3.4, p. 93 of 163). **b(4)**
- Fill weight testing, as discussed at the pre-NDA CMC meeting, will be based on an in-process test.
- The applicant was informed at the pre-NDA meeting that APSD mass balance limits of [REDACTED] based on Label Claim Emitted Dose (LCED) were too broad. In the current application for the APSD run qualification procedure, the currently proposed mass balance limits that would trigger an investigation and possible retest are [REDACTED] (i.e., [REDACTED]) of the nominal delivered dose (NDD, defined as 80 and 160 mcg for the low and high strength, respectively, see definitions provided in PDF file format, for the primary stability dataset). This limit is said to be determined by the data with [REDACTED]. It will be a review issue, but the current proposal is to allow one retest if there is a mass balance failure. Note that 8 actuations or ~720 mcg are collected for each APSD determination for the low strength product and 4 actuations (also ~720 mcg) for the high strength product. **b(4)**
- It is noted that the applicant has not provided delivered dose uniformity (DDU) acceptance criteria that are consistent with the Agency recommendations contained in the draft CMC guidance for inhalation powder drug products. They are proposing two sets of acceptance criteria. The first is based on the concepts of the parametric tolerance interval test (PTIT), originally proposed by the Agency. Unfortunately, the Agency and the industry consortium IPAC-RS has not come to agreement on what are acceptable limits for the PTIT. As a fall-back, AZ also proposes a zero tolerance DDU acceptance criteria with a retest scheme for an outlier. **b(4)**
- As agreed at the pre-NDA meeting, AZ has provided 6 months of stability data for the DP prepared with the alternated supply of devices from [REDACTED].
- Annual stability testing of the DP every 6 months is proposed for the commitment, as discussed at the pre-NDA meeting.

- Batch records and executed batch records for each strength are provided as discussed at the pre-NDA meeting.
- One “wrinkle” in the development program that was discussed at both the CMC and clinical pre-NDA meetings was the fact that the _____

Specifically, they noted that _____
 Thus, for the low strength the budesonide content was increased from _____ mg/g and for the high strength, from _____ mg/g

The metered amounts are 90 and 180 mcg so there is a hold-up of about _____ mcg, respectively, for the low and high strength of the product. Decisions on the DDU specifications will need to take into consideration that _____ of the _____ batches for each strength had the _____ budesonide target concentrations of _____ mg/g (_____ for the 90 mcg, and _____ for the 180 mcg strength) (see 3.2.P.2.2). The EF-series primary stability batches (_____ for each strength) produced in July-Aug 2003 had budesonide target concentrations of _____ mg/g.

Other Considerations

Drug Substance (NDA vs. pivotal IND clinical studies)

Since the drug substance being used for the development of the M3 Pulmicort version is the same as that used for the approved M0-ESP version, there are no questions regarding changes in site, method of synthesis, scale, purity, micronization, etc. that may impact on the fileability of the application.

Drug Product

Formulation (IND vs. NDA)

As noted above, the applicant changed the budesonide concentration in the formulation for both strengths during the development in order to achieve the targeted delivered dose. In the CMC section, these batches are identified. Of the primary stability batches, _____ for each strength, had the previous budesonide concentrations (_____ mg/g). The other _____ batches for each strength have the planned to-be-marketed concentrations of budesonide _____ mg/g). The applicant states in their application summary introduction that this change is also discussed in the clinical section of the application. The clinicians are aware of this change as it was discussed at the full pre-NDA meeting.

Manufacturer(s)/Site(s)

There has been only one manufacturer of the DP during development and it is the planned commercial manufacturer, AstraZeneca AB in Södertälje, Sweden.

b(4)

b(4)

A list of M3 90 and M3 180 batches for which batch analyses are given in tables 1 and 2 of section 3.2.P.5.4. These include all of the primary stability batches, the pivotal biobatch and clinical trial batches.

Container/closure system (IND vs. NDA)

The M3 device used for the phase 3 clinical studies are said by the applicant to have been produced with ~~_____~~ scale manufactured components. It is further stated that these inhalers were also assembled and filled with drug formulation in production lines intended for ~~_____~~ scale manufacture.

b(4)

Stability (quality and adequacy of data)

The primary stability batches were manufactured at the intended commercial production site.

