

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-929

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

NDA 21-929

NAME OF APPLICANT / NDA HOLDER

AstraZeneca LP

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMBICORT[®] pMDI

ACTIVE INGREDIENT(S)
Budesonide/formoterol fumarate

STRENGTH(S)
80 µg budesonide micronised and 4.5 µg formoterol fumarate dihydrate micronised per actuation;
160 µg budesonide micronised and 4.5 µg formoterol fumarate dihydrate micronised per actuation. ex-actuator

DOSAGE FORM

1 dose consists of 2 actuations of the pressurized metered-dose inhaler

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
6,123,924

b. Issue Date of Patent
9/26/2000

c. Expiration Date of Patent
9/26/2017

d. Name of Patent Owner
Fisons Limited

Address (of Patent Owner)
Aventis House,
50 Kings Hill Avenue Kings Hill
West Malling

City/State
Kent, England

ZIP Code
ME19 4AH

FAX Number (if available)

Telephone Number
(01732) 584000

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)
1800 Concord Pike

City/State
Wilmington, DE

ZIP Code
19803

FAX Number (if available)

Telephone Number
(800)-456-3669

E-Mail Address (if available)

General Counsel

AstraZeneca Pharmaceuticals LP

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.)	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

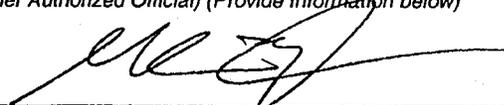
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



8/22/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Glenn M Engelmann, Vice President, General Counsel & Compliance Officer

Address

1800 Concord Pike

City/State

Wilmington DE

ZIP Code

19803

Telephone Number

(302)886-3244

FAX Number (if available)

(302) 886-1578

E-Mail Address (if available)

Glenn.Engelmann@astrazeneca.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahm/fdahm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

NDA 21-929

NAME OF APPLICANT / NDA HOLDER

AstraZeneca LP

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

SYMBICORT[®] pMDI

ACTIVE INGREDIENT(S)

Budesonide/formoterol fumarate

STRENGTH(S)

80 µg budesonide micronised and 4.5 µg formoterol fumarate dihydrate micronised per actuation;
160 µg budesonide micronised and 4.5 µg formoterol fumarate dihydrate micronised per actuation, ex-actuator

DOSAGE FORM

One dose consists of 2 actuations of the pressurized metered-dose inhaler

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,972,919

b. Issue Date of Patent
10/26/1999

c. Expiration Date of Patent
December 17, 2012

d. Name of Patent Owner
AstraZeneca AB

Address (of Patent Owner)
S-151 85

City/State
Sodertalje, Sweden

ZIP Code
SE-151-85

FAX Number (if available)

Telephone Number
01146855326000

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)
1800 Concord Pike

City/State
Wilmington, DE

ZIP Code
19803

FAX Number (if available)

General Counsel

Telephone Number
(800)-456-3669

E-Mail Address (if available)

AstraZeneca Pharmaceuticals LP

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) Claims 3, 4, 5, 11, 12, 16 and 17.	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Use for the long-term maintenance treatment of asthma in patients 12 years of age and older.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

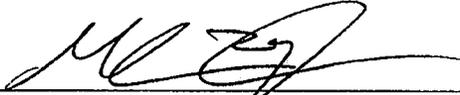
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



8/22/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Glenn M Engelmann, Vice President, General Counsel & Compliance Officer

Address

1800 Concord Pike

City/State

Wilmington DE

ZIP Code

19803

Telephone Number

(302)886-3244

FAX Number (if available)

(302) 886-1578

E-Mail Address (if available)

Glenn.Engelmann@astrazeneca.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
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- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
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First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

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2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
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NAME OF APPLICANT / NDA HOLDER

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ACTIVE INGREDIENT(S)

Budesonide/formoterol fumarate

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80 µg budesonide micronised and 4.5 µg formoterol fumarate dihydrate micronised per actuation;
160 µg budesonide micronised and 4.5 µg formoterol fumarate dihydrate micronised per actuation

DOSAGE FORM

One dose consists of 2 actuations of the pressurized metered-dose inhaler

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,674,860

b. Issue Date of Patent

October 7, 1997

c. Expiration Date of Patent

10/7/2014

d. Name of Patent Owner

AstraZeneca AB

Address (of Patent Owner)

S-151 85

City/State

Sodertalje, Sweden

ZIP Code

SE-151-85

FAX Number (if available)

Telephone Number

01146855326000

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

1800 Concord Pike

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Wilmington, DE

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19803

FAX Number (if available)

Telephone Number

(800)-456-3669

E-Mail Address (if available)

General Counsel

AstraZeneca Pharmaceuticals LP

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement:

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Claims 17, 18, 19, 22, 23, 25, 26, 27, 28, 29, 32, 33, 35 and 36 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Use for the long-term maintenance treatment of asthma in patients 12 years of age and older.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

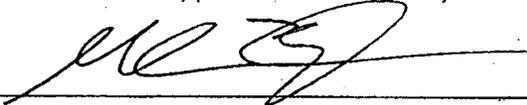
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



8/22/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Glenn M Engelmann, Vice President, General Counsel & Compliance Officer

Address

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The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahm/fdahm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 21-929

SUPPL #

HFD # 570

Trade Name Symbicort

Generic Name budesonide/formoterol

Applicant Name AstraZeneca

Approval Date, If Known July 21, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-929 Pulmicort Respules

NDA# 20-441 Pulmicort Turbuhaler

NDA# 20-831 Foradil Aerolizer

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

SD-039-0715
SD-039-0716
SD-039-0717
SD-039-0726
SD-039-0729

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

SD-039-0715 ,SD-039-0716, SD-039-0717, SD-039-0726, and SD-039-0729

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 63,394 YES ! NO
! Explain:

Investigation #2
IND # 63,394 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES
Explain:

!
! NO
! Explain:

Investigation #2

YES
Explain:

!
!
! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Colette Jackson
Title: Project Manager
Date: July 21, 2006

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Division Director, Division of Pulmonary and Allergy Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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SYMBICORT[®] (budesonide/formoterol) pMDI
NDA 21-929 Module 1

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

EXCLUSIVITY INFORMATION

AstraZeneca LP (AstraZeneca) requests 3 years of marketing exclusivity from the date of approval of SYMBICORT[®] (budesonide/formoterol) pMDI 80/4.5 µg and 160/4.5 µg for the long-term maintenance treatment of asthma in adults and patients 12 years of age and older. Exclusivity for this new drug application (NDA) is being claimed pursuant to 21 CFR 314.108(b)(4).

