CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-929

CORRESPONDENCE

DUPLICATE

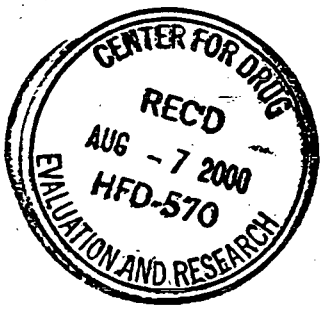
BC

AstraZeneca

Eric Couture, Ph.D.
Director, Regulatory Affairs

August 4, 2000

Robert Meyer, M.D., Director
Division of Pulmonary Drug Products
HFD-570 Room 10-B03
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Meyer:

NDA 20-929
Pulmicort Respules™ (budesonide inhalation suspension)
GENERAL CORRESPONDENCE:
RESPONSE TO REQUEST FOR INFORMATION

Please refer to our Original NDA 20-929 for Pulmicort Respules submitted November 18, 1997, and our August 7, 1998 Resubmission. Please also refer to the Agency's May 20, 1998 and February 11, 1999 approvable letters, and to our February 9, 2000 response. Reference is also made to meetings with the Agency on March 25, December 9, 1999, March 7, July 27, and 31, and August 3, 2000. Please also refer to our May 9, July 31, and August 1, and 3, 2000 faxes, and to our June 9, and July 10, 2000 responses.

Reference is also made to our August 3, and 4, 2000 faxes, and a telephone request today from Dr. Poochikian for final specification sheets for the container closure components (Attachment 1). We are also providing as requested a copy of the unannotated package insert with all ——strengths; 0.25 mg/2mL, 0.5 mg/2mL, ———— (Attachment 2), and a copy of the unannotated package insert for 0.25 mg/2mL and 0.5 mg/2mL strengths (Attachment 3). The labeling is also being provided electronically on a 3.5" diskette (Attachment 4).

An exact copy of the CMC information provided with this response is also being sent to the New England District Office.

I trust that the Agency will find this submission to be complete and acceptable in supporting the approval of the Pulmicort Respules (budesonide inhalation suspension) NDA.

AstraZeneca LP
725 Chesterbrook Blvd Wayne PA 19087-5677

Tel 610 695 1000
www.astrazeneca-us.com

Please direct any questions or requests for additional information to me at 610-695-1263 (fax 610-722-7784), or, in my absence, to James Sullivan, Regulatory Project Manager at 610-695-1423.

Sincerely,

E. Couture

Eric Couture, Ph.D.
Director, Regulatory Affairs

cc: Gretchen Trout (CDER)
Federal Express No.: 821988027650

cc: Richard Penta (New England District Office)
Federal Express No.: 821988027661

Attachment 2

17 Draft Labeling Page(s) Withheld

Attachment 3

17 Draft Labeling Page(s) Withheld

AstraZeneca

Eric Couture, Ph.D.
Director, Regulatory Affairs

[redacted] AMENDMENT
BZ

August 3, 2000

Robert Meyer, M.D., Director
Division of Pulmonary Drug Products
HFD-570 Room 10-B03
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Meyer:

NDA 20-929
Pulmicort Respules™ (budesonide inhalation suspension)
AMENDMENT TO A PENDING APPLICATION

Please refer to our Original NDA 20-929 for Pulmicort Respules submitted November 18, 1997, and our August 7, 1998 Resubmission. Please also refer to the Agency's May 20, 1998 and February 11, 1999 approvable letters, and to our February 9, 2000 response. Reference is also made to meetings with the Agency on March 25, December 9, 1999, March 7, July 27, and 31, and August 3, 2000. Please also refer to our May 9, July 31, and August 1, 2000 faxes, and to our June 9, and July 10, 2000 responses.

Please find attached our Phase IV Commitments as discussed in our August 3, 2000 teleconference.

Labeling

AstraZeneca commits to providing by February 1, 2001 (4 months post-launch) revised packaging for Pulmicort Respules. This revision will replace the statement in the current foil and carton labeling (Attachment 1) which reads "[redacted] with new wording, which will read "[redacted] (Attachment 2).

AstraZeneca plans to [redacted] 0.25 mg and 0.5 mg presentations only. Therefore, we are providing two versions of the package insert and patient instructions: one containing all [redacted] presentations (0.25 mg, 0.5 mg, and [redacted], and one containing the two presentations that will be used at launch.

Revisions to the package insert and patient instructions as discussed in the August 3, 2000 teleconference are also attached (Attachment 3). Per the Agency's request, the labeling attachments are provided electronically on CD-ROM.

AstraZeneca LP
725 Chesterbrook Blvd Wayne PA 19087-5677

Tel 610 695 1000
www.astrazeneca-us.com

Clinical

AstraZeneca commits to study and report by October 1, 2003, the effects of maintenance therapy with Pulmicort Respules at recommended doses in the indicated population (≥1 year of age) on the immunogenicity of a live virus vaccine (e.g., varicella).

