Memorandum of Telephone Facsimile Correspondence

Date: July 29, 1999

To: Eric Couture

Fax: 610-722-7784

From: Gretchen Trout (151)
Project Manager

Subject: NDA 20-746
July 13, 1999 teleconference

Reference is made to the teleconference held between representatives of your company and this Division on July 13, 1999. 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.

Eric - For your records.

INDUSTRY TELECONFERENCE MINUTES

AstraZeneca
NDA 20-746
Rhinocort Aqua (budesonide)
July 13, 1999

FDA REPRESENTATIVES

Jean Nashed, Chemistry Reviewer
Gretchen Trout, Project Manager

SPONSOR REPRESENTATIVES

Eric Couture, Regulatory Liaison Director
Cheryl Larrivee-Elkins, Director Pharmaceuticals Technology
Robert Monoghan, Regulatory Project Manager
Carolyn Russello-Callahan, Regulatory Labeling Manager
Karen Shepherd, Supply Chain Manager
Ann Smith, Product Operations Manager

BACKGROUND: The Division requested this teleconference to convey comments on the carton and container labeling, and comments on the chemistry related sections of the package insert.

First it was clarified that Astra intends to market three packages: 32 mcg/60 sprays, 32 mcg/120 sprays, and 64 mcg/120 sprays.

The following comments were with regard to the DESCRIPTION section.

1. [redacted]
2. The first sentence of the last paragraph should read "Prior to initial use, the container must be shaken gently and the pump must be primed eight times."

The following comment was with regard to the PRECAUTIONS: Information for Patients section.

1. Astra should delete reference to the [redacted] e.g., the [redacted]

The following comment was with regard to the DOSAGE AND ADMINISTRATION section.

1. The first sentence of the last paragraph should read "Prior to initial use, the container must be shaken gently and the pump must be primed eight times."

The following comment was with regard to the HOW SUPPLIED SECTION.

1. Astra should delete reference to the [redacted]

The following comments were with regard to the Carton and Container labels.

1. The space on the front panel is not used effectively (there is a lot of white space).
2. Since "Rhinocort Aqua" is part of the name, the full name should be in one color, and the graphic (wave) cannot be part of the name; e.g., it should be separated from the "A."
3. "budesonide" has to be ½ the font size and prominence of "Rhinocort Aqua."
4. The cartons for the 32 mcg and 64 mcg are too similar in appearance. The Division proposed that Astra consider using one color for each strength; e.g., "Rhinocort Aqua" 32 mcg could be all in blue, and "Rhinocort Aqua" 64 mcg could be all in green.
5. All of the Contents and additional information is on one pane, try to disperse this information and increase the size and prominence.
6. Put more emphasis on the storage conditions by either bolding or capitalizing the information.
7. Put more emphasis on "protect from light."
8. A lot of space was reserved for the UPC code, perhaps this could be made smaller and the space could be used for other information.

Astra questioned if the Division had any comments on the black arrows used to indicate that the product should be stored upright. The Division stated that we would get back to Astra on this issue, however "Store Upright" can be added to the label. *POST TELECON NOTE: The Division has no objection to using the black arrows in addition to the instruction : "Store Upright."*

The following comments were with regard to the immediate container labels.

1. Use the label space more effectively and maximize the size of the label in comparison to the vial. Astra should consider a different design for the label so that the vial does not have to be turned around to read the full drug product name.
2. The same comments as made for the cartons with regard to the different colors and the differentiation between the two strengths apply to the immediate labels.
3. The storage conditions should be more pronounced, and "protect from light" should be included.

Astra indicated that they have already printed labels and their own risk, and questioned if these changes were approvability issues, or if they could launch with the current labels and then make the changes within a specified period of time. Astra stated that they will only be launching the 32 mcg strength initially so confusion between the two strengths would not happen. They could make the changes to the labels by the time they launch the 64 mcg. The Division indicated that this will have to be discussed with the Division Director and Chemistry Team Leader.

With regard to adding "protect from light" to the immediate container label, Astra stated that they do not feel that this is necessary since the bottle is amber and coated. Astra pointed out that space on the label is limited. The Division replied that if the statement is on the carton, it is not required on the immediate container, although we recommend that it be on the immediate container as well.

The Division did not review the Patient's Instructions for Use with regard to chemistry, however Astra stated that they will be consistent with the changes made to the package insert.

Astra indicated that they will submit labeling with reference to both strengths, however when they launch just the 32 mcg, they want to remove the 64 mcg text and associated NDC numbers through an annual report. Astra questioned if this is acceptable. The Division replied that we will have to get back to them on this question.

The Division also asked Astra to follow-up on the response to our IR letter to DMF [redacted]

/S/

Gretchen Trout, Project Manager

APPEARS THIS WAY
ON ORIGINAL

Memorandum of Telephone Facsimile Correspondence

Date: July 29, 1999

To: Eric Couture

Fax: 610-722-7784

From: Gretchen Trout /S/
Project Manager

Subject: NDA 20-746
July 1, 1999 teleconference

Reference is made to the teleconference held between representatives of your company and this Division on July 1, 1999. 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.

INDUSTRY TELECONFERENCE MINUTES

AstraZeneca
NDA 20-746
Rhinocort Aqua (budesonide)
July 1, 1999

FDA REPRESENTATIVES

Jean Nashed, Chemistry Reviewer
Guirag Poochikian, Chemistry Team Leader
Gretchen Trout, Project Manager

SPONSOR REPRESENTATIVES

Eric Couture, Director Regulatory Affairs
Cheryl Larrivee-Elkins, Director Pharmaceuticals Technology
Ann Smith, Product Operations Manager

BACKGROUND: The Division issued an approvable letter for this product on June 22, 1999. Astra requested clarification on several points. Several telephone conferences were held between Dr. Couture of Astra and Ms. Trout of the Division, in addition to the July 1, 1999, telephone conference with the attendees listed above. All of the issues were addressed by July 1, 1999. The issues and the Division's comments are discussed below (the comments from the June 22, 1999, letter on which Astra requested clarification are summarized below followed by the discussion).

1.c. The Division requested t revised drug substance specification sheets for release and stability testing.

Astra questioned if the Division was requesting the same format as Astra had provided previously for the drug product in the May 18, 1999, submission. The Division confirmed that this format is acceptable.

2.a. The Division requested revised drug product specification sheets with tightened acceptance levels for [redacted] and for total specified and total impurities.

Astra questioned whether the tightening of the specifications included [redacted] The Division tightened the specifications based on data submitted on June 3, 1999, Astra explained that the values in that submission did not include [redacted] because it was not tested for at that time. Astra requested an interim specification for [redacted] of NMT [redacted] until they have adequate data to establish a new specification. Astra currently has analyzed approximately 4 batches of micronized budesonide with the range of [redacted] at [redacted] Astra will submit their proposed drug product specifications (total specified and total impurities will include [redacted] along with a justification for their proposal, to the Division for review. The Division encouraged Astra to submit data on several batches. Depending on the time of approval of the NDA, and the available data, the NDA may be

approved with interim specifications for total specified, total impurities, and [redacted]. The final method and specifications should be submitted as requested in item #6 of the June 22, 1999, letter.

4. *The Division requested a revised stability protocol to included testing in [redacted] conditions of [redacted] and change the name of the [redacted] storage condition to [redacted]*

Astra stated that the specifications were already tightened significantly based on data from 25° storage condition, and therefore they will definitely have out-of-specification results at [redacted]. The Division stated that if Astra fails at [redacted] at six months, then they would have to pass at [redacted] at 12 months. If they pass at [redacted] at 12 months, then they will not have to do a recall or field alert, because this will be part of the stability protocol. Astra agreed to include the following three conditions in their stability protocol:

[redacted]

Astra agreed to place all three conditions in their stability protocol. The Division reminded Astra that this will for the first three commercial batches, once the data are generated this will give us the criteria for establishing conditions for the post-approval batches (i.e., depending on the data, Astra would be able to submit a supplement, if warranted, to modify the stability protocol.

7.b. *The Division requested an in vitro [redacted] such as the [redacted] or [redacted]*

Astra had suggested the [redacted] however they are willing to do the [redacted] if the Division accepts that they will not be able to provide a final report by November 30, 1999, as they had agreed to previously. The Division agreed that Astra could provide a draft report for the [redacted] by November 30, 1999, followed by the final report when available.

ADDITIONAL QUESTIONS

Package Insert

Astra questioned if the wording requested by the Division in the labeling with regard to growth effects is the final class-labeling language. The Division stated that it is, and that the sponsors of the other drug products will receive their letters requesting the class-labeling language in approximately 2-3 weeks.

Safety Update

Astra questioned if they have no new information which would effect the ISS or the ISE, can they wait and submit the standard 120 day post-approval safety update. The Division stated that this was acceptable.

[redacted] /S/

Gretchen Trout, Project Manager

cc: NDA 20-746
Div. File
HFD-570/Nashed
HFD-570/Poochikian
HFD-570/trout
HFD-570/Pei
HFD-570/Vogel
HFD-570/Anthracite

Rd accepted by: Pei/7-15-99
Vogel/7-15-99
Nashed/7-15-99
Poochikian/7-19-99

MINUTES

Memorandum of Telephone Facsimile Correspondence

Date: June 10, 1999

To: Eric Couture
Director Regulatory Affairs

Fax: 610-722-7784

From: Gretchen Trout
Project Manager

Subject: NDA 20-746
June 1, 1999, teleconference

Reference is made to the teleconference held between representatives of your company and this Division on June 1, 1999. 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

IMTS #4303

INDUSTRY TELECONFERENCE MINUTES

Astra
NDA 20-746
Rhinocort Aqua (budesonide)
June 1, 1999

FDA REPRESENTATIVES

Bob Meyer, Acting Division Director
Luqi Pei, Pre-Clinical Pharmacology Reviewer
Gretchen Trout, Project Manager
Mark Vogel, Acting Pre-Clinical Pharmacology Team Leader

SPONSOR REPRESENTATIVES

ASTRA AB, Sodertalje, Sweden
George Bolcsfoldi, Director Genetic Toxicology
Ake Ryrfeldt, Senior Director Safety Assessment

ASTRA DRACO, Lund, Sweden
Mats Berglund, Director Analysis and Formulation
Claes Engelbrecht, Tox/Preclinical

ASTRA PHARMACEUTICALS, Westborough, Massachusetts
Elizabeth George, Manager Analytical Development

ASTRA PHARMACEUTICALS, Wayne, Pennsylvania
Elliot Berger, Vice President, Regulatory Affairs
Frank Casty, Business Unit Medical Director
Eric Couture, Director Regulatory Affairs
Michael Elia, Director Regulatory Affairs
Robert Monaghan, Regulatory Project Manager
Raj Sharma, Director Preclinical Sciences
Ann Smith, Manager Product and Customer Operations

BACKGROUND: The Division requested this teleconference to discuss issues related to [redacted] of budesonide. Reference is made to the submission dated May 18, 1999.

Astra began with a brief introduction, summarizing what was included in the May 18, 1999, submission.