AstraZeneca is entitled to such exclusivity as this application contains reports of new clinical investigations (other than human bioavailability and pharmacodynamic studies), conducted with budesonide and formoterol combined in a pMDI device, essential to the approval of the application and conducted by AstraZeneca. The following investigations are "essential to the approval of the application" in that the application could not be approved by FDA for the indication of the long-term maintenance treatment of asthma in patients 12 years of age and older without the following investigations:

Study SD-039-0716: A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Trial of Symbicort[®] (80/4.5 µg) versus its Mono-Products (budesonide and formoterol) in Children (≥ 6 Years of Age) and Adults with Asthma- SPRUCE 80/4.5

Study SD-039-0717: A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Trial of Symbicort[®] (160/4.5 µg) versus its Mono-Products (budesonide and formoterol) in Adolescents (≥ 12 Years of Age) and Adults with Asthma- SPRUCE 160/4.5

Study SD-039-0726: A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled Study of SYMBICORT[®] pMDI Administered Once Daily in Adults and Adolescents with Asthma- STEM

Study SD-039-0719: A Six-Month, Randomized, Open-Label Safety Study of SYMBICORT (160/4.5 µg) Compared to Pulmicort Turbuhaler in Asthmatic Children Aged Six to Eleven Years- SAPLING

Morice AH, Kukova Z, Arheden L, Beckman O. The novel budesonide/formoterol pMDI is therapeutically equivalent to budesonide/formoterol Turbuhaler(R) in children with asthma. J Allergy Clin Immunol 2005;115(suppl):S209 (abstr 833)

To the best of AstraZeneca knowledge, and based on a thorough literature search conducted on August 25, 2005, there are no other published studies or publicly available reports that are relevant to the proposed formulations and conditions of use. [Databases searched - Planet, BIOSIS Previews, EMBASE, IPAB, Ovid MEDLINE(R). Search Strategy (order, key word, (number of hits)): 1 budesonide/ (19895); 2 formoterol/ (4137); 3 (budesonide and formoterol).ti. (510); 4 symbicort\$.af. (627); 5 sym.pc. (536); 6 1 and 2 (1543); 7 3 or 4 or 5 or 6 (1977); 8 pMDI.af. (1078); 9 rapihaler\$.af. (3); 10 (pressuri\$ adj meter\$ adj dos\$.af. (1584); 11 8 or 9 or 10 (1923); 12 7 and 11 (44); 13 remove duplicates from 12 (37).]

To the best of AstraZeneca knowledge, the above-referenced clinical investigations are “new” in that they have not been relied on by the FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of any such investigations.

The above-referenced clinical investigations were “conducted or sponsored by AstraZeneca” in that AstraZeneca was the sponsor of the US investigational new drug application (IND 63,394) under which the studies were conducted or was, in the case of studies conducted outside the United States, under common ownership and control with the AstraZeneca affiliated company that conducted and sponsored the study.



Liza O'Dowd, M.D.
Senior Director Medical Research

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Badrul Chowdhury
7/21/2006 04:05:11 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

ADA # 21-929 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: September 23, 2005 Action Date: July 23, 2005

HFD 570 Trade and generic names/dosage form: SYMBICORT® (budesonide/formoterol) MDI

Applicant: AstraZeneca Therapeutic Class: 4S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Asthma

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. <u>0</u>	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. <u><6</u>	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: Pulmicort Respules® provides treatment for this age group and SYMBICORT® is not likely to be used in a substantial number of patients in that age group since the therapeutic benefit over existing treatments is unknown.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. ≥6 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. <12 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- ✓There are safety concerns
- Adult studies ready for approval
- ✓Formulation needed

Other: _____

Date studies are due (mm/dd/yy): 12/31/07

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. Adult Tanner Stage _____

Comments:

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NDA 21-621

Page 3

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-929
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-796-1654.

(revised 10-14-03)

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Colette Jackson
12/5/2005 01:57:09 PM

REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

SYMBICORT® (budesonide/formoterol) inhalation aerosol

IND Number: 63,394

NDA Number: 21-929

Indication: SYMBICORT is indicated for the long-term maintenance treatment of asthma in patients twelve years of age and older.

1. What ages are included in your deferral request?

Asthma patients 6 to <12 years of age

2. Reason for deferring pediatric studies:

AstraZeneca has included asthma patients 6 to <12 years of age in the SYMBICORT pMDI clinical program and a pediatric assessment was made, characterizing the safety and effectiveness of twice-daily SYMBICORT (80/9, 160/9 and 320/9 mcg bid) in this patient population. However, a pediatric indication (asthma patients 6 to <12 years of age) is not being sought in this NDA

3. Have pediatric drug development plans been submitted to the Agency?

Yes No

A total of 1627 children 6 to <12 years of age (950 exposed to SYMBICORT MDI) were studied in protocols D5896C00013, SD-039-0716, SD-039-0718, SD-039-0719, SD-039-0725 and SD-039-0682 and are included in the safety and efficacy evaluation in this submission.

No pediatric drug development plans have been submitted for patients <6 years of age.

4. Suggested deferred date for submission of pediatric studies

As described above, data from several clinical studies in asthma patients 6 to <12 years of age are included in this submission.

REQUEST FOR A PARTIAL WAIVER OF PEDIATRIC STUDIES

SYMBICORT® (budesonide/formoterol) inhalation aerosol

IND Number: 63,394

NDA Number: 21-929

Indication: SYMBICORT is indicated for the long-term maintenance treatment of asthma in patients twelve years of age and older.

1. What are the age ranges included in your pediatric waiver?

The age range for this waiver request is for children <6 years of age.

A pediatric deferral has been requested for asthma patients 6 to <12 years of age.

2. Reasons for waiving pediatric studies:

Per 21 CFR 314.55(3)(i):

At this time the therapeutic benefit over existing treatments in this age group is unknown, primarily due to the limitations of the current methods available to deliver the inhalation aerosol SYMBICORT in this young population; it is therefore unlikely to be used in a substantial number of patients in this age group.

The current SYMBICORT product is a fixed combination containing the glucocorticosteroid budesonide and the long-acting beta-2 agonist formoterol delivered in a HFA metered dose inhaler. As such, the two components which make up the combination (budesonide and formoterol) cannot be titrated and may not be suitable for young children. In addition, it is unlikely that very young patients have the coordination and dexterity to actuate and inhale this medication appropriately without assistance from caregivers and/or use of a supplementary device such as a spacer.

3. Justification for waiver

AstraZeneca has developed and markets a pediatric product containing the budesonide component of SYMBICORT in the form of PULMICORT RESPULES®. PULMICORT RESPULES is available in two strengths of 0.25 mg and 0.5 mg, and is indicated for the maintenance treatment of asthma and as prophylactic therapy for asthma in children 12 months to 8 years of age. Also, on the market from other sponsors is the short-acting beta-2 agonist albuterol, available as a solution for inhalation and indicated in the relief and prevention of bronchospasm in children 2 to 12 years of age with reversible obstructive airway disease. Both of these products are administered via a nebulizer.

Other products available for the treatment of asthma in children less than 6 years of age are listed below:

Treatment	Indication
SINGULAIR [®] (montelukast) Tablets	Prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older
ADVAIR DISKUS [®] (fluticasone/salmeterol)	Long-term, twice daily, maintenance treatment of asthma in patients 4 years of age and older
XOPENEX HFA [™] MDI (levoalbuterol)	Treatment or prevention of bronchospasm in patients 4 years of age and older

Based upon the availability of existing treatments AstraZeneca respectfully requests a partial waiver of studies in the pediatric subpopulation of less than 6 years of age.