The planned ~~_____~~ scale for the spheronized formulation (a.k.a. ~~_____~~ drug product) is ~~_____~~ for both strengths. The applicant states that all of the ~~_____~~ drug product and drug product batches have been produced with ~~_____~~ scale production equipment. With a ~~_____~~ drug product batch size, ~~_____~~ of the M3 90/60 and M3 180/120 inhalers can be filled, respectively. Since only ~~_____~~ inhalers are listed as filled for the ~~_____~~ primary stability batches, it is presumed that these are representative of an entire fill. ~~_____~~

b(4)

~~_____~~ Note that all were sourced from ~~_____~~. Since the applicant desires to have ~~_____~~ they were informed that they would need additional comparative stability data of at least 6 months for at least ~~_____~~ batches of DP manufactured with ~~_____~~. These data are also included in the application.

Conclusion

The PM has been instructed to inform the applicant that the fact that DMF ~~_____~~ is currently inactivated is not considered to be a filing issue, if they make a commitment to have the holder resubmit the DMF in a timely manner.

b(4)

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/s/

Craig Bertha
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Richard Lostritto
10/12/2005 05:05:08 PM
CHEMIST

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NDA 21-949

Pulmicort Turbuhaler® (budesonide) Inhalation Powder

AstraZeneca LP

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. NDA 21-949
2. REVIEW #:2
3. REVIEW DATE: 05-JUN-2006
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	12-SEP-2005
Amendment (device samples)	06-OCT-2005
Amendment (DMF reactivation letter)	17-OCT-2005

b(4)

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (partial response to CMC DR)	20-FEB-2006
Amendment (partial response to CMC DR)	28-FEB-2006
Amendment (partial response to CMC DR)	29-MAR-2006
Amendment (partial response to CMC DR)	27-APR-2006
Amendment (two responses to requests from clinical team)	04-MAY-2006 (2)
Amendment (IR spectra for component)	17-MAY-2006
Amendment (Update package)	23-MAY-2006
Amendment (Amendment re: DMF holder)	01-JUN-2006

b(4)

7. NAME & ADDRESS OF APPLICANT:

Name: AstraZeneca LP



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Address: 1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Representative: Barbara Blandin, Director, Regulatory Affairs

Telephone: 302-885-1540

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pulmicort Turbuhaler®
- b) Non-Proprietary Name (USAN): budesonide inhalation powder
- c) Code Name/# (OGD only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: glucocorticosteroid for asthma

11. DOSAGE FORM: powder, metered

12. STRENGTH/POTENCY: 90 or 180 mcg metered per actuation (corresponding emitted doses are 80 mcg budesonide or 160 mcg budesonide, respectively); low and high strength formulation assays are mg/g with the remainder lactose , respectively; low and high strengths deliver mcg of lactose , respectively, with each emitted dose.

b(4)

13. ROUTE OF ADMINISTRATION: Intrapulmonary

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

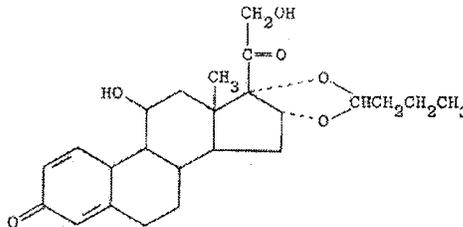
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(R,S)-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde (budesonide)