The Division then informed Astra that we do not feel the data are sufficient to support Astra's proposed specifications. Astra has data from animal (inhalation and oral) toxicology studies,

however these data do not support the proposed specifications. The inhalation data do not suppport the proposed specification because the concentration used is too low, and because of the total daily exposure in animals was lower than that in humans. The oral study did have a higher concentration of the impurity, however this is a different route of administration than what will be used in patients, and therefore it is not completely relevant. Because this degradation product is a structural alert, we are concerned about genotoxicity, and the studies which Astra has already conducted do not address genotoxicity.

The Division proposed that Astra conduct two in vitro assays - [redacted] and [redacted] assay, and submit the data with a risk assessment of the findings. Astra referred to the ICH guidelines that refer to testing at the highest dose of the substance given in the clinic. The Division agreed that this is accurate, however ICH also says that this can be modified based on the level of concern. Due to the structural alert, and since we know very little else about this compound, we have an increased level of concern.

Astra stated that they cannot lower the specifications for the [redacted] impurity, and they are already at an 18 months expiry dating period, so questioned what they need to do to qualify the impurity.

The Division requested that Astra submit the following.

1. A toxicology "discussion" based on a worst case scenario (assume that BUD [redacted] is mutagenic and/or clastogenic), and do a risk assessment compared to structurally related compounds. A discussion based on data for the inhalation route would be the most appropriate.
2. Provide a justification for the proposed specification of [redacted]
3. Conduct two in vitro tests for [redacted] using pure [redacted] (not the parent compound spiked with [redacted])

Astra stated that they would provide the discussion (#1 from above) in a minimum of two weeks. The justification (#2) would be submitted within a couple of days. The in vitro testing may be appropriate as a Phase 4 commitment, depending on the results of #1 and #2, and if an approval action is otherwise possible this review cylce.

[redacted] /S/

Gretchen Trout, Project Manager

APPEARS THIS WAY
ON ORIGINAL

HILFIKER

RECORD OF TELEPHONE CONVERSATION

Date:	October 7, 1998
Project Manager:	Hilfiker
Subject:	CMC issues related to June 25, 1998, IR letter
NDA:	20-746
Sponsor:	Astra Pharmaceuticals
Product Name:	Rhinocort Aqua (budesonide) Nasal Spray

On July 16, 1998, Linda Ng, CMC Reviewer, and Guirag Poochikian, CMC Team Leader, participated in a teleconference with members of Astra regarding several FDA comments sent to Astra in a June 25, 1998, information request (IR) letter. In regards to comments 5c, 10, 11, and 13c, Dr. Ng agreed to contact Astra upon further review of information that was submitted in reply to these comments, but did not follow up with additional contact. On September 16, 1998, Astra submitted a request for a conversation with the Division to follow up on the adequacy of the information submitted toward these comments.

FDA Participants:	David Hilfiker	Project Manager
	Eugenia Nashed	CMC Reviewer
	Guirag Poochikian	CMC Team Leader
Astra Participants:	David Pizzi	Regulatory Affairs
	Mamud Lata	Product Manager
	Kevin Gagnon	(unknown)
	Liz George	(unknown)
	Cheryl Laravie-Elkins	(unknown)
	Rob Callibrough	(unknown)

FDA suggested that the information supplied for comments 5c, 10, 11, and 13c, be discussed individually.

5. *These comments pertain to the acceptance criteria and test procedure for viscosity.*
c. *A sample of the market drug product should be submitted.*

FDA confirmed that samples have been received, but these samples are only prototype models of the container-closure system and are not filled. FDA requested filled samples in the to-be-marketed container-closure system. Astra commented that filled samples were sent on June 5, but no FDA participants have any knowledge of the receipt of these samples. Astra further replied that commercial production is in place for all components of the container-closure system, but the manufacturing line for the drug substance and fill process is not ready.

FDA asked if Astra has any remaining experimental samples that they could hand-fill preferrably with drug or otherwise with placebo solution to the appropriate fill volume. Astra confirmed that they could do that, but the samples would have to be sealed by hand. FDA confirmed that this

was satisfactory for their purpose, and further assured Astra that these samples would not be used for microbial testing.

10. These comments pertain to the [redacted] test procedure and acceptance criteria.

a. As requested previously, acceptance criteria should include the appearance as [redacted]

b. The degree and type of failure needs to be defined, restricted, and well-described in the acceptance criteria.

c. Explain/illustrate how the minimum and maximum diameters are measured.

d. Please amend the acceptance criteria to reflect actual data. Comments will be provided after evaluation of responses to present comments.

e. Ten representative [redacted] as [redacted] from different pumps should be submitted.

FDA confirmed that [redacted] were received in a June 9, 1998, submission. However, the submitted pictures do not provide an adequate depiction of the [redacted] or the evaluation method as requested in items 10b, 10c, and 10e, and FDA requested that Astra submit actual [redacted] if possible. Astra agreed.

In addition, the acceptance criteria should be revised as outlined in 10a and 10d. The supplied information suggests that Astra has adopted a fixed [redacted] distance of [redacted] to depict [redacted] geometry. FDA has previously suggested that Astra attempt a further distance of [redacted] If Astra intends to use [redacted] a justification for not using a further distance as previously suggested should be submitted. This should be supported by examples of [redacted] images from further distances obtained in comparable/identical conditions to [redacted] distance sprays.

11. Please submit the specification sheets for [redacted] Astra USA, and Astra Draco. Explain how changes in the test procedures are reflected on the specifications.

FDA confirmed receipt of tabular information regarding different testing facilities in Astra's June 15, 1998, submission. FDA requested that Astra submit in similar tabular format a complete listing of all manufacturing and testing facilities to be used in the manufacture of this drug product, including full names, telephone number, addresses, CFN numbers, and responsibilities of each facility. Astra agreed.

13. The following comments pertain to the acceptance criteria and test procedure for the pump unit.

c. Submit a copy of the ISO 2859 document.

FDA requested that Astra resubmit this document with a brief accompanying explanation of the acceptance testing of the pump units. Astra agreed.

ADDITIONAL ITEMS FOR DISCUSSION

Astra included some additional questions that were briefly described in faxes to the Division on October 5 (attachment 1) and October 6 (attachment 2).

1. In the October 5 facsimile transmission, Astra commented that the standard [redacted] test for color of the drug product was insufficient for measuring the color of drug suspensions such as Rhinocort Aqua. Because the [redacted] test relies on the transmittance of light through the sample, suspended particles will diffract light away from the detector and less light will reach the detector. The result is that a suspension will appear darker in color than a solution that is identical in color because of differences in light diffraction through a solution versus a suspension. Astra proposed to use a secondary test that relies on the reflectance of light rather than on the transmittance of light.

   Astra asked if FDA laboratories are equipped with a [redacted] instrument to measure color of a suspension using [redacted] Astra further offered to loan an instrument to FDA for the purposes of color testing. FDA could not comment on the availability of this instrument in FDA laboratories. FDA suggested that any alternative method that is employed should be related to conventionally known color standards, e.g. [redacted] color standards. Also, appropriate discriminatory acceptance criteria, which are indicative of color changes in a given range, should be submitted.

2. In the October 6 facsimile transmission, Astra proposed to change the 32 mg size container from [redacted] total sprays to 60 total sprays to accommodate the Division's recommendation that the starting dose be lowered from 128 mcg per day to 64 mcg per day (see September 2, 1998, approvable (AE) letter). The only difference will be a change in the fill volume, but no components of the container-closure system or the formulation will be affected. FDA could not comment on this matter prior to an official review of the information. Astra agreed to include both [redacted] and 60 spray samples in the package of the samples that will be submitted to the Agency.

3. Astra raised an additional issue that was left unresolved from an October 6, 1998, telephone conversation. The Division recommended that the terms "unscented and

[redacted] be removed from the DESCRIPTION section of the package insert. Astra is requesting to keep both of these terms in the labeling, because a competitor is using similar terminology for advertising.

Astra revisited the issue to better define the property of [redacted] Astra offered that [redacted] is defined as a substance which has [redacted] characteristics when at rest but gives the appearance of a [redacted] when a sheer force is applied. Astra asserts that the results of physical testing of the Rhinocort Aqua formulation supports their claim that the formulation is [redacted] and proposed to submit adequate data. FDA agreed to review the data and emphasized the importance of linking the physical parameters to its clinical relevancy. FDA suggested that Astra would have to demonstrate that this formulation is [redacted] and as importantly Astra will have to justify with supporting data how this information is clinically relevant to support its inclusion in the label. FDA further suggested that if Astra intends to support the clinical relevance of a [redacted] property, further communications with Ray Anthracite, Medical Officer, would be necessary to develop adequate protocols.

David Hilfiker
Project Manager

Attachments: (1) October 5, 1998, facsimile transmission from Astra
(2) October 6, 1998, facsimile transmission from Astra

Cc: Original NDA 20-746
HFD-570/Division File
HFD-570/Hilfiker
HFD-570/Schumaker/10-9-98
HFD-570/Nashed/10-9-98
HFD-570/Poochikian/10-9-98
HFD-570/Anthracite

/S/
10-22-98

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 1

OCTOBER 5, 1998, FACSIMILE TRANSMISSION

APPEARS THIS WAY
ON ORIGINAL

FAX

FAXED

ASTRA
Astra USA

FROM	DATE
David J. Pizzi, Associate Director	10/5/98
DEPARTMENT	FAX NO.
Regulatory Affairs	508/836-8390
TO	FAX NO.
Mr. David Hilfiker, Project Manager Food and Drug Administration	301/827-1271
SUBJECT	PAGES
Rhinocort Aqua Nasal Spray, NDA 20-746	1(1) 2

Dear Mr. Hilfiker:

Reference is made to the teleconference scheduled on Wednesday, October 7 at 3:00 p.m. with Dr. Poochikian. The purpose of the teleconference is to discuss the CMC issues for Rhinocort Aqua (NDA 20-746) which were outlined in my September 16, 1998 correspondence. Attached is an additional item, question 4b of the September 2 approvable letter that we also want to discuss during the teleconference.

Please provide this information to Dr. Poochikian.

I will contact you to confirm scheduling the teleconference.

Thank you for your cooperation in this matter.

Sincerely,

David Pizzi

att-1-

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/Astrapharm

4b. A secondary test for the intensity of the color should be developed using a more conventional method; e.g., [redacted] color test.

We are proposing to continue to analyze the final drug product for color using a [redacted] based on [redacted] as previously indicated by Astra and remain committed to loan a [redacted] instrument to the FDA laboratories upon request. Other test methods available such as [redacted] employ analysis through light transmittance versus [redacted] and result in inappropriate values that do not represent the visual color of the sample. This phenomenon occurs because of the nature of the drug suspension. Presence of the fine particles within the suspension diffract light away from the instrument detector as it passes through the sample; as opposed to translucent solutions which allow light more freely to reach the detector. The resulting [redacted] values using transmittance tests for a suspension when compared to translucent solutions are typically higher, thus suggesting the sample is visually darker than it actually is. In spite of these facts, transmittance still may be employed and specifications established in order to determine relative changes in color intensity, but values generated by conventional instrumentation employing this technique can not be considered absolute.