CMC

Chemistry, Manufacturing and Controls Phase IV Commitments items 1-10 are attached (Attachment 4).

An exact copy of the CMC information provided with this response is also being sent to the New England District Office.

I trust that the Agency will find this submission to be complete and acceptable in supporting the approval of the Pulmicort Respules (budesonide inhalation suspension) NDA.

Please direct any questions or requests for additional information to me at 610-695-1263 (fax 610-722-7784), or, in my absence, to James Sullivan, Regulatory Project Manager at 610-695-1423, or Anita Sellers, CMC Manager at 610-695-1223.

Sincerely,

Eric Couture, Ph.D.
Director, Regulatory Affairs

Sent via facsimile
cc: Gretchen Trout (CDER)
Federal Express No.: 821988027098

cc: Richard Penta (New England District Office)
Federal Express No.: 821988027087

Enclosure: CD-ROM

36 Draft Labeling Page(s) Withheld

Memorandum of Facsimile Correspondence

Date: August 3, 2000

To: Eric Couture

FAX: 610-722-7784

From: Gretchen Trout /S/

Subject: Pulmicort Respules

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error. please immediately notify us by telephone at (301) 827-1050 and return it to us at the FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857

Thank you.

As discussed at the teleconference this afternoon.

"AstraZeneca commits to study and report by October 1, 2003, the effects of maintenance therapy with Pulmicort Respules at recommended doses in the indicated population (≥ 1 year of age) on the immunogenicity of a live virus vaccine (e.g., varicella)."

2 Page(s) Withheld

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Eric Couture

Phone Number: 610-695-1263

Fax Number: 610-722-7784

FROM: Gretchen Trout

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet: 3 Date: 7-31-00

COMMENTS:

2 Page(s) Withheld

Memorandum of Facsimile Correspondence

Date: July 19, 2000

To: Eric Couture, Ph.D.
Director, Regulatory Affairs

FAX: 610-722-7784

From: Gretchen Trout 151

Subject: Labeling comments for NDA 20-929

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error. please immediately notify us by telephone at (301) 827-1050 and return it to us at the FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857

Thank you.

23 Draft Labeling Page(s) Withheld

cc: NDA 20-929
Div. File
HFD-570/Trout
HFD-570/Purucker
HFD-570/Meyer
HFD-570/Sun
HFD-570/Kim
HFD-570/Poochikian
HFD-570/Choi
HFD-570/Uppoor
HFD-570/Wilson

Drafted: GST/July 11, 2000/n:\staff\troutg\20929fax

Initialed by: Choi/7-11-00
Uppoor/7-11-00
Wilson/7-17-00
Kim/7-18-00
Purucker/7-19-00
Meyer/7-19-00
Sun/7-19-00

CORRESPONDENCE

T/Kout

RECORD OF TELEPHONE CONVERSATION

Date:	June 19, 2000
Project Manager:	Hilfiker
Subject:	**Proposed Specifications for Incoming Materials**
NDA:	20-929
Sponsor:	AstraZeneca
Product Name:	Pulmicort Respules (budesonide inhalation solution)

AstraZeneca submitted an NDA (20-929) for Pulmicort Respules on November 18, 1997. The applicant was issued an approvable (AE) action on February 11, 1999. AstraZeneca submitted a complete response to the action letter on February 9, 2000. The PDUFA due date for this application is August 10, 2000.

During a March 7, 2000, teleconference, FDA requested that AstraZeneca submit specifications for [redacted] based upon [redacted], of components of the container-closure system (i.e., [redacted]
AstraZeneca proposed submission of the [redacted] and specifications by July 10, 2000, for review prior to the action. If the NDA is otherwise able to be approved by August 10 without established specifications for [redacted], AstraZeneca requested that FDA approve the NDA with a Phase 4 commitment to submit specifications with supportive data for [redacted], no later than October 12, 2000.

Gretchen Trout, Project Manager, informed AstraZeneca that the Division would not commit to the approvability of the NDA without reviewing the [redacted] data. The acceptability for submission of [redacted] data and specifications as a Phase 4 commitment will depend on the [redacted] that are submitted in July.

AstraZeneca requested a follow-up teleconference with Guirag Poochikian, CMC Team Leader for the Division of Pulmonary and Allergy Drug Products, to clarify the information that will be available for the July 10, 2000, submission.

FDA Participants:	David Hilfiker	Project Manager
	Guirag Poochikian	CMC Team Leader, DNDC II
AstraZeneca Participant:	Eric Couture	Regulatory Affairs

Dr. Poochikian stated that the Division cannot commit to approval prior to submission of the [redacted] data, as has been communicated previously by Ms. Trout. Furthermore, the Division has not previously allowed competitors to submit [redacted] profiles and specifications as a Phase 4 commitment. At the very least, AstraZeneca will need to establish acceptance criteria for incoming materials with appropriate [redacted] data prior to approval.