Molecular formula: C₂₅H₃₄O₆
Molecular weight: 430.55 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
				7		28-SEP-2005	PM confirmed deficiency letter sent.
	Adequate					15-MAR-2006 08-MAY-2006	Review of partial response. See p. 22 of CR#2.
	Adequate					03-OCT-2005 20-MAR-2006	See p. 22 of CR#2.
	Adequate					03-OCT-2005 28-MAR-2006	See p. 22 of CR#2.
	Adequate					03-OCT-2005	See p. 5 of CR#1.
	Adequate					03-OCT-2005	See p. 5 of CR#1
	Inadequate					03-OCT-2005	See p. 23 for details regarding file status.
	Adequate					10-MAR-2004	Reviewed for use in another DPI device.
	Adequate					21-MAY-1996	Found adequate for use in manufacture of older approved Turbuhaler device for formulation contact components
	Adequate					05-OCT-2005 14-MAR-2006	See p. 22 of CR#2.
	Adequate					05-OCT-2005	See p. 5 of CR#1
	Adequate					11-OCT-2005 14-MAR-2006	See p. 22 of CR#2.
	Adequate					03-NOV-2005 30-MAR-2006	See p. 22 of CR#2.
	Adequate					05-OCT-2005	See p. 5 of CR#1

b(4)

¹ Action codes for DMF Table:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- 1 – DMF Reviewed.
- Other codes indicate why the DMF was not reviewed, as follows:
- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	63,762	AstraZeneca	Pulmicort Turbuhaler (M3)
IND	31,308	AstraZeneca	Pulmicort Turbuhaler (M0)
NDA	20-441	AstraZeneca	Pulmicort Turbuhaler (M0/M0-ESP)
IND	21,632	AstraZeneca	Rhinocort Nasal Spray
NDA	20-233	AstraZeneca	Rhinocort Nasal Spray
NDA	20-746	AstraZeneca	Rhinocort Nasal Spray
IND	44,535	AstraZeneca	Pulmicort Turbuhaler (M0)
NDA	20-929	AstraZeneca	Pulmicort Respules
IND	46,873	AstraZeneca	Budesonide Capsules
NDA	21-324	AstraZeneca	Entocort Capsules

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Not deemed necessary due to applicant analyses and stability data demonstration of relatively minor trends for all stability parameters.
EES	PAI	13-OCT-2005	Pending	
Pharm/Tox	Accept. criterion for DP impurity DP impurity	10-NOV-2005	Acceptable/L. Sancilio, Ph.D.	
Biopharm				Not necessary.
LNC				Not necessary.
Methods Validation			Pending	Forwarded on 31-MAY-2006.
DMETS				Trademark consult not necessary: product intended to replace the currently approved product of N20-441.
EA				Request for categorical exclusion under 21 CFR 25.31 (a) or (b)
Microbiology				Not necessary.

b(4)



The Chemistry Review for NDA 21-949

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **approval**, from a CMC perspective, pending an acceptable recommendation from the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None recommended.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The Pulmicort Turbuhaler M3 drug product (DP) is a multi-dose dry powder inhaler that is provided in two strengths. The drug substance is budesonide and is the same as that used for the approved Pulmicort Turbuhaler M0-ESP drug product of N20-441. Whereas the previous product was formulated strictly with budesonide, the current formulation includes ~~lactose~~ as ~~_____~~

b(4)

The lactose is micronized so that the median particle size is in a size range considered to be respirable. The low strength of the DP meters 90 mcg budesonide/actuation with a target emitted dose of 80 mcg/actuation. The high strength meters 180 mcg/act with a target emitted dose of 160 mcg/act.

The design of the M3 device is basically the same as the M0 device (used for M0-ESP variant as well) but some improvements have been made. The dose indicator is now more informative. There are numerical indications given every 20th dose and a mark every 10th dose. Both a numeral and a mark are simultaneously visible in the window so that the patient can not lose track of where they are in terms of unit life. At 10 doses prior to the end of unit life the background color of the indicator becomes red as a warning to the patient. The device does not lock out and contains a substantial overfill due to a gradual tail-off in terms of the dose delivery. Other improvements include a better seal of the cover to the device base as well as the permanent fixture of the mouthpiece to the device to prevent patient tampering. The drug product does not utilize any additional protective packaging such as a foil laminate overwrap but the device does contain an ~~_____~~ within the ~~_____~~. Relative to the approved M0 device used for the Pulmicort Turbuhaler DP of N20-441, the new M3 device used for the DP of this application includes a modification to the mouthpiece. The underside of the mouthpiece is now adjacent to a wiper that continually removes dose build-up from the underside of the mouthpiece. Specifically, the removal of the cover turns the mouthpiece approximately 120° causing the

b(4)

Executive Summary Section

wiper to remove any deposited formulation from the subsequent dose and shunting this into the inhalation channel that will deliver the current dose. It is noted that the previous versions of this product (N20-441) were known to provide occasional superpotent doses at low frequency. These doses could reach values approaching 3 mg (~19 fold greater than the labeled dose). The incorporation of the wiper has decreased the dose buildup observed for the mouthpiece by about 50%. The *in vitro* occurrence of superpotent doses has been found to be much less with the current version of the drug product.

