CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-746

CORRESPONDENCE

Trout

JUL 27 1999

NDA 20-746

Astra Zeneca
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

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

Dear Dr. Couture:

We acknowledge receipt on July 21, 1999, of your July 20, 1999, resubmission to your new drug application (NDA) for Rhinocort Aqua (budesonide) Nasal Spray.

This resubmission contains additional pre-clinical, chemistry, manufacturing and controls, and labeling information submitted in response to our June 22, 1999 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is January 21, 1999.

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

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

Trout

JUN 2 2 1999

NDA 20-746

Astra Pharmaceuticals, L.P.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

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

Dear Dr. Couture:

Please refer to your new drug application (NDA) dated July 29, 1996, received July 30, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhinocort Aqua (budesonide) Nasal Spray, 32 mcg and 64 mcg.

We acknowledge receipt of your submissions dated December 23, 1998, April 28, May 6, 18, 24, 25, and 27, and June 3 and 8, 1999. Your submission of December 23, 1998, constituted a complete response to our September 2, 1998, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to adequately address the following.

1. The following comments pertain to the drug substance.

   a. Stability data for micronized budesonide indicate that an expiry period for drug substance should be established and limited to [redacted] months. Submit copies of revised documentation that reflect this change, and specify the retest schedule and protocol that are exercised within the expiry period; i.e., [redacted] months after drug substance manufacturing.

   b. We acknowledge your commitment (amendment dated May 27, 1999) to submit by August 16,1999, a validated method for the measurement of [redacted] The method and acceptance criteria will be consistent with those applied to Pulmicort 200 Turbuhaler (NDA 20-441).

   c. Submit revised drug substance specification sheets for release and stability testing that will include individual method numbers for each analytical test procedure, as requested in comment #5 of our letter dated May 6, 1999.

2. The following comments pertain to the drug product.

a. Submit revised drug product specifications sheets with the acceptance criteria for [redacted] that reflect levels observed in primary stability batches of drug product stored for 18 months, as discussed during the June 1, 1999, teleconference. Since the [redacted] is the major contributing impurity, the acceptance criteria for total specified and total impurities should also be adjusted. Based on brief statistical evaluation of data submitted on June 3, 1999, the acceptance levels should be tightened; e.g.,

i. [redacted] for [redacted] and [redacted] for total specified and total impurities at release for each strength,

ii. [redacted] for [redacted] and [redacted] for total specified and total impurities during shelf-life for 32µg/dose strength, and

iii. [redacted] for [redacted] and [redacted] for total specified and total impurities during shelf-life for 64µg/dose strength.

b. We acknowledge your commitment to test and analyze the first twenty post- approval production batches, and to propose in a prior-approval supplemental submission, appropriate final specifications for the drug product. In particular, the [redacted] should be evaluated and tightened accordingly. The supplemental application should be provided with the available data by December 31, 1999.

c. We note that the [redacted] of the tested pump units is not very consistent, particularly for the large [redacted] We recommend that you work closely with the pump supplier to improve the consistency of the dosage performance. Statistical evaluation of the submitted data indicates that the interim specifications for [redacted] should to be tightened; e.g.,

i. average of 3 sprays from 3 bottles for Large [redacted]

ii. average of 3 sprays from 3 bottles for Very Large [redacted] and

iii. if the average for [redacted] is outside [redacted] but inside [redacted] then 3 sprays from 6 additional bottles are tested.

d. Provide a commitment to study further, and modify according to the results, the method and the acceptance criteria for the measurement of color of the drug product formulation. Submit data for [redacted] Index measurements for the suspension and the UV measurements for the filtrate that are collected on the first 20 manufacturing batches. Submit the revised method and data-based acceptance criteria in a supplemental application by December 31, 1999.

e. Tighten the interim acceptance criteria for color of the drug product, e.g., [redacted] for the 32 µg/dose strength and [redacted] for the 64 µg/dose strength.

f. Submit revised drug product specification sheets for release and stability testing after implementing all the requested changes indicated above.

3. The following comments pertain to the container closure system.

a. Provide a commitment to submit a supplemental application by December 31, 1999, that includes the results and tightened acceptance criteria for [redacted] for pump and applicator parts. The specification sheets should include limits for the [redacted] sample as well as limits per each part and per pump unit expressed in micrograms.

b. Submit revised specification sheets for incoming applicators to include the following:

i. Acceptance criteria for spray pattern that are consistent with those proposed for drug product; i.e., max/min at least [redacted]
ii. Acceptance criteria for [redacted] that are consistent with those indicated in 2(c) above for the drug product.
iii. Astra drawing [redacted] as an integral part of acceptance criteria.

4. Submit a revised stability protocol to include testing in [redacted] conditions of [redacted] and change the name of the [redacted] storage conditions to [redacted]

5. DMFs # [redacted] and [redacted] currently have inadequate status.

6. The method for determination of [redacted] impurity submitted to NDA [redacted] on May 6, 1999, has not been evaluated for this application. The final method should be submitted promptly to this NDA upon approval of [redacted] but not later than December 31, 1999.