Nonetheless, in order to develop a secondary test that is acceptable to the agency and if an [redacted] color test is still the most desirable means, we solicit suggestion from the agency with respect to the type of instrumentation that would be available to FDA laboratories so that we can customize this secondary method according to their capabilities. We further propose upon identification of the agencies capabilities, to generate [redacted] values (or another more conventional unit of measure) via the same technology and to correlate the data to values generated by the [redacted] instrumentation.

If specific details of the instrumentation or capabilities such as manufacturer or model number are not available, please provide information regarding the instrument geometry (e.g. sphere based or bi-directional) , Illuminant (e.g. daylight$_{65}$ or cool white fluorescent), and observer angle (e.g. 2° or 10°). Or, if reference in the question to a conventional method implies a visual comparison analysis instead, please indicate the extent of the agencies' requirements. Do we need to develop a traceable target range of visual color standards to accommodate this?

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 2

OCTOBER 6, 1998, FACSIMILE TRANSMISSION

APPEARS THIS WAY
ON ORIGINAL

FAX

BEST POSSIBLE COPY

ASTRA®
Astra USA

FROM	DATE
David J. Pizzi, Associate Director	10/6/98
DEPARTMENT	FAX NO.
Regulatory Affairs	508/836-8390
TO	FAX NO.
Mr. David Hilfiker, Project Manager Food and Drug Administration	301/827-1271
SUBJECT	PAGES
Rhinocort Aqua Nasal Spray, NDA 20-746	1(1) 4 pages total

Dear Mr. Hilfiker:

Reference is made to the teleconference scheduled on Wednesday, October 7 at 3:00 p.m. with Dr. Poochikian. The purpose of the teleconference is to discuss the CMC issues for Rhinocort Aqua (NDA 20-746) which were outlined in my September 16, 1998 correspondence. As currently planned, we will be discussing Questions 4b, 5c, 10, 11, and 13c of the September 2, 1998 approvable letter.

In addition to the above listed questions we request to add one more item for discussion. We propose to change the 32 mg size container from [redacted] metered sprays to 60 metered sprays. The only difference between the two dosage forms is fill volumes. All other conditions and commitments will remain the same as was described in our February 27, 1998 amendment. A copy of the amendment cover letter explaining this issue is attached for your convenience. The primary purpose for changing the container fill volume is due to the FDA's recommended starting change from 128 mcg/day to 64 mcg/day.

Please provide this information to Dr. Poochikian.

Thank you for your cooperation in this matter.

Sincerely,

att: -1-

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

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50 Otis Street
Westborough, MA

TEL:
508-366-1100

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508-366-7406

TELEX:
6810105-Coble/Astrapharm

ASTRA®
Astra USA

NDA 20-746
Rhinocort® (budesonide) Aqua Nasal Spray

AMENDMENT TO A PENDING APPLICATION

February 27, 1998

John Jenkins, MD, Director
Division of Pulmonary Drug Products
HFD-570, Document Room 10B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Jenkins:

Reference is made to our pending New Drug Application for Rhinocort (budesonide) Aqua Nasal Spray, NDA 20-746. Reference is also made to your October 29, 1997 approvable letter requesting the submission of additional chemistry and labeling information.

Attached are our responses to each of the items outlined in the approvable letter. In addition, we are also amending our application to include a new 32 mcg sample size container. For completeness of our file, we also are including four final clinical study reports and a Safety Update Report.
The following is a brief summary of the information being provided in this amendment.

Response to FDA Letter

This section includes responses to all of the chemistry questions outlined in your October 29, 1997 letter including revised and new finished product specifications, test methods and revised stability protocols.

Labeling

The container, carton, package insert, and patient's instructions for the market and physician sample products have been revised according to the Agency's comments.

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

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50 Otis Street
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508 366-1100

FAX:
508 366-7406
TELEX:
6810105-Cable/Astrapharm

Regarding the revised package insert, we are recommending to lower the starting dose in adults from 256 mcg/day to 128 mcg/day, which is the same starting dose for children. References and data supporting this change are provided. Lowering the adult starting dose to 128 mcg/day also allows for flexibility in dosing; that is, the 128 mcg/day starting dose can be increased to 256 mcg/day or lowered to 64 mcg/day as clinically needed. This change also simplifies the labeling in that the dosing range from 64 mcg to 256 mcg for adults and children is the same.

Some additional changes have also been made to other sections of the insert based upon our continuing review of our data. The revised insert has been annotated to identify the changes made.

32 mcg Sample Size Container

Currently the NDA provides for market sizes of 32 mcg and 64 mcg (containing 120 metered sprays) and a physician sample size of [redacted] Included in this amendment is information providing for a new [redacted] mcg sample size containing [redacted] metered sprays. The formulation, method of manufacture, and container/closure system for the [redacted] mcg sample size is the same as the 32 mcg market product. The only difference between the two dosage forms is fill volume. The sample size will have a fill volume of [redacted] mL compared to the 8.4 mL fill volume for the market package.

According to a teleconference held on December 18, 1997, Dr. Linda Ng, the reviewing chemist, stated that the Division will allow approval for the [redacted] mcg sample size with a commitment that Astra submit stability data on the first group of post approval production batches manufactured.

Clinical Study Reports

Final clinical reports for two U.S. studies (Study 05-3046 and 05-3047) and for two non U.S. studies (Study 05-3031 and 05-3021) are provided; the PDLs for 05-3046 and 05-3047 are available upon request. Interim reports for the two U.S. studies were submitted in the original NDA. A synopsis comparing the results of the final reports with the interim reports are also provided.

In addition, addenda for two clinical reports (05-3024 and 05-3039) are also contained in the amendment. The addenda contain additional analyses of existing data evaluating the time to maximal treatment effect of Rhinocort Aqua which is reflected in the revised package insert.

NDA 20-74
February 27, 1998

Safety Update Report

This report contains additional information from July 31, 1996 through July 31, 1997. The 120 day safety report submitted on December 3, 1996 covered the period of December 31, 1995 through July 31, 1996.

The information presented in the update report supports the original safety conclusions listed in our application and no change to the proposed package insert is required.

CRFs for Deaths and DAEs

The CRFs for patients who discontinued due to adverse events are included for the four study reports in this submission.

The labeling, clinical study reports, safety update and CRFs are also provided electronically in PDF. WordPerfect files are enclosed for Clinical Study Report 05-CR-3046 and Word files for the package insert and 05-CR-3047. The electronic files names are included in the overall table of contents.

We trust that the Agency will find this amendment to be complete and acceptable in supporting the approval of our NDA.

Please contact me at (508) 366-1100, extension 4739 or David J. Pizzi at extension 2344 if you have any further questions.

Sincerely,

Dennis J. Bucceri
Vice President
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Trout

MEMORANDUM OF TELECON

DATE: July 16, 1998

APPLICATION NUMBER: NDA 20-746

PRODCUT: Rhinocort Aqua (budesonide)

PARTICIPANTS:

FDA:	Linda Ng	Chemistry Reviewer
	Guirag Poochikian	Chemistry Team Leader
	Gretchen Trout	Project Manager

ASTRA USA:

Rob Calabro	Scientist, Formulation Development
Elizabeth George	Manager, Analytical Development
Mahmood Ladha	Project Team Leader
Cheryl Larrivee-Elkins	Manager, Formulation Development
Dave Pizzi	Associate Director, Regulatory Affairs
Sigmond Waraskiewicz	Assoc. Director, Analytical Development

ASTRA DRACO:

Claes Ahlneck	Director, Pharmaceutics-Formulation and Development
Kjell Jarring	Assistant Director, Analysis-Formulation
Kristina Johansson	Regulatory Affairs Manager
Per Niklasson	Regulatory Affairs Manager

BACKGROUND: The Division issued an information request letter to Astra on June 25, 1998. Astra requested this teleconference to discuss and clarify issues regarding questions 4, 5, 9, 10, 11, 13, 14, and 19 of that letter (see Astra's submission dated July 13, 1998).

Question 4. Re: [redacted] color test

Astra stated that due to the properties of the suspension, they could not develop an [redacted] test which would be reliable. Astra did however have an alternate method [redacted] and they questioned why this was not acceptable.

The Division replied that the [redacted] test was just an example, Astra does not have to use an [redacted] test. However, we do not have a feel for what the numbers proposed by Astra based on their test mean; e.g., the color test they supplied is for [redacted] and they proposed a specification of [redacted] This means that, for

example, 100 or 1000 could pass, instead there should be a range. Astra should submit samples with values of [redacted] so that we can understand what the values mean, and set a range for the acceptance criteria. Astra agreed.

The Division then referenced a component that Astra refers to for this test which is not a common component, the Division questioned if it is commercially available. Astra replied that it is and that they could loan it to the FDA if necessary. The Division replied that if we agree to the specifications, then Astra can use this component, however an alternate method for our purposes would be useful.

Question 5.a. Re: release and shelf life viscosity.

The Division stated that Astra submitted a lot of data for this, however a lot of the batches submitted were not U.S. to-be-marketed concentration or strength. The specifications need to be revised to be based on what is to-be-marketed. The Division explained that acceptance criteria should always be set on the to-be-marketed product. Astra replied that they had used the ancillary data (data other than for the U.S. to-be-marketed product) to provide justification for the specification. However, Astra agreed to revisit the data and discuss this internally.

Question 5.b. Re: Viscosity affects on [redacted] and surface tension.

The Division stated that for the [redacted] data, the data is varied and we are trying to understand the cause for the variation. Viscosity was suggested as a possible reason for the variation. The Division asked Astra to comment on this. Astra replied that data were collected in Sweden on samples made at different concentrations to span viscosity. They looked at weight of dose and [redacted] and there was very little difference in viscosity, therefore they do not think that it effects weight of dose or [redacted] The Division stated that we would like to see data based on the marketed product, and the specification should be set so that future batches can be reproduced reliably. Astra stated that they understood.

Question 5.c. Re: Market product sample.

Astra wanted to know if the Division reviewed the market product samples which were already submitted on June 9, 1998. The Division replied that this question was repeated in the letter so

that the comment was formally conveyed (it had previously been requested unofficially). The Division confirmed that the market product samples were received and there are no additional comments on this at this time.

Question 9. Re: Establish a range for application orifice.

The Division explained that Astra has stated that they conduct a form functionality test prior to release. The Division stated that Astra should include acceptance criteria and a test for the size of orifice.

Question 10. Re: [redacted]

Astra wanted to know if the data they had already submitted with regard to [redacted] is acceptable, because in response to the June 25, 1998, letter they will resend the same information. The Division replied that we have received what Astra submitted, but it has not yet been reviewed so we cannot comment at this time. The Division stated if we have further comments or questions we will convey them to Astra.

Question 11. Re: Specification sheets.

Again the Division stated that we have received the specification sheets submitted by Astra but they have not yet been reviewed.

