CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-929

CHEMISTRY REVIEW(S)

12/7/05

CHEMISTRY NDA FILEABILITY CHECK

NDA: 21-929

Applicant: AstraZeneca LP

Letter Date: September 23, 2005

FILING REVIEW
DATE: November 25, 2005

TO: N21-929 File

THROUGH: Blair Fraser, Ph.D.
Branch Chief DPA-I, Branch II

FROM: Alan C. Schroeder, Ph.D.
Chemistry Reviewer
DPA-I, Branch II

SUBJECT: Filing Review for N21-929 Symbicort (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

IS THE CMC SECTION OF APPLICATION FILEABLE? **yes**, although stability data are quite limited. See comments for applicant at the end of this review.

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 application organized adequately?	X		Follows CTD format.
2	Is the application indexed and paginated adequately?	X		
3	On its face, is the application legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		CFNs were provided where available.
5	Is a statement provided that all facilities are ready for GMP inspection?	X		See form 356h
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	?		Majority of stability batches are with 6 months of stability data; uncertain whether this will be

				sufficient to support requested 12 mo. expiry (review issue)
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			See specific notes regarding agreements below (review issue)
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		See P.2.2 (pg. 42)
14	Is there a Methods Validation package?	X		Although this is a 6 page "package" since the contents are cross-referenced to other parts of the NDA.
15	Is a separate microbiological section included?		X	There are microbial limits, however, for each d.s. and for the d.p.
16	Have all DMF References been identified?	X		Apparently yes. See QOS. DMFs included are for CCS components: valve, can, , actuator, shield, foil laminate and desiccant. In addition, DMF —— is for the propellant.

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X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-*_____

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/s/

Alan Schroeder
12/7/2005 10:15:30 AM
CHEMIST

Blair Fraser
12/7/2005 11:23:26 AM
CHEMIST

7/21/06

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

DATE: July 21, 2006

TO: Division File System

FROM: Prasad Peri, Ph.D,

SUBJECT: Carton, Foil pouch, Shield, and Dose tracking card labels submitted July 20, 2006.

AstraZeneca submitted amended labels for the above mentioned presentations in response to the Agency's comments communicated in a teleconference dated July 19, 2006.

AstraZeneca has significantly changed the graphics and color schemes for the above labels. The newly proposed labels provide a good contrast for the trade name and the strength compared to the previous versions.

Submission dated July 11, 2006, contained the proposed immediate container label that was found acceptable.

From a CMC standpoint, I find their proposed labels acceptable and recommend this issue be closed.

Prasad Peri

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/s/

Prasad Peri
7/21/2006 12:35:32 PM
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Blair Fraser
7/21/2006 02:07:05 PM
CHEMIST

4/19/06

SYMBICORT
(budesonide/formoterol fumarate dihydrate)
Inhalation Aerosol
NDA 21-929

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

Applicant: AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Indication: long-term maintenance treatment of asthma in patients 12 years of age and older.

Presentation: Two strengths

SYMBICORT 80/4.5 contains 80 mcg of budesonide and 4.5 mcg of formoterol fumarate dihydrate per emitted dose.

SYMBICORT 160/4.5 contains 160 mcg of budesonide and 4.5 mcg of formoterol fumarate dihydrate per emitted dose.

Each strength is contained in a pressurized aluminum canister fitted with a ——— valve, a shield, a red plastic actuator body with white mouthpiece, and an attached gray dust cap. Each canister contains 120 inhalations and has a net fill weight of 9 grams.
Each canister is packaged in a foil overwrap pouch, with desiccant sachet, inside a carton.

Each strength is also represented in a 60 actuation presentation as physician's samples only.

EER Status: **Acceptable** 7-Jul-2006

Consults:

Biometrics:	PTIT as alternate method for content uniformity; Do not recommend, 7-Apr-2006
Pharm/Tox:	Drug substance impurities qualified, 22-May-2006 Extractables and leachables qualified, 23-May-2006
EA:	Categorical exclusion granted under 21 CFR 25.31(b)
DMETS:	requested 28-Oct-2005
DDMAC:	requested 31-Oct-2005
Microbiology:	Recommend approval, 14-Feb-2006

Methods Validation: Method validation package is provided. Samples will be requested for method validation study to be conducted by FDA laboratories.