AstraZeneca stated that [redacted] profiles for all incoming materials will be provided in the July 10, 2000, submission. [redacted] data cannot be obtained until [redacted] AstraZeneca remains interested in a Phase 4 commitment to provide [redacted] data and specifications post-approval.

Dr. Poochikian emphasized that FDA may not allow [redacted] data to be submitted as a Phase 4 commitment if the [redacted] do not assure FDA that there is minimal risk in approving the drug product without the [redacted] data. If AstraZeneca decides to pursue approval in the absence of [redacted] data, they are assuming a large risk and should not blame the FDA if approval is withheld due to the [redacted] results and absence of [redacted] data. Dr. Couture acknowledged that AstraZeneca assumes the risk in this proposal and will defer to FDA's decision based on the [redacted] data.

Dr. Couture mentioned that one additional item will be included in the June 9 submission to FDA. AstraZeneca will be proposing to alter the specification for MMD (particle size) based on further data generated from the analysis of [redacted] batches. (The previous specification was proposed based on [redacted] batches.) AstraZeneca will not propose widening the specification, but rather shifting the specification range. Dr. Poochikian stated that the proposal sounds reasonable, but will depend on the supportive data.

David Hilfiker
Project Manager

/S/ 6/26/00

Cc: Original NDA 20-929
HFD-570/Division file
HFD-570/Hilfiker
HFD-570/Trout
HFD-570/Kim
HFD-570/Poochikian/6-23-00

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20929

DF

MINUTES OF TELECONFERENCE

AstraZeneca
NDA 20-929
Pulmicort Respules
May 22, 2000

FDA REPRESENTATIVE

Gretchen Trout, Project Manager

SPONSOR REPRESENTATIVE

Eric Couture, Regulatory Affairs

BACKGROUND: On March 7, 2000, representatives from the Division and AstraZeneca held a teleconference to discuss outstanding chemistry deficiencies for this NDA. AstraZeneca submitted a facsimile on May 9, 2000 (see attached) with their proposed plan of action to respond to the Division's requests for information.

Following an internal meeting to discuss the May 9, 2000, facsimile I telephoned Dr. Couture to inform him of the following.

The Division will not commit to the approvability of AstraZeneca's proposed response; however, the more data they can provide us as early as possible, the more likely they will be able to obtain a favorable action. The Division agrees to the submission of specific data by June 9, 2000, and by July 10, 2000. Whether or not we will agree to a Phase 4 commitment to provide the remaining data in October (i.e, following approval), will depend on the data submitted by July 10, 2000.

I also informed Dr. Couture that the Division intends to proceed with labeling negotiations so that we can be prepared for an approval action. This does not mean that AstraZeneca will receive approval this cycle.

Dr. Couture indicated that he understood.

/S/

Gretchen Trout
Project Manager

AstraZeneca

Fax

To	Gretchen Trout, Project Manager	**Fax number**	301-827-1271
Company	Pulmonary Division, CDER		
From	Jim Sullivan Regulatory Project Manager	**Fax number**	610-722-7784
Date	May 9, 2000; 14:55	**Total pages**	1 (9) Including cover
Subject	General Correspondence: Response to FDA Request for Information		

CONFIDENTIAL

Dear Gretchen:

Please refer to our NDA 20-929 for Pulmicort Respules™ (budesonide inhalation suspension), and the February 9, 2000 response to the Agency's February 11, 1999 approvable letter. Reference is also made to the March 7, 2000 teleconference where the Agency requested additional information on [redacted]. Please find attached a draft proposed plan of action to respond to the Agency's request for information.

Please forward this information to Dr. Poochikian and Dr. Kim. I welcome the opportunity to have a brief discussion with Dr. Poochikian and/or Dr. Kim to discuss the proposed plan and timing.

Please direct any questions or requests for additional information to me at 610-695-1203 (fax no. 610-722-7784), or in my absence, to James Sullivan, Regulatory Project Manager, at 610-695-1423.

Sincerely,

E. Couture

Eric Couture, Ph.D
Director, Regulatory Affairs

AstraZeneca L.P.
725 Chesterbrook Blvd
Wayne, PA 19087

Tel +1 610 695 1000

AstraZeneca

NDA 20-929
Pulmicort Respules™ (budesonide inhalation suspension)

AstraZeneca proposes the following strategy and timelines to address the Agency's request for additional information during the 7 March 2000 teleconference. Reference is made to item numbers per the 9 February 2000 submission.

AstraZeneca commits to provide by 9 June 2000:

Response to Item 3c: [redacted]

[redacted]

Response to Item 4: [redacted]

- Updated DMF authorization letters
- The appropriate DMF contact persons and fax numbers have been provided to the Agency as requested.

In addition, [redacted] Stability reflecting storage through [redacted] at 25°C/40% RH in new [redacted]) Respule will be provided.