7. The following comments pertain to [redacted] of budesonide.

   a. Conduct an in vitro [redacted] that complies with the ICH guidelines regarding [redacted] design and validity. Specifically, the study must meet ICH requirements for [redacted] and must be done in both the presence and absence of the [redacted]

   b. Conduct an in vitro [redacted] that complies with ICH guidelines, such as the [redacted]

   c. Commit to providing the results of both of the above studies to the Agency by November 30, 1999. Additional evaluation of [redacted] of budesonide may be necessary if the above testing yields positive results.

8. Submit revised draft labeling as indicated in the attached marked-up label.

Additional labeling comments will be forwarded following satisfactory resolution of the above issues.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an [illegible] ference with this Division to discuss what further steps need to be taken before the application may be approved.

You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely yours,

Robert J. Meyer, M.D.
Acting Director
Division of Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

12 **Page(s) Redacted**

Draft

Labeling

Trout

NDA 20-746

MAY – 6 1999

Astra Pharmaceuticals
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

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

Dear Dr. Couture:

Please refer to your pending July 29, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhinocort Aqua (budesonide) Nasal Spray.

We also refer to your submission dated December 23, 1998.

We have completed our review of the Chemistry, Manufacturing and Controls section(s) of your submission and have the following comments and information requests.

1. It is noted that micronization and testing of the drug substance for commercial product is performed by [redacted], whereas the micronization and testing for clinical and stability batches was performed by Astra Production Chemicals AB (APH; CFN #96-10565). Confirm that [redacted] will be the only site involved in the micronization and testing of the drug substance. Demonstrate equivalency of the micronized drug substance from [redacted] and APH by submitting the following:

   a. Acceptance testing protocols, along with specifications and Certificate of Analysis from supplier(s), for the incoming drug substance (non-micronized and micronized if applicable).

   b. Description of micronization process, equipment and in-process controls with emphasis on differences between the two sites. Table format is preferred.

   c. Acceptance criteria for the micronized drug substance for release and stability testing prior to formulation. This should also include acceptance criteria for [redacted]

d. Supporting release and stability data for micronized drug substance and drug product manufactured from drug substance micronized at [redacted] and APH.

2. Establish acceptance criteria for impurities in the drug product. Specify each impurity equal to or greater than [redacted] Include acceptance criteria for individual and total specified impurities, individual and total unspecified impurities, and total impurities, in addition to the "Degradation products". Impurities of drug substance synthesis that do not increase during storage should be listed in the drug product specifications as a reference, and should be included in the total impurities.

3. Change the abbreviated name for degradation compound [redacted] from [redacted] to the more informative name, [redacted] of budesonide. We are concerned with relatively high levels (up to [redacted] of this decomposition compound in the drug product, since it constitutes structural concern for [redacted] and [redacted] Provide a short summary of any corrective actions implemented to slow down the [redacted] Also, submit data on the levels of this degradation product present in the pre-clinical batches or any other data for toxicological qualification of this impurity.

4. The method [redacted] for color measurement in the reflectance mode does not distinguish adequately between the 1 month old and 30 months old samples. In fact, it does not demonstrate correlation between the age of the drug product sample and the "color" reading. Submit systematic stability data, if available. Improve the discriminatory power of the method; e.g., include measurements in several different metamerism indexes like Tint/Tint Difference and [redacted] Index. In addition, the method could be supplemented with measurements on the drug product filtrate in the [redacted] mode.

5. A unique number should be designated for each analytical test procedure employed for testing of every attribute. The numbering system should permit logical tracking of subsequent changes introduced with time to each testing procedure. Drug substance and drug product specification sheets (release and stability) should be modified to include references to the analytical test procedures utilized for a given test and to the testing site. For example:

Parameter	Test Procedure (number)/ Testing site (CFN number)	Acceptance criteria

6. The following comments pertain to the performance of the dosage form.

   a. We acknowledge your commitment to test and analyze the first twenty post-approval production batches and to propose, in a prior-approval supplemental submission, appropriate final acceptance criteria for parameters pertaining to the performance of the drug product dosage.

   b. Based on currently presented data, the proposed interim acceptance criteria for [redacted] should be tightened and revised to include range of values for [redacted]. Also, a [redacted] profile for [redacted] which according to proposed criteria may account for [redacted]% of total volume, has to be adequately addressed; e.g., [redacted] for [redacted] and for all [redacted] may be included, in addition to [redacted] Submit revised specifications with supporting data.

   c. Based on submitted data, revise the acceptance criteria for [redacted] as follow:
      Number % of budesonide particles [redacted] at least [redacted] and
      Number % of budesonide particles [redacted] at least [redacted]

   d. Tighten the acceptance criteria for drug product viscosity based on currently submitted data.

   e. Tighten the proposed acceptance criteria for the ratio of the maximal to minimal diameter of the [redacted]

7. The following comments pertain to the container closure system.

   a. Significantly tighten the proposed acceptance criteria for [redacted] for pump parts extracted with [redacted] Provide acceptance criteria for [redacted] expressed as micrograms per container part, in addition to the acceptance limits for [redacted] of tested sample.

