

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-949

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 21-949	
		NAME OF APPLICANT / NDA HOLDER AstraZeneca LP	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) PULMICORT TURBUHALER®			
ACTIVE INGREDIENT(S) budesonide		STRENGTH(S) 90 mcg and 180 mcg	
DOSAGE FORM dry powder 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 6,027,714		b. Issue Date of Patent 2/22/2000	c. Expiration Date of Patent 1/9/2018
d. Name of Patent Owner Astra Akticbolag		Address (of Patent Owner) S-151 85	
		City/State Södertälje	
		ZIP Code Sweden	FAX Number (if available)
		Telephone Number 01146855326000	E-Mail Address (if available)
e. <u>Name of agent or representative</u> 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) <input checked="" type="checkbox"/> General Counsel AstraZeneca Pharmaceuticals LP		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)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> 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) 7 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.)

DOSAGE AND ADMINISTRATION

PULMICORT TURBUHALER should be administered by the orally inhaled route in asthmatic patients age 6 years and older.

INDICATIONS AND USAGE

PULMICORT TURBUHALER is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age or older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of those patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

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

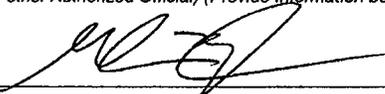
6. Declaration Certification

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.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Glenn M. Engelmann, General Counsel	
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.

Appears This Way
On Original

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.htm>.

First Section

Complete all items in this section.

I. 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.

- 1c) 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.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 21-949	
		NAME OF APPLICANT / NDA HOLDER AstraZeneca LP	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) PULMICORT TURBUHALER®			
ACTIVE INGREDIENT(S) budesonide		STRENGTH(S) 90 mcg and 180 mcg	
DOSAGE FORM dry powder 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 6,287,540		b. Issue Date of Patent 9/11/2001	c. Expiration Date of Patent 1/9/2018
d. Name of Patent Owner Astra Aktiebolag		Address (of Patent Owner) S-151 85	
		City/State Södertälje	
		ZIP Code Sweden	FAX Number (if available)
		Telephone Number 01146855326000	E-Mail Address (if available)
e. <u>Name of agent or representative</u> 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) <input checked="" type="checkbox"/> General Counsel AstraZeneca Pharmaceuticals LP		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)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> 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) 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.)

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

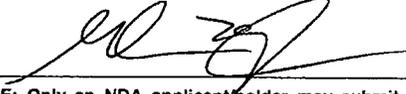
6. Declaration Certification

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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.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Glenn M. Engelmann, General Counsel	
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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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 # 21-949

SUPPL #

HFD # 570

Trade Name Pulmicort Turbuhaler M3

Generic Name budesonide

Applicant Name AstraZeneca

Approval Date, If Known June 30, 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# 20-929

Pulmicort Respules

NDA# 20-441

Pulmicort Turbuhaler

NDA# 20-746

Rhinocort Aqua

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#

NDA#

NDA#

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-004-0620

SD-004-0726

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-004-0620
SD-004-0726

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 # 63762 YES ! NO
! Explain:

Investigation #2
IND # 63762 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: June, 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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this page is the manifestation of the electronic signature.**

/s/

Badrul Chowdhury
7/12/2006 04:18:16 PM

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AstraZeneca LP
1800 Concord Pike
Wilmington, DE 19850-5437

PULMICORT TURBUHALER® M3 (budesonide inhalation powder)
NDA 21-949

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

EXCLUSIVITY INFORMATION

1. Exclusivity Claim

AstraZeneca LP claims an exclusivity period of three years for this new drug application.

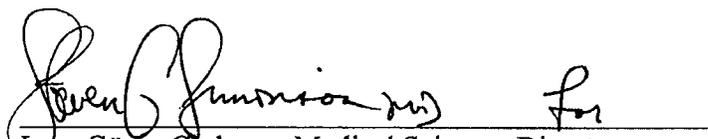
2. Authority for Exclusivity Claim

Exclusivity for this new drug application is being claimed pursuant to 21 CFR 314.108(b)(4).

3. Information Demonstrating this Application Contains New Clinical Investigations Conducted or Sponsored by the Applicant that are Essential to the Approval of this New Drug Application.

(a) Certification of New Clinical Investigations

AstraZeneca LP certifies that to the best of its knowledge, each of the clinical investigation(s) included in this new drug application meets the definition of "new clinical investigation" set forth in 21 CFR Section 314.108(a).


Lars-Göran Carlsson, Medical Sciences Director

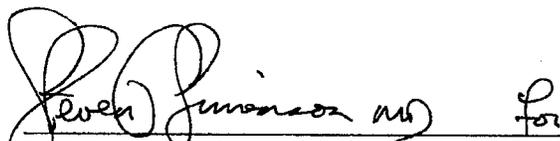
(b) Essential to Approval

(i) Literature Search

There are no published studies or publicly available reports of clinical investigations known to AstraZeneca LP through a literature search that are relevant to the conditions for which approval is being sought.

(ii) Certification

AstraZeneca LP certifies that it has thoroughly searched the scientific literature and, to the best of its knowledge, there are no published studies or publicly available reports that provide a sufficient basis for the approval of the conditions for which approval is being sought without reference to the new clinical investigations in this new drug application.



Lars-Göran Carlsson, Medical Sciences Director

(c) Conducted or Sponsored by the Applicant.

AstraZeneca LP is the sponsor named in Form FDA 1571 for IND 63,762 under which the new clinical investigations essential to the approval of this new drug application were conducted.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA # 21-949 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: September 12, 2005 Action Date: July 12, 2005

HFD 570 Trade and generic names/dosage form: Pulmicort Turbuhaler® (budesonide inhalation powder)

Applicant: AstraZeneca Therapeutic Class: 5S

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. 0 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. <6 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 Pulmicort Turbuhaler M3 does not represent a therapeutic benefit over existing treatments and is not likely to be used in a substantial number of patients in that age group.

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. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ 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): _____

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. ≥6 Tanner Stage _____
Max Adult kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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NDA 21-949

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 21-949
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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/s/

Colette Jackson
12/5/2005 02:11:07 PM

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Debarment Certification
PULMICORT TURBUHALER® M3 (budesonide inhalation powder)

1.3.3 DEBARMENT CERTIFICATION

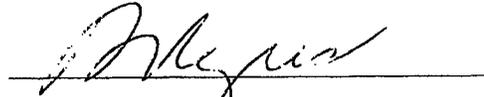
Re: NDA 21-949

PULMICORT TURBUHALER® M3 (budesonide inhalation powder)

Debarment Certification Statement

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca LP (AstraZeneca), that we did not use and will not use in connection with this New Drug Application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,



Anthony Rogers, Vice President
Regulatory Affairs
AstraZeneca

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REQUEST FOR CONSULTATION

TO (Division/Office):
**Division of Drug, Marketing, Advertising and
Communication (DDMAC)
WO Bldg 22 Rm. 1400**

FROM:
Colette Jackson
Project Manager
Division of Pulmonary and Allergy Products

DATE
September 19, 2006

IND NO.

NDA NO.
21-949

TYPE OF DOCUMENT
N

DATE OF DOCUMENT
August 31, 2006

NAME OF DRUG
budesonide inhalation powder

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Inhaled Corticosteroid

DESIRED COMPLETION DATE
December 31, 2006

NAME OF FIRM: AstraZeneca Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input checked="" type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Labeling Review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This is a request for an evaluation and review of the package insert, carton, and container labeling for the newly proposed names PULMICORT FLEXHALER (first choice) and ~~_____~~

This submission is electronic only and is located in the EDR in the submissions dated August 31, and September 12, 2006. The September 12, 2006, submission is the PI with only their preferred name.

PDUFA DATE: March 1, 2007

CC:
Archival NDA 21-949
HFD-570/Division File
HFD-570/Jackson

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
 MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

b(4)

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/s/

Colette Jackson
9/19/2006 02:33:16 PM

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REQUEST FOR CONSULTATION

TO (Division/Office):
**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
WO Rm 4414**

FROM:
Colette Jackson
Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

DATE September 7, 2006	IND NO.	NDA NO. 21-949	TYPE OF DOCUMENT N	DATE OF DOCUMENT August 31, 2006
NAME OF DRUG budesonide inhalation powder		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Glucocorticosteroid	DESIRED COMPLETION DATE January 12, 2007

NAME OF FIRM: AstraZeneca

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

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 (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

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"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <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
--	---

V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
-----------------------------------	--------------------------------------

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This is a request for a consult on AstraZeneca's NDA 21-949 for budesonide inhalation powder. Their first choice is PULMICORT FLEXHALER; second choice is "_____". This submission is electronic only and is located on the EDR under the SLR-001 submission dated August 31, 2006. The August 31, 2006, submission contains the proposed names, carton and container labeling. AstraZeneca will submit the package insert in a submission to follow.

b(4)

PDUFA DATE: March 1, 2007

ATTACHMENTS:

CC:

Archival NDA 21-949
HFD-570/Division File
HFD-570/Jackson

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Colette Jackson
9/7/2006 01:25:20 PM

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-949 Efficacy Supplement Type SE- Supplement Number		
Drug: Pulmicort (budesonide) Turbuhaler M3		Applicant: AstraZeneca
RPM: Colette Jackson	HFD-570	Phone # 6-1230
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:		
• Review priority	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
• Chem class (NDAs only)	5	
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
7/12/2006		
❖ Special programs (indicate all that apply)		
<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2		
❖ User Fee Information		
• User Fee	<input checked="" type="checkbox"/> Paid UF ID number <u>3006182</u>	
• User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
• User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	12/5/2005

General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	(x) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	
<ul style="list-style-type: none"> Status of advertising (approvals only) 	(x) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	(x) Yes () Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	() None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	7/5/2006
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	7/11/2006
<ul style="list-style-type: none"> Original applicant-proposed labeling 	9/12/2005
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	5/18/2006
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Applicant proposed 	7/11/2006, 7/10/2006, and 9/12/5005
<ul style="list-style-type: none"> Reviews 	
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
	10/28/2005, 11/23/2005, 1/25/2006, 3/3/2006, 3/13/2006, 5/1/2006, 5/10/2006, 6/23/2006, 7/5/2006, and 7/10/2006
❖ Memoranda and Telecons	
	6/27/2006 (Minutes faxed 7/11/2006)
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	9/8/2004 (CMC), 12/6/2004
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	
<ul style="list-style-type: none"> Other 	
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> Date of Meeting 	
<ul style="list-style-type: none"> 48-hour alert 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (<i>indicate date for each review</i>)	CMC-6/6/2006 P/T- 5/22/2006 MO- 5/31/2006 DD- 7/11/2006
❖ Clinical review(s) (<i>indicate date for each review</i>)	11/2/2005, 5/17/2006, and 6/23/2006
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	
❖ Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	
❖ Risk Management Plan review(s) (<i>indicate date/location if incorporated in another rev</i>)	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	12/5/2005
❖ Demographic Worksheet (<i>NME approvals only</i>)	
❖ Statistical review(s) (<i>indicate date for each review</i>)	10/27/2005 and 5/18/2006
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	11/3/2005 and 5/19/2006
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) (<i>indicate date for each review</i>)	10/12/2005 and 1/11/2006
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	
• Review & FONSI (<i>indicate date of review</i>)	
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	
❖ Facilities inspection (provide EER report)	Date completed: (x) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (x) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	10/20/2005 and 5/19/2006
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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The product subject of this application is called by AstraZeneca as the M3 product. The M3 product differs from the two predecessor products (described in the CMC section below). AstraZeneca also wishes to introduce two dosage strengths of the product, 180 mcg and 90 mcg. The 180 mcg strength product delivers 160 mcg from the mouthpiece, which is similar to the currently marketed Pulmicort Turbuhaler 200 mcg, which also delivers 160 mcg from the mouthpiece. The 90 mcg product would be new dosage strength. In support of the 90 mcg product AstraZeneca partly relies on the clinical studies conducted with the M0 Pulmicort Turbuhaler 100 mcg dosage strength. This approach is acceptable because the Division had originally concluded that clinical data with the 100 mcg product were adequate.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substance budesonide is a well known compound and is already approved for use in orally inhaled products. The M3 product contains an _____ dry powder formulation of budesonide in _____ lactose _____ contained in a reservoir type device that delivers multiple doses of a _____ powder blend of micronized budesonide and micronized lactose

b(4)