A preliminary draft of the Table of Contents for this submission is provided on the following page:

PROPOSED TABLE OF CONTENTS FOR 9 JUNE 2000 SUBMISSION PAGE

4 Page(s) Withheld

Memorandum of Telephone Facsimile Correspondence

Date: May 15, 2000

To: Eric Couture, Ph.D.

Fax: 610-722-7784

From: Gretchen Trout
Project Manager

Subject: NDA 20-929
March 7, 2000 teleconference

Reference is made to the teleconference held between representatives of your company and this Division on March 7, 2000. Attached is a copy of our final minutes for that teleconference. These minutes will serve as the official record of the teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1058.

Thank you.

APPEARS THIS WAY
ON ORIGINAL

INDUSTRY TELECONFERENCE MINUTES

DATE: March 7, 2000
NDA: 20-929
PRODUCT: Pulmicort Respules (budesonide nebulizing suspension)
SPONSOR: AstraZeneca

FDA PARTICIPANTS:

Chong-Ho Kim, Chemistry Reviewer
Guirag Poochikian, Chemistry Team Leader
Gretchen Trout, Project Manager

SPONSOR PARTICIPANTS:

Eric Couture, Director, Regulatory Liaison
Jim Sullivan, Regulatory Affairs

BACKGROUND: The Division requested this teleconference to discuss Astra's submission dated February 9, 2000, containing responses to the Division's February 11, 1999, approvable (AE) letter. NOTE: the numbers and letters refer to the Division's comments from the AE letter, and Astra's corresponding responses.

The Division informed Astra that we are reviewing their amendment, and there are still some deficiencies. They are as follows.

3.a. Provide compositions of ——— For example, there are other components in the ——— we want all of the components not just what comes in contact with the product.

3.c. Provide acceptance criteria and test methods for ——— Acceptance criteria should be modified to reflect the observed data. The Division referenced tables 8, 9, and 10.

4. DMFs——— were reviewed and found inadequate. The Division will issue deficiency letters this week. The DMF holders should respond as quickly as possible.

6.b. Astra's proposed limits are too high. USP standards are not intended for inhalation dosage forms. This is very important. We need procedural information: time, temperature, duration, etc.

ADDITIONAL INFORMATION

[redacted]

Astra questioned if the Division could comment on the expiry and the foil labeling. The Division replied that we cannot comment on that because the [redacted] may effect the expiration dating period. We will not comment until we have all of the data.

/S/

Gretchen Trout
Project Manager

Cc: Orig. NDA 20-929
Div. File
HFD-570/Kim
HFD-570/Poochikian
HFD-570/Trout

Drafted: GST/March 23, 2000

Rd initial by: Kim/April 3, 2000
File name: 20929tel

MINUTES/CORRESPONDENCE

Trout

FEB 23 2000

NDA 20-929

AstraZeneca
725 Chesterbrook Blvd.
Wayne PA, 19087-5677

Attention: Eric Couture, Ph.D.
Director, Regulatory Affairs

Dear Dr. Couture:

We acknowledge receipt on February 10, 2000, of your February 9, 2000, resubmission to your new drug application (NDA) for Pulmicort Respules (budesonide inhalation suspension).

This resubmission contains additional chemistry, manufacturing, and controls information submitted in response to our February 11, 1999, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is August 10, 2000.

If you have any questions, call me at (301) 827-1058.

Sincerely yours,

/S/

Gretchen Trout
Project Manager
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-929
HFD-570/Div. Files
HFD-570/G.Trout
HFD-570/Kim
HFD-570/Poochikian
HFD-570/Purucker
HFD-570/Meyer
HFD-570/Uppoor
HFD-570/Sun
HFD-570/Wilson
HFD-570/Elashoff
DISTRICT OFFICE

Drafted by: GST/February 22, 2000
Initialed by: Jani/2-22-00

final: Trout/2-23-00
filename: n:\staff\troutg\20929c2

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)

NDA 20-929

SEP 14 1998

Astra USA, Inc.
P.O. Box 4500
Westborough, MA 01581-4500

Attention: Dennis Bucceri
Vice President
Regulatory Affairs

Dear Mr. Bucceri:

We acknowledge receipt on August 11, 1998, of your August 7, 1998, resubmission to your new drug application (NDA) for Pulmicort Respules (budesonide inhalation suspension), 0.25 and 0.5 mg.

This resubmission contains additional information submitted in response to our May 20, 1998, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is February 11, 1998.

If you have any questions, contact Mr. David Hilfiker, Project Manager, at (301) 827-1046.

Sincerely yours,

/S/

Cathie Schumaker, R.Ph.
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-929
HFD-570/Div. Files
HFD-570/Hilfiker
HFD-570/Schumaker/9-9-98
HFD-570/Trout
DISTRICT OFFICE

/S/ H 9-10-98

Drafted by: HFD-570/Hilfiker/9-8-98
final: HFD-570/Hilfiker/9-10-98
filename: c:\my_documents\n20929\98-09-08.acltr.doc

ACKNOWLEDGEMENT (AC)

/S/

9/13/97.