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1104/08

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Alan C. Schroeder, Ph.D., Reviewing Chemist, Branch II, DPAI, ONDQA
E-mail Address: alan.schroeder@fda.hhs.gov
Phone: (301)-796-1749
Fax: (301)-796-9747

FROM: FDA
Division of Pharmaceutical Analysis, HFD-920
James Allgire
Room 1002
1114 Market Street
St. Louis, MO 63101

Through: B. J. Westenberger, Deputy Director, HFD-920
Phone: (314)-539-3869

SUBJECT: Methods Validation Report Summary

Application Number: NDA 21-929

Name of Product: Symbicort (budesonide and formoterol fumarate) Inhalation Aerosol
80 mcg budesonide/4.5 mcg formoterol fumarate dehydrate (emitted dose), and
160 mcg budesonide/4.5 mcg formoterol fumarate dehydrate (emitted dose)

Applicant: AstraZeneca LP

Applicant's Contact Person: Liuda Shtohryn, PharmD, CMC Regulatory Affairs Director

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

Telephone: 302-885-4108 Fax: 302-886-2822

Date NDA Received by DPA: 5/30/2007

Date Samples Received by DPA: 8/08/2007

Date Analytical Completed by DPA: 1/03/2008

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments:

See page 2 for Cover memo
See page 3 for Summary of Results

NDA 21-929
Symbicort® MDI

Please refer to your submission dated August 30, 2007, which requested an extension of your pediatric deferral date. We have the following comment.

Your deferred pediatric assessment required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required post-marketing study commitment. While we understand there may be a delay in submitting the post-marketing pediatric assessment and agree that it is reasonable, we can not change the due date of a post-marketing commitment.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-796-1230.

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Drafted: CCJ/September 20, 2007
Initialed: Barnes/ September 21, 2007
Starke/ September 24, 2007
Gilbert-McClain/September 24, 2007

Finalized: CCJ/September 24, 2007

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/s/

Colette Jackson
9/24/2007 02:47:08 PM
CSO

8/8/07



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

METHODS VALIDATION MATERIALS RECEIVED

NDA 21-929

Liuda Shtohryn, PharmD
CMC Regulatory Affairs Director
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Shtohryn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SYMBICORT (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol, 80 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose) and 160 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose) and to our May 31, 2007 letter requesting sample materials for methods validation testing.

We acknowledge receipt on August 8, 2007 of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have any questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (james.allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

James F Allgire
8/8/2007 04:12:40 PM

5/31/07



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

REQUEST FOR METHODS VALIDATION MATERIALS

NDA 21-929

Liuda Shtohryn, PharmD
CMC Regulatory Affairs Director
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Shtohryn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SYMBICORT (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol, 80 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose) and 160 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose).

We will be performing methods validation studies on SYMBICORT (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol, 80 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose) and 160 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose) as described in NDA 21-929.

In order to perform the necessary testing, we request the following sample materials and equipments:

Drug Product

SYMBICORT pMDI 80/4.5, 120 actuations – 50 units
SYMBICORT pMDI 160/4.5, 120 actuations – 50 units
Placebo pMDI – 2 units

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (james.allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

James F Allgire
5/31/2007 05:41:10 PM

5/10/07

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

CONSULTATIVE REQUEST FOR METHODS VALIDATION

TO: FDA
Division of Pharmaceutical Analysis, HFD-920
Attn: Nick Westenberger
Room 1002
1114 Market Street
St. Louis, MO 63101

FROM: Alan C. Schroeder, Ph.D., Reviewing Chemist, Branch II, DPAI, ONDQA
E-mail Address: alan.schroeder@fda.hhs.gov
Phone: (301)-796-1749
Fax.: (301)-796-9747

Through: Dr. Blair Fraser, Director, DPAI, ONDQA
Phone: (301)-796-1671

SUBJECT: Methods Validation Request

Application Number: **NDA 21-929**

Name of Product: Symbicort (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol
80 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose), and
160 mcg budesonide/4.5 mcg formoterol fumarate dihydrate (emitted dose)

Applicant: AstraZeneca LP

Applicant's Contact Person: Liuda Shtohryn, PharmD, CMC Regulatory Affairs Director

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

Telephone: 302-885-4108 Fax: 302-886-2822

The link to the electronic Methods Validation Package is the following: \\Cdsub1\21929\N_000\2006-08-31\cm\cmctoc.pdf

Date NDA Received by CDER: **9/23/2005**

Chemical/Therapeutic Type: 4S

Date of Amendment(s) containing the MVP: **8/31/2006**

Special Handling Required: No

DATE of Request: **5/22/2007**

DEA Class: N/A

Requested Completion Date: **12/31/07**

PDUFA User Fee Goal Date: **7/23/06**

This is to confirm the suitability of the proposed manufacturing controls as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request Form*. Upon receipt of the samples, please notify the review chemist via email to the email address cited above. Perform the tests indicated in item 3 of the attached *Methods Validation Request Form* as described in the accompanying MV package. In addition to including a summary of laboratory results, please also include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes. All information relative to this application is to be held confidential as required by 21 CFR 314.430.

Because of statutory time limits for processing applications, we request your report to be submitted promptly upon completion, but not later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. Please promptly advise the reviewing chemist of the date the validation process begins. If the requested completion date cannot be met, please promptly notify the reviewing chemist.

Upon completion of the requested validation/verification, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying memoranda). At the bottom of the report signed by the laboratory director or by someone designated by the director, place the filing code: **"MR/Method Validation Report."** Send by overnight courier to the above reviewing chemist.

ENCLOSURE: *Methods Validation Request Form.*

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-

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/s/

Michael Folkendt
5/29/2007 05:13:41 PM

DSI CONSULT: Request for Clinical Inspections

Date:

To: Ni Aye Khin, M.D., Branch Chief, GCP1, HFD-476
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

cc: Joanne L. Rhoads, M.D., Director, DSI, HFD-45
Badrul Chowdhury, M.D., Ph.D., Director, HFD-570

From: Colette Jackson, Regulatory Health Project Manager, HFD-570
Division of Pulmonary and Allergy Products

Subject: Request for Clinical Site Inspections
NDA 21-929
AstraZeneca
Symbicort (budesonide/formoterol fumarate dehydrate) Metered Dose
Inhaler

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Edward E. Lisberg, M.D. Spartanburg Pharmaceutical Research 126 Dillon Drive Spartanburg, SC 29307	SD-039-0716	18	Asthma
Sanchayita Tripathy, M.D. Clinical Research of the Ozarks 509 East 10th Street Rolla, MO 65401	SD-039-0716	21	Asthma

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Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Edward M. Kerwin, M.D. Clinical Research Institute of Southern Oregon, PC 3860 Crater Lake Avenue, Suite B Medford, OR 97504	SD-039-0717	15	Asthma
Mark H. Ellis, M.D. Children's Hospital of Orange County 725 West LaVeta Orange, CA 92868	SD-039-0717	12	Asthma
Mark H. Ellis, M.D. Children's Hospital of Orange County 725 West LaVeta Orange, CA 92868	SD-039-0729	3	Asthma

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) May 1, 2006. We intend to issue an action letter on this application by (division action goal date) June 25, 2006. The PDUFA due date for this application is July 23, 2006.

Should you require any additional information, please contact Colette Jackson at 301-796-1230.

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/s/

Colette Jackson
1/4/2006 03:16:37 PM

NDA 21-929
Symbicort (budesonide/formoterol)

Please refer to your September 23, 2005, new drug application (NDA) for Symbicort (budesonide/Formoterol). We also acknowledge receipt of your submission dated July 19, 2006. We have the following preliminary labeling comments and/or recommendations. Submit revised draft labeling incorporating the changes listed below.

Product Label:

- 1. Replace lines 321-322 with the following:

“systemically absorbed. In health subjects, 34% of this metered dose was deposited in the lung (as assessed by plasma concentration method and using a budesonide containing dry-powder inhaler) with an absolute systemic availability of 39% of the metered dose. Peak steady-state plasma concentration of budesonide administered by dry powder inhaler in”

The above change captures the data completely as in the budesonide dry powder inhaler label.