_____The M3 product is similar to the currently marketed M0-ESP Pulmicort Turbuhaler with some differences. The major difference is the addition of lactose in the formulation. Some minor differences include change in the spheronization process, inclusion of a dose counter (as opposed to an indicator), and change in the mouthpiece designed to decrease drug retention. There are two strengths of the product, one designed to deliver 160 mcg budesonide per inhalation and the other designed to deliver 80 mcg budesonide per inhalation. The two devices are identical with the exception of dose-counter wheel starting point. The delivered amount of the drug is altered by the concentration of budesonide in the formulation. The drug substance budesonide is manufactured in an AstraZeneca facility in Sweden. The final drug product is also manufactured in an AstraZeneca facility in Sweden. All relevant DMFs associated with the manufacture of the drug product are adequate or sufficient information has been supplied directly by the applicant. The manufacturing and testing facilities associated with this drug product have acceptable EER status.

There were several CMC issues identified by the CMC review team early in the review period and were communicated to AstraZeneca in a discipline review letter. AstraZeneca resolved these issues and the CMC team recommends an approval action. I concur with this recommendation. There is one CMC issue worth noting. The in vitro aerodynamic particle size distribution for the M3 product is sensitive to flow rates. The fine particle dose (i.e., the respirable dose) stays relatively stable between flow rates of 60 to 80 L/min, but drops to 40-50% at flow rate of 30 L/min. This flow dependent change in particle size distribution is unlikely to have clinical impact. Flow dependent change in particle size distribution is often seen with dry powder inhalers. The currently marketed M0-ESP also has similar in vitro characteristics. The flow resistance of the M3 product is similar to the M0-ESP product; the resistance of the M3 being about 6% greater. The mean inspiratory flow rate that children with asthma between the ages of 6 to 17 years can generate through the device is 72.5 L/min (range 19.1 to 103.6 L/min). These factors

was used, which was 400 mcg twice-daily for M0-ESP Pulmicort Turbuhaler. _____

_____ That dose was 200 mcg once-daily. It should be noted that once-daily is not a recommended starting dose for Pulmicort Turbuhaler. The clinical studies that are considered pivotal to approval of this application are these two studies and the clinical pharmacology study SD-004-0601 mentioned above. Detailed review of these studies and other supporting studies can be found in Dr. Kaiser's clinical review, Dr. Starke's clinical team leader review, and in Dr. Gebert's statistical review. The clinical team and the statistical team have concluded that these studies along with the knowledge of prior clinical studies conducted with M0 Pulmicort Turbuhaler support approval of the M3 product, but not as a switch product to the currently marketed Pulmicort Turbuhaler. The clinical team and the statistical team recommend an approval action on this application and I concur with this recommendation.

b(4)

The two clinical studies mentioned above are briefly commented on in the following sections. The design and conduct of these studies are briefly described, followed by efficacy and safety findings and conclusions.

Design and conduct of the efficacy and safety studies (SD-004-0620 and SD-004-0726):
Study SD-004-0620 was double-blind, placebo-controlled, parallel group in design, conducted in the United States and Asia (Indonesia and Philippines) in patients 18 years of age and older with mild-to-moderate asthma who had recently used inhaled corticosteroids for at least 3 months. The study had a 5-40 day single-blind placebo run in period, followed by 12-week double blinded treatment period. The treatment arms were M3 budesonide inhalation powder 360 mcg twice-daily, M3 budesonide inhalation powder 180 mcg once-daily, M0-ESP Pulmicort Turbuhaler 400 mcg twice-daily, M0-ESP Pulmicort Turbuhaler 200 mcg once-daily, and placebo. The two higher doses of the two products and the two lower doses of the two products deliver the same amount of budesonide to the patient. During conduct of the study AstraZeneca increased the budesonide content of the M3 products by about 5% to match the M0-ESP Pulmicort Turbuhaler device. The change was small and is not expected to impact on the study conclusion. The reviewers also did various ancillary analyses and did not see a clinical impact of the change from these alternative analyses. The primary endpoint in the study was change from baseline in the pre-dose FEV1 averaged over the treatment period. The study was designed to have 105 patients per treatment arms to give 90% power to detect a 0.23 L mean difference for the primary endpoints at two-sided alpha-level of 0.05. Safety assessment included recording of adverse events, vital signs, physical examinations, and clinical laboratory measures. Plasma budesonide concentration was measured at pre-defined time points in a subset of patients to define the pharmacokinetic parameters. A total of 621 patients (72.5% in the United States) were randomized approximately equally to the five treatment arms. The mean FEV1 at screening was 74% predicted and at randomization was 65% predicted. Approximately 40% to 75% patients completed the study with notably more completers in the budesonide treatment arms compared to placebo.

Table 1. Study SD-004-0620, Pre-dose FEV1 (L) results

Treatment	n	Baseline mean	Change from Baseline	Difference from placebo	
				LS mean	95% CI
M3 360 mcg BID	128	2.14	0.30	0.18	0.10 to 0.26
M0-ESP 400 mcg BID	128	2.15	0.36	0.24	0.16 to 0.32
M3 180 mcg QD	119	2.09	0.19	0.07	- 0.01 to 0.16
M0-ESP 200 mcg QD	110	2.19	0.27	0.15	0.06 to 0.23
Placebo	114	2.14	0.12		

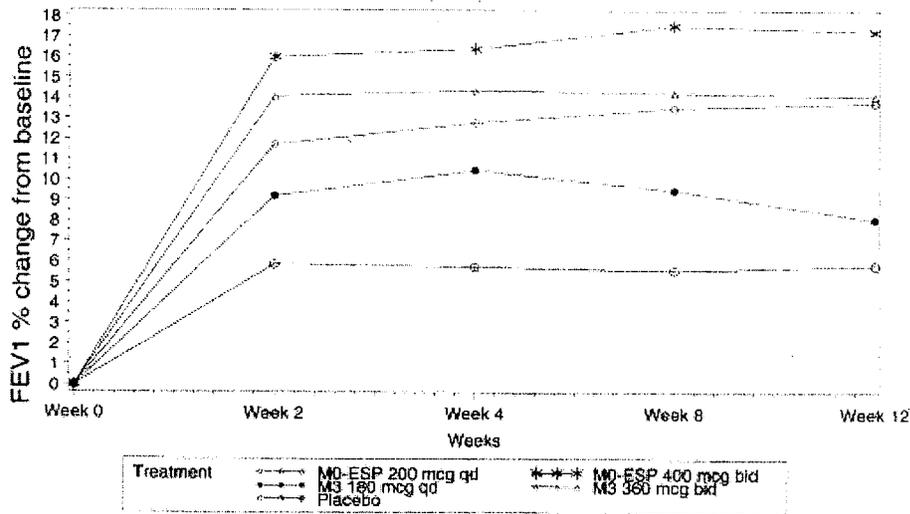
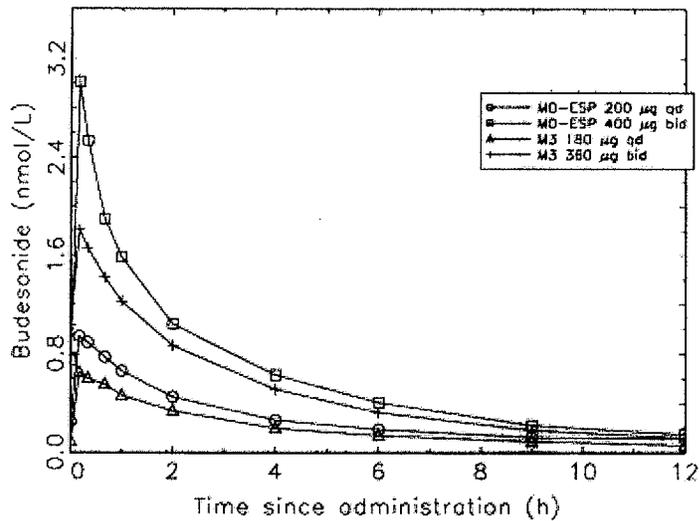


Figure 1. Study SD-004-0620, Percent change from baseline in FEV1 by week, LOCF, ITT



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Figure 2. Study SD-004-0620, Mean budesonide plasma concentration curves

Table 2. Study SD-004-0620, selected secondary endpoints

	M3 360 mcg BID	M0-ESP 400 mcg BID	M3 180 mcg QD	M0-ESP 200 mcg QD	Placebo
Change from baseline					
AM PEF (L/min)	18.0	25.2	8.0	6.3	- 9.2
PM PEF (L/min)	13.5	22.0	6.8	5.9	- 5.7
Daytime symptom score	- 0.71	- 0.82	- 0.61	- 0.65	- 0.38
Nighttime symptom score	- 0.52	- 0.57	- 0.48	- 0.39	- 0.24
Albuterol use	- 1.76	- 2.14	- 1.26	- 1.37	- 0.41
% subjects in treatment group					
% patients meeting asthma discontinuation criteria	14.6 %	15.5 %	24.8 %	29.2 %	47.9 %

Table 3. Study SD-004-0726, Pre-dose FEV1 (% predicted) results

Treatment	n	Baseline mean	Change from Baseline	Difference from placebo	
				LS mean	95% CI
M3 360 mcg BID	90	84.2	5.8	5.4	3.2 to 7.6
M0-ESP 400 mcg BID	98	86.6	4.1	4.3	2.1 to 6.4
M3 180 mcg QD	103	84.7	2.7	2.4	0.2 to 4.5
M0-ESP 200 mcg QD	101	84.4	2.9	2.5	0.4 to 4.7
Placebo	101	84.4	0.4		

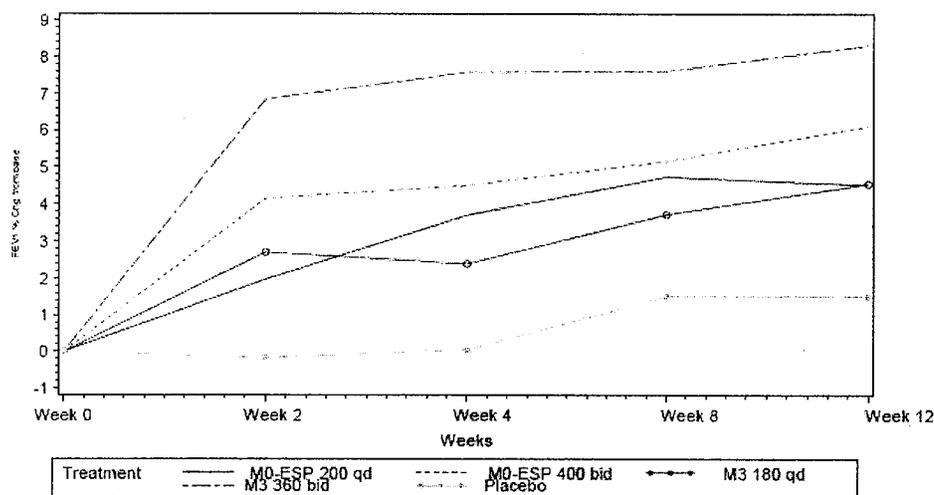


Figure 3. Study SD-004-0726, Percent change from baseline in FEV1 by week, LOCF, ITT