Original Submission: 23-Sep-2005

Post-Approval Agreements:

The applicant agrees to the following post-marketing agreements:

1. To provide a full detailed assessment of the stability trend in fine particle dose (based on stability data through 18 months) in October 2006,

2. To reevaluate acceptance criteria for unmicronized and micronized formoterol fumarate dihydrate drug substances and drug product within 1 year of the approval of this NDA,

3. To study the long term stability for the one-time study of drug product canisters stressed ,

4. To provide a reassessment of the drop testing of canisters and to report the data,

5. To modify the method for leakage rate (in October 2006),

6. To submit data for the proposed actuator by the end of September 2006 as a CBE-30 supplement if the NDA has been approved prior to that time (The actuator used in NDA studies is no longer available.),

7. To extend the expiration dating period beyond 12 months in a prior approval supplement based on real time data,

8. To evaluate options for improving the sensitivity (LOQ) for the (leachable) assay and to limit to less than (this was requested in our pharm/tox consult review),

9. To provide an updated methods validation package not later than September 4, 2006.

10. To provide the Agency with their understanding of the Agency's PTIT proposal for dose content uniformity (DCU), for confirmation. If possible, they will evaluate the Agency's PTIT proposal for DCU, based on data collected in the first year post approval; this will be performed within 1 year of the approval date.

Drug Substance:

Budesonide, a corticosteroid, has the chemical name (R,S)-11β,16α,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 430.5 grams/mole, an empirical formula of $C_{25}H_{34}O_6$, and a mixture of two epimers (22R and 22S). The budesonide micronized drug substance used for manufacture is the same as that for approved Pulmicort Turbuhaler (NDA 20-441).

Formoterol fumarate dihydrate, a β_2- adrenergic receptor agonist, has the chemical name (R*,R*)-(±)-N-[2-hydroxy-5- [1-hydroxy-2-[[2-(4- methoxyphenyl)-1-methylethyl] amino] ethyl] phenyl] formamide, (E)-2-butendioate(2:1), dihydrate. Formoterol fumarate dihydrate (2:1 salt) is a white to off-white powder; is slightly soluble in water from pH 4-8; has an octanol-water partition coefficient at pH 7.4 of 2.6; has a formula weight of 840.9 grams/mole; and has an empirical formula of $C_{42}H_{56}N_4O_{14}$. Formoterol (free base) is a racemic mixture of the 2 isomers α1R, α2R and α1S, α2S (designated R*,R*) giving 4 stereoisomers; has an empirical formula of C19H24N2O4; has a molecular weight of 344.4 grams/mole; and displays two pKa values at 25°C of 7.9 for the phenolic group and 9.2 for the amino group.

Formoterol fumarate dihydrate and formoterol fumarate dihydrate micronized drug substances have been shown to be stable for 36 months during long-term storage at 25°C/60% RH in a well-closed aluminum container. The retest periods for these drug substances are currently ——.

Conclusion: Drug substance is acceptable.

Drug Product:

Symbicort Inhalation Aerosol is a Metered Dose Inhaler (MDI). The final container is an aluminum canister —— containing a suspension of the two micronized drug substances, along with excipients, in a —— propellant. The suspension containing micronized budesonide, micronized formoterol fumarate dihydrate, Povidone K25 (suspending agent), and PEG 1000 (lubricant) is maintained in —— propellant (HFA-227) under pressure in the final container.

Noteworthy, for an inhalation product, are the use of HFA-227 (apaflurane; 1,1,1,2,3,3,3-heptafluoropropane) as a new propellant and the use of Povidone K25 (polyvinylpyrrolidone K25) and PEG 1000 (polyethylene glycol 1000) as new excipients.

The drug product has two presentations:

SYMBICORT 80/4.5* contains 80 mcg of budesonide and

4.5 mcg of formoterol fumarate dihydrate per emitted dose (120 actuations).

SYMBICORT 160/4.5* contains 160 mcg of budesonide and 4.5 mcg of formoterol fumarate dihydrate per emitted dose (120 actuations).