- 2. Delete the paragraph contained in lines 555-563. This is captured in lines 551-553, and lines 565-567. The paragraph contained in lines 555-563 describes the Figures in the Clinical Study section that is not necessary or appropriate for this section. Note that similar data for other products of this class are not further elaborated or described as you are proposing.
- 3. Line 810: We recommend that you consider replacing “eg” by “e.g.,” in this line and elsewhere in the label.
- 4. Lines 819-820: Replace “13176” with “13,176” and replace “13179” with “13,179.” This change reflects the insertion of a comma. Make similar changes elsewhere where large numbers appear.
- 5. Line 1177: Strike out the full word “recommended”.
- 6. We suggest that you replace lines 537-542 with the following:

“While the pharmacodynamic effect is via stimulation of beta-adrenergic receptors; excessive activation of these receptors commonly leads to skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.”

This change is meant to improve readability and to remove the term ~~_____~~ from this section.

Medication Guide:

8. Delete the following two sentences starting on line 202:

The Medication Guides follow standardized language, which these sentences do not match. In addition, the first sentence is factually incorrect in that the Medication Guide is required for the safe and effective use of the product. The second sentence is redundant.

9. You should be aware that the Medication Guide has a 10 point font size requirement.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-796-1230.

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/s/

Colette Jackson
7/20/2006 05:02:52 PM
CSO

Colette Jackson
7/20/2006 05:03:20 PM
CSO

7/17/06

NDA 21-929
Symbicort

NDA 21-929
Symbicort Inhalation Aerosol
Draft comments 7/17/06

The following comments are preliminary comments. We will have further labeling comments to be discussed at the teleconference of July 19, 2006. Line numbers refer to your annotated labeling and Medication Guide of July 11, 2006.

1. The following comments pertain to the package insert. Your proposed package insert contains some information that is either not present in the labels of drugs of the same class, not supported by substantial data, not supported by clinical data, or irrelevant to the drug product. Remove this information, as listed below. In addition, some information present in the labels of drugs in the same class is missing from your proposed product label. Add that information, as listed below.

2

- a. Lines 141, 321, and 347-351. Add language from the Pulmicort Turbuhaler and/or new language from Budesonide Inhalation Aerosol that is missing.
- b. Lines 355-362 and 498-503. Include language present in Foradil label that is missing.

2. The following comment pertains to the Medication Guide. We refer you to our fax of July 10, 2006. Replace lines 40-51 with the language as shown in our fax of July 10.

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/s/

Sandra Barnes
7/17/2006 05:48:24 PM
CSO

7/16/06

NDA 21-929
Symbicort (budesonide/formoterol)

Please refer to your September 23, 2005, new drug application (NDA) for Symbicort (budesonide/Formoterol). We also acknowledge receipt of your submission dated June 27, 2006. We have the following preliminary labeling comments and/or recommendations for the proposed Medication Guide. Submit revised draft labeling incorporating the changes listed below and shown in the attached labeling.

1. The two highlighted areas on lines 254 and 382 will need to be changed to match wording that will be proposed for the PI, as discussed at the June 29, 2006, labeling teleconference.
2. Figure 4 shows the mouth open, but the instructions in the text state to close the lips around the mouthpiece. Please address this.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-796-1230.

Enclosure: Recommendations to the Proposed Medication Guide

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 X Draft Labeling

 Deliberative Process

*Withheld Track Number: Administrative-*_____

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/s/

Colette Jackson
7/10/2006 05:20:19 PM
CSO

7/5/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 21-929

AstraZeneca Pharmaceuticals LP
P.O. Box 8355
Wilmington, DE 19803-8355

Attention: Mark A. DeSiato
Director of Regulatory Affairs

Dear Mr. DeSiato:

Please refer to your September 23, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbicort (budesonide/formoterol fumarate dihydrate) MDI.

We also refer to your submissions dated October 21, November 2, and 8, and December 8, and 27, 2005, and January 30, April 13, 19, and 27, May 10, 15, and 31, and June 1, and 14, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide updated specifications for drug product and for drug product components.
2. Provide an agreement that you will extend the expiration dating period beyond 12 months in a prior approval supplement based upon real time data, because of the limited leachables data currently available and the indication of a decreasing trend in fine particle mass.
3. We encourage you to improve the sensitivity (LOQ) for the _____ assay, and to limit _____ in the _____ components to less than _____
4. Provide an agreement to provide within two months of this letter, an updated Methods Validation package, including all of the usual information (or hypertext links to that information) such as analytical procedures, validation reports, composition, specifications, information supporting the integrity of the reference standards, and a summary flow chart of the synthesis of formoterol fumarate dihydrate and a list of known impurities/side reaction products. Information that may be submitted to the laboratories along with the samples, when requested, includes batch numbers, quantities of samples, certificates of analysis, and MSDS information.
5. Provide an updated stability protocol for the first three commercial stability batches to include leachables testing over multiple time points across the proposed shelf life, as agreed in the April 13, 2006, amendment.

6. This comment pertains to your agreement to consider the Agency's PTIT proposal for a specification for dose content uniformity, based on data collected during the first year post-approval for this drug product.

If you will not have collected the appropriate data to assess the PTIT approach and specification in the first year post-approval, due to the nature of the approved dose content uniformity specification, then you are released from this agreement. If you can find a way to consider the Agency's PTIT approach, then the Agency will provide any additional information about this approach that you need.

7. The review of the latest amendment in ~~_____~~ : DMF ~~_____~~ which pertains to the actuator, will be deferred pending your future submission to this NDA for this source of the actuator.

If you have any questions, call Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

Blair A. Fraser, Ph.D
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Alan Schroeder
7/5/2006 04:40:43 PM
Signed for Blair Fraser, Ph.D.

NDA 21-929
Symbicort (budesonide/formoterol)

Please refer to your September 23, 2005, new drug application (NDA) for Symbicort (budesonide/Formoterol). We also acknowledge receipt of your submissions dated January 19, March 7, and June 16, 2006. We have the following preliminary labeling comments and/or recommendations. Note that there are several locations where we have asked you to supply new data points or new information.

1. Please submit a Medication Guide, which will replace the 'Patient Package Insert' and the 'Summary of Information for Patients'.

Comments regarding the PI:

2. Overall, we have tried to make the paragraph order and wording read in such a way that a reader can match it with other inhaled corticosteroid/long-acting beta agonist drug products.
3. Replace all references to *Patient's Instructions for Use* with references to the *Medication Guide*.
4. Please note that in several areas of the label we are requesting additional information, numbers or figures. Replace and 'xx' with the appropriate number, and add the requested figure to the Clinical Studies subsection.
5. Regarding the DESCRIPTION section:
 - a. Add information regarding instructions to shake prior to use. Update the appropriate section with the correct numbers. Note that similar information is requested in the PRECAUTIONS: Information for Patients subsection and the DOSAGE AND ADMINISTRATION section.
 - b. Add information regarding the number of actuations for each fill weight/presentation.
 - c. Since your product was never developed as a CFC formulation, information stating that it does not contain CFCs is not necessary.
 - d. Remove statements regarding what Symbicort does not contain. These statements are unnecessary,
6. Regarding the CLINICAL PHARMACOLOGY section and the Clinical Studies subsection:

 - b. We have changed the references in each study to the Symbicort dosage strength rather than to the dose used. Update the Legends in all tables and figures to refer to Symbicort and other active treatments by dosage strength and dose administered, e.g. Symbicort 160/4.5, 2 inhalations twice daily.
 - c. Withdrawal due a predefined asthma event had originally been a primary endpoint and is an important, clinically meaningful endpoint. We have added information

and a table for each study regarding withdrawals and patients who qualified for withdrawal due to a predefined asthma event.