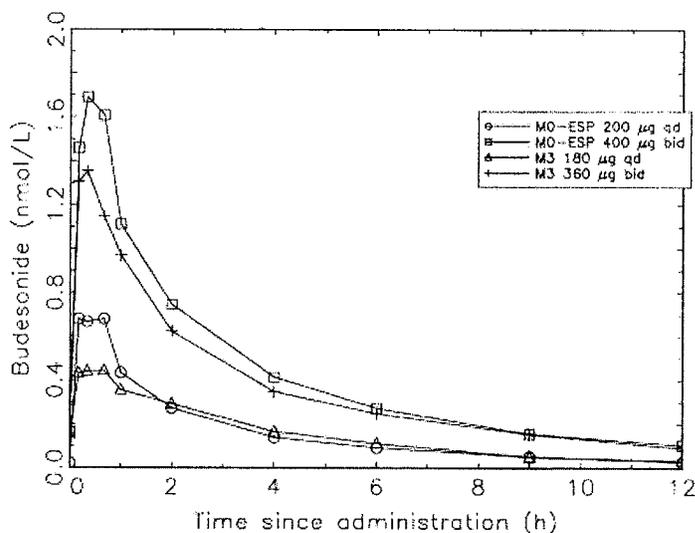


Figure 4. Study SD-004-0726, Mean budesonide plasma concentration curves

The starting doses for the M3 product for adults and for children can be recommended based on the two studies conducted by AstraZeneca to support the M3 product along with the prior clinical studies conducted by AstraZeneca with the M0 product.

In adults ages 18 years and older a starting dose of 360 mcg twice daily is supported by the study SD-004-0620 discussed above along with previous studies conducted by AstraZeneca with the M0 product. In some adult patients a downward titrated dose or a starting dose of 180 mcg twice daily can also be recommended. Although the 180 mcg twice daily dose was not studied with the M3 product, a study with the M0 product in adults (GHBA-165) submitted to the original Pulmicort Turbuhaler NDA showed that 100 mcg twice daily dose was statistically superior to placebo. Therefore, 180 mcg metered dose twice daily from the M3 product, which would be higher than 100 mcg metered dose twice daily from the M0 product, would likely be efficacious in adults.

In children ages 6 to 17 years a starting dose of 360 mcg twice daily is supported by the study SD-004-0726 discussed above, and an additional lower dose of 180 mcg twice daily is supported based on extrapolation and by previous studies conducted by AstraZeneca with the M0 product. Although the 180 mcg twice daily dose was not studied with the M3 product, this additional lower starting dose can be recommended as the preferred starting dose without qualification because it is generally known that for this class of drugs the dose in children is lower than in adults. In addition, in study SD-004-0726 conducted in children with the M3 product, the 180 mcg once daily dose separated statistically from placebo (Table 3). Furthermore, a study with the M0 product in children (GHBA-168) that was submitted to the original Pulmicort Turbuhaler NDA showed that 100 mcg twice daily dose was statistically superior to placebo. In children the 180 mcg twice daily will be recommended as the starting dose with a statement that in some patients the 360 mcg twice daily may also be appropriate.

b(4)

b(4)

Safety findings and conclusion:

The review of the submitted data and other sources did not reveal any new or unusual trends. Budesonide is marketed in the United States for use in patients with asthma and its safety characteristics are well understood. The adverse events profile reported by patients in the two studies was typical for this class of drug. Adverse events reported more commonly by patients in the budesonide group compared to patients in the placebo group were nasopharyngitis, upper respiratory tract infection, oral candidiasis, etc. These events are typically seen with orally inhaled corticosteroids due to local effects. The systemic safety of the M3 product is supported by extrapolation from the M0-ESP product since the pharmacokinetic results showed that the M3 product produced comparable (study SD-004-0601) or less (studies SD-004-0620 and SD-004-0726) exposure to budesonide compared to the M0-ESP product.

Data Quality, Integrity, and Financial Disclosure

No DSI audit for the clinical studies sites were conducted because budesonide is not a new molecular entity, budesonide is already approved for the treatment of asthma, the clinical studies conducted to support this application were routine and straight forward, and during review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements. There was one investigator who had significant financial interest in AstraZeneca. Review of the efficacy and safety data of that particular investigators' site did not show any suspicious trends.

Pediatric Considerations

AstraZeneca is seeking approval for ages 6 years and above and requested waiver of pediatric studies for patients below 6 years of age. The deferral and waiver was granted on filing the application. Budesonide is already approved for patients 1 years of age and older in an age appropriate Pulmicort Respules formulation. The current dry powder formulation is not an appropriate formulation for children younger than 6 years of age and it does not provide any therapeutic benefit over existing products.

b(4)

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Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 11, 2006

To: Barbara Blandin	From: Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number: 302-886-2822	Fax number: 301-796-9718
Phone number: 302-885-1540	Phone number: 301-796-1230

Subject: NDA 21-949 June 27, 2006, Teleconference Minutes

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES XNO

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MEMORANDUM OF TELECON

DATE: June 27, 2006

APPLICATION NUMBER: NDA 21-949

BETWEEN:

Name: Bertil Andersson, PhD, Global Product Director
Barbara Blandin, Director, Regulatory Affairs
Christopher Blango, Sr. Director Strategic Development
Eric Couture, PhD, Executive Director, Regulatory Affairs
Torgny Gustafsson, PhD, Global Director, Regulatory Affairs
Mike Gillen, RPh, Director, Clinical Pharmacology, Experimental Medicine
Richard Jahn, MS, Associate Director, Regulatory Affairs
Carolyn Russello-Callahan, Associate Director Labeling, Regulatory Affairs
Steven Simonson, MD, Senior Medical Director, Clinical Research
Tom Uryniak, MS, Biostatistics Leader, Respiratory/GI
Piet Vervaet, MD, Senior Safety Medical Director, Clinical Research

Phone: 1-866-222-5350

Representing: AstraZeneca Pharmaceuticals

AND

Name: Badrul A. Chowdhury, M.D. Ph.D., Division Director
Peter Starke, M.D., Clinical Team Leader
James Kaiser, M.D., Clinical Reviewer
Sayed Al Habet, Ph.D., Clinical Pharmacology Reviewer
Emmanuel Fadiran, Ph.D., Clinical Pharmacology Team Leader
Craig Bertha, Ph.D., Chemistry Reviewer
Ruthanna Davi, M.S., Statistical Team Leader
James Gebert, Ph.D., Statistical Reviewer
Colette Jackson, Project Manager
Division of Pulmonary and Allergy Products

SUBJECT: NDA 21-949 Labeling Discussion

The FDA referred to AstraZeneca's labeling submission dated June 13, 2006, which stated that AstraZeneca disagrees with the FDA's opinion that the NDA data shows that this is not a switchable product. The FDA stated that we still uphold our opinion of the interpretation of the data, and therefore still conclude that the products are different. The FDA stated that many other products which involved a switch program, such as CFC to HFA, have encountered the same conclusion that the new to-be-marketed product is a stand-alone product. The M3 is a stand-alone product based upon the clinical trial data.

AstraZeneca asked why the FDA views this as a different product. The FDA explained that in

order for this application to be considered a true switch program the data would have to show 1
identical dose response curves. This was not the case. The adolescent-adult trial showed
notably lower efficacy of the M3 product compared to the M0-ESP. These differences were seen
both in the primary and secondary endpoints. The pediatric trial, conducted in patients who were
relatively well, was unable to show a meaningful separation of the two devices.

The FDA discussed the remaining portions of the label, relaying our recommended changes.
AstraZeneca stated they would take the FDA recommendations under consideration and submit
revised labeling within the next few days.

POST-MEETING NOTE:

AstraZeneca submitted revised labeling on June 29, 2006. The FDA responded to that
submission with a facsimile dated July 5, 2006.

Colette Jackson
Project Manager

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FACSIMILE TRANSMITTAL SHEET

DATE: July 10, 2006

To: Barbara Blandin	From: Colette Jackson
Company: AstraZeneca Pharmaceuticals	Division of Pulmonary and Allergy Products
Fax number: 302-886-2822	Fax number: 301-796-9718
Phone number: 302-885-1540	Phone number: 301-796-1230

Subject: NDA 21-949

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NDA 21-949
budesonide inhalation powder

Please refer to your September 12, 2005, new drug application (NDA) for budesonide inhalation powder. We also acknowledge receipt of your submission dated July 7, 2006. We have the following labeling recommendation to the PRECAUTIONS, Pediatric Use subsection, lines 1057 to 1071 of your July 7, 2006, submission:

b(4)

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

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DATE: July 5, 2006

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Phone number: 302-885-1540	Phone number: 301-796-1230
Subject: NDA 21-949	

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- a. We do not accept your proposal to include the text in lines 1064-1065, “and the projected final height was identical in both groups.”
 - b. In order for FDA to accept the text in lines 1060-1064 ending with the word “velocities” you must propose labeling that will place the results in context to help in the interpretation of the results. Such labeling may include reference to the fact that patients may have attained puberty during the course of the study, the unequal use of corticosteroids in the treatment groups, etc.
 - c. We remind you that labeling containing statements related to effects on growth have previously been submitted to NDA 20-441, S-006, for Pulmicort Turbuhaler. Final agreed-upon labeling for growth should also be submitted to the NDA for Pulmicort Turbuhaler.
 - d. Describe the derivation of 500 pediatric subjects treated with “inhaled budesonide” but not with TRADENAME.
4. In the ADVERSE REACTIONS section, Adverse Event Reports from Other Sources subsection, lines 1149 and 1172-1173, you refer to the comparator device as ~~_____~~ and “a different budesonide-containing dry powder inhaler.” We refer you to our facsimile dated June 23, 2006, in which we advised you to choose and apply a consistent terminology to distinguish Pulmicort Turbuhaler from TRADENAME throughout the package insert. **b(4)**
5. Regarding the DOSAGE AND ADMINISTRATION section:
- a. In lines 1294-1295 remove the qualifier ‘ ~~_____~~ ’ **b(4)**
 - b. We acknowledge your statement of justification for the inclusion of a starting dose for adults of TRADENAME, 180 mcg BID. Your proposal to include this dose regimen for adults is under Agency review and consideration.

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

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 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 23, 2006

To: Barbara Blandin	From: Colette Jackson
Company: AstraZeneca Pharmaceuticals	Division of Pulmonary and Allergy Products
Fax number: 302-886-2822	Fax number: 301-796-9718
Phone number: 302-885-1540	Phone number: 301-796-1230

Subject: NDA 21-949

Total no. of pages including cover: 32

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NDA 21-949
budesonide inhalation powder

Please refer to your September 12, 2005, new drug application (NDA) for budesonide inhalation powder. We also acknowledge receipt of your submission dated June 13, 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.