*4.5 mcg formoterol fumarate dehydrate is equivalent to 3.7 mcg formoterol (free base)

The final drug product is overwrapped in an aluminum foil laminate pouch containing a desiccant sachet. The materials of construction of the drug product include: the aluminum can with a actuator made of ; and valve components

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

A method validation package, describing the test methods and validation procedures, including information supporting the reference standard, is provided and will be updated by the applicant by September 4, 2006. Samples of the drug substance and drug product will be requested for the method validation study to be conducted in the FDA laboratories.

Pending approval of the tradename, the package insert, container labels, and carton labels are acceptable.

Adequate stability data were provided to support a 12 month expiration date.

The applicant adequately responded to all comments and requests for information.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval.**

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

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/s/

Blair Fraser
7/19/2006 05:25:05 AM
CHEMIST

7/18/06

NDA 21-929

Symbicort (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

AstraZeneca LP

Alan C. Schroeder, Ph.D.
Office of New Drug Quality Assessment

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Chemistry Assessment **13**

Chemistry Review Data Sheet

1. NDA 21-929

2. REVIEW #2:

3. REVIEW DATE: July 18, 2006

4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	23-SEP-2005
Amendment	21-OCT-2005
CMC filing review	07-DEC-2005
Filing Review Letter	06-DEC-2005
CMC telecon	13-DEC-2005
Amendment	27-DEC-2005
CMC telecon	11-JAN-2006
Amendment	30-JAN-2006
CMC IR Letter #1	08-MAR-2006
CMC IR Letter #2	12-APR-2006
CMC IR Letter #3	04-MAY-2006
CMC IR Letter #4	24-MAY-2006
CMC IR Letter #5	08-JUN-2006
CMC IR Letter #6	05-JUL-2006

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6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	13-APR-2006
Amendment (clarification requested by Applicant)	19-APR-2006
Amendment	27-APR-2006
Amendment	10-MAY-2006
Amendment	15-MAY-2006
Amendment	31-MAY-2006
Amendment	01-JUN-2006
Amendment	14-JUN-2006
Amendment	12-JUL-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	AstraZeneca LP
Address:	1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355
Representative:	Mark A. Desiato Director, Regulatory Affairs
Telephone:	302-885-1386

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Symbicort Inhalation Aerosol
b) Non-Proprietary Name (USAN): budesonide and formoterol fumarate dihydrate inhalation aerosol
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4 (New combination)
- Submission Priority: S

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

10. PHARMACOL. CATEGORY:

budesonide – anti-inflammatory corticosteroid
formoterol fumarate – long-acting selective beta2-adrenergic agonist

(SYMBICORT is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older.)

11. DOSAGE FORM: inhalation aerosol

12. STRENGTH/POTENCY:

80 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose), and
160 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose)

13. ROUTE OF ADMINISTRATION: inhalation

14. Rx/OTC DISPENSED: _x__Rx ___OTC

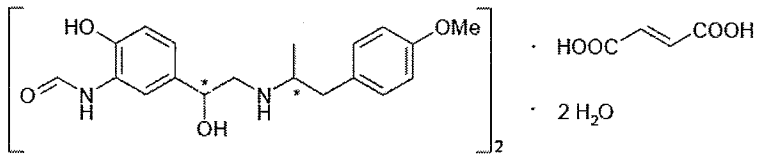
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X____Not a SPOTS product

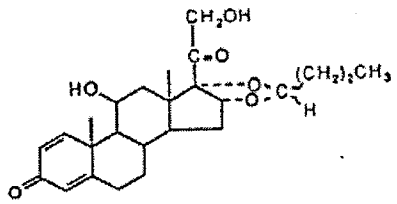
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Figure 1 Structure of formoterol fumarate dihydrate



Structure of budesonide:

Structural formula



Budesonide is a corticosteroid designated chemically as
(RS)-11β, 16α, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is C25H34O6 and its molecular weight is 430.5.