   b. Provide a brief explanation for the ISO 2859 document tables (Pages 5-051 and 52 of December 23, 1998 submission) for the acceptance testing procedure for the pump units, as discussed during a teleconference on October 7, 1998.

c. Specify who is responsible for the acceptance testing of different parts of the container closure system, and specify what percentage of your yearly production (referred to drug product) is being/will be tested to verify Certificates of Analysis from suppliers.

d. Refer to comment 6.b. on [redacted] for the drug product. The above comments equally apply to the acceptance criteria for incoming pumps and actuators. Modify the specifications accordingly.

e. Provide supportive data to justify the proposed acceptance criteria (i.e., [redacted] for the size of the orifice of the applicator.

f. Submit revised acceptance criteria sheets for pumps and actuators with all the requested changes. Include appropriate supportive data. Tabular format, consistent with the specification sheets for drug product is preferred (see comment #5 above).

8. The following comments pertain to the proposed post-approval stability protocol (Attachment 6, pp. 1-225 to 1-228).

a. Acceptance criteria for stability testing (stability specification sheets) constitute an integral part of the stability protocol and should be submitted along with the list of tested parameters (attributes) and references to the testing methods and testing intervals (see example given for drug product in item 5). If all the parameters and methods are identical to those submitted as a drug product specifications (Attachment 2), an appropriate reference should be made.

b. Modify the protocol for the first three production batches to include [redacted] for all parameters. Also, provide results of drug product stability testing (6 months, minimum of 4 data points) on batches stored at [redacted] and collected for all parameters according to the final methods.

c. Omission of the 3-and 9-months testing intervals proposed for analysis of second and subsequent year batches is inappropriate at this time, since several methods and acceptance criteria are still under modification. Such a proposal should be submitted, including supportive data, as a prior-approval supplemental submission when an adequate database (collected according to the full protocol, including [redacted] is available.

9. Submit revised drug product specification sheets for release and stability testing after implementing all the requested changes. Provide adequate release and stability data (in the same revised format, if possible) to support the proposed acceptance criteria for the drug product.

10. Deficiency comments are being forwarded to the holders of DMF #'s [redacted] and [redacted]

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

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary Drug Products, (HFD-570)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Trout

NDA 20-746

JAN 11 1999

Astra Pharmaceuticals
725 Chesterbrook Boulevard
Wayne, PA 19087-5677

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

Dear Dr. Couture:

We acknowledge receipt on December 23, 1998, of your December 23, 1998, resubmission to your new drug application (NDA) for Rhinocort Aqua (budesonide) Nasal Spray.

This resubmission contains additional Chemistry, Manufacturing, and Controls (CMC) information, and revised labeling, submitted in response to our September 2, 1998, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is June 23, 1999.

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

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

SEP - 2 1998

NDA 20-746

Astra Pharmaceuticals, L.P.
50 Otis Street
Westborough, MA 01581-4500

Attention: Dennis Bucceri
Vice President
Regulatory Affairs

Dear Mr. Bucceri:

Please refer to your new drug application (NDA) dated July 29, 1996, received July 30, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhinocort Aqua (budesonide) Nasal Spray, 32 µg and 64 µg.

We acknowledge receipt of your submissions dated February 27, March 6, April 2, May 6, May 14, June 9, and June 15, 1998. Your submission of February 27, 1998, constituted a complete response to our October 29, 1997, action letter. The user fee goal date for this application is September 2, 1998.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues.

1. State the source of the drug substance used in the stability studies of the drug product. Data for stability batches of the drug product prepared from each drug substance source should be submitted.

2. Include the microbial limits test description (Attachment 4, page 178 of the February 27, 1998, submission) as part of the USP <61> microbial limits test in the test procedures section for the drug product.

3. The following comments pertain to the [redacted] acceptance criteria and test procedure.

   a. The acceptance criteria for the [redacted] procedure should also include individual sprays, as well as the average as is currently reported. Since the average is the mean of 9 measurements, the specification should be adjusted to reflect the data for both tier 1 and tier 2.

   b. Define the background number, how it is obtained, and whether it is fixed or

a new background sample is run each day.

4. The following comments pertain to the [redacted] index [redacted] test procedure.

   a. Based on the updated stability data, a range should be proposed for the acceptance criteria of the [redacted] test procedure.

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

5. The following comments pertain to the acceptance criteria and test procedure for viscosity.

   a. As previously requested, the release and shelf-life viscosity should be adjusted to reflect observed data for the to-be-marketed product.

   b. It is not clear how the viscosity affects the [redacted] and surface tension of the drug product. Due to the high variation in the proposed viscosity acceptance criteria for the drug product, the acceptance criteria and test procedures for the excipients should be submitted. Appropriate specifications should be submitted for the excipients that affect viscosity of the drug product.

6. The specifications for the delivered dose and number of medicated actuations for the various strengths and sizes should be revised as follows.

   a. For the delivered dose test procedure, the specification should be modified as follows.

      In the third paragraph (for doses 1 and 2), replace [redacted] with "and," and replace [redacted] with "within."

   b. For the number of medicated actuations, the specification should be modified as follows.