Memorandum of Telephone Facsimile Correspondence

Date: April 21, 1998

To: Dennis Bucceri
Vice President, Regulatory Affairs
FAX # 508-836-8390

From: Gretchen Trout (b) (1) (b) (1)
Project Manager

Through: Cathie Schumaker
Chief, Project Management Staff

Subject: Pulmicort Respules

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error. please immediately notify us by telephone at (301) 827-1050 and return it to us at the FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857

Thank you.

Please refer to your pending November 18, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Pulmicort Respules (budesonide nebulizing suspension) 0.25, 0.5 [redacted] mg.

The following requests for information are with regard to microbiology issues identified during review of your NDA.

1. [redacted]

2. [redacted]

3. Does the drug product suspension support microbial growth?

If you have any questions, please contact Ms. Gretchen Trout, Project Manager, at (301) 827-1058.

cc: Orig. NDA 20-929
Div. File
HFD-570/Kim
HFD-570/Poochikian
HFD-570/Trout
HFD-805/N. Sweeney

drafted: GST/April 20, 1998/n:\staff\troutg\20929.2fax

CORRESPONDENCE

FAX

ASTRA®
Astra USA

FROM	DATE
Murad Husain	4/23/98
DEPARTMENT	FAX NO.
Regulatory Affairs	(508) 836-8390
TO	FAX NO.
Gretchen Trout Division of Pulmonary Drug Products	(301) 827-1271
SUBJECT	PAGES
NDA 20-929/Pulmicort Respules	1(2)

Dear Gretchen,

As follow-up to our phone conversation on Monday, May 20, 1998, below is a list of questions seeking clarification of some of the CMC comments from the Division's 4/15/98 letter.

Per your request, this fax also provides our response to Dr. Brad Gillespie's question from April 7, 1998 regarding "n.e." (not existing) entries on the Table of Investigational Formulations - Pharmacokinetic Studies.

CMC:

We would like clarification of the Division's following comments (numbers correspond to that of the Division's letter of April 15, 1998):

Comments 5.b.: Is the Division's recommendation for the specifications of particle size of the drug product based on the initial batch analysis data (e.g., Certificates of Analyses) or the stability data? We ask this question, because the stability data does not support the recommended specifications.

Comment 11.: To qualify [redacted] of [redacted] namely [redacted] the primary stability batches of the drug product were packaged in [redacted] from these two sources. The stability data collected from the drug product packaged with [redacted] was provided in the original NDA Volume 1.007, page 7, Item 3.B.9.a under Primary Stability Data and page 263 (page 268 in PDF), Item 3.B.9.b.10 under Special Stability Studies. Please clarify the Division's comment.

MAILING ADDRESS:
Astra USA, Inc.
P.O. Box 4500
Westborough, MA 01581-4500

OFFICE:
50 Otis Street
Westborough, MA

TEL:
508-366-1100

FAX:
508-366-7406

TELEX:
6810105-Cable/Astropharm

FROM	DATE	PAGES
Murad Husain	4/23/98	2(2)

Comment 14.: This comment is not clear. Please note that, the drug product specifications for the test to be performed during stability study, which are listed on the proposed stability protocol, and the corresponding specifications listed on the drug product *Specifications* submitted under NDA item 3.B.7.a., are the same.

Comment 18.: Please clarify what the Division meant by "appropriate studies need to be performed to qualify the [redacted]
Please note that the [redacted] Study was submitted in the original NDA Volume 1.007, page 260 (page 265 in PDF), Item 3.B.9.b.9. under Special Stability Studies.

Investigational Formulation - Pharmacokinetic Studies:

Response to Dr. Brad Gillespie's question regarding the "n.e" entries in the table for the Investigational Formulations - Pharmacokinetic Studies in Volume 1.17, page 59 (telephone contact dated 4/7 and 4/14/98) are as follows:

[redacted]

Please call me at (508) 836- 8403 for additional information and clarification.

Sincerely,

Murad Husain
Associate Director
Regulatory Affairs

NDA 20-929

APR 15 1998

Astra USA, Inc.
P.O. Box 4500
Westborough, MA 01581-4500

Attention: Dennis Bucceri
Vice President
Regulatory Affairs

Dear Mr. Bucceri:

Please refer to your pending November 18, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Respules (budesonide inhalation suspension) 0.25 mg, 0.5 mg, and 1.0 mg.

We also refer to your amendment dated January 15, 1998.

We have completed our review of the Chemistry, Manufacturing, and Controls section of your submission and have identified the following deficiencies.

The following comments pertain to the proposed drug product specifications and test methods.

1. The proposed specification for [redacted] is not justified; the specification should be significantly tightened to reflect the observed data. In addition, a relationship of the proposed [redacted] to a certain reference [redacted] standard should be established.