Formoterol fumarate dihydrate is a selective beta2- agonist designated chemically as (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4- methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate. The empirical formula of formoterol is C42H56N4O14 and its molecular weight is 840.9.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate		DMF is referenced in LOA only for an organic extractables method which has not been the subject of a recent deficiency. Note: Extractable/ leachable information is in this application. Additional information in other DMFs (see below).
	III			1	Adequate	6/1/2006	
	III			3	Adequate	2/22/2006	Adequate for this NDA based on Dr. Rogers review. Note that this NDA also addresses controls for extractables and leachables
	III			1	Adequate	7/14/2006	
	III			1	Adequate	6/01/2006	
	III			3	Adequate	2/22/2006	Dr. Rogers' review
	III			1	Adequate	2/13/2006	

Chemistry Review Data Sheet

	III		1	Adequate	5/23/2006	
	III		1	Adequate	6/07/2006	
	III		1	Adequate	7/11/2006	
	III		1	Inadequate (review of response withheld pending future NDA submission for new actuator.)	2/27/2006	Dr. Shaw This DMF is not needed for approval of this NDA, which does not provide for source of the
	III		1	Adequate		5/30/2006
	III		7	N/A		Review not needed (note A)
	IV		1	Adequate	6/28/2006	

Note that there are other supporting DMFs that support some of the DMFs listed above. These supporting DMFs are listed in the appropriate DMF reviews.

Note A – DMF is for DMF Holder provided information to AstraZeneca in this NDA, that complies with 21 CFR 177.1660 (polyester resins) and 21 CFR 178.3297 (colorant for polymers). No additional information is needed since the shield does not come in contact with the drug formulation or with the patient's mouth.

[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
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 63,394	Symbicort MDI

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Recommend against acceptance of applicant's PTIT proposal for dose content uniformity	4/24/2006	MeiYu Shen Yi Tsong
EES	Acceptable	7/07/2006	S. Adams
Pharm/Tox	The following are qualified in the drug product: formoterol-related impurities and degradants, budesonide-related impurities and degradation products, residual solvents), and foreign particles and the known leachables and extractables including	5/22/06 and 5/23/2006 (2 reviews)	Timothy W. Robison
Biopharm	N.A.		
Labeling			DMETS and DDMAC labeling consults submitted by project manager.
Methods Validation	Not yet requested		Updated MV package will be provided NLT September 4, 2006.
OPDRA	N.A.		
EA	Satisfactory.		Categorical exclusion requested in original NDA and found satisfactory in the present review.
Microbiology	Approval	2/14/2006	Anastasia G. Lolas

The Chemistry Review for NDA 21-929

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from a CMC perspective.

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

The following post-marketing agreements have been made by the applicant:

1. To provide a full detailed assessment of the stability trend in fine particle dose (based on stability data through 18 months) in October 2006,

2. To reevaluate acceptance criteria for unmicronized and micronized formoterol fumarate dihydrate drug substances and drug product within 1 year of the approval of this NDA,

3. To study the long term stability for the one-time study of drug product canisters stressed at (to be reported in their annual report),

4. To provide a reassessment of the drop testing of canisters and to report the data,

5. To modify the method for leakage rate in October 2006),

6. To submit data for the proposed actuator manufactured by the end of September 2006 as a CBE-30 supplement if the NDA has been approved prior to that time (The actuator used in NDA studies is no longer available.),

7. To extend the expiration dating period beyond 12 months in a prior approval supplement based on real time data,

8. To evaluate options for improving the sensitivity (LOQ) for the assay and to limit to less than (this was requested in our pharm/tox consult review),

9. To provide an updated methods validation package not later than September 4, 2006.

10. To provide the Agency with their understanding of the Agency's PTIT proposal for dose content uniformity (DCU), for confirmation. If possible, they will evaluate the Agency's PTIT proposal for DCU, based on data collected in the first year post approval; this will be performed within 1 year of the approval date.

II. Summary of Chemistry Assessments

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

Symbicort Inhalation Aerosol is a MDI with HFA-227 (apaflurane; 1,1,1,2,3,3,3-heptafluoropropane) as the propellant and two new excipients (for an inhalation product), PEG 1000 (polyethylene glycol 1000) and Povidone K25 (polyvinylpyrrolidone K25). HFA-227 is apparently not yet used in a marketed drug product in the USA. Both micronized drug substances are present in the drug product suspension as suspensions, and this makes it important to control the solid state properties of the drug substances.

The drug product has four presentations: 2 strengths (80/4.5 and 160/4.5, budesonide/formoterol fumarate dihydrate, expressed as µg of drug delivered from the mouthpiece) and two fill sizes (60 and 120 actuations). The 60 actuation presentations are only for physicians' samples. Each dose is 2 actuations and the proposed dosage is 2 actuations twice a day.