      In the third paragraph (for doses 119 and 120), replace [redacted] with "and" and replace [redacted] with "within."

In the fifth paragraph: "The average of each of the beginning and end values is 27.2 - 36.8 µg (±15% of label claim)."

7. The following comments pertain to the acceptance criteria and test procedure for the content and impurities assay of the drug product.

   a. Acceptance criteria should be set for the ratio of the two isomers of budesonide in the budesonide assay for content.

   b. The two peaks, claimed to be process impurities on the [redacted] as [redacted] should be referenced and listed as process impurities in the test procedure.

   c. All peaks above the claimed quantitation limit should be included in the total. A statement to indicate such should be included in the test procedure.

   d. All unknown impurities at or above [redacted] should be specified.

   e. Acceptance criteria for impurities should be revised as follows:

   32 µg/dose: NMT [redacted] total
   NMT [redacted]
   NMT [redacted]
   No other individual impurity [redacted]
   All peaks above the claimed quantitation limit should be included in the total.

   64 µg/dose: NMT [redacted]
   NMT [redacted]
   NMT [redacted]
   No other individual impurity [redacted]
   All peaks above the claimed quantitation limit should be included in the total.

8. No relationship exists between the asymmetry and tailing values for potassium sorbate in the table on page 49 of the February 27, 1998, submission. For example, 2.4 asymmetry is equal to 1.6 tailing and 2.1 asymmetry is equal to 1.6, 1.5, 1.7, or 1.8 tailing. Provide the calculations for asymmetry and tailing factors. The formula for calculation should be included in the method.

9. The acceptance testing for the dimensions of the applicator should include an

established range for the orifice.

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

    a. As previously requested, 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 and illustrate how the minimum and maximum diameters are measured.

    d. Amend the acceptance criteria to reflect actual data. Additional comments pertaining to this test and specification will be provided after evaluation of your responses to these comments.

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

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

12. The following comments pertain to the pump components and container.

    a. As requested previously, clarify the role of [redacted] in the [redacted] which is provided to [redacted]

    b. DIN [redacted] (mentioned in Table 1, page 74, Attachment 11 of the February 27, 1998, submission to include possible deviations of the stainless spring wires) should be submitted.

    c. The composition of the green coloring of the bottle coating, or a letter of authorization to an appropriate DMF for this information, should be provided.

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

    a. Specifications should be submitted which include acceptance criteria and test procedures for extractables for the pump unit. Data should be submitted to

justify the acceptance criteria before additional comments can be made.

b. The location of the data for extractables of pump parts and resin in DMF [ ] should be stated. Currently, DMF [ ] remains inadequate.

c. Submit a copy of the ISO 2859 document.

14. The following comments pertain to the particle size distribution test procedure.

a. Clarify how an "event" for the [ ] test procedure is performed.

b. Provide representative photographs of the two strengths indicating the presence of drug substance and cellulosic particles. The magnification and size should be specified.

c. Explain the discrepancy observed in the number of particles [ ] between the data for the drug substance and the data for the drug product batches (Attachment 14, page 115).

d. A standard mixture of particle sizes should be included as part of system suitability testing for the [ ] test procedure.

e. The specification for the [ ] will be finalized after the above issues are resolved.

15. Revised specifications for the drug product and container/closure should be submitted, after taking into account all of our comments.

16. A commitment to re-evaluate acceptance criteria for testing of the drug product and the pump unit will only be considered after complete evaluation of all supporting data. Amending the acceptance criteria requires prior agreement and justification.

17. The stability protocol should be revised to clearly designate the proposed storage orientation.

18. Include two batches of the drug product made from each of the two sources of drug substances in stability studies.

19. Explore and implement appropriate improvements to the current design of the applicator. The actuating finger-positions are not firm.

20. We remind you of our previous comments related to NDA [redacted] pertaining to your environmental assessment, that calculations should be based on all budesonide-containing products for the estimated concentration of drug substance at point of entry into the aquatic environment.

21. The printing area of the immediate container labels should be enlarged so that the font size can be increased for better legibility.

22. The following comments pertain to the carton label.

    a. The prominence of "budesonide" in the name should be increased relative to "Rhinocort."

    b. The priming information and target dose weight should be included.

    c. The word [redacted] should be replaced by "spray."

23. Make changes as indicated in the revised draft package insert enclosed with this letter and the revised draft Patient's Instructions enclosed in our June 25, 1998, letter. Additional labeling may be forthcoming following our review of the information requested above.

    The Division is currently finalizing class labeling regarding the potential effects of inhaled and intranasal corticosteroids on growth in children. Additional labeling comments will be forthcoming once the class labeling language is finalized.

Although not required for approval, we strongly encourage you to conduct additional clinical studies to address the following comments as part of the continuing development and evaluation of this drug product.

Current data suggests that total daily doses of 32 µg through 256 µg are equally effective for patients 18 years of age and older. *Post hoc* exploratory analyses suggest that there may be less efficacy in younger patients, or that efficacy may require higher doses in younger patients. The mean minimum effective doses should be separately established for adults (18 years of age and above), for adolescents (12 to 18 years of age), and for children (6 to 11 years of age) through additional [redacted] studies.