Question 13.c. Re: ISO 2859 document.

The ISO 2859 Level 1 inspection table submitted by Astra has been received, but not reviewed as of this time.

Question 14.d. Re: [redacted] system suitability.

Astra explained that they have concerns for setting up a standard what materials they should use. Astra believes that the only standard available to them regularly are [redacted] for the size ranges proposed. The Division responded that [redacted] in the range that Astra is claiming to use for analysis is acceptable.

Question 19. Re: applicator design.

Astra stated that they have looked into redesigning the applicator to add wings, and everything else about the applicator would remain the same. However, Astra stated that the round applicator that they used is commercially available and meets specifications. Astra expressed concern about the NDA not being

approved based on the design of the applicators, and stated that if this is the case they will most likely object. The Division replied that we are concerned that once this product is on the market and in the hands of consumers that we will be receiving complaints from consumers, so careful consideration should be given to this issue. Astra stated that they want to implement the winged applicator as soon as possible, however they cannot commit to have the appropriate supporting data prior to the September 2, 1998, userfee due date for this application.

The Division pointed out that there are two issues with regard to the applicator: wings and the wobbliness of the applicator. Astra replied that one other product on the market has more of a wobble than the Rhinocort Aqua applicator. The Division explained that the pump units for most other products are screw on caps in a single piece, furthermore this was discussed with the clinical team and they also have concerns with regard to this. The Division's concern is the applicator which attaches to the metal cap, if there is a lot of wobble, could effect the stem. The Division questioned if Astra could tighten where it attaches to the metal part. Astra referenced Flonase which is similar to their product, however Flonase was transferred to this Division after approval. The Division restated that our concern is how the design will effect the functionality of the pump unit in the long run (in the hands of the consumers). Astra stated that they will look into the issue further.

CONCLUSION: Astra intends to respond to the June 25, 1998, information request letter within 4-6 weeks (although this needs to be discussed with their colleagues in Sweden). The prototype to add the wings on the applicator will be available in August, by the firm may not be able to have the redesigned pump ready within that response timeframe.

The Division and Astra agreed that Astra should call with any further questions that they have in order to assist them in fully responding to the letter.

/S/

Gretchen Trout
Project Manager

APPEARS THIS WAY
ON ORIGINAL

Trout

Division of Pulmonary Drug Products
Food and Drug Administration

Telephone Conversation Note

NDA No. 20746

Attendants: David Pizzi, Astra UAS (508-366-1100 Ext. 2344)
Luqi Pei, Ph.D., FDA /S/ 5/5/98

Date: May 4, 1998
Initiated by: David Pizzi

Subject: Safety assessment of the inactive ingredients in Rhinocort:

Notes:

On May 4 and 5, 1998, Mr. David Pizzi, a new program manager for Rhinocort in Astra, asked me to update him and clarify issues related to the Agency's request for Astra to conduct a safety evaluation of the inactive ingredients.

Background:

In a pre-NDA meeting held on December 6, 1998, Astra and the Agency agreed that as a phase 4 commitment Astra would conduct a 6 month inhalation toxicity study in rats to evaluate nasal toxicity of two inactive ingredients: polysorbate 80 and potassium sorbate. The agency would review the data for safety evaluation of the inactive ingredients once the study results became available. Astra has recently completed the above mentioned study. Its results were submitted to the Agency under another application (NDA No. [redacted] and reviewed by Mark Vogel, Ph.D. and a pharmacologist reviewer in the Division (Review dated April 28, 1998). The study appeared clean. The study report, however, has not been submitted to the Rhinocort application (NDA 20746). The Astra should update the Rhinocort application and conduct a safety evaluation of these inactive ingredients present in the Rinocort product, based on the available information.

David Pizzi called back for further clarification (on May 4, 1998). He later (May 5, 1998) asked for a fax copy of Divisional request. Mrs. Trout agreed to take care of the fax.

HFD-570/Dr. Sheevers/ Mrs. Trout

Memorandum of Telephone Facsimile Correspondence

Date: January 16, 1998

To: Dave Pizzi

Fax: 508-898-9289

From: Gretchen Trout
Project Manager

Subject: NDA 20-746
Rhinocort Aqua
Telecon dated December 18, 1997

Reference is made to the teleconference held between representatives of your company and this Division on December 18, 1997. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-1058.

Thank you.

IMTS #2084

MEMORANDUM OF TELECON

DATE: December 18, 1997

APPLICATION NUMBER: NDA 20-746

PRODCUT: Rhinocort Aqua (budesonide)

PARTICIPANTS:

ASTRA USA:

John Cook	Project Team Leader
Mahmood Ladha	Project Manager
Cheryl Larrivee-Elkins	Manager, Formulation Development
Larry Paglia	Senior Director, Quality Assurance CMC
Dave Pizzi	Associate Director, Regulatory Affairs
Roberta Tucker	Director, Regulatory Affairs
Sigmond Waraskiewicz	Assoc. Director, Analytical Development

ASTRA DRACO:

Claes Ahlneck	Director, Pharmaceutics-Formulation and Development
Kjell Jarring	Assistant Director, Analysis-Formulation
Kristina Johansson	Regulatory Affairs Manager
Hans Nilsson	Assoc. Director, Pharmaceutics-Formulation and Development
Gordon Santesson	Project Team Leader

FDA:	Linda Ng	Chemistry Reviewer
	Gretchen Trout	Project Manager

BACKGROUND: Astra submitted a meeting request on December 9, 1997, to discuss and clarify issues with regard to questions 1, 3, 11, 19, 21, and 23, of the Division's October 29, 1997, approvable letter. Astra's specific questions/comments from the December 9, 1997, meeting request are attached for reference.

Dr. Ng addressed Astra's questions in order (where agreements were reached following discussion, the agreement is in bold type).

1. The [redacted] DMF is under review.

3. The two concentrations should be as equal as possible.

Astra replied that they are confident their method is acceptable however they can tighten the sample or standard concentration if necessary. Dr. Ng stated the Division likes to see that they are equal because this removes any bias to the method. **Astra replied that they will make adjustments to the test method for the January submission (response to the approvable letter).**

3.b. Astra explained that their data system for the primary stability slope utilized in the calculation for a concentration using two standards, which yield data points which are similar. Therefore they need an additional point which is different to draw the slope. The other point which was chosen is 0.0. The response factor is the area standard divided by the concentration of the standard. The slope is equivalent to response factor. Astra stated that have a table which they can include in the January submission with calculated response factor and slope, or they can change the method to response factors. In summary: Astra has two standards and they use 0.0 to get the slope and use it as a conversion factor for calculating assay values. Dr. Ng replied that she understood what Astra was doing, however the day to day assay of the sample may not always pass through 0.0, which is why the Division is concerned about using a calculation where they are forcing the line through 0. **Astra replied that they will tighten the sample concentration and the standard concentration to make them similar and then will convert calculation to the response factor, and this should nullify this question (3.b.). Dr. Ng agreed.**

11.a. Astra explained that all impurities and degradants are detected so the total will be greater than the sum of [redacted] and [redacted] Dr. Ng informed Astra that this statement should be reflected in the response to the approvable letter. Dr. Ng also stated that Astra should remember that the total specification is greater than the sum of those two impurities, but in reality the levels may be much lower than the specification. Astra replied that as a result of including in the total everything above the limit of quantitation than the sum is higher. Dr. Ng explained that the total is often less than the sum because of the presence of varying levels of different impurities. The sum of the two actual impurities is not equal to the sum of the specification for the two. **Astra replied that they will review their stability data and provide something in writing.**

11.b. Dr. Ng informed Astra that they should not use stability data at [redacted] to set the specification, they need to use the 25°. Astra clarified that the specifications have to be revised to include 24 months of 25° data. Dr. Ng replied that this was

correct.

19.a. Dr. Ng explained that question was generated because Astra has generated production batches with limited data (some tests were added later). Astra has complete data from only two timepoints which makes it difficult to have a good feel of what is happening. Astra replied that that they understood.

21. Dr. Ng explained that the proportionality data was requested because Astra is using the 32 mcg and 64 mcg products interchangeably and we need data to support that they are equivalent. Astra replied that they never anticipated using the two dosage strengths interchangeably and they thought this had been clarified previously. **Astra and the Division both agreed that they will follow-up with their respective teams and re-address this issue.**

23. Yes, the Division has completed review of the [redacted] DMF amendments.

With regard to Astra's additional question on an additional sample size, 32 mcg for [redacted] ([redacted] fill volume), Dr. Ng replied it was acceptable for Astra to proceed with this and they will need to provide a commitment on the stability data. Astra agreed.

[redacted]
/S/

Gretchen Trout
Project Manager

APPEARS THIS WAY
ON ORIGINAL

AQUA CMC ISSUES
ITEMS FOR DISCUSSION

Question 1: **Re: [redacted] DMFs**

Has the FDA completed their review of the [redacted] DMF amendments submitted on October 13, 1997.

Question 3: **Re: Sample and Standard concentrations**

What is considered to be acceptable for the sample and standard concentrations to be similar.

Question 3b: **Re: [redacted] linear regression calculations**

We want to explain that our linear regression calculation forcing the line through zero is equivalent to the external standard method.

Question 11a: **Re: Product impurities**

We want to explain why the total impurities/degradents reported in the stability data is greater than the sum of the [redacted] and the [redacted] of budesonide.

Question 11b: **Re: Specifications for impurities**

Please clarify. The specifications established for the impurities are reflective of the actual stability data collected under [redacted] month conditions.

Questions 19a: **Re: Post approval stability protocol**

Please clarify why inverted storage conditions are required for production batches. Data collected from inverted storage conditions were already provided in the primary stability data package.

Question 21: **Re: Proportionality Data**

Please clarify, we do not fully understand what data are needed.

Question 23: Re: [redacted] DMF

Has the FDA completed their review of the [redacted] DMF amendments submitted on June 3 and August 26, 1997.

NEW DOSAGE FORM

Currently the NDA provides for market sizes of 32 mcg and 64 mcg (containing 120 metered sprays) and a physician sample size of [redacted] mcg containing [redacted] metered sprays. We are proposing to include in our January amendment information to provide for a new [redacted] mcg sample size containing [redacted] metered sprays. The formulation, method of manufacture, and container/closure system for the [redacted] mcg sample size is the same as the 32 mcg market product. The only difference between the two dosage forms is fill volume. The sample size will have a fill volume of [redacted] mL compared to the 8.4 mL fill volume for the market product. Based on this will the FDA allow approval for the [redacted] mcg sample size with a commitment to submit stability data on the first group of post approval production batches.

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA 20-746
Div. File
HFD-570/Ng
HFD-570/Poochikian
HFD-570/Trout
HFD-570/Anthracite
HFD-570/Honig

drafted: GSTrout/December 30,

rd initial by: Ng/1-15-98

TELECON correspondence

Memorandum of Telephone Facsimile Correspondence

Date: October 28, 1997

To: Roberta Tucker

Fax: 508-898-9289

From: Gretchen Trout
Project Manager

Subject: NDA 20-746
Rhinocort Aqua
October 7, 1997 Telecon

Reference is made to the telecon held between representatives of your company and this Division on October 7, 1997. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting/telecon. If you have any questions or comments regarding the minutes, please call me at (301) 827-1058.