2. The method for [redacted] should indicate [redacted] viewed. In addition, the proposed specification should be tightened to reflect actual data and there should be an upper limit; e.g., NMT [redacted]

3. The following comments pertain to the specification and test method for Edetate Disodium Dihydrate.

   a. The retention time target of [redacted] is too close to the [redacted] We recommend that the target retention time be increased to greater than [redacted]

b. Please provide information about the [redacted] observed levels) found in method [redacted]

c. Please state whether any other [redacted]

d. The proposed specification does not reflect the stability data. The specification should be tightened to [redacted]

4. The content uniformity specification should be clearly spelled out and be reflective of the data of multiple batches. Moreover, the content uniformity test method should be described in detail. An appropriate method number or procedure number should be assigned.

5. The following comments pertain to the specifications and test method for "Particle Size of Budesonide Micronized API and Budesonide Inhalation Suspensions by [redacted]

a. Please provide reproducibility data and the reports [redacted] which were referenced in the validation studies. In addition, provide particle size distribution analysis printouts of different batches.

b. Batch analysis data indicate that the proposed specifications should be significantly tightened; e. g.,

MMD:	[redacted]
d < [redacted]	NLT [redacted]
d < [redacted]	NLT [redacted]
d < [redacted]	NMT [redacted]

6. The following comments pertain to the impurities and degradation products.

a. The specifications should be tightened to reflect the stability data as follows:

Total:	NMT [redacted]
[redacted]	NMT [redacted]
[redacted]	NMT [redacted]
Individual unspecified impurity:	NMT [redacted]
Total unspecified impurity:	NMT [redacted]

b. The LODs and LOQs for degradation products are too high. We strongly recommend that the analytical method be improved.

The following comments pertain to manufacturing.

7. Please provide the correct name and address, including zip code, of the contract facility, [redacted]

8. Please provide information (composition and compatibility with the formulation components) on the [redacted] used for manufacturing.

The following comments pertain to the container and closure system.

9. The application should include references to authorized drug master files (DMFs) for each of the [redacted] The information should include complete compositions, sources, acceptance/release criteria, test methods, data, etc.

10. The application should contain compositions, appropriate acceptance specifications, test methods and data for each of the packaging components [redacted]

Once the suppliers' test results are confirmed through multiple batches using appropriate test methods, shipments of packaging components may be accepted based on Certificates of Analysis (COAs) from the supplier. However, in the latter case, the results of COAs should be periodically validated on a preset schedule.

11. Equivalency of secondary packaging from different sources should be established, documented, and data submitted in terms of [redacted]

12. The following comments pertain to the [redacted]

[redacted]

The following comments pertain to the drug product stability.

13. The stability protocol provided does not contain a specification and test for [redacted] This parameter should be a part of the stability protocol.

14. Acceptance criteria for stability should be the same as those for drug product specifications on shelf-life.

15. It is stated that since there was some difficulty in [redacted] of storage; Pulmicort Respules are recommended to be stored "upright". Please provide an explanation for the cause of the [redacted] problem.

16. Please provide information (nature, extent, etc.) about the [redacted] found in samples stored for [redacted] at 40°C/30% RH (Table 32, page 100, vol. 1.7). What will be the impact at [redacted] Please also provide the detection method for the [redacted]

17. [redacted] study between [redacted] was reported. A study of [redacted] condition and its impact on the particle size distribution, [redacted] is recommended (see comment 16. above).

18. Appropriate studies need to be performed to qualify the [redacted] used for [redacted] is recommended. Please also refer to comments 9. and 10. above.

19. The stability commitment and protocols should be updated; [redacted] accelerated stability should be added to the protocol.

20. It is stated that deviations that do not affect the safety and efficacy of the product will be promptly discussed with the FDA's District Office according to 21 CFR 314.81(b)(1)(ii) in the post approval stability commitment (page 305, vol. 1.7). A statement "stability failures will also be discussed with the review division" should be added to the paragraph.

21. Updated stability data and protocol should be provided.

The following comment pertains to the Environment Assessment.

22. Regarding a request for categorical exclusion of environmental assessment, please provide actual calculations which should include all the budesonide containing products for the estimated concentration of the drug substance at the point of entry into the aquatic environment.

The following preliminary comments pertain to the labeling.

23. The established name should be revised to "budesonide inhalation suspension."

24. The tab portion of each unit should be extended/enlarged to allow [redacted]

25. The fact that the [redacted] (See comment 18. above).

We would appreciate your prompt written response so we can continue our evaluation of your NDA. Please note, however, that while we are providing these comments to you at this time in order to allow you as much time as possible to address them, providing a response to these comments will not necessarily preclude the issuance of an action letter. You are encouraged to contact this Division for assistance in addressing the above issues.

If you have any questions, please contact Ms. Gretchen Trout, Project Manager, at (301) 827-1050.