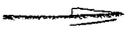
- d. We have the following comments regarding the Selected Secondary Efficacy Variables table (now Table 2):
 - i. We have added albuterol rescue use and average daily symptom score results from Study 1, but removed symptom-free days.
 - ii. Update the table so that the order of columns matches that of Table 1, i.e. Symbicort, the free combination of budesonide and formoterol, budesonide, formoterol, and placebo.
 - iii. Update the footnote to state that the results were based on last available data.
 - e. Add the appropriate numbers to the Asthma Quality of Life Questionnaire paragraph in Study 1.
 - f. Add a Figure in Study 2 similar to that of Figure 1 for Study 1. Show the N for each visit and EOT, as currently represented in Figure 1. Note our previous comment about the legend for this figure.
 - g. In the Onset of Action subsection,
 We have therefore deleted this statement. Insert the appropriate number for the median time to onset of a clinically significant (>15% improvement in FEV₁) bronchodilatory effect. Note that similar information is requested in the PRECAUTIONS: Information for Patients subsection.
7. Regarding the PRECAUTIONS section:
- a. Clinical studies represented in the PRECAUTIONS: Short-Acting Beta2-Agonists subsection should include the three 12-week, double-blind, placebo-controlled US clinical studies. Update the appropriate numbers in this subsection.
 - b. We were unable to confirm the numbers of patients exposed to intranasal and systemic corticosteroids while being treated with Symbicort, as represented in the represented in the PRECAUTIONS: Intranasal and Systemic Corticosteroids subsection. Update the numbers in this subsection. State which safety pooling you are using, e.g. Pool 5, and clarify where you have submitted the data to the NDA.
 - c. Justify inclusion of the last sentence of the Intranasal and systemic corticosteroids subsection referring to differences in adverse event rates in patient taking or not taking these medications.
 - d. Regarding the Pediatric Use subsection:
 - i. Update the numbers of patients exposed to Symbicort.
 - ii. We agree with adding class language for the potential of inhaled corticosteroids to cause a growth effect.
- 

While we agree with adding information regarding the growth effect of orally inhaled budesonide in pediatric patients to this subsection based on data from the published literature, justify why the statement regarding long-term effects and projected adult height should be included in the absence of primary data. We have therefore removed this information and substituted the class labeling.

- e. We have added appropriate geriatric wording to the Geriatrics section. Update the numbers of geriatric patients exposed to Symbicort, as per our previous comment.
8. Regarding the ADVERSE REACTIONS section:
 - a. Update the Adverse Event table to represent only patients exposed to BID dosing in the 3 placebo-controlled 12-week studies. Specifically, the numbers of patients exposed to budesonide 80 mcg, should be changed, as indicated.
 - b. Information for instances of cataracts and glaucoma in patients on orally inhaled budesonide comes from AERS reports.
9. Regarding the DOSAGE AND ADMINISTRATION section:

Include information directing physicians and patients to use the appropriate dosage strength for a given selected dosage. We have updated the wording in this section to reflect that the maximum dosage should not be achieved by use of the 80/4.5 mcg dosage strength.

We recently received the full size versions of the carton and container labeling on June 19, 2006. We have not yet completed our review of this labeling information. Until then, we are unable to comment regarding legibility, including legibility of specific statements and of the immediate container. Nevertheless, we have the following comments:

10. We recommend that you remove the picture (of three persons, one of whom is holding a banner) from all labeling.
11. The words "Inhalation Aerosol" in the name should be the same font size as that for "Budesonide/Formoterol".
12. The established name should be represented in a font of the same prominence as the proprietary name.
13. The dosage strength of Symbicort should appear on the same line and in the same font as the proprietary name, i.e. "Symbicort 160/4.5" or "Symbicort 80/4.5".
14. The established name on the carton should be the same as that in the PI and on the container labeling. Change  to "formoterol fumarate dihydrate", and include the dosage strength of each component, i.e. "budesonide 160 mcg / formoterol fumarate dihydrate 4.5 mcg" or "budesonide 80 mcg / formoterol fumarate dihydrate 4.5 mcg".
15. Remove the separate line with the dosage strength, currently represented as "160/4.5 mcg" or "80/4.5 mcg", since it is confusing and the dosage strength of each component is not matched with the component (see previous comment).

16. The space for “lot number” and “expiration date” should be labeled as such.
17. The warning statements for “drugs in dispensers pressurized by gaseous propellants” are missing, as required by 21 CFR 369.21. Add this information to the carton labeling.
18. The shield label contains different font sizes for the 160 or 80 mcg dose of budesonide than for the 4.5 mcg dose of formoterol. Change the font size to that both are the same.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-796-1230.

Enclosure: Recommendations to the Proposed Label

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6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative-_____

Drafted: CCJ/June 22, 2006
Initialed: Barnes/June 22, 2006
Starke/June 22, 2006
Schroeder/June 22, 2006
Peri/June 22, 2006
Al Habet/June 22, 2006
Fadiran/June 22, 2006
Guo/June 22, 2006
Davi/June 22, 2006
Robison/June 22, 2006
Sun/June 22, 2006
Chowdhury/June 22, 2006

Finalized: CCJ/June 22, 2006
Filename: 21929 Labeling fax.doc

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/s/

Colette Jackson
6/22/2006 04:39:38 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: (Division/Office) DPAP/OND Dr. Joseph Sun, Pharm./Tox Supervisor			FROM: Alan C. Schroeder/ONDQA	
DATE: 6/12/2006	IND NO.:	NDA NO.: 21-929	TYPE OF DOCUMENT: Original NDA & Amendment	DATE OF DOCUMENT: 9/23/2005 and 4/13/2006
NAME OF DRUG: Symbicort Inhalation Aerosol		PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG: 4S	DESIRED COMPLETION DATE: ASAP
NAME OF APPLICANT: AstraZeneca.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY _____		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> REPOSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW xOTHER (Specify below) pharm/tox assess. of leachables
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY			<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary) This is a formal consult request, which was previously discussed with you informally. Please evaluate leachables for safety, based upon maximum allowed acceptance criteria in the drug product. See attached Table 10 from the April 13, 2006, amendment. For additional information, see responses in the 4/13/2006, amendment to our comments #2b(i) and 2b(ii). This information is in the electronic document room. The following extractables are not routinely observed as leachables, and therefore, are not included in our consult (unless you have a specific concern about them): Please evaluate for drug product safety, an impurity _____ I. The information about this is to be placed in a separate review of supporting DMF _____ Please write a memo to file and put it in DFS for N21-929, indicating that a non-clinical review of DMF _____ was written in support of N21-929 and regarding an impurity: _____ I. Please don't include confidential information from the DMF in the NDA review or memo to file.				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY <i>Check one</i> <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

cc: QNDQA/ASchroeder/BFraser
DPAP/JSun/TRobison/CJackson

1 Page(s) Withheld

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative

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/s/

Blair Fraser
6/12/2006 05:11:53 PM

NDA 21-929
Symbicort

Please refer to your September 23, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbicort (budesonide/formoterol fumarate dihydrate) MDI.