The potential impact of Rhinocort Aqua on growth retardation should be quantified in prepubescent children at the lowest commercially available daily dose of 64 µg.

You are strongly encouraged to consult the Division of Pulmonary Drug Products regarding the design of these additional studies before they are initiated.

Please submit a sample of the to-be-marketed drug product.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus at the time of your response to this letter will facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

11 **Page(s) Redacted**

Draft

Labeling

NDA 20-746

JUN 25 1998

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

Attention: Dennis Bucceri
Vice President,
Regulatory Affairs

Dear Mr. Bucceri:

Please refer to your pending July 29, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhinocort Aqua (budesonide) Nasal Spray.

We also refer to your submissions dated February 27 and May 14, 1998.

We have completed our review of the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests.

1. Please state the source of the drug substance used in the stability studies of the drug product. Stability batches of the drug product prepared from each drug substance source should be submitted.

2. Please include the microbial limits test description (Attachment 4, p. 178 of the February 27, 1998 submission) as part of the USP <61> microbial limits test in the test procedures section of the drug product.

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

   a. The acceptance criteria for [redacted] test procedure (page 71 of the February 27, 1998 submission) should include individual sprays, as well as the average as is reported. In addition, the specification should be adjusted to reflect the data for both tier 1 and tier 2.

   b. Explain what the background number is, how it is obtained, and if it is fixed or a background sample is run each day.

4. These comments pertain to the [redacted] index [redacted] test procedure.

   a. Based on the updated stability studies data, a range should be proposed for the acceptance criteria of the [redacted] test procedure.

   b. Please relate the intensity of the color using a more conventional method; e.g., [redacted] An alternate method could be developed due to lack of available equipment in the FDA laboratories.

5. These comments pertain to the acceptance criteria and test procedure for viscosity.

   a. As requested previously, the release and shelf life viscosity should be adjusted to reflect observed data for the market product.

   b. It is not clear how the viscosity affects the [redacted] and surface tension of the drug product. Due to the high variation in the proposed viscosity acceptance criteria for the drug product, the acceptance criteria and test procedures for the excipients should be submitted. Appropriate specifications should be submitted for the excipients that affect viscosity of the drug product.

   c. A sample of the market drug product should be submitted.

6. The appropriate statements for the specifications of the various strength and sizes for the delivered dose and number of medicated actuations should be revised.

   For delivered dose test procedure, the revised statement should read: (3rd paragraph) If 2 or 3 of the values are outside [redacted] (±20% of label claim) with no value outside [redacted] (±25% of label claim) and the average is within [redacted] (±15% of label claim) then 20 additional bottles are tested (for doses 1 and 2).

   For number of medicated actuations, the revised statements should read: (3rd paragraph) If 2 or 3 of the values are outside [redacted] (±20% of label claim) with no value outside [redacted] (±25% of label claim) and [redacted] (±15% of label claim) then 20 additional

(5th paragraph) The average of each of the beginning and end (see item 13) values is 27.2 - 36.8 µg (±15% of label claim).

7. These comments pertain to the acceptance criteria and test procedure for the content and impurities assay of the drug product.

   a. Acceptance criteria should be set for the ratio of the two isomers of budesonide in the assay of budesonide for content.

   b. The two peaks claimed to be process impurities on the [redacted] as [redacted] and [redacted] should be referenced and listed as process impurities in the test procedure.

   c. All peaks above the claimed quantitation limit should be included in the total. A statement to indicate such should be included in the test procedure.

   d. All unknown impurities at [redacted] should be specified.

   e. Acceptance criteria for impurities should be revised as follows:

   32 µg/dose:
   NMT [redacted] total
   NMT [redacted]
   NMT [redacted]
   No other individual
   All peaks above the claimed quantitation limit should be included in the total.

   64 µg/dose:
   NMT [redacted] total
   NMT [redacted]
   NMT [redacted]
   No other individual [redacted]
   All peaks above the claimed quantitation limit should be included in the total.

8. No relationship exists between the asymmetry and tailing values for potassium sorbate in the table on p. 49 of the February 27, 1998 submission. For example, 2.4 asymmetry is equal to 1.6 tailing and 2.1 asymmetry is equal to 1.6, 1.5, 1.7 or 1.8 tailing. Please provide the calculations for

asymmetry and tailing factors. The formula for calculation should be included in the method.

9. The acceptance testing for the dimensions of the applicator should include an established range for the orifice.

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.

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.

12. The following comments pertain to the pump components and container.

    a. As requested previously, please clarify the role of [redacted] in the [redacted] which is provided to [redacted]

    b. DIN [redacted] mentioned in table 1, p. 74, Attachment 11 of the February 27, 1998, submission, to include possible deviations of the [redacted] should be submitted.

    c. The composition of the green coloring of the bottle coating should be provided. Alternately, a DMF reference could be provided.