Regarding the Package Insert:

1. Throughout the Package Insert, choose and apply a consistent terminology to distinguish the marketed Pulmicort Turbuhaler drug product from TRADENAME. For example, you may choose to use terminology such as “another marketed formulation of budesonide dry powder inhaler” or “approved formulation of budesonide dry powder inhaler”, or choose to use the Pulmicort Turbuhaler trade name.
2. Please note that in several areas of the label we are requesting additional information, numbers or figures. Replace ‘xx’ with the appropriate number, and add the requested figures to the Clinical Studies subsection.
3. Regarding the DESCRIPTION section: Add information regarding the number of actuations for each fill weight/presentation.
4. Regarding the Clinical Studies subsection:
 - a. We have changed the references in each study to the TRADENAME dosage strength rather than to the dose used. Please update the legends in all tables and figures to refer to TRADENAME by dosage strength and dose administered, e.g. TRADENAME 180 mcg, 2 inhalations twice daily.
 - b. For Study 0620, replace the current graphic with figure displaying a line graph of by-treatment group mean changes from baseline in FEV₁ over time. Use the observed data only, not the LOCF data. Display the following treatment groups: TRADENAME 180 mcg, 2 inhalations bid; budesonide dry powder inhaler [i.e. Pulmicort Turbuhaler M0-ESP] 200 mcg, 2 inhalations bid; and placebo. At the right side of this graph display the point estimates for the primary efficacy analysis, change from baseline in by-treatment group means averaged over the treatment period. Include a footnote displaying the p-value for the primary efficacy comparison for the M3 only, indicating that it was calculated using last-observation-carried-forward (LOCF) methods. The footnote should also mention that the two products result in the same delivered dose of 160 mcg. Along with the Week designation on the horizontal axis, provide the sample sizes used for calculation of the plotted means at each time point. The sample size for the point

estimates for the primary efficacy analysis should be those from the LOCF analysis.

- c. For Study 0726, replace the current graphic with a figure similar to that requested above, except that the graph should display by-treatment group mean changes from baseline in percent predicted FEV₁ over time, and the legend should reflect the dosage strength of TRADENAME used in this study.
5. Regarding the PRECAUTIONS section, justify the statement regarding a lack of taste with TRADENAME. You may need to assess whether TRADENAME can be tasted and revise the bullet point regarding the potential for a lack of sensation if needed.

a. Regarding the Pediatric Use subsection:

- i. Add the appropriate numbers of patients studied with inhaled budesonide and with TRADENAME.
- ii. We agree with adding class language for the potential of inhaled corticosteroids to cause a growth effect.

We note, however, that the class language for the potential to cause growth effects includes a statement that ~~_____~~

~~_____~~

~~_____~~ 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 without your providing the primary data for Agency review and analysis. We have therefore removed this information and substituted the class labeling.

b(4)

6. Regarding the ADVERSE REACTIONS section:

- a. The text below the table should reflect data to be imported from the Pulmicort Turbuhaler package insert. Please verify if it is appropriate to include *flu syndrome* and *dyspepsia*, perhaps due to rounding. We have added several adverse event terms to the paragraph naming the events at a greater incidence in the 800 mcg BID treatment arm as compared to the 400 mcg BID treatment arm, consistent with the table of adverse events in the approved Pulmicort Turbuhaler package insert.
- b. ~~_____~~
- c. Information from AERS reports for instances of cataracts and glaucoma in patients on orally inhaled budesonide is new information.

b(4)

7. Regarding the DOSAGE AND ADMINISTRATION section:

a. The second paragraph must address the clinical differences that make TRADENAME a stand-alone drug product, and that may result in dosage and administration differences when patients are transitioned between the currently marketed Pulmicort Turbuhaler and TRADENAME. We have modified this paragraph to clarify these differences.

b. ~~_____~~

c. ~~_____~~

b(4)

Regarding the Carton and Container labeling:

8. Submit updated labeling in its actual size with TRADENAME substituted for Pulmicort Turbuhaler. Until then, we are unable to comment regarding legibility, including legibility of specific statements and of the immediate container.

9. Remove the picture that currently appears within the proprietary and established names.

10. The proprietary name should be in the same font throughout. The dosage strength of TRADENAME should appear in the same font as the proprietary name, i.e. "TRADENAME 180 mcg" or "TRADENAME 90 mcg".

11. The number of doses on the carton labeling should be presented in a larger font.

12. The established name on the carton and container should be the same as that in the PI, i.e., the established name should include the dosage strength. Change '~~_____~~' to "budesonide inhalation powder, 180 mcg" or "budesonide inhalation powder, 90 mcg".

b(4)

13. Address the fact that the physicians samples for both dosage strengths have white or yellow fonts on teal or violet backgrounds, making legibility a problem.

Regarding the Patient Instructions for Use:

14. Replace "Pulmicort Turbuhaler" with TRADENAME.

b(4)

15. Replace "~~_____~~" with "health care provider" or a similar term.

16. Regarding “Important points to remember about [TRADENAME]”: Add safety advice consistent with any updates or modifications to the package insert.
17. Regarding “Further information about TRADENAME”: See the first comment in item 6 (above) regarding the taste of the product.
18. Add a section, worded to be consistent with the adverse reactions section of the proposed package insert, titled “What are the most common side effects of TRADENAME?”

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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26 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Colette Jackson
6/23/2006 04:13:27 PM
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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: May 19, 2006

To: Colette Jackson, Regulatory Project Manager
Division of Pulmonary and Allergy Products

From: Michelle Safarik, PA-C, Regulatory Review Officer
Iris Masucci, PharmD, Labeling Reviewer
Division of Drug Marketing, Advertising, and Communications

Subject: NDA 21-949
DDMAC labeling comments for Pulmicort Turbuhaler (budesonide inhalation powder) 180 mcg and 90 mcg

Per your consult request dated October 19, 2005, DDMAC has reviewed the proposed product labeling (PI), proposed patient package insert (PPI), and the following proposed carton and container labeling for Pulmicort Turbuhaler: 180 mcg container sample, 180 mcg container, 180 mcg carton sample, 180 mcg carton, 90 mcg container sample, 90 mcg container, 90 mcg carton sample, and 90 mcg carton. While this proposed labeling addresses the 90 mcg and 180 mcg dosage strengths of Pulmicort Turbuhaler, DDMAC has reviewed the entire label and are thus commenting on other sections of the label that were approved in the Pulmicort Turbuhaler 200 mcg label.

PI

General Comments

b(4)

8 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Michelle Safarik
5/18/2006 03:54:50 PM
DDMAC REVIEWER

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 10, 2006

To: Barbara Blandin	From: Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number: 302-886-2822	Fax number: 301-796-9718
Phone number: 302-885-1540	Phone number: 301-796-1230
Subject: NDA 21-949	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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NDA 21-949
Pulmicort Turbuhaler

We are reviewing your NDA submission dated September 12, 2005, and we have the following requests in order to facilitate the clinical review of studies.

1. Regarding testing for effects of the Pulmicort Turbuhaler M3 on plasma cortisol:
 - a. For trials SD-004-0210, SD-004-0600, SD-039-0667, SD-039-0668, and SD-039-0673, submit line listings by treatment group of plasma cortisol values and the results of ACTH testing (when done). Define the reference range for each trial's testing and clearly mark the subject values that fell outside reference range. Briefly describe the ACTH testing protocol, including the dose of ACTH administered.
 - b. Identify the constituents of the placebo for trials SD-004-0620 and SD-004-0726. Explain why Table 2 of the clinical trial reports for these trials states that the placebo for M0-ESP contained excipients.
2. Provide a summary of procedures for trials for which this information is not included in your integrated summary of safety. These trials include but may not be limited to: SD-005-0601, SD-004-0210, SD-004-0600, SD-039-0667, SD-039-0668, and SD-039-0673. This information can be in the form of text, a table of procedures, or other.
3. Regarding information relevant to the evaluation of safety in trials 850-CR-0280 and D525400007, please provide tabulations of the numbers of subjects and their percents of treatment groups (i.e., dose level) of:
 - a. Subjects treated solely with one dose level of the device.
 - b. Nonfatal serious adverse events with respect to dose and organized by organ class and then by preferred term.
 - c. Discontinuations for adverse events organized as in item 3b.
4. Provide a cumulative table of exposure, similar to Table 1 of the Safety Update Report for the clinical program to October 31, 2005.

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

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/s/

Colette Jackson
5/10/2006 10:47:02 AM
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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 1, 2006

To: Barbara Blandin	From: Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number: 302-886-2822	Fax number: 301-796-9718
Phone number: 302-885-1540	Phone number: 301-796-1230
Subject: NDA 21-949	

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

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NDA 21-949

INFORMATION REQUEST LETTER

AstraZeneca Pharmaceuticals
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Barry Sickles
Executive Director, Regulatory Affairs

Dear Mr. Sickles:

Please refer to your September 12, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Turbuhaler (budesonide inhalation powder) M3.

We also refer to your submissions dated September 16, October 6, 17, and 18, November 3, and December 19, 2005, and January 9, 26, and February 20, 2006.

We are reviewing the Clinical and Chemistry, Manufacturing and Controls sections 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 comparative *in vitro* ~~midstack~~ data in terms of the fine particle dose and midstack particle dose for the M3, M0, and M0-ESP drug products, determined at flow rates between 30-100 L/min. It is understood that historical data may be referenced for the M0 version as it has not been manufactured recently.
2. Provide data with regard to the typical inspiratory flow rates expected for adults and children of various age groups, e.g. 6-8 years, 8-10 years, 10-12 years, etc., both for healthy subjects and patients with moderate to severe persistent asthma.
3. Proposed labeling includes the statement that peak inspiratory flow rates in the subjects in the pediatric trial were 72.5 [19.1 – 103.6] L/min. Describe the methodology you used to determine these values.

b(4)

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

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sandra Barnes
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 13, 2006

To: Luida Shtohryn	From: Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number: 302-886-2822	Fax number: 301-796-9718
Phone number: 302-885-4108	Phone number: 301-796-1230
Subject: NDA 21-949	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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NDA 21-949
Pulmicort Turbuhaler

Please refer to your September 12, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Turbuhaler (budesonide inhalation powder) DPI.

We also refer to your submission dated February 20, 2006, which requested clarification of comment 16a of our January 25, 2006, Discipline Review Letter. We have the following comment.

The Agency is supportive of the PTIT approach for delivered dose uniformity testing, as elaborated at the Advisory Committee meeting held in October 2005. However, the Agency does not agree to the specifics of your approach to PTIT for the Pulmicort Turbuhaler M3 application, specifically the proposed acceptance criteria. The PTIT approach and acceptance criteria that the Agency will agree to were provided in the Oct. 2005 Advisory Committee meeting. Therefore, the PTIT approach can remain as an alternate test for delivered dose uniformity only if the Agency proposed acceptance criteria are adopted for the specification.

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

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/s/

Colette Jackson
3/13/2006 10:08:57 AM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 3, 2006

To: Barbara Blandin	From: Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number: 302-886-2822	Fax number: 301-796-9718
Phone number: 302-885-1386	Phone number: 301-796-1230
Subject: NDA 21-949	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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NDA 21-949
Pulmicort Turbuhaler

We are reviewing your NDA submission dated September 12, 2005, and we have the following requests in order to facilitate the clinical review of studies.