We also refer to your submissions dated May 10, and June 1, 2006. We have the following comments. We request a prompt response in order to continue our evaluation of your NDA.

1. This pertains to your response dated June 1, 2006, to Comment 1 of our IR letter dated May 24, 2006. Revise the proposed specification for dose content uniformity as follows.

2. Request the holder of DMF _____ to respond to our previous letter on or before June 9, 2006. Ask them to fax an exact copy of their official amendment to the attention of Dr. Alan Schroeder at 301-796-9747, as well as to submit the official amendment through the normal process.

3. _____ DMFs _____ are deficient and the Agency has faxed letters to them on June 6, 2006. Please request that they provide complete responses in an expeditious manner.

4. This pertains to your response of May 10, 2006, to comment 4 of our information request letter dated April 12, 2006. Our main concern was that a normal stability time point schedule should be incorporated into the stability protocol. Annual maintenance stability testing may be performed as described in the revised stability commitment in this amendment, for the first three production batches, with the exception that such future annual testing may be limited to stability storage conditions of 25°C/60%RH. Please resubmit an appropriate annual maintenance stability protocol based upon this approach. This annual protocol may be reassessed in a supplemental application after the data for the first three production batches are analyzed.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-796-1230.

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/s/

Colette Jackson
6/8/2006 11:07:41 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 6, 2006

TO: Collette Jackson, Regulatory Project Manager
Peter Starke, M.D., Medical Team Leader
Division of Pulmonary and Allergy Products, HFD-570

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Ele Ibarra-Pratt, R.N., MPH
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-929

NME: No

APPLICANT: AstraZeneca LP

DRUG: Symbicort® 80/4.5 and 160/4.5 Inhalation Aerosol (budesonide/formoterol inhalation aerosol)

THERAPEUTIC CLASSIFICATION: 4S

INDICATION: Maintenance treatment of asthma

CONSULTATION REQUEST DATE: 01/04/06

DIVISION ACTION GOAL DATE: 06/23/06

PDUFA DATE: 07/23/06

I. BACKGROUND:

Symbicort MDI is a combination of the corticosteroid budesonide and the long-acting beta₂-agonist formoterol. The dry powder inhaler (DPI) form of Symbicort is currently marketed internationally, and the two components of Symbicort are also marketed separately. Pulmicort Turbuhaler (budesonide) DPI is

approved for asthma in the U.S. and Oxis Turbuhaler (formoterol) DPI is marketed for asthma outside the U.S.

The studies selected for audit include two pivotal studies; protocols SD-039-0716 and SD-039-0717. Protocol SD-039-0716 included subjects who were at least 6 years of age with a documented clinical diagnosis of asthma for at least 6 months, as defined by the American Thoracic Society. Subjects were stratified by age group, and randomized to one of four arms: a fixed combination of budesonide/formoterol, one of its mono-products (budesonide or formoterol) or placebo. Protocol SD-039-0717 is similar to SD-039-0716. However, subjects were randomized to one of the following 5 arms: fixed combination budesonide/formoterol, budesonide pMDI, formoterol TBH, budesonide pMDI and formoterol TBH, or placebo. The primary efficacy parameter was the average FEV1 12-hour post-treatment for both studies. Safety parameters include incidence of adverse events, serious adverse events, discontinuations due to adverse events, results of laboratory testing, and electrocardiograms.

There was concern in the pivotal trials about the comparator arm formoterol in its DPI presentation, unlike Symbicort and budesonide comparators that were administered as MDIs, in evaluating the contribution of the formoterol to the combination product. Therefore, protocol SD-039-0729, an open-label 4-week treatment study, was developed to address this concern and selected for audit. The objective of SD-039-0729 was to compare the bronchodilating effect of formoterol given via Symbicort pMDI vs. formoterol administered via the Oxis Turbuhaler, by assessing the average 12-hour FEV1 in adults subjects with asthma.

Site selection was generally based on the total number of subjects enrolled at the center, whether the results of the primary endpoints were discrepant in comparison to the other centers, and whether financial interests were disclosed. Dr. Ellis disclosed a significant equity interest, and is therefore included in the audit.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol #	Insp. Date	EIR Received Date	Final Classification
Edward Lisberg, MD (18)	River Forest, IL	SD-039-0716	3/14-3/23/06	5/10/06	VAI
Sanchayita Tripathy, MD (21)	Rolla, MO	SD-039-0716	2/7-2/10/06	3/14/06	NAI
Edward Kerwin, MD (15)	Medford, OR	SD-039-0717	2/6-2/10/06	3/24/06	VAI
Mark Ellis, MD (12)	Orange, CA	SD-039-0717	1/11-1/25/06	4/20/06	NAI
Mark Ellis, MD (3)	Orange, CA	SD-039-0729	1/11-1/25/06	4/20/06	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

A. Protocol SD-039-0716

- Edward E. Lisberg, M.D.
 7420 Central Avenue
 Suite 2020
 River Forest, IL 60305

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b. Limitations of inspection: There were no limitations noted during this inspection.

c. General observations/commentary:

The inspection documented that the CI did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. For example, subject 6011, at study visit 3, the 600 minute post-dose FEV1 fell by 21% from baseline. However, the CI did not conduct the follow-up visit the following morning to determine whether the subject would meet the criteria for study withdrawal, as required by the protocol. Additionally, for subject 6008 at study visit 4 (12/11/2002), the pre-dose FEV1 fell by 22% from baseline. However, the CI did not promptly withdraw the subject from the study; subject was withdrawn on 12/18/2002.

There were no serious adverse events or deaths reported from this site. The data listings were compared with source documents on site; no discrepancies were noted. A Form FDA 483, Inspectional Observations, was issued at the end of inspection.

d. Assessment of data integrity: The data from this site appear acceptable.

C. Protocol SD-039-0717 and Protocol SD-039-0729

Mark H. Ellis, M.D.
725 West La Veta Avenue, Suite 100
Children's Hospital Of Orange
Orange, CA 92868

Dr. Ellis was selected for audit due to significant disclosure of financial interests.

a. What was inspected: For protocol SD-039-0717, a total of 13 subjects were enrolled; one dropped out at study visit 2 (subject E7014014). For protocol SD-039-0729, a total of 3 subjects were enrolled at this site.

b. Limitations of inspection: There were no limitations noted during this inspection.

c. General observations/commentary: There were no significant deviations noted and the data listings were consistent with source documents on site. Adverse events were appropriately reported. An audit of the subjects' records was conducted; the data listings were compared with source documents on site. A Form FDA 483, Inspectional Observations, was not issued at the end of inspection.

d. Assessment of data integrity: The data from this site appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, the sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol and signed informed consent. The inspection documented minor protocol violations at sites 15 and 18. There were no significant discrepancies noted with the data listings and source documents at each site.

The data submitted in support of this NDA appear to be acceptable.

Follow-up action: None needed.

{See appended electronic signature page}

Elenita Ibarra-Pratt, RN, MPH
CSO

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Elinita Ibarra-Pratt
6/6/2006 11:30:19 AM
CSO

Leslie Ball
6/12/2006 09:44:02 PM
MEDICAL OFFICER

5/04/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 21-929

AstraZeneca Pharmaceuticals LP
P.O. Box 8355
Wilmington, DE 19803-8355

Attention: Mark A. DeSiato
Director of Regulatory Affairs

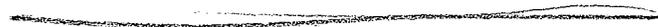
Dear Mr. DeSiato:

Please refer to your September 23, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbicort (budesonide/formoterol fumarate dihydrate) MDI.