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

    a. Specifications which include acceptance criteria and test procedures for extractables for the pump unit should be submitted. Data to justify the acceptance criteria should be submitted before comments can be made.

    b. The location of the data for extractables of pump parts and resin in DMF [redacted] should be stated.

    c. Submit a copy of the ISO 2859 document.

14. The following comments pertain to the [redacted] procedure.

    a. Clarify how an "event" for the [redacted] procedure is performed.

    b. Provide representative photographs of the two strengths indicating the presence of a drug substance and a cellulosic particles. The magnification and size should be specified.

    c. Explain the discrepancy observed in the number of particles [redacted] between the data for the drug substance and the data for the drug product batches (Attachment 14, p. 115).

    d. It is recommended that a standard mixture of particle sizes be included as system suitability testing for the [redacted] test procedure.

    e. The specification of the [redacted] will be finalized after the issues raised above are resolved.

15. Revised specifications for the drug product and container/closure which include the acceptance criteria and test procedures requested for the NDA should be submitted.

16. Commitment to re-evaluate acceptance criteria for testing of drug product and pump unit will only be considered after complete evaluation of all supporting data. Amendment to acceptance criteria requires prior agreement and justification.

17. Instead of either upright or inverted position for storage, the stability protocol should be revised to state only one storage position.

18. Please commit to put two batches of the drug product made from each of the two sources of drug substances in stability studies.

19. Please explore and implement appropriate improvements to the current design of the applicator. The actuating finger-positions are not firm and the upper section of the applicator wobbles.

20. We remind you of the comments related to NDA [redacted] for submission of calculations based on all budesonide-containing products for the estimated concentration of drug substance at point of entry into the aquatic environment.

21. The printing area of the immediate labels should be increased so as to enable the print size to be enlarged for better legibility.

22. These comments pertain to the carton label.

    a. The prominence of "budesonide" in the name should be increased relative to "Rhinocort."

    b. The priming information and target dose weight should be included.

    c. The word [redacted] should be replaced by "spray".

23. Please make changes as indicated on the attached copy of the Patient's Instructions.

24. The holder of DMF [redacted] has been informed of comments.

We would appreciate your prompt written response so we can continue our evaluation of your NDA. Please note that additional labeling comments will follow.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

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

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader, DNDC II for the
Division of Pulmonary Drug Products, (HFD-570)
DNDC 2, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment

APPEARS THIS WAY
ON ORIGINAL

2 **Page(s) Redacted**

Draft

Labeling

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Roberta Tucker

Phone Number: 508-366-1100

Fax Number: 508-898-9289

FROM: Hretchen

DIVISION OF PULMONARY DRUG PRODUCTS

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

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

Total number of pages, including cover sheet: 2 Date: 3/27/98

COMMENTS: Robby - per our earlier conversation, please do conversions for Aqua based on the attached table.

Body weights & Conversion factors for preclinical labeling, DPDP (10/30/97)

Body Weights	
Age (years)	Weight (kg)
0-1	3
2-3	12
4-5	16
6-11	20
12-adult	50
Adopted from: National Center for Health Statistics, monthly vital statistics report 25:1, 1976	

Conversion Factors – HUMAN mg/kg to mg/m^2	
Age (years)	Conversion factor (Km)
0-11	25
12-adult	37
Adopted from: Freircich EJ, et al., 1966, Cancer Cemother Repts 40 (4):219:244.	

Conversion Factors – ANIMAL mg/kg to mg/m^2	
Animal	Conversion factor (Km)
mouse	3
hamster	4
rat	6
guinea pig	8
rabbit	12
monkey (small)	12
dog	20
Adopted from: Freircich EJ, et al., 1966, Cancer Cemother Repts 40 (4):219:244.	

APPEARS THIS WAY
ON ORIGINAL

MAR 23 1998

NDA 20-746

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

Attention: Dennis J. Bucceri
Vice President
Regulatory Affairs

Dear Mr. Bucceri:

We acknowledge receipt on March 2, 1998, of your February 27, 1998, resubmission to your new drug application (NDA) for Rhinocort (budesonide) Aqua Nasal Spray.

This resubmission contains additional chemistry, manufacturing, and controls information, as well as revised draft labeling, clinical study reports, the safety update report, and case report forms for deaths and discontinuations due to adverse events, submitted in response to our October 29, 1997, action letter.

We consider this a complete, class 2 response to our October 29, 1997, action letter. Therefore, the user fee goal date is September 2, 1998.

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

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

MAR - 6 1998

NDA 20-233, 20-441, 20-746

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

Attention: Dennis Bucceri
Vice President
Regulatory Affairs

Dear Mr. Bucceri:

Please refer to your approved new drug applications submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhinocort (budesonide) Nasal Spray, 50 µg (NDA 20-233), Rhinocort Aqua Nasal Spray, 32 and 64 µg (NDA 20-746), and Pulmicort (budesonide) Dry Powder Inhaler, 200 and 400 µg (NDA 20-441).

We also refer to Astra studies 05-2071 and 05-3046 submitted to NDA 20-746 regarding the growth effects of chronically dosed intranasal budesonide in children.