1. Please explain the rules used to calculate last observation carried forward (LOCF) values in datafiles _PULM02 for studies SD-004-0620 (0620) and SD-004-0726 (0726). There appear to be inconsistencies in how the LOCF approach was applied to these data such as the following:
 - a. There are missing values for FEV₁ at visits 3 through 6 (FEV₃, FEV₄, FEV₅, and FEV₆) in studies 0620 and 0726. We understand that certain FEV₁ values may be missing because the baseline and FEV₂ values are not carried forward. Please explain why there are missing values for FEV₄ through FEV₆. We recognize that some but not all are explainable by the occurrence of unassigned visit values.
 - b. There appear to be inconsistencies in the methods for carrying forward values when there are unassigned visit values. Sometimes when there is an unassigned visit value you do not carry forward (for example, subject E0004018 in trial SD-004-0620), but at other times a value is carried forward (an example, subject E0014004 in trial SD-004-0620). Please explain.
2. Compliance with treatment was measured by means of an electronic "logpad." Please submit logpad data, including these compliance data, as a data set or data sets, or submit the locations of these data in previously submitted data sets.

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

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/s/

Colette Jackson
3/3/2006 11:59:41 AM
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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 25, 2006

To: Barbara Blandin	From: Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Drug Products
Fax number: 302-886-2822	Fax number: 301-796-9718
Phone number: 302-885-1540	Phone number: 301-796-1230

Subject: NDA 21-949 Discipline Review Letter

Total no. of pages including cover: 7

Comments:

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NDA 21-949

DISCIPLINE REVIEW LETTER

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

Attention: Barry Sickles
Executive Director, Regulatory Affairs

Dear Mr. Sickles:

Please refer to your September 12, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Turbuhaler M3.

We also refer to your submissions dated October 6, and October 17, 2005.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1.

2.

3.

4.

b(4)

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

- e. Revise the labels for the containers to include a warning that the device must be stored with the cover tightly in place at all times when not in use (e.g., Keep tightly closed).
- f. Indicate the position on the four container labels where the lot number and expiration date will be located.
- g. Provide clarification of how and with what printed information the strength of the product will be included on the inhaler (not the cover) as described in the “Dosage” section of the Patient’s Instructions for Use.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified and subject to change as we finalize our review of your application. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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/

Richard Lostritto
1/25/2006 01:20:50 PM

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Is the application affected by the Application Integrity Policy (AIP)? YES xNO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? xYES NO

• Was form 356h included with an authorized signature? xYES NO

If foreign applicant, both the applicant and the U.S. agent must sign.

• Submission complete as required under 21 CFR 314.50? xYES NO
If no, explain:

• If an electronic NDA, does it follow the Guidance? xYES NO

If an electronic NDA, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format?

Modules 1 through 5 were submitted electronically.

Additional comments:

Module 1 provided also in paper.

• If in Common Technical Document format, does it follow the guidance? xYES NO

• Is it an electronic CTD?(eCTD not currently available) xYES NO

If an electronic CTD, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format?

All parts were submitted in electronic format.

Additional comments:

• Patent information included with authorized signature? xYES NO

• Exclusivity requested? xYES, 3 years NO

Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? xYES NO

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . ."

• Financial Disclosure information included with authorized signature? xYES NO
(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

• Field Copy Certification (that it is a true copy of the CMC technical section)? xYES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? xYES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: IND 63,762; ~~_____~~ **b(4)**
- End-of-Phase 2 Meeting(s)? Date(s) _____ xNO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s) xYES Date(s) _9/8/04 (CMC), 12/6/04_
 If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? xYES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? YES xNO
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? xN/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? xN/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? xN/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? xN/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? xYES NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? xYES NO
- If parenteral product, consulted to Microbiology Team (HFD-805)? YES xNO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Is the rate at which the product’s active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a “Paragraph IV” certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

- _____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
- _____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
 - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

	YES	NO
--	-----	----
 - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

	YES	NO
--	-----	----
 - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

	N/A	YES	NO
--	-----	-----	----
 - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

	N/A	YES	NO
--	-----	-----	----
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
 - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

	YES	NO
--	-----	----
 - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

	YES	NO
--	-----	----
 - EITHER
 The number of the applicant's IND under which the studies essential to approval were conducted.

	YES, IND # _____	NO
--	------------------	----

 OR
 A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

	N/A	YES	NO
--	-----	-----	----
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

	YES	NO
--	-----	----

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 18, 2005

BACKGROUND:

NDA 21-949 is the result of a Phase 4 commitment for NDA 20-441. IND 63,762 is the referenced IND for Pulmicort Turbuhaler.

ATTENDEES:

Attendees:

Badrul A. Chowdhury, M.D., Ph.D., Division Director, DPADP
Peter Starke, M.D., Clinical Team Leader, DPADP
James Kaiser, M.D., Clinical Reviewer, DPADP
Lawrence Sancilio, Ph.D., Pharmacology/Toxicology Reviewer
Joseph Sun, Ph.D., Pharmacology/Toxicology Team Leader
Sayed Al Habet, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer
Emmanuel Fadiran, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer
James Gebert, Ph.D., Statistical Reviewer
Ruthanna Davi, Ph.D., Statistical Team Leader
Colette Jackson, Project Manager

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	James Kaiser
Secondary Medical:	Peter Starke
Statistical:	James Gebert
Pharmacology:	Lawrence Sancilio
Statistical Pharmacology:	
Chemist:	Craig Bertha
Environmental Assessment (if needed):	
Biopharmaceutical:	Sayed Al Habet
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Manager:	Colette Jackson
Other Consults:	DDMAC

Per reviewers, are all parts in English or English translation? xYES NO
If no, explain:

CLINICAL

FILE X

REFUSE TO FILE _____

- Clinical site inspection needed: YES xNO
- Advisory Committee Meeting needed? YES, date if known _____ xNO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

		xN/A	YES	NO
CLINICAL MICROBIOLOGY	FILE _____	REFUSE TO FILE _____		xN/A
STATISTICS	FILE <u>X</u> _____	REFUSE TO FILE _____		
BIOPHARMACEUTICS	FILE <u>X</u> _____	REFUSE TO FILE _____		
	• Biopharm. inspection needed:		YES	xNO
PHARMACOLOGY	FILE <u>X</u> _____	REFUSE TO FILE _____		
	• GLP inspection needed:		YES	xNO
CHEMISTRY	FILE <u>X</u> _____	REFUSE TO FILE _____		
	• Establishment(s) ready for inspection?		xYES	NO
	• Microbiology	xYES	NO	N/A

ELECTRONIC SUBMISSION:
 Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

- _____ The application is unsuitable for filing. Explain why:
- X_____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
- _____ No filing issues have been identified.
- X_____ Filing issues to be communicated by Day 74.

ACTION ITEMS:

1. Document no filing issues conveyed to applicant by Day 74.

Colette Jackson
Regulatory Project Manager, HFD-570

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/s/

Colette Jackson
12/5/2005 02:12:31 PM
CSO

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 23, 2005

To: Barbara Blandin	From: Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Drug Products
Fax number: 302-886-2822	Fax number: 301-796-9718
Phone number: 302-885-1540	Phone number: 301-796-1230

Subject: NDA 21-949 Filing Letter

Total no. of pages including cover: 4

Comments:

Document to be mailed: xYES NO

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FILING REVIEW LETTER

NDA 21-949

AstraZeneca Pharmaceuticals
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Barry Sickles
Executive Director, Regulatory Affairs

Dear Mr. Sickles:

Please refer to your September 12, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Turbuhaler (budesonide inhalation powder) M3.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 11, 2005, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

We note that the dose content of the test article was increased during trial SD-004-0620 to the dose content proposed for marketing. We further note that the to-be-marketed formulation was not studied in trial SD-004-0726.

We are providing the above comment to give you preliminary notice of a potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We have the following requests for information:

1. Please describe the basis for the selection of case report forms submitted in the application.
2. Statistical summaries presented in section 7.3 of the trial SD-004-0620 final report do not agree in all cases with analyses in tables to which they refer. For example, Tables 45-47 from the final report cite the change from baseline in FEV₁ for the once-a-day M3 inhaler ~~_____~~ g fill as 0.28 and the change from baseline for the twice-a-day subgroup using M3 ~~_____~~ g fill as 0.38. However, the data

b(4)

table from which you state this value derives (Table 11.2.1.1.6) shows the treatment averages of 0.23 and 0.30, respectively.

- a. Please clarify what data sets were used to generate tables in section 7.3 of the final report for trial 0620.
- b. If the tables in the final report are incorrect, please submit corrected versions to the NDA.
- c. The values of the variables CONTENT and _CONTENT in files _PULM02 and _DIARY02 in folder SD-004-0620 are inconsistent. For some subjects the value is missing in one data set and present in another, for others neither data set contains a value (Subjects 4007, 4009, 4010, 4011, 4030, 4041, 4043, 4044, and 4053). Specify correct values for subjects 4007, 4009, 4010, 4011, 4030, 4041, 4043, 4044, and 4053.
- d. Please identify the data sets that specify for all subjects whether they received the g or g M3 inhaler. If such a data set has not been submitted, please submit it.

b(4)

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Eugene Sullivan
11/23/2005 03:07:20 PM
For Badrul Chowdhury

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: <i>(Division/Office)</i> J. Sun, Ph.D., Team Leader (HFD-570)			FROM: Craig M. Bertha, Ph.D. (ONDQA, Div. 1)	
DATE 11/10/05	IND NO. 63,762	NDA NO. N21-949	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT 12-SEP-2005
NAME OF DRUG Pulmicort Turbuhaler (budesonide) Inhalation Powder		PRIORITY CONSIDERATION 3	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE 01/10/05
NAME OF FIRM: 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"/> RESPONSE 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 <input checked="" type="checkbox"/> OTHER <i>(Specify below)</i>
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"/> <i>IN-VIVO</i> 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"/> CASE REPORTS OF SPECIFIC REACTIONS <i>(List below)</i> <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	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate, from the pharmacology/toxicology perspective, the adequacy of the acceptance criteria of <u> </u> of the impurity in the drug product. This would limit the maximum daily dose exposure to less than <u> </u> mcg. This molecule has a structural alert for mutagenicity.				
cc: Orig. NDA # 21-949 HFD-570/Div. File HFD-810/RLostritto/BFraser/CBertha HFD-570/JSun/LSancilio HFD-570/SBarnes/CJackson				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY <i>(Check one)</i> <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

b(4)

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/s/

Blair Fraser

11/10/2005 12:24:08 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-949

AstraZeneca Pharmaceuticals
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Barry Sickles
Executive Director, Regulatory Affairs

Dear Mr. Sickles:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Pulmicort Turbuhaler (budesonide inhalation powder) M3

Review Priority Classification: Standard (S)

Date of Application: September 12, 2005

Date of Receipt: September 12, 2005

Our Reference Number: NDA 21-949

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 11, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 12, 2006.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request within this application for a partial waiver of pediatric studies. We have reviewed your partial waiver request and agree that a waiver is justified only for pediatric studies in patients zero to

NDA 21-949

Page 2

less than 6 years of age for Pulmicort Turbuhaler® M3 for asthma since Pulmicort Respules® provides treatment for this age group and Pulmicort Turbuhaler M3 does not represent a therapeutic benefit over existing treatments and is not likely to be used in a substantial number of patients in that age group.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/ Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, Ph.D.
Director
Division of Pulmonary and Allergy Drug Products, HFD-570
Office of Drug Evaluation II
Center For Drug Evaluation and Research

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/s/

Badrul Chowdhury
10/28/2005 10:22:40 AM

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S. B. [Signature]
10/21/05

TO (Division/Office):
**Division of Drug, Marketing, Advertising and
Communication (DDMAC)**
400 Bldg 22 Rm. 1400

FROM:
Colette Jackson
Project Manager
Division of Pulmonary and Allergy Products

DATE October 19, 2005	IND NO.	NDA NO. 21-949	TYPE OF DOCUMENT N	DATE OF DOCUMENT September 12, 2005
NAME OF DRUG Pulmicort Turbuhaler (budesonide)	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Inhaled Corticosteroid	DESIRED COMPLETION DATE May 20, 2006	
NAME OF FIRM: AstraZeneca Pharmaceuticals				

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE—NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Labeling Review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

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 OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This is a request for an evaluation and review of the package insert, carton, and container labeling for Pulmicort Turbuhaler®. This submission is electronic only and is located in the EDR in the submission dated September 12, 2005.