The container closure system consists of a canister sealed with a metering valve . The valve "typically" delivers of suspension formulation per actuation. There is a "shield component" which fits on the end of the canister, and an actuator/mouthpiece.

The actuator mouthpiece (including the spray orifice) has not been changed throughout development of this drug product. The drug product is overwrapped in an aluminum foil laminate pouch containing a desiccant sachet.

The materials of construction of the drug product include the following: aluminum can actuator and valve components made of the

A number of changes have been made in the drug product after Phase 3 studies (see below and see later in this review for a discussion in the Pharmaceutical Development Section).

Manufacture and control of one of the two drug substances, micronized budesonide, is cross-referenced to AstraZeneca's approved NDA 20-441 (Pulmicort Turbuhaler).

AstraZeneca has its own (new) manufacturing process for the other drug substance, formoterol fumarate dihydrate. Formoterol has 2 asymmetric carbons.

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

This information is from the proposed package insert (based on Agency requested modifications).

The proposed expiration dating period in the original NDA is 12 months.

C. Basis for Approvability or Not-Approval Recommendation

This section presents highlights of the more significant issues for this application.

There were a number of changes made in the drug product between Phase 3 clinical batches and the NDA stability batches. The applicant has provided data to compare the performance of the two products (delivered dose uniformity data and aerodynamic particle size distribution data). Overall, the release data for performance attributes between clinical and commercial batches are quite similar, although some batch to batch variability is observed. Overall, the stability data from clinical batches do not appear to be substantially different from the primary NDA stability data. In certain cases (e.g., some APSD/fine particle dose data), the clinical batch stability data may be somewhat tighter in terms of variability when compared to the NDA stability data (although there are fewer data points for the clinical batches). Observed variability and occasional outliers in the delivered dose uniformity results and the aerodynamic particle size distribution results were discussed with the medical officers (DPAP): the result was that no clinical concerns were identified.

One of the significant concerns about the drug product during the IND studies was the sensitivity of the valve to stress testing during manufacture (e.g . This problem appears to have been resolved. See further explanation of this in Chemistry Review #1 for this NDA, including the Executive Summary. A post-marketing agreement (as mentioned earlier in this summary) will confirm this by studying the long term stability for the one time study of drug product canisters stressed at .

The applicant has proposed a parametric tolerance interval test (PTIT) approach for the dose content uniformity (DCU) specification. This approach falls considerably short of the PTIT standard that has been proposed by the Agency at the October 2005 Pharmaceutical Science Advisory Committee Meeting. Therefore, the applicant has dropped this specification at the Agency's request. They will instead use their alternative "counting test" specification for DCU, with a modification of the outlier test based upon their data and based upon their proposal to store and ship the drug product in an inverted orientation. This gives an improved data set in terms of outliers, relative to the data set that includes upright storage. The carton will be labeled to indicate the proper storage position. Based on data collected during the first year post-approval, the applicant has agreed to revisit the PTIT approach within a year of approval of this NDA, to see if the FDA approach may be implemented.

The applicant has informed the Agency that their actuator/mouthpiece supplier will no longer provide this component, and that they have been qualifying a new supplier. At the time of the NDA submission, they did not have data available yet to support this change. Appropriate comparative data for the mouthpiece and the drug product will be proposed in a CBE-30 supplement if the information is provided after approval of this NDA.

A direct comparison of leachables and extractables data are necessary in order to support an extractables/leachables correlation between drug product components and the drug product itself. Because the current leachables data are so limited over the time of the stability study, an agreement has been made by the applicant to include leachables testing to the stability protocol for the first three commercial stability batches of the 60-actuation product presentations. This is an important issue, since leachables testing will not be performed routinely on the drug product, rather the extractables from the container closure components will be controlled. The acceptability of this approach depends upon the establishment of an extractables/leachables correlation (to show that when device components have extractables controlled at certain levels, then corresponding drug product leachables are controlled to safe levels). For this product, the extractables/leachables correlation will need to be confirmed after approval. The pharmacologist/toxicologist has found the maximum levels (permitted by the acceptance criteria) of specified leachables to be safe.