Sincerely yours,

/S/

Guirag Poochikian, Ph.D.
Chemistry Team Leader, DNDC II
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-929
HFD-570/Div. Files
HFD-570/CSO/G.Trout
HFD-570/Kim
HFD-570/Poochikian
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: GST/April 9, 1998/n:\staff\troutg\20929.let

Initialed by: Schumaker/4-10-98
Kim/4-13-98
Schroeder (for Poochikian)/4-14-98

final: Trout/4-15-98

INFORMATION REQUEST (IR)

Memorandum of Telephone Facsimile Correspondence

Date: January 30, 1998

To: Dennis Bucceri
Vice President, Regulatory Affairs
FAX # 508-836-8390

From: Gretchen Trout /S/
Project Manager

Subject: Pulmicort Respules

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error. please immediately notify us by telephone at (301) 827-1050 and return it to us at the FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857

Thank you.

Please refer to your pending November 18, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Pulmicort Respules (budesonide nebulizing suspension) 0.25, 0.5 and [redacted] mg.

To assist us in our review of the clinical pharmacology and biopharmaceutics section of your submission, we request that you provide the following information.

1. [redacted] are reported out in terms of pmol, not in units of concentration. It appears that in some cases, [redacted] of plasma were used and in others, [redacted] mL. Thus, it is difficult to interpret assay performance data. All assay validation data should be converted to pmol/L.

2. Data to describe variability at the individual points of the standard curve were not included. Individual standard curve data should be provided, including all calculated plasma concentration values. Additionally, descriptive estimates of mean, maximum, minimum and %CV should be included for all standard concentrations.

We would appreciate your prompt written response so we can continue evaluation of your NDA.

If you have any questions, please contact me at (301) 827-1058.

APPEARS THIS WAY
ON ORIGINAL

cc: Orig. NDA 20-929
Div. File
HFD-570/Gillespie
HFD-570/Trout

drafted: GST/January 30, 1998/n:\staff\troutg\20929.2fax

rd initial by: Schumaker/ /S/ 1/30/98
Gillespie/ /S/ 1/30/98

CORRESPONDENCE

Memorandum of Telephone Facsimile Correspondence

Date: January 16, 1998

To: Dennis Bucceri
Vice President, Regulatory Affairs
FAX # 508-836-8390

From: Gretchen Trout /S/
Project Manager

Subject: Pulmicort Respules

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error. please immediately notify us by telephone at (301) 827-1050 and return it to us at the FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857

Thank you.

Please refer to your pending November 18, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Pulmicort Respules (budesonide nebulizing suspension) 0.25, 0.5 and [redacted] mg.

To assist us in our review of the pharmacology and toxicology section of your submission, we request that you provide your justification for conducting the 3-month toxicity study (study No. 97058-1) in dogs aged 5 to 6 weeks for the proposed pediatric population [redacted]

We would appreciate your prompt written response so we can continue evaluation of your NDA.

If you have any questions, please contact me at (301) 827-1058. [redacted]

APPEARS THIS WAY
ON ORIGINAL

cc: Orig. NDA 20-929
Div. File
HFD-570/Tripathi
HFD-570/Trout

drafted: GST/January 14, 1998/n:\staff\troutg\20929.fax

rd initial by: Schumaker/1-13-98
Tripathi/1-14-98
Sun/1-15-98

CORRESPONDENCE

NDA 20-929

DEC 19 1997

Astra USA, Inc.
P.O. Box 4500
50 Otis Street
Westborough, MA 01581

Attention: Dennis Bucceri
Vice President
Regulatory Affairs

Dear Mr. Bucceri:

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 Respules (budesonide nebulizing suspension), .25 mg, 0.5 mg, [redacted]

Therapeutic Classification: P

Date of Application: November 18, 1997

Date of Receipt: November 20, 1997

Our Reference Number: NDA 20-929

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 19, 1998, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations you may request an informal conference 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 application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Ms. Gretchen Trout, Project Manager, at (301) 827-1058.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

Cathie Schumaker
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Orig. NDA 20-929
Div. File
HFD-570/Trout
HFD-570/Chu
HFD-570/Meyer
HFD-570/Elashoff
HFD-570/Wilson
HFD-570/Tripathi
HFD-570/Sun
HFD-870/Gillespie
HFD-870/Chen
HFD-570/Kim
HFD-570/Poochikian

Drafted by: GSTrout/Dec. 11, 1997/n:\staff\troutg\20929.let

Final Typed by: LGrimshaw/12-17-97

ACKNOWLEDGEMENT (AC)

Trout

INDUSTRY MEETING MINUTES

Astra
NDA 20-929
Pulmicort Respules (budesonide inhalation suspension)
December 9, 1999

FDA REPRESENTATIVES

Chong-Ho Kim, Chemistry Reviewer
Bob Meyer, Division Director
Guirag Poochikian, Chemistry Team Leader
Mary Purucker, Medical Reviewer
Gretchen Trout, Project Manager