The airflow resistance of the device can be considered to be midrange compared to other known DPI devices. The *in vitro* dose delivery data are relatively insensitive to the testing flow rate over a range of 30 – 80 L/min, however, the *in vitro* aerodynamic particle size distribution (APSD) of the delivered dose from the device is quite sensitive to flow rates below 60 L/min. Whereas a flow rate of 80 L/min does not appreciably alter the APSD of the delivered dose, a flow rate of 30 L/min results in less than half of the fine particles of drug substance retained at 60 L/min. This is not an uncommon observation for an inhalation powder drug product considering that it is the patient's inhalation that provides the only energy to deagglomerate the formulation and produce respirable particles of the drug substance. The mean peak inspiratory flow (PIF) generated by asthmatic children aged 6-17 was 72.5 [19.1 – 103.6 L/min]. This is somewhat lower than what the label claims for the approved M0-ESP version of the product, where asthmatic children aged 6-15 had a mean PIF of 82 [43-125 L/min]. Flow resistance of the new M3 device is about 6% greater than the older M0-ESP device.

It is noted that the applicant has also provided data to support the use of _____ for the device.

b(4)

B. Description of How the Drug Product is Intended to be Used

The drug product is designed to deliver 80 mcg (90 mcg metered) or 160 mcg (180 mcg metered) of budesonide per actuation along with the _____ lactose _____. The proposed dosing (note that label claim for DPIs is given as the metered dose) is reproduced in the table from the package insert.

b(4)

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
------------------	---------------------------	--------------------------

b(4)



Executive Summary Section

The patient is instructed to prime the device (loading dose only) prior to the initial use and to replace the cover after each use in order to protect the remaining formulation. Other specifics about orientation during dose loading and inhalation are included in the patient's instructions for use.

The proposed expiry period for the drug product is 30 months and this is supported by the stability data supplied.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C.Bertha/ONDQA/6/5/06
B.Fraser/ONDQA _____
C.Jackson/DPAP

C. CC Block

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Craig Bertha
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Blair Fraser
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MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC
HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 27-JUN-2006

TO: N 21-949 File

THROUGH: Blair Fraser, Ph.D.
ONDQA Branch Chief

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer, ONDQA

SUBJECT: Addendum to Chemistry Review #2 re: 22-JUN-2006, Amendment of N21-949
regarding DMF — and — supplier



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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

NDA 21-949

Pulmicort Turbuhaler® (budesonide) Inhalation Powder

AstraZeneca LP

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

- 1. NDA 21-949
- 2. REVIEW #:1
- 3. REVIEW DATE: 22-DEC-2005
- 4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
N/A	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	12-SEP-2005
Amendment (device samples)	06-OCT-2005
Amendment (DMF reactivation letter)	17-OCT-2005

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7. NAME & ADDRESS OF APPLICANT:

Name: AstraZeneca LP
1800 Concord Pike
Address: P.O. Box 8355
Wilmington, DE 19803-8355
Representative: Barry Sickels
Telephone: 302-885-5895

8. DRUG PRODUCT NAME/CODE/TYPE:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- a) Proprietary Name: Pulmicort Turbuhaler®
b) Non-Proprietary Name (USAN): budesonide inhalation powder
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: glucocorticosteroid for asthma

11. DOSAGE FORM: powder

12. STRENGTH/POTENCY: 90 or 180 mcg metered per actuation (corresponding emitted doses are 80 mcg budesonide or 160 mcg budesonide, respectively); low and high strength formulation assays are mg/g with the remainder lactose , respectively; low and high strengths deliver mcg of lactose , respectively, with each emitted dose.