Thank you.

APPEARS THIS WAY
ON ORIGINAL

IMTS #1808

MEMORANDUM OF TELECON

DATE: October 7, 1997

APPLICATION NUMBER: NDA 20-746

PRODCUT: Rhinocort Aqua (budesonide)

PARTICIPANTS:

ASTRA:	Rob Calabro	Pharmaceutical Scientist-Formulation Development
	Cheryl Larrivee-Elkins	Manager, Formulation Development
	Dave Paglia	Senior Director
	Dave Piazzi	Associate Director, Regulatory Affairs
	Roberta Tucker	Director, Regulatory Affairs
	Michael Bayard (Consultant)	Bayard Development Co.
FDA:	Ray Anthracite	Medical Reviewer
	Linda Ng	Chemistry Reviewer
	Guirag Poochikian	Chemistry Team Leader
	Gretchen Trout	Project Manager

BACKGROUND: Astra submitted a meeting request on October 1, 1997, to discuss the method they are developing for evaluating particle size and to solicit suggestions from the Division of alternate methods or technologies.

Astra began by providing an update of their current position. Astra explained that they have used traditional methods, for example [redacted] however they have not been able to distinguish between the budesonide particles and the cellulose particles in the suspension. Astra is looking into using [redacted] Astra is trying to measure the particles without altering the final product in anyway, and they are having difficulty because of the small particle size in the presence of similar sized excipient. The methods Astra has considered can be used, however they do not lend themselves to quality control measures because they are very time consuming methods.

Dr. Ng replied that a control on particle size is needed, and questioned if Astra has considered any other techniques. Astra replied that they looked at [redacted] and looked at using [redacted] which was not successful. Astra also indicated that they have looked at competitors' products with these methods and it was difficult to distinguish the drug

substance particles in the competitors' products as well. Astra's bottom line is that they have looked at several methods, and while it is possible to differentiate between the drug substance and the cellulose particles, none of the methods are adequate for quality control because they are too time consuming and/or are too operator dependent.

Dr. Poochikian replied that from a regulatory viewpoint it is important that we can assure that the product, batch to batch, is reproducible. In addition, upon aging (since the product is a suspension) we need to assure that the particle morphology does not change, because we do not know what the impact of any changes would be. Therefore, we need some type of control, even semi-quantitatively, to provide us with some assurance. The Division does recognize the inherent difficulties, and we realize that microscopy is a tedious process, and may not be amenable to quality control.

Dr. Poochikian referred to Astra's October 1, 1997 submission where they stated (Under Question 4a.) that they propose "the following investigation to obtain and provide data to ascertain a change, if any, in the [redacted] of the suspended budesonide in the final product:..." Dr. Poochikian asked for clarification on this statement. Astra explained that the current technique they are looking is they have 6 batches which they follow on stability. They also have a 24 month timepoint for the primary stability batch, which will mature in December. Astra is interested in seeing if there are any changes with aging. Astra submitted samples to the consultant and Dr. Bayard stated that the comparison was almost exact, and that differentiation was at the μm size range. The samples were stained and the overlap at this range is approximately 2%. They are addressing the formulation and comparing it to bulk drug substance.

Dr. Bayard explained that they are using a stain for methyl cellulose which works well after drying, however he does not like a dye because it may alter the drug substance.

Dr. Poochikian questioned what kind of controls Astra has for the drug substance. Astra replied that it is released under the same acceptance criteria as Pulmicort.

Astra again stated that they can only differentiate between the two substances after drying. They looked for drug substance before and after, using an [redacted] however they have not looked at other stains. Astra stated that they can look at other stains if necessary. Astra

questioned if we want them to stain the cellulose preferentially or the drug substance (being aware that staining the drug substance preferentially might alter the properties). Dr. Ng replied that a control is needed, however, it is up to Astra to determine how to provide the control.

Astra questioned if it would be acceptable for them to measure the bulk drug substance and the cellulose particles separately. Dr. Ng replied that they need to measure the drug substance individually within the formulation - it is the drug substance which is being controlled.

Astra asked for suggestions on methods or technologies which other companies might have used. Dr. Ng replied that the information is proprietary. Dr. Poochikian added that it is a difficult task, and again stated that a semi-quantitative controls might be adequate for the time being. Dr. Bayard asked if Astra could submit something with different precision ranges to see if they would be acceptable. Dr. Poochikian replied that we will compromise on an interim basis, and Astra should continue to work on new technologies and staining procedures.

/S/
Gretchen Trout
Project Manager

Trout

RECORD OF TELEPHONE CONVERSATION

NDA NUMBER: #20-746 DATE: 2 September, 1997

INITIATED BY: _X_ APPLICANT __FDA

FIRM NAME: Astra USA

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Dave Pizzi and Ross Rocklin, M.D.

TELEPHONE NUMBER: (508)366-1100 x2344

1600 hours:

The discrepant Rhinocort Aqua systemic availability information given in the label and in Volume 1, Page 25 of NDA #20-746 has been resolved. The correct information about systemic availability can be found in the original Rhinocort NDA in Volume 1, Pages 89 & 90; Volume 12, Page 91K; and, Volume 15, Page 174.

The following table summarizes this information. 'Metered dose' was the ex valve dose and 'delivered dose' was the ex mouthpiece dose. Where the spacer device was used, 'delivered dose' was the dose exiting the spacer.

SYSTEMIC AVAILABILITY OF VARIOUS BUDESONIDE FORMULATIONS		
Formulation Administration	Systemic Availability	
	Delivered Dose (%)	Metered Dose (%)
Rhinocort Nasal Inhaler (pMDI)	23	14
Rhinocort Turbuhaler (dpMDI)	40	22
Rhinocort Aqua	34	33
Pulmicort Turbuhaler (dpMDI)	39	34
Pulmicort (pMDI) with Nebuhaler	35	34

The self-selected-control study of budesonide on growth inhibition submitted with the Pulmicort NDA, #20-441, used both the dpMDI Turbuhaler and the pMDI with spacer. The information above indicates that the metered dose of both results in about the same systemic availability, which is about the same as for Rhinocort Aqua.

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

RECORD OF TELEPHONE CONVERSATION

IND NUMBER: #20-746 DATE: January 24, 1997

INITIATED BY: __APPLICANT _X_FDA

FIRM NAME: Astra USA

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Dave Pizzi

TELEPHONE NUMBER: (508)366-1100 x2344

1400 hours:

I initiated the call to request clarification of pivotal study 05-3038 in two areas, serum cortisol determinations and dose-response verification. The FAX that is attached describes the details of these requests. In addition, Dr. Albert Chen, the Bio-Pharmacology reviewer posed some questions of his own and planned to send them in a follow-up FAX to the sponsor. Mr. Pizzi was told that the responses were not required immediately. He was also encouraged to discuss any required clarification of our requests with us, as well as any difficulty that the requests themselves may pose.

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
IND
HFD-570/Division File
HFD-570/Team Leader/Honig
HFD-570/Medical Reviewer/Anthracite
HFD-570/BioPharm Reviewer/Chen
HFD-570/CSO/Trout

APPEARS THIS WAY
ON ORIGINAL

January 24, 1997

Dear Mr. Pizzi:

While reviewing trial 05-3038, I found two areas that I believe would benefit from slightly different analytic approaches. These same analytic approaches are applicable to other trials that investigated the same end points. To avoid confusion, I have specified these analyses in this communication which will reach you by FAX following our phone conversation on the same topic.

Serum Cortisol

The data in Volume 31, Page 229, Table 43, can be configured to answer other questions pertinent to the detection of adrenal suppression. The basal cortisol at visit #1 can be compared with the basal cortisol at visit #4, represented by a percent change, to detect any suppression in this basal value over the duration of treatment. In addition, the percent increase in the Cortrosyn stimulated cortisol levels at the two visits can be compared to determine if response to this stimulation had been suppressed over the four weeks. The table below shows one way these analyses may be presented.

ADJUSTED MEAN CHANGES IN BASAL (PreStim) AND CORTROSYN STIMULATED (Stim) LEVELS FOR ALL PATIENTS AT BASELINE (Visit 1), AFTER FOUR WEEKS OF TREATMENT (Visit 4) AND THE CHANGE IN BASAL CORTISOL OVER THE TWO VISITS (Visit 4-1)

Treatment	Visit 1 (Baseline)			Visit 4			Visit 4-1
	PreStim	Stim	Stim-PreStim (%)	PreStim	Stim	Stim-PreStim (%)	PreStim Dif (%)
Placebo	349	709	50.78	384	703	83.07	9.11
MN (all) Budesonide	374.75	715.75	47.69	409.75	713.75	74.51	8.54
32 µg	419	735	42.99	443	734	65.69	5.42
64 µg	368	733	49.80	414	726	75.36	11.11
128 µg	339	678	50.00	377	685	81.70	10.08
256 µg	373	717	47.98	405	710	75.31	7.90

Please repopulate this table with correct values, if these are not, and construct two more similar tables for pediatric patients aged 6-17 years, inclusive, and for adult patients with ages ≥ 18 years. It would be appreciated if other trials that measured serum cortisols, with or without stimulation, were similarly analyzed and submitted; e.g., [redacted]

[1]

APPEARS THIS WAY
ON ORIGINAL

Dose-Response

This analysis is found in Volume 31, Pages 93, 154 & 253 and uses linear regression of NIS on only the lowest (32 µg) and highest (256 µg) dose levels. Please redo the analysis to include all four dose levels.

The SAS data sets used to construct responses to these requests and the SAS macro programming employed should be copied to magnetic, preferably, or optical computer disks and forwarded to the FDA statistician on this project, Dr. Ted Guo. If you would like further clarification on these subjects, please do not hesitate to contact me at my personal office phone: (301)827-1081.

Yours very truly,

/S/

Raymond F. Anthracite, M.D.

APPEARS THIS WAY
ON ORIGINAL

T ROUT

OCT 2 1996

MEMORANDUM OF TELECON

DATE: October 2, 1996

APPLICATION NUMBER: NDA 20-746

PARTICIPANTS:

ASTRA USA: D. Bucceri, R. Tucker, D. Pizzi, R. Rocklin, R. Cintron, P Tandon

ASTRA Sweden: P. Brennan, S. Josson, R. Brattsand, A. Ryerfeldt, G. Santesson, C. Karlsson, K. Englebrect, B. Lindmark, S. Edsbacker

FDA: Luqi Pei, Hilary Sheevers, Mike Sevka, Gretchen Strange

Dr. Pei informed Astra, that following a preliminary review of the pharmacology/toxicology section of NDA 20-746, the Division has concerns about two of the inactive ingredients: potassium sorbate and polysorbate 80. Specifically, potassium sorbate has never been approved for nasal use, and polysorbate 80 is being used by Astra at concentrations 5x the approved level. Dr. Pei indicated that the Division had previously been concerned with the level of polysorbate and Astra had supplied the final report for the expert panel for cosmetics, and the federal register statement for use of potassium sorbate for vaginal products. The current Division policy requires additional studies or information to support the level of polysorbate 80 and potassium sorbate.