NDA stability data provided to this NDA show a decreasing trend on stability in fine particle dose with some batches, which have data close to the lower end of the proposed acceptance criteria range at the 12 month stability time point. As indicated above under item I.B., a full detailed stability assessment based on 18 months of data will be provided in October 2006, relative to the apparent stability trend in fine particle dose. Some ameliorating factors are as follows. Available stability data to date suggest that a significant amount of the change in fine particle dose takes place within 3 months after storage, and it is claimed that the supportive stability data show no significant change during the second year of storage. In addition, the acceptance criteria for fine particle dose was modified somewhat based on additional summary stability data provided in the January 30, 2006, amendment. The applicant will only extend the initial 12 month expiration dating period in a prior approval supplement based upon real time data.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

A.Schroeder/ONDQA/7-18-2006
B.Fraser/ONDQA/_____
C.Jackson/DPAP/Date

C. CC Block

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Alan Schroeder
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7/19/2006 05:18:04 AM
CHEMIST

4/24/06

NDA 21-929

Symbicort (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

AstraZeneca LP

Alan C. Schroeder, Ph.D.
Office of New Drug Quality Assessment

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1. NDA 21-929

2. REVIEW #1:

3. REVIEW DATE: April 19, 2006

4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC filing review	07-DEC-2005
CMC telecom	13-DEC-2005
CMC telecon	11-JAN-2006
CMC IR Letter #1	08-MAR-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	23-SEP-2005
Amendment	21-OCT-2005
Amendment	27-DEC-2005
Amendment	30-JAN-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	AstraZeneca LP
Address:	1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355
Representative:	Mark A. Desiato Director, Regulatory Affairs
Telephone:	302-885-1386

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Symbicort
b) Non-Proprietary Name (USAN): budesonide/formoterol inhalation aerosol
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4 (New combination)
- Submission Priority: S

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

10. PHARMACOL. CATEGORY:

budesonide – anti-inflammatory corticosteroid
formoterol fumarate – long-acting selective beta2-adrenergic agonist

(SYMBICORT is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older.)

11. DOSAGE FORM: inhalation aerosol

12. STRENGTH/POTENCY:

80 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose), and
160 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose)

13. ROUTE OF ADMINISTRATION: inhalation

14. Rx/OTC DISPENSED: _x__Rx ___OTC

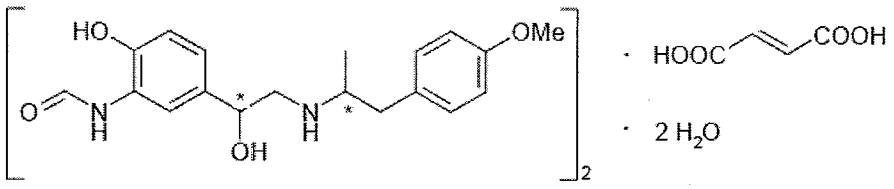
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

_X___Not a SPOTS product

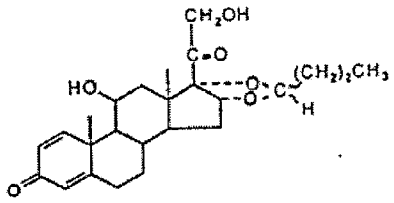
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Figure 1 **Structure of formoterol fumarate dihydrate**



Structure of budesonide:

Structural formula



Budesonide is a corticosteroid designated chemically as (RS)-11β, 16α, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is C25H34O6 and its molecular weight is 430.5.

Formoterol fumarate dihydrate is a selective beta2- agonist designated chemically as (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4- methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate. The empirical formula of formoterol is C42H56N4O14 and its molecular weight is 840.9.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III	—	—	3	Adequate		— referenced in LOA are only for an organic extractables method — which has not been the subject of a recent deficiency. Note: Extractable/ leachable information is in this application.

Chemistry Review Data Sheet

							Additional information in other DMFs (see below).
	III			1	Inadequate	3/3/2006	
	III			3	Adequate	2/22/06	Adequate for this NDA based on Dr. Rogers review. Note that this NDA also addresses controls for extractables and leachables
	III			1	Inadequate	2/9/06	Review by Dr. Art Shaw
	III			1	Inadequate	3/2/06	
	III			3	Adequate	2/22/06	Dr. Rogers' review
	III			1	Adequate	2/13/2006	
	III			1	Inadequate	2/13/2006	
	III			1	Inadequate	2/13/2006	Dr. Shaw's review
	III			1	Inadequate	2/5/2006	Dr. Shaw's review
	III			1	Inadequate	2/27/2006	Dr. Shaw
	III			7	See comments.		per Dr. Shaw, not reviewable due to inadequate LOA (see letter for DMF
	III			7	N/A		Review not needed (note A)
	IV			3	Inadequate	1/14/2005	No response to deficiency letter dated Jan. 24,

Chemistry Review Data Sheet

							2005
Note that there are other supporting DMFs that support some of the DMFs listed above. These supporting DMFs are listed in the appropriate DMF reviews.							