We also refer to your submissions dated October 21, November 2, and 8, and December 8, and 27, 2005, and January 30, April 13, 19, and 27, and May 10, and 15, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1.



2. Provide an agreement to reconsider the Agency's proposed PTIT approach to control of dose content uniformity, based on data collected over the first year post-approval, provided that the Agency's proposed acceptance criteria may be adopted for the specification.
3. It is noted that the listed methods in your response for periodic testing of valve extractables are methods for leachables in the drug product. Provide the methods for valve extractables, as previously requested. (Response to our comment 4l(vi) from our March 8, 2006, IR letter in your amendment dated April 13, 2006.)

If you have any questions, call Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

Blair A. Fraser, Ph.D
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser
5/24/2006 12:56:09 PM

NDA 21-929
Symbicort

We are reviewing your NDA submission dated September 23, 2005, and we have the following requests in order to facilitate our review. The following requests pertain to study SD-039-0715.

1. Specify the timing which the following assessments were performed in relation to study drug administration at visits 1-6: spirometry, 12-lead ECG.
2. Provide a table similar to Table 53 on page 146 of study SD-039-0719 listing the following ECG parameters: heart rate, QT, QTcB, QTcF.

If there are any questions, please contact Colette Jackson, Project Manager, at 301-796-1230.

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Colette Jackson
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 21-929

AstraZeneca Pharmaceuticals LP
P.O. Box 8355
Wilmington, DE 19803-8355

Attention: Mark A. DeSiato
Director of Regulatory Affairs

Dear Mr. DeSiato:

Please refer to your September 23, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbicort (budesonide/formoterol fumarate dihydrate) MDI.

We also refer to your submissions dated October 21, November 2, and 8, and December 8, and 27, 2005, and January 30, and April 13, 19, and 27, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We also remind you of our comments in our information request letter dated March 8, 2006. The comments below are cross-referenced (in parentheses) to comments in our Information Request letter of March 8, 2006. We request a prompt written response in order to continue our evaluation of your NDA.

- 1. The following comments pertain to specifications for leachables. (Comment 2d(ii))
a. Place a footnote on the drug product specification sheet for leachables, to indicate that certain known leachables (among others) are controlled by the acceptance criterion for ...
b. Explain the origin of ... since it has been observed as a leachable, but it has not been detected as an extractable in the ... components.
c. Clarify the rigorousness of the extractables methodology employed, in consideration of the fact that certain leachables, ... appear at substantially higher levels as leachables in the primary stability batches than as extractables.

- d. Clarify if there are any other significant known extractables that are controlled in the category of _____' besides those identified in your data tables for the NDA stability studies.
2. Provide the composition of the mouthpiece colorant, _____, as requested in our March 28, 2006, telecon. (Comment 2e(i))
3. The variability for formoterol fumarate deposited on the throat of the cascade impactor, as well as on _____ at the end of canister, seems to be higher than expected. Indicate what has been done/is being done to reduce this variability. (Comment 4k)
4. This pertains to acceptance criteria for the valves, which include an AQL of 0 for mean results. Clarify that the mean actuation weights for through life testing are actually determined and evaluated relative to the specification, separately at the beginning, middle and end of canister, so that the mean remains a mean of two actuations, as for within batch testing. (Comment 4.l (v))
5. Provide the weight of each valve component.
6. Provide an agreement to periodically validate the test results shown on the Certificate of Analysis for the excipient HFA 227 propellant. (Comment 4g)

If you have any questions, call Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

Blair A. Fraser, Ph.D
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser
5/4/2006 03:24:24 PM

NDA 21-929
Symbicort

Please refer to your September 23, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbicort (budesonide/formoterol fumarate dihydrate) MDI.

We also refer to your submission dated April 19, 2006, which requested clarification of comments 2.a. and 9 of our April 12, 2006, Information Request Letter. We have the following comments.

1. The APSD comparison is adequate, except that the summary should also include a concise comparison of the variabilities of the individual data generated by each method (comment 2.a.).
2. Your approach for issue 2.f. in our March 8, 2006, IR letter is adequate to address the stability part of comment 9 in our April 12, 2006, letter. In addition, however, provide a concise comparison of *release data* for clinical and commercial batches to show drug product performance. You may suggest other approaches to respond to comments 2.f. and 9.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-796-1230.

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/s/

Colette Jackson
4/28/2006 09:58:21 AM
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NDA 21-929
Symbicort

We are reviewing your NDA submission dated September 23, 2005, and we have the following requests in order to facilitate our review. The following requests pertain to studies 716 and 717.

1. Provide, in written format, subject identification numbers for subjects who qualified for early withdrawal from the studies according to the protocol specified discontinuation criteria (as recorded on the ASTEXAC case report form). For each of these subjects, include the timepoint at which the discontinuation criteria were satisfied. Also, indicate whether each of these subjects was actually withdrawn and if so the timepoint at which the withdrawal occurred. In addition, provide this information electronically including the subject identification number (USUBJID and SUBJECT), the date the discontinuation criteria were satisfied, an indicator variable for the withdrawal status of each patient, and the date the withdrawal occurred. These dates should be consistent with the date in variable `_TERM_DT` in your disposition data set.
2. Provide analyses and figures describing the co-primary efficacy endpoint, baseline-adjusted 12-hour FEV1, at the week 12 time point including only subjects who never qualified for withdrawal from the study as recorded on ASTEXAC case report form irrespective of whether the subject continued in the study or not. The figures should be similar to that displayed as Figure 3 in your proposed label. The analyses should be similar to those provided in Tables 27 and 28 in Section 7.2.1.1 of the study report for study 716; and in Tables 28 and 29 in Section 7.2.1.1 of the study report for study 717.
3. If the number of subjects described as a result of comment 1 is different from the information included in Table 41 in Section 7.2.2.1 of the study report for study 716 or Table 38 in Section 7.2.2.1 for study 717, provide an updated version of these tables.

If there are any questions, please contact Colette Jackson, Project Manager, at 301-796-1230.

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/s/

Colette Jackson
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CSO

MEMORANDUM OF TELECON

DATE: March 28, 2006

APPLICATION NUMBER: NDA 21-929 SYMBICORT (budesonide/formoterol) pMDI

BETWEEN:

Name: Mark DeSiato, Regulatory Affairs Director
Luida Shtohryn, PharmD, Director, CMC Regulatory Affairs
Andy Ludzik, BSc, Team Manager, Analytical Development
Rob Whyard, Associate Director, Pharmaceutical Project Management
Tara Chapman, PharmD, Regulatory Affairs Associate Director
Rob Jansen, Team Manager, Product Development
Dennis Sandell, PhD, Associate Principal Scientist, Analytical Development
AstraZeneca Pharmaceuticals (AZ)

Phone: 1-866-208-4528

AND

Name:

Alan Schroeder, Ph.D., CMC Reviewer
Prasad Peri, Ph.D., Pharmaceutical Assessment Lead
Colette Jackson, Project Manager
Division of Pulmonary and Allergy Products

SUBJECT: To discuss the FDA's March 8, 2006, Information Request (IR) Letter.

BACKGROUND: The Agency sent an IR Letter to AstraZeneca on March 8, 2006. AstraZeneca (AZ) requested clarification of the letter as outlined in their March 15, 2006, correspondence which included a meeting request and briefing package. The contents of the March 15, 2006, communication are in italics, and the discussion that follows is in normal font.