Ms. Tucker stated that Astra had previously supplied information on potassium sorbate to the Division and in a follow-up telecon with Dr. Sancilio he had accepted Astra's position. Dr. Pei responded that he was aware of the conversation, however the current guidelines for an inactive ingredient not used for the intended route requires a 6 month chronic toxicology study. Dr. Sheevers added that the earlier decision was not scientifically sound because it had been based on a single use vaginal product. The Division cannot make the leap from a short-term vaginal product to a long-term exposure nasal product such as Rhinocort Aqua. Astra was told that if they can find data in the literature that will address the safety concerns, they should please submit it, and the Division will evaluate it quickly so as not to slow the product development process.

Mr. Bucceri stated that Astra does have additional information, both from the literature and from their own files. Astra will submit what they have to the Division to see if it is sufficient. Dr. Sheevers specified that what would be most helpful are studies of a long duration in animals by the appropriate route. Studies by other routes would be helpful, however they would not adequately address the concerns.

/S/

Gretchen Strange
Project Manager

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

151
9-17-96

TO (Division/Office) Dan Boring HFD-530			FROM: Gretchen Strange HFD-57-	
ember 16, 1996	IND NO.	NDA NO. 20-746	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT July 30, 1996
NAME OF DRUG Rhinocort Aqua Nasal Spray		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE September 30, 1996

NAME OF FIRM Astra USA

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURINGCHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*

nomenclature review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY 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,]CIATED DIAGNOSES
- : REPORTS OF SPECIFIC REACTIONS *(List below)*
- ,IPARATIVE 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/SPECIAL INSTRUCTIONS:

cc: Orig. NDA, Div File, HFD-570/Ng/Sevka/Strange/Schumaker

SIGNATURE OF REQUESTE	METHOD OF DELIVERY *(Check one)*
151	☒ MAIL ☐ HAND SEP 17 1996
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

APPEARS THIS WAY
ON ORIGINAL

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Pulmonary Drug Products	**HFD-570**
Attention: Gretchen Strange	**Phone:** 7-1058
Date: September 16, 1996	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Rhinocort Aqua Nasal Spray	**NDA/ANDA#** 20-746

Established name, including dosage form:

Rhinocort (budesonide) Aqua Nasal Spray

Other trademarks by the same firm for companion products:

Rhinocort (budesonide)

Indications for Use (may be a summary if proposed statement is lengthy):

management of symptoms of seasonal and/or perennial allergic rhinitis in adults and children six (6) years and older.

Initial Comments from the submitter (concerns, observations, etc.):

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. December 95

APPEARS THIS WAY
ON ORIGINAL

TROUT

FDA

MEMORANDUM

FROM: Mark Vogel, HFD-570 (Pulmonary), PKLN, 10B-45 827-1094
TO: NDA 20-746, Rhinocort Aqua Nasal Spray
DATE: June 22, 1999
RE: Pharmacology/Toxicology Team Leader Memo

/S/
6·22·99

The original action recommendation for this application, from a Pharmacology/Toxicology perspective, was approval, as indicated in Hilary Sheevers' Pharm/Tox team leader memo, dated October 20, 1997. One outstanding issue and two additional issues have been addressed since that date. These issues are addressed below:

Excipients: This formulation contains polysorbate 80, and potassium sorbate, neither of which has been used previously in inhalation or intranasal products. The applicant agreed to conduct nonclinical safety studies of these ingredients in animals by the inhalation route. A 6-month inhalation study of potassium sorbate and polysorbate 80 in rats was submitted to NDA [redacted] and reviewed by Mark Vogel (review dated April 28, 1998). The relevance of the study results to the present application were reviewed by Luqi Pei (review #3, dated August 14, 1998). There was no systemic toxicity and no local effects on the nasal cavity attributable to these excipients. Based on a comparison of nasal cavity surface areas in rats and humans the local concentrations at the highest doses tested in rats were 5-15 fold greater than the maximum expected human exposures. Thus, the safety of these excipients has been established and the issue is resolved.

Amended Dose Ratios: After the original Pharm/Tox labeling review of this product the maximum recommended daily dose in pediatric patients has been decreased from 256 to 128 µg per day. The dose ratios in the labeling relating doses used in animal studies to maximum recommended human clinical doses have been changed appropriately to reflect the change in the recommended pediatric dosage.

Budesonide [redacted] Impurity: Specifications for degradants of budesonide were originally addressed in Pharm/Tox review #2, dated June 29, 1996. Based on the ICH guidance for impurities in drug products, a limit of up to [redacted] was considered appropriate. Subsequently, the Division adopted a practice of examining the structures of impurities to determine whether any known structural alerts for mutagenicity or carcinogenicity are present. The CMC reviewer determined that [redacted]

[redacted] is an [redacted] recommended that it be renamed [redacted] of budesonide, and noted the [redacted] as a structural alert for mutagenicity and carcinogenicity. The applicant has agreed to conduct [redacted] in vitro [redacted] of [redacted] The applicant has agreed to conduct these studies by November 30, 1999. Additional evaluation of the [redacted] potential of [redacted] of budesonide may be needed if the above tests yield positive results. In the mean time, the applicant presented a risk assessment for [redacted] of budesonide based on published literature for other [redacted] This assessment demonstrates that the proposed specifications for [redacted] of budesonide would limit the anticipated daily exposure to this compound to levels that are similar to the levels of [redacted] exposure considered safe based on [redacted] assumptions. Since [redacted] is a more potent mutagen and carcinogen than other [redacted] the anticipated exposure to [redacted] of budesonide does not present a safety concern.

Overall, the application is recommended for approval from a Pharmacology/ Toxicology standpoint. The safety of this budesonide formulation will be re-evaluated upon submission of the [redacted] studies. Based on the existing risk assessment of [redacted] of budesonide, using conservative "worst case" assumptions, it is unlikely that the outcome of those studies would result in a recommendation that lower limits on this impurity are necessary.

cc: NDA 20-746 Division File
HFD-570/L. Pei
HFD-570/G. Trout
HFD-570/M. Vogel

APPEARS THIS WAY
ON ORIGINAL

Trout

Memorandum

To: NDA 20-746, Rhinocort Aqua Nasal Spray
From: Hilary V. Sheevers - Pharm./Tox. Team Leader
Re: Team Leader NDA Summary, HFD 570
Date: October 20, 1997

151

Rhinocort Nasal Spray is an intranasal aqueous formulation of the potent glucocorticoid budesonide . The proposed indication for Rhinocort Nasal Spray is for the treatment of seasonal or perennial allergic rhinitis. Patients are expected to be 6 years old or greater, and the maximum dose is 256 µg/day. The active ingredient has previously been approved and marketed (first in 1982), including the nasal inhaler formulation of Rhinocort.

Overall Recommendation (Pharm/Tox): Approval

Outstanding Issue:

- Two inactive ingredients, Polysorbate 80 and potassium sorbate, have not been used previously in intranasal/inhalation products and were not included in preclinical safety tests. These two ingredients are being evaluated for safety in a Phase IV commitment; the studies have already been started and are expected to be submitted within a year. (The phase IV commitment was allowed because we had at one time indicated that we would accept the sponsor's argument that the ingredients were safe because of their use in vaginal and cosmetic products.)

Summary of Significant Preclinical Studies:

A large set of preclinical studies were performed for previously approved products, including Rhinocort Nasal Inhaler and Pulmicort Turbuhaler. Of particular relevance to this NDA are the findings in the **chronic toxicity studies,** which were typical of other glucocorticosteroids. Changes included atrophy of the thymus, adrenals, and lymph nodes, depression of the HPA axis, and increased liver glycogen. In an intranasal irritation study in dogs, no irritation was noted.

Reproduction studies of budesonide resulted in decreased pre-and post-natal viability (SC doses, 20-80 µg/kg/day). Budesonide (SC) was teratogenic and embryocidal in rabbits and rats. At 25-500 µg/kg/day, budesonide induced fetal loss, decreased pup weights, and skeletal abnormalities in rats. These findings are consistent with expected reproductive effects of steroids. Additionally, the studies were performed subcutaneously and we may expect the nasal

formulations to reach lower systemic levels than seen with the SC studies. In a rat inhalation study, no teratogenic or embryocidal effects were seen at 250 µg/kg. (No PK data was collected in these studies, and thus blood level comparisons cannot be made.)

Two drinking water **carcinogenicity studies** were performed for earlier formulations. In a 91-week mouse study, budesonide at up to 200 µg/m2/day was not carcinogenic. In a 2-year Sprague-Dawley rat study, budesonide caused a statistically significant increase in gliomas in the males at 300 µg/m2/day, but not at lower doses or in females. A repeated study in males at the high dose did not confirm the finding of gliomas, although an increase in hepatocellular tumors was noted. A third study in male Fischer-344 rats at the same dose level did not demonstrate increased incidences of either tumor types.

Genotoxicity studies (a battery of 6 assays) were all negative.

Labeling changes are noted in detail in the pharmacology review (i.e., labeling review of 10/7/97). The changes were made to update the label and reflect recent language conformities. The primary pharm/tox reviewers for Pulmicort (L. Sancilio) and Rhinocort Aq (L. Pei) reviewed the label together, and agreed upon the proposed labeling language.

Overall, the submission is recommended for approval from a pharm/tox standpoint. At submission of the Phase IV studies, the safety of this formulation of budesonide will be re-evaluated.

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 20-746
D.V. file
HFD-570/Sheevers
PEI
TROUT

MEMORANDUM OF TELECON

DATE: February 4, 1997

APPLICATION NUMBER: NDA 20-746

PARTICIPANTS:
ASTRA USA: Dennis Bucceri
FDA: Gretchen Trout

On January 24, 1997, the Division sent a request for information to Astra via facsimile. Number 2. of that correspondence asked for additional information from 5 studies. After the facsimile was sent, it was discovered that one of the study numbers was possibly incorrect. I called Mr. Bucceri and informed him that the Division requested information from study 050-CR-3002, however, we now believe that the study we require information on is study 52-CR-3002. I informed Mr. Bucceri that the study we are interested in is a pharmacokinetics of budesonide study. Mr. Bucceri stated that he would check and make sure the correct information is sent to us.