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13. ROUTE OF ADMINISTRATION: Intrapulmonary

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

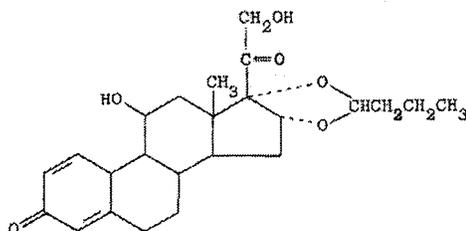
(R,S)-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde (budesonide)



CHEMISTRY REVIEW



Chemistry Review Data Sheet



Molecular formula: $C_{25}H_{34}O_6$

Molecular weight: 430.55 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
					Inadequate	28-SEP-2005	PM confirmed deficiency letter sent.
					Inadequate	03-OCT-2005	PM confirmed deficiency letter sent.
					Inadequate	03-OCT-2005	PM confirmed deficiency letter sent.
					Adequate	03-OCT-2005	
					Adequate	03-OCT-2005	
					Inadequate	03-OCT-2005	PM confirmed deficiency letter sent.
					Adequate	10-MAR-2004	Reviewed for use in another DPI device.
					Adequate	21-MAY-1996	Found adequate for use in manufacture of older approved Turbuhaler device for formulation contact components
					Inadequate	05-OCT-2005	PM confirmed deficiency letter sent.
					Inadequate	05-OCT-2005	
					Inadequate	11-OCT-2005	PM confirmed deficiency letter sent.
					Inadequate	03-NOV-2005	PM confirmed deficiency letter sent.
					Adequate	05-OCT-2005	

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¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

The Chemistry Review for NDA 21-949

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be **approvable** from a CMC perspective. Comments in the draft letter should be forwarded to the applicant and should be adequately addressed prior to the approval of the application.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None recommended at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The Pulmicort Turbuhaler M3 drug product (DP) is a multi-dose dry powder inhaler that is provided in two strengths. The drug substance is budesonide and is the same as that used for the approved Pulmicort Turbuhaler M0-ESP drug product of N20-441. Whereas the previous product was formulated strictly with budesonide, the current formulation includes lactose _____ as a _____

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_____ The low strength of the DP meters 90 mcg budesonide/actuation with a target emitted dose of 80 mcg/actuation. The high strength meters 180 mcg/act with a target emitted dose of 160 mcg/act.

The design of the M3 device is basically the same as the M0 device (used for M0-ESP variant as well) but some improvements have been made. The dose indicator is now more informative. There are numerical indications given every 20th dose and a mark every 10th dose. Both a numeral and a mark are simultaneously visible in the window so that the patient can not lose track of where they are in terms of unit life. At 10 doses prior to the end of unit life the background color of the indicator becomes red as a warning to the patient. The device does not lock out and contains a substantial overfill due to a gradual tail-off in terms of the dose delivery. Other improvements include a better seal of the cover to the device base as well as the permanent fixture of the mouthpiece to the device to prevent patient tampering. The drug product does not utilize any additional protective packaging such as a foil laminate overwrap but the device does contain an _____ within the _____ Relative to the approved M0 device used for the Pulmicort Turbuhaler DP of N20-441, the new M3 device used for the DP of this application includes a modification to the mouthpiece. The underside of the mouthpiece is now adjacent to a wiper that continually removes dose build-up from the underside of the mouthpiece. Specifically, the removal of the cover turns the mouthpiece approximately 120° causing a wiper

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on the underside to remove any deposited formulation from the subsequent dose and shunting this into the inhalation channel that will deliver the current dose. It is noted that the previous versions of this product (N20-441) were known to provide occasional superpotent doses at low frequency. These doses could reach values approaching 3 mg (~19 fold greater than the labeled dose). The incorporation of the wiper has decreased the dose buildup observed for the mouthpiece by about 50%. The applicant will be asked to characterize the frequency of superpotent doses observed for this current product.