DISCUSSION:

The Division requested, particularly for comments 3 and higher, that AZ make their responses succinct and to the point, as much as possible. For revised methods, include a detailed list of all changes for each method made relative to the method submitted in the original NDA, and state that no other changes have been made. AZ stated that they intend to respond for most of the comments by the end of April, and asked the Division if this would be acceptable. The Division stated that the review will be based upon time, resources, and priority, and urged AZ to respond as soon as possible. The Division also noted that additional CMC comments will be forthcoming in a second IR letter.

CLARIFICATION OF COMMENTS ON QUALITY SECTION

Introduction

AstraZeneca requests clarification of the following comments that have been made in the FDA Information Request Letter (8 March 2006) for NDA 21-929 for SYMBICORT® pressurized metered dose inhaler (pMDI). FDA comments are provided in bold text followed by AstraZeneca requests for clarification in normal text.

Comment 2.a

The change in manufacturing of the actuator will need to be submitted in a supplement after approval of this NDA. Appropriate data supporting that change, including adequate comparative performance data for drug product and CMC data for the actuator itself, will need to be reviewed and approved prior to implementing the change.

AstraZeneca understands the "change in manufacturing of the actuator" to mean the change in supplier, [redacted]. Is this correct? If so, please note that [redacted] notified AstraZeneca of their intention to cease supply to the pharmaceutical industry in September 2004. Due to the timing of this announcement, it was not possible to have fully validated commercial actuation counter (AC) actuator components, [redacted] available for the NDA submission. As stated in the NDA (refer to 'AC actuator changes' in 'P.2.4 Pharmaceutical Development – Container Closure System') commercial tooling for the shield component, AC body and AC mouthpiece dust cap will be implemented and qualified [redacted]. The mouthpiece commercial tooling was qualified at [redacted] and has been transferred and re-qualified at [redacted]. A fully automatic line will be implemented and qualified [redacted]. Is the review of these data required for approval?

Discussion:

The Division confirmed that this comment refers to the change in supplier [redacted].

Review of data pertaining to the mouthpiece (and to the drug product manufactured with this mouthpiece) [redacted] (and compared to data for the mouthpiece from [redacted]), and to the drug product manufactured with this mouthpiece) are needed for approval of the new mouthpiece supplier. AZ requested further clarification, noting that the same mold tool for the mouthpiece has been transferred to [redacted], thereby producing the same components. The suppliers are also the same. The data submitted are representative of the commercial supply. The Division stated that [redacted] is still considered a new site and comparative data are needed. The re-qualification process at the new site was not complete at the time of NDA submission. AZ stated that the re-qualification process has now been completed and that they could have all the data (APSD, DDU, etc.) on all [redacted] batches of the product made with those actuators by September 2006, and asked if this could be submitted as a prior approval or a changes being effected supplement. The Division stated that the data could be submitted as a CBE-30 if the NDA has been approved by that time.

Comment 2.c.(i)

Assess the purity profile of representative batches of polyethylene glycol for impurities that may not be controlled by the NF monograph, assess the safety of impurity levels found, and propose controls for impurities in addition to those in the NF monograph, as appropriate.

AstraZeneca has assessed the purity profile of polyethylene glycol as described by the NF monograph. In addition, the polyethylene glycol meets the purity requirements of the European Pharmacopoeia, which additionally controls _____ to a limit of _____. AstraZeneca has also previously confirmed with our supplier that all possible impurities are certified on every certificate of analysis. Beyond these compendial requirements for purity, we request the Agency to please provide guidance as to any specific impurities that are of concern.

Discussion:

The Division noted that this was a general question. Note that the amount of polyethylene glycol per actuation is _____. Therefore, we have concerns about the purity profile of this excipient just as we would for a drug substance. The Division suggested AZ utilize good scientific judgment, review the literature, evaluate the batches of the excipients and see whether other impurities are present. (For example, there may be _____ etc.) The Division suggested AZ look at purity profile first. Then, whether control is necessary for additional impurities will be a review issue (i.e., the data will be evaluated and a decision will then be made). AZ stated that they will work to characterize any additional impurities in representative batches by reasonable means. This is a _____ well known impurity profile. The Division noted that this approach sounded reasonable, but it will be a review issue (i.e., the data will need to be evaluated when they are available).

Comment 2.e.(i)

Provide a letter of authorization for the appropriate DMF _____ with a reference to submission dates and page numbers for relevant information for your mouthpiece/actuator which was used in clinical and NDA stability drug product batches. Clarify whether specific actuator/mouthpiece colorants and resins identified in the NDA, as well as their suppliers, were those used for clinical and stability batches of drug product.

In September 2004, _____ notified AstraZeneca of their intention to cease supply to the pharmaceutical industry before they had filed their DMF containing information specific to AstraZeneca's product, consequently no DMF is available from _____. AstraZeneca can supply information on the materials used for the actuator, mouthpiece colorants, and resins, as well as their suppliers, and we can confirm that these were used for clinical and stability batches of drug product. Is there any additional information that the Agency requires?

Discussion:

The Division stated that appropriate information should be in the NDA for the drug product used in the clinical and NDA stability studies, and for comparison with the same information for the proposed new supplier of the mouthpiece/actuator. Besides the information that AZ identified, specify any additives added by mouthpiece/actuator fabricator and the quantitative composition of the mouthpiece/actuator. AZ clarified that no other suppliers of raw materials (i.e., resin, pigments) suppliers have been or will be used for the fabrication of the mouthpiece, and there are no additives used in fabrication. AZ stated that they have all of the qualitative information. AZ stated they do not have access to the quantitative information. _____ needs to supply this in their DMF and AZ intends to reference to their DMF. AZ stated they will contact _____ to make sure the information has been or will be submitted to the DMF.

Comment 2.f

Provide summary stability data (individual and mean data) and individual stability data, for clinical batches of drug product.

AstraZeneca has provided summary stability data (mean data) at key time points for the clinical batches in the NDA. These data, together with discussion of trends observed, may be found in the following documents:

- *“P.8.3 Supportive Stability Data For Drug Product” - In this document, the stability data for the 2 commercial scale clinical batches (ie, P6501A and P6502A) are summarized and discussed as supportive stability data. This document also contains stability data for 4 pilot scale clinical batches (ie, P6037, P6186, P6039 and P6040) summarized and discussed as development stability data.*
- *“P.2 Pharmaceutical Development, Attachment 11: Evaluation Of Critical SYMBICORT pMDI Batches” - For the clinical batches that were not part of a stability study (including batches of the SYMBICORT _____ testing was carried out subsequent to their use in pivotal studies at the Agency's request. The approximate age at retest of these batches ranged from _____ months. Mean data are summarized in this document.*

Since the summaries provided in the NDA are available to assess trends in the clinical batches, AstraZeneca suggests that only the individual data be provided for the supportive stability studies (ie, individual stability data for all time points tabulated for batches P6501A, P6502A, P6037, P6186, P6039 and P6040). These data will comprise approximately 400 pages.

Does the Agency agree with AstraZeneca's proposal to provide only the individual stability data for the available clinical batches of drug product, with cross-reference to the stability summaries already provided in the NDA?

If the Agency disagrees with AstraZeneca's proposal, please provide guidance on the required presentation of these data with respect to depth of information required (eg, all available time points and orientations, for all test parameters) and format (ie, NDA format or the format used for data provided in the submission dated 30 January 2006).