PDUFA DATE: July 12, 2006

CC:
Archival NDA 21-949
HFD-570/Division File
HFD-570/Jackson

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

M. [Signature] 10/21/05

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/s/

Colette Jackson
10/21/2005 03:19:32 PM

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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 5, 2005

To: Peggy Berry	From: Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Drug Products
Fax number: 302-886-2822	Fax number: 301-827-1271
Phone number: 302-886-8991	Phone number: 301-827-9388
Subject: 12/6/04 Meeting Minutes for IND 63,762 pre-NDA meeting	

Total no. of pages including cover:

Comments:

Document to be mailed: xYES NO

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 6, 2004

TIME: 1:00 PM

LOCATION: Food and Drug Administration/Conference Room B

APPLICATION: IND 63,762/ Pulmicort Turbuhaler M3/AstraZeneca

TYPE OF MEETING: Pre-NDA (non-CMC) Meeting

FDA ATTENDEES, DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

Badrul A. Chowdhury, M.D., Ph.D., Division Director
John H. Gunkel, M.D., Clinical Reviewer
Peter Starke, M.D., Clinical Team Leader
Sandra Suarez, Ph.D., Clinical Pharmacology/Biopharmaceutics
Emmanuel Fadiran, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader
Sue Jane Wang, Ph.D., Acting Statistical Team Leader
James Gebert, Ph.D., Statistical Reviewer
Colette Jackson, Project Manager

ASTRAZENECA ATTENDEES AND TITLES:

Peggy Berry, Director, Regulatory Affairs
Lars-Göran Carlsson, MD, Product Medical
Torgny Gustafsson, PhD, Global Director, Regulatory Affairs
Richard Jahn, Associate Director, Regulatory Affairs
Richard Leff, MD, Senior Medical Director, Clinical Research
Lawrence McDermott, MD, Associate Director, Clinical Research
William Mezzanotte, MD, Executive Director, Clinical Research
Piet Vervaet, MD, Senior Safety Medical Director, Clinical Research

BACKGROUND: The purpose of this meeting is to discuss the content and format of the non-CMC information to be provided in the NDA filing. On December 3, 2004, the Division sent written responses to the questions posed in the meeting package via facsimile (see attachment). On December 4, 2004, AstraZeneca (AZ) sent their corresponding clarifications (in bold italics) below via secure e-mail and the discussion follows. (**POST-MEETING NOTE:** AZ officially submitted their clarifications in a letter dated December 7, 2004, serial number 063).

DISCUSSION:

The Division stated that the purpose of sending Division responses and comments before the meeting was to allow the Sponsor the opportunity to clarify issues and to provide focus for the meeting, not to raise new questions. The Division explained to AZ that their response (“clarification correspondence”) sent via secure e-mail could not be commented on at this time. The clarification correspondence includes additional questions for which the Division has not had sufficient time for review, and the Division cannot agree or disagree as requested in the correspondence.

Below are the original questions posed by AZ. Each numbered question is followed by the Division’s faxed response, AZ’s clarification, and the discussion of the remaining issues.

The Division referred to question 6-1 and the Division’s response as outlined in the facsimile sent to AZ.

CLINICAL AND STATISTICAL INFORMATION

- 6-1. Does the Agency agree with AstraZeneca’s proposal to only provide the pivotal clinical study reports (SD-004-0620 and SD-004-0726) in Module 5 of the NDA and to incorporate the remaining 10 study reports into the Pulmicort Turbuhaler M3 NDA by cross-reference only?**

No. The NDA should include both the pivotal and non-pivotal study reports and clinical data necessary to support the M3 switch and proposed new labeling. In particular, Studies 04-3020A (GHBA-165) and 04-3023A (GHBA-168) are essential to approval of the 90 mcg dosage strength.

Your proposed labeling retains the perspective of the previous product presentations. Instead, it should primarily represent the current M3 product presentation. Specifically, the M3 clinical studies should be comprehensively described, and efficacy and safety information should be prominently displayed in charts and/or figures. The M0 information should be preserved, but it should follow the M3 information.

The Division then referred to AZ’s clarification for 6-1.

- 6-1.**
AstraZeneca agrees to include studies 04-3020A (GHBA-165) and 04-3023A (GHBA-168) within Module 5 of the NDA. The CSRs that will be included in Module 5 are now:

SD-004-0620

SD-004-0726

SD-004-0601

04-3020A (GHBA-165)

04-3023A (GHBA-168)

Please refer to 11-5 regarding the format for the submission of the 100 mcg bid dosing regimen, 04-3020A (GHBA-165) and 04-3023A (GHBA-168) studies.

The 1-yr and 5-yr open label study CSRs, 850-CR-0280 and D525400007 are being included by cross-reference.

PK studies per comment 5-1, SD-004-0600 and SD-004-0708 are being included by cross-reference.

Regarding all other studies please refer to 7-1.

Regarding the Agency's package insert comment, please see response 10-2.

Does the Agency agree with this plan?

Discussion:

The Division confirmed that AZ would include studies 04-3020A and 04-3023A electronically, but the study reports will be scanned and submitted as pdf files. The Division asked if there would be a Table of Contents (TOC) linkage. AZ stated that there will be TOCs with electronic links to each section of the reports, but there will be no links for lower levels of organization (e.g., individual data tables). The Division stated that this is acceptable.

The Division stated that it is acceptable for the 1-year and 5-year open label study CSRs to be included by cross reference. AZ noted that the 1-year study has been submitted and that the 5 year study is now completed and the submission should be forthcoming in the near future. AZ stated that it does not plan to include information from those two studies in the package insert. The Division asked AZ to briefly describe the study objectives. AZ replied that the 1-year study measured height, cortisol levels, and included an ophthalmic examination. The 5-year study was more limited; adverse events and minimal laboratory analyses were collected. The 5-year study, which included adult and pediatric subjects, had a high rate of attrition. AZ regards this study as for information purposes only and not in support of labeling claims, and therefore plans to submit the study to the IND and not the NDA submission. The Division stated that in order to support the NDA and to provide additional safety information, the 5-year study report summary should be provided with the NDA. The Division noted that AZ's proposed NDA involves a new dosage strength for Pulmicort Turbuhaler, as well as the switch program to the M3, and both must be supported in the NDA.

The Division asked AZ if the across study comparison of the PK of Pulmicort Turbuhaler M3 and Pulmicort Turbuhaler MO-ESP was still under consideration. AZ stated that a cross study comparison would be included as well as the population PK analysis of all

available data from Pulmicort Turbuhaler M3, Pulmicort Turbuhaler MO, and Pulmicort Turbuhaler MO-ESP.

Discussion then turned to the proposed package insert (PI). As stated in its response to the original question 6-1 from AZ, the Division stated that the PI should primarily reflect the new M3 product and be written from that perspective. The currently proposed PI retains and emphasizes the information about the current and previous Pulmicort products, while only briefly mentioning the new M3 product. Patients will be using the new M3 product, which involves major changes from previous product presentations, and the PI should provide that information, especially when describing the clinical trials. AZ stated that their perspective of the PI is that it should not create confusion for the clinician. AZ believes that if the data demonstrate PK and clinical comparability, it is better not to duplicate results in the PI. The Division suggested AZ look at the PIs of other programs involved in switch programs as models for handling the PI. The Division understands that AZ cannot compose a final label until all the data and results are available, but recommends that more information about M3 be included in the label. At a minimum, the M3 clinical studies should be described in more detail. AZ stated that the current PI includes dosing information from the earlier product presentations that were not studied with M3 so that retaining the current perspective would assist the clinician in dosing with the M3 product. The Division acknowledged this point and stated that it is in fact a review issue, as elaborated further in the discussions of questions 6-2 and 7-1. Nevertheless, the Division reiterated the fact the M3 will replace previous presentations of the Turbuhaler. While information from previous presentations is critical to efficacy and safety, once the previous presentations are no longer marketed the M3 product PI must stand alone. Therefore, the PI should be written from the frame of reference of the M3 presentation.

The Division then referred to question 7-1 and the Division's response as outlined in the facsimile sent to AZ.

SAFETY INFORMATION

7-1. Does the Agency agree with AstraZeneca's proposal regarding: a) the studies (SD-004-0620, SD-004-0726, and SD-004-0601) that will contribute safety data to the Summary of Clinical Safety, and b) that the safety data will not be pooled across these studies?

No. As stated in the response to 6-1, the Summary of Clinical Safety will need to support the proposed labeling. Other study reports are required, specifically, safety data from patients who received the 100 mcg dosage in studies 04-3020 and 04-3023 should be included in the Summary of Clinical Safety. The Division would also like to see summary safety data from patients who received M3 in the other studies.

We recommend that a table of adverse events be included in the package insert for the pooled 12-week M3 Phase 3 studies, similar to the table of adverse events

in the current package insert. See 6-1 regarding the perspective of the new package insert.

The Division then referred to AZ's clarification for 7-1.

7-1.

a) AstraZeneca agrees to pool the data across the two pivotal M3 studies SD-004-0620 and SD-004-0726 by total daily dose (placebo, M3 180 mcg qd, M3 360 mcg bid, M0-ESP 200 mcg qd, and M0-ESP 400 mcg bid). All adverse event data including SAEs and discontinuations due to adverse events will be pooled and presented in the Summary of Clinical Safety. The remaining safety data from these two studies will be summarized by study.

Does the Agency agree with this plan?

b) Data from the 100 mcg bid M0 arms from studies 04-3020A (GHBA-165) and 04-3023A (GHBA-168) will be pooled. All adverse event data including SAEs and discontinuations due to adverse events will be pooled and presented in the Summary of Clinical Safety. The remaining safety data from these two studies will be summarized by study.

Does the Agency agree with this plan?

c) AstraZeneca agrees to include safety summaries for the patients who received Pulmicort Turbuhaler M3 in the following studies:

SD-004-0210

SD-039-0667

SD-039-0668

SD-039-0673

These studies are not placebo controlled and have an active comparator (Pulmicort Turbuhaler M2 or Symbicort Turbuhaler M3) that is not currently approved in the U.S.

- The summaries will be formatted by key variable, and described by each individual study. Due to the limited relevance of these studies for the proposed labeling, only the following key variables are suggested for inclusion: AEs (including SAEs discontinuations due to AEs), cortisol, and ACTH testing.***
- The CSRs for the studies above will be included by cross-reference.***

Does the Agency agree with this plan?

Discussion:

AZ asked for Division concurrence about pooling AE-related data but not other safety data (e.g., vital signs). The Division generally concurred and suggested that AZ pool as

much data as doses and populations allow. The Division also concurred in including safety summaries from the other four studies mentioned for the patients who received M3 in those studies.