The airflow resistance of the device can be considered to be midrange compared to other known DPI devices. The *in vitro* dose delivery data are relatively insensitive to the testing flow rate over a range of 30 – 80 L/min, however, the *in vitro* aerodynamic particle size distribution (APSD) of the delivered dose from the device is quite sensitive to flow rates below 60 L/min. Whereas a flow rate of 80 L/min does not appreciably alter the APSD of the delivered dose, a flow rate of 30 L/min results in less than half of the fine particles of drug substance retained at 60 L/min. This is not an uncommon observation for an inhalation powder drug product considering that it is the patient's inhalation that provides the only energy to deagglomerate the formulation and produce respirable particles of the drug substance. The mean peak inspiratory flow (PIF) generated by asthmatic children aged 6-17 was 72.5 [19.1 – 103.6 L/min]. This is somewhat lower than what the label claims for the approved M0-ESP version of the product, where asthmatic children aged 6-15 had a mean PIF of 82 [43-125 L/min].

The applicant has provided data to support the use of _____ for the device. Apart from some issues with regard to _____ the included data supports th_____

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B. Description of How the Drug Product is Intended to be Used

The drug product is designed to deliver 80 mcg (90 mcg metered) or 160 mcg (180 mcg metered) of budesonide per actuation along with the _____ lactose _____. The proposed dosing (note that label claim for DPIs is given as the metered dose) is reproduced in the table from the package insert.

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Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
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The patient is instructed to prime the device (loading dose only) prior to the initial use and to replace the cover after each use in order to protect the remaining formulation. Other specifics about orientation during dose loading and inhalation are included in the patient's instructions for use.

The proposed expiry period for the drug product is 30 months and this is supported by the stability data supplied.

C. Basis for Approvability or Not-Approval Recommendation

The original M0 and the intermediate M0-ESP drug products that were approved in 1997 and 2000, respectively, had formulation consisting of the budesonide drug substance alone. And due to the small amounts of budesonide needed for dosing, the metering reproducibility achievable by the device design was limited. The M0-ESP version uses the previous M0 device iteration upon which the current M3 device design was based. Because there was a medical benefit associated with the use of the budesonide product, the Agency approved the original budesonide-only formulated M0 product, even though the dose delivery acceptance criteria needed to pass a sufficient number of manufactured batches were wider than was typically necessary or approved for drug products to be taken by the oral inhalation route. This was done with the provision of a commitment by AstraZeneca to undertake a development program to improve the dose delivery reproducibility of the drug product. The M0-ESP intermediate product provided some improvement in dose reproducibility due to the "enhanced spheronization process" used to manufacture the budesonide-only formulation. The current M3 formulation contains lactose as a ~~carrier~~, and along with the improvements made to the delivery device, the new product presentation provides further improvement in dose delivery. The following table reproduced from supplement S-010 of N20-441 demonstrates the magnitude of the improvement in dose delivery variability realized (see lower RSDs for the M3 versions).

Table 1.1. Dose content uniformity for all Pulmicort Turbuhaler products

Product	Doses 1-10		Middle 10 doses		Last 10 doses		Frequency (%) of doses outside			
	mean (%LC)	RSD (%)	mean (%LC)	RSD (%)	mean (%LC)	RSD (%)	no. of doses ⁴	±20% LC	±25% LC	±35% LC
M3 90/60 ¹	98	7.7	101	7.5	101	8.1	900	0.7	0.1	0.0
M3 180/60 ¹	98	7.5	102	7.2	100	8.5	900	1.0	0.1	0.0
M3 180/120 ¹	97	7.3	104	6.9	100	8.3	900	1.3	0.2	0.0
M0-ESP 200/60 ²	100	10.4	n.a. ⁵	n.a.	103	12.2	4740	8.0	3.9	1.0
M0-ESP 200/200 ³	97	11.2	n.a.	n.a.	102	13.4	8640	12.0	6.1	1.4
M0 200/200 ³	101	13.9	n.a.	n.a.	103	18.4	9240	27.5	13.2	5.0

¹ Data normalized against batch average since the M3 products were not yet optimized with respect to overall dose level.

² Mixed data set containing dose 1, doses 1-10, dose 60 and doses 60-69.

³ Mixed data set containing dose 1, doses 1-10, dose 200 and doses 200-209.