Note A – DMF is for [redacted] DMF Holder [redacted] has provided information to AstraZeneca in this NDA, that [redacted] complies with 21 CFR 177.1660 (polyester resins) and 21 CFR 178.3297 (colorant for polymers). No additional information is needed since the shield does not come in contact with the drug formulation or with the patient's mouth.

[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
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 63,394	Symbicort MDI

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			Pending review for PTIT (for DCU)(2/21/06 formal consult; informal consult 2/2/06)
EES			Pending (11/9/05 submitted)
Pharm/Tox			Pending (3/14/06 consult) – formoterol d.s. impurities; d.p. impurities and degradation products and foreign particles.
Biopharm			
LNC			DMETS and DDMAC consults submitted by project manager.
Methods Validation			
OPDRA			
EA			Categorical exclusion requested in original NDA and found satisfactory in the present

			review.
Microbiology	Approval	2/14/2006	Anastasia G. Lolas

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The Chemistry Review for NDA 21-929

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable from a CMC perspective. Two IR letters have been sent to the applicant and the issues should be satisfactorily addressed. These two IR letters are equivalent to a DR letter. Approvability is also pending satisfactory pharmacology/toxicology consult review, biometrics consult review, EER and labeling. A pharm/tox consult for leachables is deferred pending additional information that has been requested.

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

Agreements in several areas are being requested (see IR letters). These include the following agreements: to add leachables testing to the post-approval stability protocol for the first 3 commercial stability batches, to reevaluate acceptance criteria for drug substances and drug product within 1 year of the approval of this NDA, to study the long term stability for the one time study of drug product canisters stressed at ——— and to report the data, to modify the method for leakage rate ——— , and to submit lot numbers, sample quantities and certificates of analysis when samples are requested for methods validation.

II. Summary of Chemistry Assessments

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

Symbicort Inhalation Aerosol is a MDI with HFA-227 (apaflurane; 1,1,1,2,3,3,3-heptafluoropropane) as the propellant and two new excipients (for an inhalation product), PEG 1000 (polyethylene glycol 1000) and Povidone K25 (polyvinylpyrrolidone K25). Both micronized drug substances are present in the drug product suspension as suspensions, and this makes it important to control the solid state properties of the drug substances.

The drug product has four presentations: 2 strengths (80/4.5 and 160/4.5, budesonide/formoterol fumarate dihydrate, expressed as µg of drug delivered from the mouthpiece) and two fill sizes (60 and 120 actuations). Each dose is 2 actuations and the proposed dosage is 2 actuations twice a day.

The container closure system consists of a canister sealed with a metering valve The valve "typically" delivers of suspension formulation per actuation. There is a "shield component" which fits on the end of the canister, and an actuator/mouthpiece. The drug product is overwrapped in an aluminum foil laminate pouch containing a ——— desiccant sachet.

The materials of construction of the drug product include the following: aluminum can actuator and valve components made of the

A number of changes have been made in the drug product after Phase 3 studies (see below and see later in this review for a discussion in the Pharmaceutical Development Section).

Manufacture and control of one of the two drug substances, micronized budesonide, is cross-referenced to AstraZeneca's approved NDA 20-441 (Pulmicort Turbuhaler).

AstraZeneca has its own (new) manufacturing process for the other drug substance, formoterol fumarate dihydrate. Formoterol has 2 asymmetric carbons.

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

This information is from the proposed package insert.

The proposed expiration dating period in the original NDA is 12 months. Additional presentations of stability data have been requested, and there is concern about fine particle stability in some batches (see item C, below).

C. Basis for Approvability or Not-Approval Recommendation

This section presents highlights of the more significant issues for this application.