I would like to inform you that a working group comprised of members of the Division of Pulmonary Drug Products and the Division of Metabolic and Endocrine Drug Products has been formed to gather and evaluate all published and proprietary information on the systemic effects of intranasal and inhaled corticosteroids in human subjects. The working group has been tasked with the development of class labeling for inhaled and intranasal corticosteroid drug products related to the potential effects of these products on growth in children. The working group has also been tasked with the development of recommendations and guidance regarding the appropriate study design(s) and duration to evaluate possible systemic effects of inhaled and intranasal corticosteroid drug products (e.g., studies of adrenal function, growth studies in children, etc.).

We are in the process of planning a joint advisory committee meeting to discuss these topics. This meeting is now tentatively scheduled for late July of 1998. The success of the meeting will require participation by the pharmaceutical industry and will be greatly aided by full public discussion of all relevant and available data.

We recognize that the data from Astra studies 05-2071 and 05-3046 may be considered to be proprietary information. We would like your permission to include these findings in our discussion at the upcoming advisory committee meeting. Similar requests will be made of other pharmaceutical companies with relevant proprietary data. We fully anticipate that the pharmaceutical industry will be given an opportunity at this meeting to make presentations of data relevant to the discussion.

We look forward to your cooperation and participation in this extremely important discussion. If you have any questions, please contact Mr. David Hilfiker, Project Manager, at (301) 827-1046.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

OCT 29 1997

NDA 20-746

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

Attention: Dennis Bucceri
Vice President,
Regulatory Affairs

Dear Mr. Bucceri:

Please refer to your new drug application dated July 29, 1996, received July 30, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhinocort Aqua (budesonide) Nasal Spray 32 and 64 mcg.

We acknowledge receipt of your submissions dated October 10, November 1, 4, 5, 8, 15, 20, 21, and 27, and December 3, 1996, and January 22, March 6, April 17, May 9 and 22, June 3, 13, and 16, September 8, 16, and 30, and October 7 and 15, 1997. The original user fee goal date for this application was July 30, 1997. Your submission of June 16, 1997 extended the user fee goal date to October 30, 1997.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following information.

1. [redacted] holder of DMFs [redacted] and [redacted] relating to the starting material and drug substance respectively, has been notified of comments.

2. The RSD for the system suitability testing for the [redacted] test procedure should be tightened.

3. The following pertain to all [redacted] test procedures.

   a. It is recommended that the sample and standard concentrations be kept similar.

   b. The following supporting data should be submitted with your statement that linear regression forcing the line through zero is appropriate.

(1) Show that the non-zero y-intercept is not statistically different from zero.

(2) Provide the 95% confidence interval around the non-zero y-intercept.

(3) State your plan if any non-zero intercept is observed.

4. Submit the microbial limits test procedure as performed by your analysts to enable duplication by the FDA laboratories.

5. The Number of Medicated Actuations Through Life of Container should be retained for release and stability. Elimination of this test procedure is not recommended.

6. The following comments pertain to the [redacted] specification.

   a. The specification for the [redacted] test procedure should be tightened to reflect data; e.g., the range for the [redacted] could be [redacted]

   b. The specification sheet should be modified to reflect the change.

7. Include the test procedure on [redacted] index [redacted] and all updates on specification and test procedures in the revised specification sheet.

8. The pump delivery (weight of formulation/dose) test procedure should be retained on the specification sheet.

9. For the microbial limits test, the absence of specific pathogens should also include salmonella. The specification sheet and test procedure should be revised.

10. Based on the submitted viscosity data, the shelf life viscosity specification should be [redacted] The release specification may be adjusted accordingly.

11. The following comments pertain to the specification and test procedure for impurities.

a. The sum of the indicated impurities is less than the total impurities in the stability data. If any peaks at fixed [redacted] are consistently observed, these should be listed with the [redacted] indicated.

b. Specification for impurities: total [redacted] of budesonide should be tightened to reflect the data. Limits for other individual impurities should be [redacted]

c. Clarify the source of the observed peaks before [redacted] Impurities, known and unknown, related to the drug substance should be monitored and thus impurities should start at a lower [redacted] than [redacted]

12. The following comments pertain to the budesonide and potassium sorbate test procedures.

a. Clarify how many samples covering 100 runs exceed a tailing factor of [redacted] for potassium sorbate.

b. USP recommends a tailing factor of [redacted] The tailing factor should be set accordingly.

13. The following comments pertain to the [redacted] test and specification for acceptance of the pump as well as for release and stability of the drug product.

a. For the [redacted] specification, it is stated that if one fails out of 10 samples, test 20 more. State the degree of failure which will allow for the testing of the 20 samples.

b. Individual raw data to support the [redacted] should be submitted.

c. The distance between the orifice of the pump and the surface of deposition is more discriminating using a distance between [redacted] rather than [redacted] Specification could be proposed to also include that appearance should be [redacted]

14. The proposed Standard Operating Procedures for Astra USA and Astra Draco for tracking specification and numbered methods, with their respective changes, as used by the [redacted] Laboratories should be submitted.

15. The letter dated January 14, 1993, by [redacted] vol 2, p. 6, states that stainless steel spring wire grade [redacted] complies with CFR 177.2470 which is for [redacted] Please clarify what role [redacted] plays in the stainless steel.