AZ asked whether the studies may be cross-referenced or whether the study reports should be included in the NDA. The Division stated that whatever supports the NDA should be included in it, and asked AZ to explain exactly what cross-referencing would entail. AZ explained that data sets for the legacy studies might not be available in a form that would allow electronic submission. The Division stated that this could be a review problem. The Division stated that it will be necessary to submit all evidence supporting the 90 mcg dose of M3 in order to allow for adequate review of the data. AZ stated its belief that all clinical data supporting the lower dose had already been fully reviewed and with the original NDA and from a clinical standpoint was complete to support approval. The Division stated that that is an incorrect understanding. It was previously examined by the Division as part of the original NDA review, but since AZ did not request action on this dose, a regulatory action on this dose was never taken and the dose was not included in the labeling. The Division stated that in addition to the complete study reports, review of the lower dosage form will require submission of data sets and SAS transport files. AZ expressed concern about whether that will be possible. The Division stated that if it is not possible, AZ should reconsider submitting the lower dosage form. The Division stated that the data quality is of issue and the original data needs to be included in the NDA.

The Division referred to question 7-2 and the Division's response as outlined in the facsimile sent to AZ.

7-2. Does the Agency agree with AstraZeneca's proposal to maintain adverse events coding consistency within each study by a) leaving data from study SD-004-0601 and its respective Item 11 dataset in the Astra Adverse Events Dictionary (AAED) and b) presenting the data from studies SD-004-0620 and SD-004-0726 using MedDRA (in the version available in the clinical study reports)?

The Division agrees.

The Division then referred to AZ's clarification for 7-2.

7-2. AstraZeneca will maintain adverse event coding consistency within each study, for all studies that we agreed to include in the NDA per Comments 6-1 and 7-1.

Does the Agency agree with this plan?

The Division agreed with AZ's clarification for question 7-2.

The Division referred to question 8-1 and the Division's response as outlined in the facsimile sent to AZ.

ADMINISTRATIVE INFORMATION

8-1. Does the Agency agree with the request for a pediatric waiver for children under the age of 6 years?

Requests for pediatric waivers and deferrals are made at the time the NDA is submitted.

The Division then referred to AZ's clarification for 8-1.

8-1. AstraZeneca plans to request a waiver at the time the NDA is submitted. Does the Agency foresee any issues with approving this request?

AZ asked the Division if there could be an issue with obtaining a waiver. The Division stated that it is too early to comment. The Division stated that the determination will be made based on whether other pediatric studies might be needed, and that cannot be determined at this time. This would be a review issue.

The Division referred to question 10-1 and the Division's response as outlined in the facsimile sent to AZ.

LABELING

10-1. Does the Agency agree with AstraZeneca's proposal to retain the commercial tradename of "Pulmicort Turbuhaler"?

The product's trade name will be consulted for review by the Division of Medical Errors and Technical Support, but we do not anticipate major obstacles to retaining the current trade name.

The Division then referred to AZ's clarification for 10-1.

10-1. To facilitate the consultation, should AstraZeneca submit a request or any information regarding the tradename directly to the Division of Medical Errors and Technical Support?

The Division suggested that the tradename consult be initiated at the time of the NDA submission. AZ asked whether the Division was signaling that there might be an issue, and the Division replied that at this time we do not foresee any trade name issues.

The Division referred to question 10-2 and the Division's response as outlined in the facsimile sent to AZ.

10-2. Does the Agency agree with AstraZeneca's labeling strategy for:

a) retaining the Pulmicort Turbuhaler M0 and M0-ESP product data;

The Division agrees with retaining the previous product data, but see the previous comments about the perspective of the new package insert.

b) expressing the doses and addressing the comparability of Pulmicort Turbuhaler M0 and M0-ESP and Pulmicort Turbuhaler M3 data;

As stated, the M3 studies should be more prominently and comprehensively described.

c) adding the 90 mcg bid dosage regimen in children and adults; and

As previously indicated, labeling for the 90 mcg bid dosage regimen will be a review issue.

d) adding the safety data for Pulmicort Turbuhaler M3 adverse events in study SD-004-0620 (adults) that occurred at a frequency $\geq 5\%$ and greater than placebo in the text of the PI?

See previous response regarding a table of adverse events for the M3 studies. We recommend that you choose a frequency less than 5% for the presentation of adverse events; for example, $\geq 3\%$.

The Division then referenced AZ's clarification for 10-2, which was previously discussed with question 6-1.

10-2.

In regard to the perspective of the package insert as commented on by the FDA in comment 6-1, AstraZeneca believes that the safety and efficacy profile of Pulmicort Turbuhaler is best represented by the currently approved package insert and therefore the M0 information cannot be relegated to supportive information only. The most relevant M3 information to the prescriber is the comparability between the M3 and M0-ESP data from the pivotal studies SD-004-0620 and SD-004-0726.

AstraZeneca recognizes the Agency's request to make the M3 data more prominent; however, until the data from the current program is available for review, AstraZeneca does not believe it is possible to assess the ultimate format for presentation. For example, AstraZeneca has concerns that the inclusion of two adverse event tables in the package insert may be confusing to prescribers if the information is redundant.

AstraZeneca would like to come to a common understanding of the objectives in integrating new information into the package insert.

The Division referred to the Division's additional comment as outlined in the facsimile sent to AZ, as well as the discussion with question 6-1.

Additional Comment

The NDA must include detailed information about the modification of budesonide content targets made during the course of the Phase 3 clinical studies with the M3 drug product. You must specify when the change(s) was made, provide in vitro data before and after the change(s), and describe which products were used in which clinical studies and at what times.

The Division then referred to AZ's clarification for the additional comment.

Additional Comments.

AstraZeneca agrees to provide the requested information in the CMC section of the NDA. The clinical section (formulation development) will contain a cross-reference to the CMC section. AstraZeneca is planning to request a CMC meeting to discuss this with the Agency in 1Q05, as discussed at the September 8, 2004 CMC pre-NDA Meeting.

Does the Agency agree with this plan?

The Division stated that since there were CMC changes during the study, AZ would need to provide a detailed summary of the trial as it pertains to the CMC issue.

The Division referred to question 11-5 and the Division's response as outlined in the facsimile sent to AZ.

PROPOSED FORMAT OF THE ELECTRONIC SUBMISSION

11-5 Does the Agency agree with AstraZeneca's proposal to only submit Item 11 datasets and Item 12 for studies SD-004-0620, SD-004-0726, and SD-004-0601, and not for any Pulmicort Turbuhaler M0, M0-ESP, or M3 studies that are being incorporated by cross-reference?

Yes. This information should also be included for 04-3020A and 04-3023A. Item 12 CRFs need to include deaths, serious adverse events, and withdrawals due to adverse events.

The Division then referred to AZ's clarification for 11-5.

11-5.

The studies that included the 100 mcg bid dosing regimen, 04-3020A (GHBA-165) and 04-3023A (GHBA-168), are legacy studies. At the time of submission, study reports were not required to be submitted electronically, and therefore, they are not available in this format. AstraZeneca proposes to add bookmarking to the highest level of the TOC, and to provide the contents of Item 11 and 12 as pdf files since the original NDA submission contained paper. Hypertext linking would not be included.

Does the Agency agree with this plan?

The Division agreed with AZs clarification for question 11-5.

Before concluding the meeting, AZ asked the Division to focus on question 6-2. The Division referred to question 6-2 and the Division's response as outlined in the facsimile sent to AZ.

6-2. Does the Agency agree that the previous demonstration of clinical efficacy of 100 mcg bid (80 mcg delivered) of Pulmicort Turbuhaler M0 in children and adults will result in the approval of Pulmicort Turbuhaler M3 at a dose of 90 mcg bid (80 mcg delivered) in children and adults provided that the data from studies SD-004-0620 and SD-004-0726 support approval of the M3 product otherwise?

Although the Division's previous review supported the efficacy of the 100 mcg bid dosage strength, the NDA for Pulmicort M0 did not include the 100 mcg dosage strength in the proposed labeling. Therefore, the studies will now have to be evaluated to determine what information can be supported in the proposed labeling about this dosage strength. For example, we note that no studies with the lower dosage strength have been conducted in patients not receiving inhaled corticosteroids (i.e., bronchodilators alone), yet the lower dose of M3 is proposed for those patients. This will be a review issue.

AZ stated that there are no studies with the lower dose strength with patients receiving bronchodilators alone. AZ has completed one study with the M2 version of Pulmicort in a non-US study that evaluated 100 mcg BID versus placebo in the mild asthmatic population, and asked the Division if this study could be of use in the NDA for support of the 100 mcg dose. The Division stated that the M2 product presentation has never been reviewed in the US and therefore we cannot comment as to whether its data is supportive. The Division stated that if AZ decides to submit this information in support of the 100 mcg dose in their forthcoming NDA, then all of the CMC information would need to be provided as well.

AZ stated that the design of the 2 legacy trials should support the 100 mcg BID dose in mild asthmatics, since 200 mcg is established as a maintenance dose. The Division asked AZ if there is any 100 mcg BID data in patients receiving only bronchodilators. AZ stated that they have 100 mcg BID data in the pediatric and adult populations, but only for patients on inhaled corticosteroids. The Division stated that this would be a review issue.

The Division noted that the sponsor was including region in the model for the primary efficacy analysis and will be summarizing results by region (US and South East Asia). The Division stated that treatment by region interaction should be included in the model and discussed in the Study report.

The Division asked AZ as to their timeframe for the submission of the NDA. AZ stated they plan to submit the NDA by end of third quarter 2005.

Colette Jackson
Minutes Preparer

Attachement: December 3, 2004, facsimile sent to AZ.

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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 3, 2004

To: Peggy Berry	From: Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Drug Products
Fax number: 302-886-2822	Fax number: 301-827-1271
Phone number: 302-886-8991	Phone number: 301-827-9388

Subject: IND 63,762 Responses to Meeting Questions

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IND 63,762

Pulmicort Turbuhaler M3 (budesonide inhalation powder)

AstraZeneca

Attached are the FDA responses to your questions (in bold italics) regarding Pulmicort Turbuhaler M3. You have the option of canceling our meeting of December 6, 2004, if these answers are clear to you. If you choose to have the meeting (or change it to a telecon), we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please notify the Division as soon as possible whether you are canceling the meeting.

NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

4-1. a) ***Common Technical Document (CTD) Module 4 will not be included in the submission, since all relevant pharmacology/ADME/ toxicology documentation has been previously submitted. Tabular summaries for ADME/toxicology studies will be included in the CTD (Section 2.6.5 and 2.6.7) and written summaries (Sections 2.6.1, 2.6.2, 2.6.4, 2.6.6) will provide a description of each relevant non-clinical study, cross-references to the application number, serial number where appropriate, and submission date. Does the Agency agree with the approach for providing the non-clinical information?***

Yes, we agree.

b) ***Does the Agency agree that based on previous NDA submissions/approvals, there is sufficient pre-clinical support for the NDA approval of Pulmicort Turbuhaler M3?***

Yes, we agree.

Additional Comment:

Address qualification of impurities exceeding ICH recommended thresholds, leachables, and extractables.

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

5.1 ***AstraZeneca intends to include clinical pharmacology study SD-004-0601 and pivotal studies with pharmacokinetic or pharmacodynamic components (studies SD-004-0620 and SD-004-0726) in the submission. All other supportive clinical***

pharmacology information will be cross-referenced to NDA 20-441 and IND 63,762. Does the Agency agree with this approach?