/S/

Gretchen Trout

cc: Original NDA 20-746
Div. File
HFD-570/Chen
HFD-570/Trout

TELECON

APPEARS THIS WAY
ON ORIGINAL

Trout

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
DIVISION OF PHARMACEUTICAL EVALUATION II

Date: Jan. 24, 1997

To: Ms. Gretchen Trout, CSO (HFD-570)

Through: Team Leader, Dale Conner, Pharm.D. (HFD-870) 1/24/97

From: Tien-Mien Chen, Ph.D. (HFD-870) 01/24/97

RE: NDA 20-746 for Rhinocort Aqua (budesonide) Nasal Spray, 32 and 64/spray

During my review of Human Pharmacokinetics and Bioavailability section of NDA 20-746 for missing in the NDA submission (budesonide) Nasal Spray, 32 and 64/spray, I realized that there was missing information on Rhinocort Aqua formulations, batch/lot sizes, etc., that were used in the pivotal clinical trials and pivotal pharmacokinetic studies. Therefore, the following biopharm comment should be communicated to the sponsor ASAP.

COMMENT: (Needs to be conveyed to the sponsor):

On page 65, Volume 1.1 of NDA 20-746 for Rhinocort Aqua (budesonide) Nasal Spray, it is stated under Item 2.F. Investigational Formulations that investigational formulations were used in pivotal clinical trials and that information about investigational formulations is included in the Drug product section. However, the above information is not found. Therefore, it is recommended that the sponsor provide responses to the following biopharm requests. If any of the following information has been included in the submitted NDA, please provide the page and volume Nos.

1. For Rhinocort Aqua (budesonide) Nasal Spray formulations only, please provide the compositions of the investigational formulations (other than the to-be-marketed formulations of 32 and 64 μg/spray) used in the pivotal clinical trials and in the pharmacokinetic (PK) studies.

2. Provide a summary table(s) for the batches/lots of Rhinocort Aqua (budesonide) Nasal Spray used in the pivotal clinical trials (please provide study Nos.) and also in the PK studies (Nos. 850-CR-2119, 050-CR-3002, 08-CR-3017, 52-CR-3036, and 05-CR-3040). The table(s) should 1) include batch/lot Nos., sizes, and dates and site(s) of manufacture and 2) identify which formulation(s) used, if it is not the to-be-marketed. In addition, please indicate what will be the full-scale production size batch for commercial use. Ideally, the batches/lots used

Ideally, the batches/lots used in the pivotal PK studies should represent >1/10 of what a full-scale production batch size should be.

3. Was the to-be-marketed 32 µg/spray formulation of Rhinocort Aqua ever used in the pivotal clinical trials (please provide study Nos.) and also in any PK studies?

4. Was the dosage (or therapeutic) equivalence, e.g., between 2 x 32 µg/spray and 1 x 64 µg/spray of Rhinocort Aqua, ever demonstrated in the pivotal clinical trials (please provide study Nos.) or was a bioequivalence study for 2 x 32 µg/spray vs. 1 x 64 µg/spray or 4 x 32 µg/spray vs. 2 x 64 µg/spray, ever conducted ?

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 20-746, HFD-570 (Trout), HFD-870 (D. Conner, T.M. Chen)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

(Division/Office)			FROM:	
Biometrics, Dr. Ted Guo			L. Ng /S/ 7-7-97	
DATE 7/3/97	IND NO.	NDA NO. 20-746	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 6-16-97
NAME OF DRUG Rhinocort Aqua Nasal Spray		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE End of August

NAME OF FIRM

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☑ OTHER *(Specify below)*

/S/ 7/7/97

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- SSOLUTION
- — 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 ASSESSEMENT 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/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Info on stability is found on p. 195 – 305, vol 1 of 2.

Please evaluate the following parameters to support expiration dating period :-

assay, impurities/degradation products ; weight loss and [redacted] assay.

cc: Orig NDA 20-746
HFD-570 / Div
HFD-570 / Ng, Trnt, Schwartz.

SIGNATURE OF REQUESTER /S/	METHOD OF DELIVERY *(Check one)* ☐ MAIL ☑ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

TEAM LEADER MEMORANDUM

TO:	NDA 20-746
THROUGH:	John K. Jenkins, MD
FROM:	Peter K Honig, MD
RE:	Rhincort AQ
DATE:	August 31, 1998

/S/

/S/

8/31/98

From a clinical perspective, the Rhinocort AQ application remains approvable. Please refer to Dr. Anthracite's review dated August 31, 1998 for a more detailed discussion of the additional clinical data submitted by the sponsor in response to the first 'approvable' letter. The most significant clinical development impacting this application concerns the proceedings of the recent joint PADAC/MEDAC Advisory Committee (July 30-31, 1998). At that time, the effect of inhaled corticosteroids on growth in children was discussed extensively and the committee agreed that class labeling of inhaled corticosteroids was supported. The committee also agreed, in principle, that children should receive the lowest effective dose of inhaled corticosteroids required to effectively manage their disease.

The material in the Rhinocort AQ resubmission contains final, complete data from a long-term, open-label, PAR extension study in which children aged 6-17 years were treated with daily doses of 256 micrograms of Rhinocort AQ for up to 52 weeks. The control group received Nasalcrom. The small but discernable and statistically significant difference in effect on linear growth in prepubertal children was previously reviewed and supports the principle of dosing children with the lowest dose required for effective disease management. The final study report also contains new, previously unreviewed information regarding the effect of Rhinocort AQ on bone mineral density. X-rays of the left hand and wrist as well as bone densitometry evaluations of the lumbar vertebrae were obtained at randomization and after one year of treatment with Rhinocort AQ or Nasalcrom. Mean normalized lumbar bone mineral density increased less in the Rhinocort AQ groups and the analysis of the subgroup of prepubertal children barely missed statistically significant differences ($p = 0.0698$) from the Nasalcrom controls. The differences between hand/wrist skeletal age and chronological age were consistently numerically greater in the Rhinocort AQ cohort as a whole and in the pubertal and prepubertal subsets. Statistically significant differences were not achieved for any analysis. Although the clinical consequences of these findings are not known, this study demonstrates an additional, quantifiable systemic effect of inhaled corticosteroids and supports the principle of administering the lowest effective dose to any individual patient.

The clinical review of the remainder of the data contained in the resubmission did not reveal any additional insights or raise any additional concerns regarding the safety and tolerability of Rhinocort AQ

Team Leader Recommendation: The Rhinocort AQ application remains approvable from a clinical perspective. Extensive labeling comments have previously been forwarded to the sponsor. Based on the PADAC/MEDAC discussions and the data contained in the Rhinocort AQ application, the DOSAGE AND ADMINISTRATION section should be further revised to recommend the use of lowest effective doses that have been developed for market with allowances for titration to higher doses if maximum benefit has not been achieved. The action letter should also strongly encourage that additional studies be conducted to demonstrate the lowest mean effective dose for the pediatric population and to more precisely quantify the effect of Rhinocort AQ (at the lowest approved dose) on linear growth in children. These studies should not be prerequisites for approval; however, they should be designated as Phase 4 commitments in the final approval letter.

cc:
NDA20-746/Division File
HFD-570/MO/Anthracite/Honig
HFD-570/PM/Hilfiker

APPEARS THIS WAY
ON ORIGINAL

Trout

TEAM LEADER MEMORANDUM
Addendum

TO:	NDA 20-746
THROUGH:	John K. Jenkins, MD
FROM:	Peter K Honig, MD
RE:	Rhincort AQ
DATE:	October 7, 1997

/S/ 10/7/97

/S/ 10/8/97

In order to evaluate the approvability of the pediatric claim for Rhinocort AQ in the treatment of seasonal and perennial allergic rhinitis, *post hoc* efficacy analyses of children 6-12 were conducted for Studies 3038 and 3039. Please refer to Dr. Guo's Statistical review for details. To summarize, in SAR trial 3038, the sponsor studied 94 children between the ages of 6 and 12 and 73 of these were randomized to active doses for four weeks. This constituted 23.2% of the total treated population. When comparing the mean effect size for the primary endpoint (change from baseline in Nasal Index Score at endpoint), it is apparent that doses below 128 ug/day are less effective. This contrasts the findings in the adult population and is summarized in the table below.

Age Group	32 ug/day	64 ug/day	128 ug/day	256 ug/day
6-12 (n=94)	-0.339	0.075	-1.006	-0.0871
13-17 (n=81)	-0.786	-0.570	-0.964	-0.1370
18+ (n=230)	-0.970	-1.096	-0.955	-1.260

Subgroup analyses in study 3039 (a 6 week PAR trial) yielded similar results except that, in this case, daily doses below 256 ug/day did not result in treatment effects that were comparable to all doses of Rhinocort AQ tested in the adult population over 18 years of age. The results are summarized in the table below.

Age Group	32 ug/day	64 ug/day	128 ug/day	256 ug/day
6-12 (n=133)	-0.417	-0.426	-0.194	-0.943
13-17 (n=86)	-0.225	-0.534	0.250	-0.267
18+ (n=254)	-0.884	-0.745	-0.864	-0.835

Week-by-week analyses yielded similar results for both studies. No inferential testing versus placebo was conducted on these subgroups.

Team Leader Conclusion: It appears that adult patients have a greater mean improvement over placebo and that the threshold dose of Rhinocort AQ may be higher in children below 12 years of age than in adults. In adults all doses of Rhinocort AQ provide comparable mean effects versus placebo. In contrast, it appears that only doses greater than or equal to 128 ug/day provide comparable mean changes to those seen in the adult population. The reasons for this difference are not apparent and somewhat counterintuitive. It should be remembered that this is a *post hoc* analysis of non-randomized patients and, as such, subject to bias.

Rhinocort AQ is approvable for the pediatric population aged 6-12. Adequate numbers of children have been studied for efficacy and safety. It remains to be determined how the product will be labeled with regard to dosing recommendations for the pediatric as well as the adult population. All doses appear to be effective in the adult population. The only distinguishing feature may be the time to maximum effectiveness which is demonstrated for the 256 ug/day dose at 2 weeks in both studies. This difference is no longer evident at the three week evaluation timepoint. In children with SAR, mean maximum effectiveness is achieved at Week 2 for doses of 128 ug and 256 ug per day. By the third week, this distinction is no longer evident. This relationship is not evident in children aged 6-12 in PAR trial 3039.

Team Leader Recommendation: Rhinocort AQ should be approved. Labeling should recommend that adults and children over the age of 12 should be started on a dose of 256 ug/day. If no improvement is seen after 2 weeks, the medication should be discontinued. If improvement is seen, the dose should be reduced to the lowest effective dose for that patient. For children aged 6 to 12, the recommended starting dose should be [redacted] ug/day. If no improvement is seen after 2 weeks, the medication should be discontinued. If improvement is seen, the dose should be reduced to the lowest effective dose for that patient.

cc:
NDA20-746/Division File
HFD-570/MO/Anthracite/Honig
HFD-570/PM/Trout

APPEARS THIS WAY
ON ORIGINAL

TEAM LEADER MEMORANDUM

TO: NDA 20-746
THROUGH: John K. Jenkins, MD
FROM: Peter K Honig, MD
RE: Rhincort AQ
DATE: July 14, 1997

Concur, need further analysis of pediatric data to address what indicated age is approvable
7/14/97

/S/
7/23/97

Rhinocort AQ is approved in 34 foreign countries. Two dose strengths (32 ug and 64 ug per spray) have been developed for the US market. Single dose studies investigating the clinical pharmacokinetics of Rhinocort AQ were conducted and a comparison to other budesonide formulations are presented in the table below. These data indicate that single 400 ug doses of Rhinocort AQ provide comparable exposures to those seen after 800 ug of budesonide from the Pulmicort Turbohaler and less than those seen after dosing with Rhinocort-CFC.