⁴ The number of tested doses is maximized for each product, to give as representative data as possible. Hence the varying numbers.

⁵ Not analyzed, since the middle doses are not included in the specification for M0 and M0-ESP.

Although the approval of this application will ultimately result in improved dosing reproducibility for the Pulmicort Turbuhaler that is marketed, there are certain standards of quality and other related information that must be considered.



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There are several issues that are covered in this review that are currently under discussion either within a PQRI working group (APSD retesting and mass balance scenarios) or between the Agency and the IPAC-RS (delivered dose uniformity standards and the Parametric Tolerance Interval Test). As no resolution has been reached yet in either case, the proposals in this application for the related controls and testing schemes were evaluated based on the data alone from a purely quality control view point, with consideration given to the controls for the currently approved Pulmicort Turbuhaler M0 product (N20-441), and the quality levels found acceptable for other inhalation drug products. The DDU acceptance criteria are evaluated below starting on p. 111. One complicating factor is that some of the earlier drug product batches had assay targets that were lower than the current proposals for both strengths. As such the resultant dose delivery data for these batches is shifted below the target on average, complicating the evaluation of the DDU acceptance criteria. For perspective, the reader should keep in mind that the approved product marketed for the last 7 years or so had the occasional failure for the DDU acceptance criteria (Pulmicort Turbuhaler with the M0 device). These acceptance criteria required that ~~all~~ of the individual dose determinations be within ~~100~~% of the label claim emitted dose with no values outside of ~~100~~%. In addition, there was some allowance for values even outside of ~~100~~% for samples tested in the stability studies but the numbers for acceptance were to be based on a continually updated database (see S-010 for N20-441 for more details). The APSD retest scenario and mass balance controls are evaluated below starting on p. 98.

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This review has taken into consideration the history of the older versions of this product that have been marketed for many years. Based on the extensive information and data that have been provided in this application, it is now considered to be **approvable**. From a CMC perspective, approval will be recommended when the applicant addresses the deficiency comments in the attached draft letter at the end of this review.

A summary of the more important CMC issues included in the attached draft letter:

- The zero tolerance delivered dose uniformity acceptance criteria justification is based on a dataset that includes batches that were prepared with target formulation assays below what is proposed to be marketed. This tends to broaden the acceptance criteria obtained from the applicant's derivation.
- The zero tolerance delivered dose uniformity acceptance criteria include an "outlier" replacement scheme. The allowed upper limit for the "outlying" value should be justified by the applicant with data.
- Labeling instructs that patients must inhale with the device in the upright (mouthpiece up) or horizontal position, but it is unclear from the configuration of the *in vitro* dose delivery device and the data presented that the applicant has characterized the dose delivery with the device in either of these orientations.
- Robustness studies, which characterize the performance after dropping, have not been included in the application. Due to the multiple alterations to the device, this data should be provided to address any change in ruggedness that may impact on the performance for



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patients. Similarly, the effect of the mechanical challenge test to simulate shipping did not address any impact on the *in vitro* aerodynamic particle size distribution (APSD) of emitted doses.

- Additional studies should be performed to address the apparently large effects observed when drug product is tested *in vitro* for dose delivery and APSD with increasing environmental humidity. For example, testing at 25°C/75%RH lead to 25% decreases in the fine particle dose (FPD) when compared to test results obtained with a condition of 25°C/30%RH.
- Multiple supporting Drug Master Files have been reviewed and were found to be deficient. These include those for the [redacted], as well as the [redacted] and the manufacture of various raw materials used in the [redacted]. In addition, there are inconsistencies noted with regard to the [redacted] in the DMFs from the [redacted].
- Sampling for APSD testing is currently inadequate with only [redacted] per batch and the mass balance acceptance criterion needs revision based on data from batches prepared at the current proposed assay target.
- Key dimensional tolerance limits for the component of the device responsible for dose metering are too permissive based on the data that have been provided and should be tightened accordingly.

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III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C.Bertha/ONDQA/12/22/05
 B.Fraser/ONDQA _____
 C.Jackson/DPAP

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C. CC Block

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