Yes, we agree.

5.2 ***Does the Agency agree with the proposed analyses and presentation of the pharmacokinetics data as outlined in this document?***

Yes, we agree.

CLINICAL AND STATISTICAL INFORMATION

6-1. ***Does the Agency agree with AstraZeneca's proposal to only provide the pivotal clinical study reports (SD-004-0620 and SD-004-0726) in Module 5 of the NDA and to incorporate the remaining 10 study reports into the Pulmicort Turbuhaler M3 NDA by cross-reference only?***

No. The NDA should include both the pivotal and non-pivotal study reports and clinical data necessary to support the M3 switch and proposed new labeling. In particular, Studies 04-3020A (GHBA-165) and 04-3023A (GHBA-168) are essential to approval of the 90 mcg dosage strength.

Your proposed labeling retains the perspective of the previous product presentations. Instead, it should primarily represent the current M3 product presentation. Specifically, the M3 clinical studies should be comprehensively described, and efficacy and safety information should be prominently displayed in charts and/or figures. The M0 information should be preserved, but it should follow the M3 information.

6-2. ***Does the Agency agree that the previous demonstration of clinical efficacy of 100 mcg bid (80 mcg delivered) of Pulmicort Turbuhaler M0 in children and adults will result in the approval of Pulmicort Turbuhaler M3 at a dose of 90 mcg bid (80 mcg delivered) in children and adults provided that the data from studies SD-004-0620 and SD-004-0726 support approval of the M3 product otherwise?***

Although the Division's previous review supported the efficacy of the 100 mcg bid dosage strength, the NDA for Pulmicort M0 did not include the 100 mcg dosage strength in the proposed labeling. Therefore, the studies will now have to be evaluated to determine what information can be supported in the proposed labeling about this dosage strength. For example, we note that no studies with the lower dosage strength have been conducted in patients not receiving inhaled corticosteroids (i.e., bronchodilators alone), yet the lower dose of M3 is proposed for those patients. This will be a review issue.

- 6-3. *Provided studies SD-004-0620 and SD-004-0726 demonstrate comparable efficacy, safety, and systemic exposure to Pulmicort Turbuhaler M0-ESP, does the Agency agree that both presentations of the Pulmicort Turbuhaler M3 product can be used to fulfill the dosing regimens in the currently approved Pulmicort Turbuhaler M0-ESP package insert and the proposed 90 mcg bid dosing regimen?*

Yes, for the 180 mcg dosage strength. See response to 6-2 for the 90 mcg dosage strength.

SAFETY INFORMATION

- 7-1. *Does the Agency agree with AstraZeneca's proposal regarding: a) the studies (SD-004-0620, SD-004-0726, and SD-004-0601) that will contribute safety data to the Summary of Clinical Safety, and b) that the safety data will not be pooled across these studies?*

No. As stated in the response to 6-1, the Summary of Clinical Safety will need to support the proposed labeling. Other study reports are required, specifically, safety data from patients who received the 100 mcg dosage in studies 04-3020 and 04-3023 should be included in the Summary of Clinical Safety. The Division would also like to see summary safety data from patients who received M3 in the other studies.

We recommend that a table of adverse events be included in the package insert for the pooled 12-week M3 Phase 3 studies, similar to the table of adverse events in the current package insert. See 6-1 regarding the perspective of the new package insert.

- 7-2. *Does the Agency agree with AstraZeneca's proposal to maintain adverse events coding consistency within each study by a) leaving data from study SD-004-0601 and its respective Item 11 dataset in the Astra Adverse Events Dictionary (AAED) and b) presenting the data from studies SD-004-0620 and SD-004-0726 using MedDRA (in the version available in the clinical study reports)?*

The Division agrees.

- 7-3. *Since no Pulmicort Turbuhaler M3 post-marketing data exists, does the Agency agree with AstraZeneca's proposal for populating the post-marketing section of the CTD as described in Section 7.7?*

The Division agrees.

- 7-4. *Does the Agency agree with AstraZeneca's request to waive the requirement for submission of a 4-month safety update report, since all studies in the Pulmicort*

Turbuhaler M3 clinical program will be completed at the time of the submission?

While acknowledging that no ongoing studies with M3 are planned, the 4-month safety update regulation applies to the molecular entity and is required. You may choose to populate this section in a manner similar to the post-marketing section.

ADMINISTRATIVE INFORMATION

8-1. *Does the Agency agree with the request for a pediatric waiver for children under the age of 6 years?*

Requests for pediatric waivers and deferrals are made at the time the NDA is submitted.

8-2. *Does the Agency agree with the plan to provide standard Periodic Safety Update Reports and not to provide any additional risk management plan?*

The Division agrees.

LABELING

10-1. *Does the Agency agree with AstraZeneca's proposal to retain the commercial tradename of "Pulmicort Turbuhaler"?*

The product's trade name will be consulted for review by the Division of Medical Errors and Technical Support, but we do not anticipate major obstacles to retaining the current trade name.

10-2. *Does the Agency agree with AstraZeneca's labeling strategy for:*
a) retaining the Pulmicort Turbuhaler M0 and M0-ESP product data;

The Division agrees with retaining the previous product data, but see the previous comments about the perspective of the new package insert.

b) expressing the doses and addressing the comparability of Pulmicort Turbuhaler M0 and M0-ESP and Pulmicort Turbuhaler M3 data;

As stated, the M3 studies should be more prominently and comprehensively described.

c) adding the 90 mcg bid dosage regimen in children and adults; and

As previously indicated, labeling for the 90 mcg bid dosage regimen will be a review issue.

d) adding the safety data for Pulmicort Turbuhaler M3 adverse events in study SD-004-0620 (adults) that occurred at a frequency $\geq 5\%$ and greater than placebo in the text of the PI?

See previous response regarding a table of adverse events for the M3 studies. We recommend that you choose a frequency less than 5% for the presentation of adverse events; for example, $\geq 3\%$.

Additional Comment

The NDA must include detailed information about the modification of budesonide content targets made during the course of the Phase 3 clinical studies with the M3 drug product. You must specify when the change(s) was made, provide in vitro data before and after the change(s), and describe which products were used in which clinical studies and at what times.

PROPOSED FORMAT OF THE ELECTRONIC SUBMISSION

11-1. Does the Agency agree with the proposed TOC of the electronic NDA submitted in the CTD format for Pulmicort Turbuhaler M3 (see Appendix 14.3)?

Yes, we agree with the following notations:

- 1) You show the list of investigators in Module 1. Place the list in Module 5.3 and in your Module 2 Summaries, provide links to the appropriate investigator entry(ies).
- 2) Place any current and approved labeling for the comparator(s) in the "Listed Drug" Labeling section(s) 1.14.3
- 3) The proposed TOC does not appear to include patient listings. Patient listings should be included in the NDA; they may be included as appendices to the study reports. The proposed TOC is otherwise acceptable.

11-2. Does the Agency agree with AstraZeneca's plans in Section 11.1 to cross reference to other applications that are not electronic or in CTD format?

Yes, we agree.

11-3. Consistent with the Agency feedback from the June 28, 2004, Symbicort IND ~~pre~~-NDA meeting, does the Agency agree with AstraZeneca's proposal that patient narratives will only be presented one time in the respective CSR contained within Module 5, and that the patient narratives discussed in the summary documents within Module 2 will be included by electronic hypertext link?

Yes, we agree.

11-4. Consistent with the Agency feedback from the June 28, 2004, Symbicort pre-NDA meeting, does the agency agree with AstraZeneca's proposal not to submit patient profiles because Item 11 datasets are being provided?

Yes. Patient Profiles for a group or subset should be available if requested by the Reviewer.

11-5. Does the Agency agree with AstraZeneca's proposal to only submit Item 11 datasets and Item 12 for studies SD-004-0620, SD-004-0726, and SD-004-0601, and not for any Pulmicort Turbuhaler M0, M0-ESP, or M3 studies that are being incorporated by cross-reference?

Yes. This information should also be included for 04-3020A and 04-3023A. Item 12 CRFs need to include deaths, serious adverse events, and withdrawals due to adverse events.

11-6 Consistent with the Agency feedback from the June 28, 2004 Symbicort pre-NDA meeting, does the Agency agree to accept individual datasets that approach the 100 MB in size?

Yes, we agree.

11-7 Does the Agency agree with the AstraZeneca's proposal in Section 11.4 to only include Item 12 CRF's for any deaths, serious adverse events, and withdrawals due to adverse events for the 3 studies being submitted in the NDA?

See the response to 11-5.

If there are any questions, please contact Colette Jackson, Regulatory Health Project Manager, at 301-827-9388.

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 Gunke/December 2, 2004
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 Suarez/ December 2, 2004
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 Pei/December 2, 2004
 McGovern/December 2, 2004
 Chowdhury/December 3, 2004

Finalized: CCJ/December 3, 2004

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Drafted: December 10, 2004

Initialed by:

Gunkel/December 14, 2004

Starke/ December 16, 2004

Suarez/ December 14, 2004

Fadiran/ December 14, 2004

Gebert/ December 13, 2004

Wang/ December 13, 2004

Chowdhury/January 3, 2005

Finalized: CCJ/January 3, 2005

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 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: September 15, 2004

To: Luida Shtohryn	From: Colette Jackson
Company: AstraZeneca.	Division of Pulmonary and Allergy Drug Products
Fax number: 302-886-2822	Fax number: 301-827-1271
Phone number: 302-885-4108	Phone number: 301-827-9388

Subject: September 8, 2004, Meeting Minutes

Total no. of pages including cover: 15

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 8, 2004
TIME: 2:00 PM
LOCATION: Food and Drug Administration/ Conference Room B
APPLICATION: IND 63,762/Pulmicort Turbuhaler/AstraZeneca
TYPE OF MEETING: Chemistry, Manufacturing and Controls (CMC) Pre-NDA Meeting

FDA ATTENDEES:

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

Craig Bertha, Ph.D., Chemistry Reviewer
Badrul A. Chowdhury, M.D., Ph.D., Director
Eric Duffy, Ph.D., ONDC Director
Colette Jackson, Project Manager
Richard Lostritto, Ph.D., Supervisory Chemist
Mobin Tawakkul, DHHS Emerging Leader/Visiting Student

ASTRAZENECA ATTENDEES AND TITLES:

Diane Alleva, PhD, Director, US Regulatory CMC
Bertil Andersson, PhD, Global Product Director
Peggy Berry, Director, Regulatory Affairs
Chris Blango, Sr. Director, Strategic Development
Richard Jahn, Associate Director, Regulatory Affairs
Thomas Lööf, Associate Director, Pharmaceutical & Analytical R&D
Luida Shtohryn, PharmD, Team Director, Regulatory CMC
Pelle Ström, PhD, Associate Principal Scientist, Product Development
Anders Törngren, PhD, Associate Principal Scientist, Analytical Development

BACKGROUND: The purpose of this meeting is to discuss AstraZeneca's CMC concerns in preparation for submitting their new drug application (NDA) for Pulmicort Turbuhaler M3.

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12 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Drafted by: CCJ/SEPTEMBER 9, 2004

Initialed by:

Bertha/September 10, 2004

Lostritto/ September 10, 2004

Chowdhury/September 14, 2004

final: CCJ/SEPTEMBER 15, 2004

MEETING MINUTES

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