Drug Product and Dose (n)	Cmax (ng/ml)	Tmax (hr)	AUC_{0-t} (ng-hr/ml)
Rhinocort AQ 400 ug (15)	0.43	0.67	1.81
Rhinocort CFC 800 ug (15)	0.22	2.04	1.32
Pulimcort TBH 800 ug (16)	0.46	0.39	2.04
Rhinocort AQ 256 ug (12 children)	0.71	0.70	2.37

Two multicenter, double-blind, placebo controlled, parallel-group, pivotal clinical trials were conducted in support of efficacy. In each of the trials, the primary efficacy endpoint was the nasal index score (NIS) evaluated over the entire double-blind evaluation period (Overall Analysis). The NIS consisted of the sum of the three individual symptom scores rhinorrhea, sneezing and nasal congestion each scored on a conventional 0-3 symptom scoring scale. Study 3038 was 6 week study evaluating daily budesonide doses of 32 ug, 64 ug, 128 ug, and 256 ug in adults and children down to six years of age with seasonal allergic rhinitis (SAR). Placebo consisted of vehicle control without active drug. Patients had to have at least two of the symptoms included in the NIS and one of these had to be of at least moderate severity (i.e. 2 out of possible maximum score of three) during four days out of seven in the run-in period. Four hundred and six patients were randomized to the four week double-blind period. The results of the primary efficacy analysis are shown below.

Treatment arm (n)	Mean Baseline NIS	Adjusted Mean Change in NIS
Placebo (83)	4.9	-0.77
32 ug/day (78)	5.0	-1.64*
64 ug/day (79)	5.0	-1.54*
128 ug/day (83)	5.1	-1.57*
256 ug/day (82)	5.1	-1.82*

*p<0.05

The sponsor defined the pediatric subset of the study population as those patients between the ages of 6 and 17 years of age. There were approximately 35 patients per treatment arm (range 32-38) for this age population and, when compared to adults (>18 years), the treatment effect was consistently and notably lower for active drug and

placebo. For the 'pediatric' subset, statistical significance versus placebo was demonstrated only for the 256 ug/day treatment group whereas, for the adults, statistical significance versus placebo was seen for all budesonide groups. It is unknown the number of pediatric patients between the ages of six and twelve who participated in this trial.

Study 3039 was identical in design and conduct to the previous study with the exception that the patients had perennial allergic rhinitis (PAR) who were studied over a six week double-blind period. 478 patients were randomized to placebo or 32 ug, 64 ug, 128 ug, or 256 ug of budesonide once daily. 46% of these were 'pediatric' patients between the ages of six and seventeen. The results of the primary efficacy analysis are shown below.

Treatment arm (n)	Mean Baseline NIS	Adjusted Mean Change in NIS
Placebo (96)	6.3	-1.53
32 ug/day (97)	6.0	-2.25*
64 ug/day (92)	6.3	-2.06*
128 ug/day (92)	6.0	-2.01
256 ug/day (97)	6.1	-2.29*

*p<0.05

Similar to the findings of the SAR trial, the 'pediatric' subset analysis demonstrated the mean effect to be lower in the pediatric age group and no budesonide treatment was statistically superior to placebo. A post hoc onset of action analysis was performed in which the NIS (adjusted mean change from baseline) was analyzed separately at three timepoints after the first dose of medication. These results are presented below.

	24 Hours	48 Hours	72 Hours
Placebo	-0.44	-0.65	-0.76
32 ug/day	-1.02	-1.12	-1.33
64 ug/day	-0.94	-1.07	-1.25*
128 ug/day	-0.90	-1.07	-1.17
256 ug/day	-1.16*	-1.13*	-1.28*

*p<0.05

Several other active comparison, placebo-controlled supportive studies were submitted. These included Studies 3006 (Rhinocort AQ versus Rhinocort MDI), 3011 (Rhinocort AQ versus non-US beclomethasone), 3030 (Rhinocort AQ versus non-US fluticasone), 3012 (Rhinocort AQ 32 versus 256/day in PAR), and 3024 (Rhinocort AQ versus non-US azelastine in PAR). These all supported the contention that Rhinocort AQ is effective in the management of seasonal and perennial allergic rhinitis.

The general safety and tolerability of Rhinocort AQ was supported by a safety database of nearly 8000 patients and normal volunteers of which approximately 3300 received one or more doses of Rhinocort AQ. Of those, 662 individuals were exposed to the highest proposed dose for marketing (256 ug/day). The vast majority of all patients were exposed to drug for a period of three to six weeks (median= 22 days) although some patients were exposed to Rhinocort AQ for up to 60 months in uncontrolled studies. The safety analyses indicate that Rhinocort AQ is well tolerated. The only adverse events that exhibited evidence of a dose-related effect were 'nasal irritation' and epistaxis. Known steroid effects were evaluated more specifically. As part of Study 3038, basal and cosyntropin stimulated cortisols were evaluated on a subset of the patients before and after 4 weeks of double-blind treatment. 237

Rhinocort AQ patients and 62 placebo patients were evaluated. The data analyses indicated that none of the proposed doses of Rhinocort AQ suppressed basal or stimulated cortisol production. Urinary cortisols collected over 24 hours were part of the safety assessments for other trials. In Study 3006, a three week SAR trial in adults, demonstrated that the 24 urine cortisol production shoed little difference between active treatment groups (256 and 400 ug/day of Rhinocort AQ) and placebo. These findings are similar to those found in Study 3011 in which 24-hour urine cortisols were evaluated in patients receiving Rhinocort AQ (256 ug/day), beclomethasone nasal spray (400 ug/day) or placebo for three weeks. A long-term, uncontrolled study of children with PAR revealed that treatment with Rhinocort AQ, at doses up to 256 ug/day, resulted in decreased rates of growth (height and weight) when compared to healthy, historical controls. This finding is difficult to interpret due to the uncontrolled nature of the study. The concern is mitigated because growth suppression studies conducted in support of the Pulmicort application (NDA 20-441) do not indicate that budesonide exposures which would occur as a result of the use of Rhinocort AQ would be likely to pose a significant problem.

The worldwide post-marketing experience with intranasal budesonide formulations was scrutinized. 460 reports involving 655 adverse events have been received from 1983 through January 1996. Of particular concern are 47 to 75 reports of nasal septum perforation and 16 to 26 reports of epistaxis (duplicate reporting may be in effect).

Team Leader Conclusions: Rhinocort AQ has been demonstrated to be effective in the treatment of seasonal and perennial allergic rhinitis. The lowest effective dose that will be available for marketing is 64 ug/day (one spray per nostril once daily). There is no evidence of dose response or incremental benefit above 32 ug/day. Doses up to 256 ug/day appear to be safe from a perspective of HPA and growth suppression. Dose related safety issues may include local effects such as epistaxis and nasal septum irritation/perforation. There do not appear to be any gender, age, or race related differences in efficacy or safety.

Team Leader Recommendation: The Rhinocort AQ application is approvable from a clinical perspective. In order to evaluate the approvability of the pediatric claim, the sponsor should be asked to break down the numbers of patients studied between the ages of 6 to 9 and 9 to 12 years of age. A post hoc efficacy analysis of children 6-12 should be conducted for Studies 3038 and 3039. Labeling comments will be dealt with in a separate review.

cc:
NDA20-746/Division File
HFD-570/MO/Anthracite/Honig
HFD-570/PM/~~Bernes~~Truitt

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: September 30, 1999

FROM: Gretchen Trout /S/
Project Manager

SUBJECT: Memo to File

TO: NDA 20-746

Reference is made to teleconferences held between representatives of the Division of Pulmonary Drug Products, and Astra Zeneca, on July 13 and 26, 1999 with regard to cartons and container labels for this product. It was agreed between the Division and Astra during these teleconferences that Astra would be allowed to launch their product line with the 32 mcg strength product using the immediate container labeling identical to that submitted to the NDA on December 23, 1998. However, within three months of launch, Astra would have to utilize their revised carton and container labels, submitted on July 30, 1999, which incorporated the changes requested by the Division.

For administrative reasons, the Division requested that Astra resubmit, in one submission, the package insert, patient's instructions for use, and launch carton and container labels. Astra complied in the submission dated September 24, 1999. On September 27, 1999, Astra submitted the final version of the carton and container labels (to be implemented within three months of launch).

Cc: NDA 20-746
Div. File
HFD-570/Trout

Rd initial by: Schumaker 9-30-99

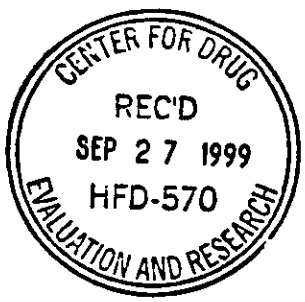
APPEARS THIS WAY
ON ORIGINAL

AstraZeneca

Eric Couture, Ph.D.
Director, Regulatory Liaison

September 27, 1999

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 20-746
Rhinocort® Aqua™ (Budesonide) Nasal Spray
Labeling Submission: Response to FDA Request for Information

Please refer to our July 29, 1996 New Drug Application for Rhinocort Aqua (Budesonide) Nasal Spray, 32 mcg and 64 mcg, to our teleconferences on July 13 and July 26, 1999 to discuss issues related to the label and carton, to our submissions to FDA dated July 20, July 30, August 30, and September 24, 1999, and to our conversations with Ms. Gretchen Trout on September 22 and September 23, 1999.

In our teleconference dated July 26, 1999, FDA agreed to permit AstraZeneca LP, upon approval, to launch Rhinocort Aqua (Budesonide) Nasal Inhaler 32 mcg/ 60 sprays presentation with the existing bottle label. As part of this agreement, AstraZeneca LP will revise this label no later than 3 months following the launch date as per FDA directions. A sample of the revised version of this label is attached. The carton has already been revised according to FDA request as per the teleconference of July 26, 1999.

As requested by FDA in our conversations on September 22 and 23, 1999, attached are copies of the following items:

- Carton and "new" 32 mcg/60 spray bottle label (previously submitted on July 30, 1999).
- Carton and "new" bottle labels for all other 32 and 64 mcg presentations (same as previously submitted on September 24, 1999).

AstraZeneca LP
725 Chesterbrook Blvd Wayne PA 19087-5677

Tel 610 695 1000
www.astrazeneca-us.com

Please direct any questions or comments to me at (610) 695-1263 or, in my absence, to Robert Monaghan, Senior Regulatory Project Manager at (610) 695-4227.

Sincerely yours,

R Monaghan FOR:

Eric Couture, Ph.D.
Director, Regulatory Liaison

Enclosure
cc: Gretchen Trout, Regulatory Project Manager

Sent via courier

APPEARS THIS WAY
ON ORIGINAL