There were a number of changes made in the drug product between Phase 3 and the the NDA stability batches. The applicant has provided a limited amount of graphical data to compare the performance of the two products (dose content uniformity data based on delivered dose 1 and aerodynamic particle size distribution data) which appear quite similar (perhaps with more scatter in the clinical batches compared to the proposed commercial batches), and they have provided the results of statistical analysis which do not show a statistically significant difference in either performance parameter, between the clinical and proposed commercial batches). There is a small difference, not considered consequential, in delivered dose through life (2% and 3% increase for the commercial product and the clinical product, respectively.) This applies to both drug substances. Mean fine particle dose
label claim in the commercial product relative to the pivotal clinical batches for formoterol fumarate dihydrate. *Additional comparisons of release and stability data are being requested to confirm the lack of a substantitive difference between the two versions of the drug product, because of the number of changes that were made.* The changes between the clinical and NDA stability batches are described in this review.

Executive Summary Section

It is noted by the applicant that the mouthpiece component (including the orifice) has been kept constant from phase 3 through the commercial product.

One of the significant concerns addressed with the sponsor during the IND studies was the sensitivity of the valve to stress testing during manufacture . See summary of CMC IND minutes for this product in the NDA filing review for N21-929. This sensitivity had resulted in problems in the product's ability to meet delivered dose uniformity acceptance criteria. The problem was attributed to deformation between valve body and gathering ring . This was considered to be result in a lack of robustness of the valve to conditions that may be encountered during shipping or patient handling. This approach appears to have been successful in resolving the problem based on data provided in this NDA. These include a small amount of stability data in a study in which drug product was maintained at then placed on stability (unwrapped) for 3 months at 25°C/60% RH. Mechanical robustness of the valve is demonstrated In addition, drug product stability data are provided from the stressed primary NDA stability batches, and this also demonstrates the robustness of the drug product.

The applicant has proposed a parametric tolerance interval test (PTIT) approach for the delivered dose uniformity specification. This approach falls considerably short of the PTIT standard that has been proposed by the Agency at the October 2005 Pharmaceutical Science Advisory Committee Meeting. Therefore, the applicant has been asked to drop this specification and to use their alternative "counting test" specification for dose content uniformity, with a modification on the outermost limits based upon their data and based upon their proposal to store and ship the drug product in an inverted orientation. This gives an improved data set in terms of outliers, relative to the data set that includes upright storage. The carton will be labeled to indicate the proper storage position.

The applicant has informed the Agency that their actuator/mouthpiece supplier will no longer provide this component, and that they have been qualifying a new supplier. At the time of the NDA submission, they did not have data available yet to support this change. Appropriate comparative data for the mouthpiece and the drug product will have to be provided and reviewed in order to make this change.

A direct comparison of leachables and extractables data are necessary in order to support an extractables/leachables correlation between drug product components and the drug product itself. In addition, because the leachables data are so limited over the time of the stability study, an agreement is needed to include leachables testing to the stability protocol for the first three commercial stability batches. This is an important issue, since leachables testing will not be performed routinely on the drug product and the acceptability of this depends upon the establishment of an extractables/leachables correlation (to show that when device components have extractables controlled at certain levels, then corresponding drug product leachables are controlled to safe levels).

Explanation and investigation are needed for the decreasing trend on stability in fine particle dose with some batches, which have data close to the lower end of the proposed acceptance criteria range at the 12 month stability time point. Concern is that these batches will drop out of specification by the next timepoint.

Explanation is requested for the observed higher variability in delivered dose on stability than at release.

Explanation is needed for very low outliers on stability in one batch, attributed to the automated test method.

The two active ingredients are deposited on the inside walls of the canister and on valve components as the drug product is used. The applicant needs to demonstrate the stability of the deposited drugs over the use

life of the product, especially if the canister were to be dropped. If drug may be resuspended from deposits on the container closure components, then there is the possibility of overdosing.

A number of supporting DMFs for this application are deficient and the DMF holders have been notified. These include DMFs for HFA-227 propellant, valve components, canister, canister actuator and foil laminate.

Other comments have been included in the IR letter dated March 8, 2006 and in the IR letter sent in April, 2006.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

A.Schroeder/ONDQA/4-19-2006
B.Fraser/ONDQA/_____
C.Jackson/DPAP/Date

C. CC Block

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