SPONSOR REPRESENTATIVES

Diane Alelva, Director, Product Industrialization
Bertil Andersson, Global Product Director, Pulmicort
Frank Casty, Global Medical Leader
Eric Couture, Director, Regulatory Liaison
Mario Cruz-Rivera, Director, Drug Development
Donna Dea, Respiratory Therapeutic Area Regulatory Leader
John Lally, Leader, Product Certification
Cheryl Larrivee-Elkins, Leader, Manufacturing Technical Services
Robert Monaghan, Senior Regulatory Project Manager
Jessica Sjunnesson, Responsible Pharmacist, AstraZeneca R&D
Thomas Lööf, Pharmaceutical Project Leader

BACKGROUND: Astra requested this meeting to discuss the issue of [redacted] in the Pulmicort Respules. Reference is made to the submission dated November 15, 1999. Reference is also made the facsimile dated December 8, 1999 (see attachment 1) regarding dispensed dose.

Astra indicated that their response to the Agency's February 11, 1999, approvable letter is complete with the exception of responding to the issue of [redacted]

Astra made a presentation (see attachment 2) showing what tests were conducted and the resulting data collected. The shaded areas in the tables indicate new data not previously submitted to the Agency.

Astra explained the various testing done and provided some clarifications.

VISUAL INSPECTION: [redacted] respule strips were randomly selected from each lot, and all [redacted] were visually inspected. For the visual inspection, the inspectors just indicated whether or not [redacted] were seen, the [redacted] were not counted. Inspectors were pre-qualified to detect [redacted]

MICROSCOPIC: During the microscopic evaluation, one respule per strip was evaluated and the [redacted] were counted. The data on tables 4 and 5 are from microscopic evaluations and the number of respules evaluated were made up of the 9 controls plus all of those respules identified visually (see table 2) as having [redacted]

DISPENSED DOSE (data from the December 8, 1999, facsimile) was collected by taking 5 respules from a strip and dispensing each one individually into its own container. Each respules was analyzed separately. The data from this lot (1990902702) is atypical and this lot is on stability. The previous [redacted] loss in dose was corrected with the new respule design (a respule with decreased headspace).

DROPLET SIZE DISTRIBUTION (graph) shows data from three respules with visual [redacted], and three without. A LC Parijet Plus nebulizer with a flow rate of 28.2 was used. Astra stated that statistically there was no difference in droplet size distribution between the respules with [redacted], and those without.

All the data are from lots manufactured at the United States Westboro facility (this is the only facility that can manufacture sterilized budesonide).

Particles of less than [redacted] are not specifically controlled, however, particles of this size are always seen in clusters. The Division stated that it would be appropriate to have a complete profile on the size and numbers of [redacted] including the [redacted] range. Astra replied that it is very difficult to measure the [redacted] range. The Division questioned how the current respules compare to the clinical batches with regard to [redacted] in the [redacted] range. Astra replied that they will discuss this internally.

The Division feels that Astra has enough data to develop a fixed, final specification. Astra should include the specification in their response to the approvable letter. Astra stated that they would like to collect their database overtime to see what is happening so that they can distinguish atypical batches. However, they can consider shortening their original proposal of two years stability data. The Division replied that by the time of approval we would like to be as close to a final specification as we can get, the specifications can be changed later, if necessary, with a prior approval supplement.

With regard to dispensed dose, the Division pointed out that the 0.25 mg product has the least number of [redacted], and yet is the most prone to problems with loss of dose. Astra may need to treat the 0.25 mg product individually (currently they average all [redacted] strengths). Astra stated that they do not have a dispensed dose specification, however they do have dispensed dose data. In general [redacted] of the dose is dispensed and they have not seen a difference between the batches with [redacted] and those without.

CONCLUSIONS:

1. The Division cannot discuss acceptance criteria until the data are reviewed.
2. Particle size distribution needs to be controlled.
3. The Division will consider whether controls should be on individual respules or on a mean.
4. It may be more appropriate to have separate specifications for the different strengths.

/S/

Gretchen Trout, Project Manager

Attachment 1

AstraZeneca

Fax

To	Ms. Gretchen Trout Project Manager	**Fax number**	301-8271271
Company	Pulmonary Division		
From	Dr. Eric Couture	**Fax number**	610-722-7784 Astra 301-897-2559 Marriott
Date	8 December, 1999; 15:44	**Total pages**	~~1(1)~~ 1(3) including cover
Subject	Response to FDA Request		

Dear Ms. Trout:

Please refer to your request today for clarification on dispensed dose for Pulmicort Respules (budesonide inhalation suspension).

Please call if you have any further questions.

Sincerely yours,

E Couture

Eric Couture, Ph.D

Director, Regulatory Liaison

AstraZeneca L.P.
725 Chesterbrook Blvd
Wayne, PA 19087

Tel +1 610 695 1000