16. The following comments pertain to the acceptance testing of the pump unit.

    a. Under the Appearance testing, it is not acceptable to allow an AQL [redacted] for functional defects; i.e., missing part, cracks, etc.

    b. Include in the test procedure a statement as to the test sample used for the function test of spray pattern for pump acceptance, submission dated September 16, 1997, p. 107.

    c. Specification and test procedures for extractables in different solvents and chemical testing for the acceptance of the components of the pump units should be proposed to ensure the quality and reproducibility of the pump units. For chemical testing the attributes indicated in the USP are acceptable.

17. As requested previously in item 7.e. of the March 12, 1997 letter, a properly designed study with data on priming and repriming after different periods of specified rest, at different storage orientations, should be submitted. The issue of number of actuations to prime and reprime, number of lapse days permitted before the full initial priming actuations must be addressed.

18. The following comments pertain to the stability data.

    a. Comments on the expiration dating period will be deferred pending resolution of updated stability data on [redacted] and microscopic evaluation.

b. Please submit updated stability data.

19. Submit a revised post-approval stability protocol which includes the following, using the format as in Pulmicort Turbuhaler, NDA 20-441.

a. Commit to perform stability testing on the first three production commercial batches and on a specific number of marketed batch(es) (to be proposed) per year thereafter. The first three production batches should have both upright and inverted positions. Future batches beyond the first three commercial production batches may be exempt from multiple storage positions if the data justify a single position.

b. The specification for edetate disodium should be finalized in the protocol. The protocol should also include the [redacted] and microscopy test procedures.

c. Commitments should apply to all sizes/strengths.

20. The following comments pertain to the PVC coating of the glass bottle.

a. Information on the composition, quality of material, thickness of the coating, and assurance/controls (specification and test procedures) that the inside of the bottle would not be exposed to the coating material should be provided. The information submitted on June 16, 1997, vol 2, p. 171 is inadequate.

b. Do the components of the green opaque bonded PVC coating material meet CFR requirements for food packaging? Appropriate references, if any, should be provided.

21. Provide, in tabular form, the available individual raw data in µg of budesonide for delivery per dose or actuation, and [redacted] to show proportionality between the 32 and the 64 µg sizes. Batch number, time period of testing relative to manufacturing date, clinical vs. stability batch should be indicated.

22. In view of your intended change in facilities for post-approval testing, provide, in tabular form, which tests are performed in which facilities for release and stability. Any change in sites will require a post-approval supplement unless clearly defined in the NDA.

23. The holder of DMF [redacted] has been informed of comments.

24. The following preliminary comments pertain to general labeling.

    a. The name should be "Rhinocort Aqua (budesonide) Nasal Spray, 32 mcg or 64 mcg" for all labeling.

    b. The cap and relevant parts should be identified by their color.

    c. The warning statement "Do not spray in eyes" should be included in the HOW SUPPLIED section, Patients' Instruction for Use, and in the package label. Warning statements not to freeze the product and that the product should be kept away from light should also be included.

    d. The priming information should be included and supported by data. (See comment 17. above for details). The priming information should be included in the DESCRIPTION, DOSAGE AND ADMINISTRATION sections of the package insert, Patient's Instruction for Use, and in the package label.

    e. Contradictory storage temperature ranges are stated in the package insert vs. cartons and should be corrected.

    f. The statement "Shake well before use" should be in bold letters in the HOW SUPPLIED section, Patient's Instruction for Use, immediate container label and the carton label.

25. The immediate container label should be redesigned to include at a minimum the following information.

a. The size and prominence of budesonide in the name should be increased relative to "Rhinocort."

b. A statement to read the attached Patient's Instructions for Use should be included.

c. 8.4 mL should be listed as "Net contents: 8.4 mL" and separate from "120 sprays."

d. A statement on storage conditions should be included.

e. The statements "For intranasal use only" and "shake well before use" should be included.

26. The carton label should include the recommended dose information in addition to the information stated above in comment 24.

27. The Patient's Instruction for Use should include the following information.

a. The instructions for spray pump preparation should have a section title so as to provide clear instructions.

b. A statement to discard the product after 120 sprays should be included.

c. A storage statement should be included.

28. The immediate container and carton label for the physician sample should be submitted.

29. Additional comments on the physician's package insert and Patient's Instructions for Use are indicated in the attached marked-up labels.

Please be aware that the labeling comments we are providing are preliminary, and additional comments may follow. Please submit a copy of your revised label on diskette, in addition to a hard copy.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ATTACHMENT

APPEARS THIS WAY
ON ORIGINAL

31 **Page(s) Redacted**

Draft

Labeling

Memorandum of Telephone Facsimile Correspondence

Date: July 2, 1997

To: Dennis Bucceri
FAX # 508-836-8390

From: Gretchen Trout
CSO, Division of Pulmonary Drug Products

Through: Dale Conner
Team Leader, Clinical Pharmacology and Biopharmaceutics

Subject: NDA 20-746 Rhinocort Aqua

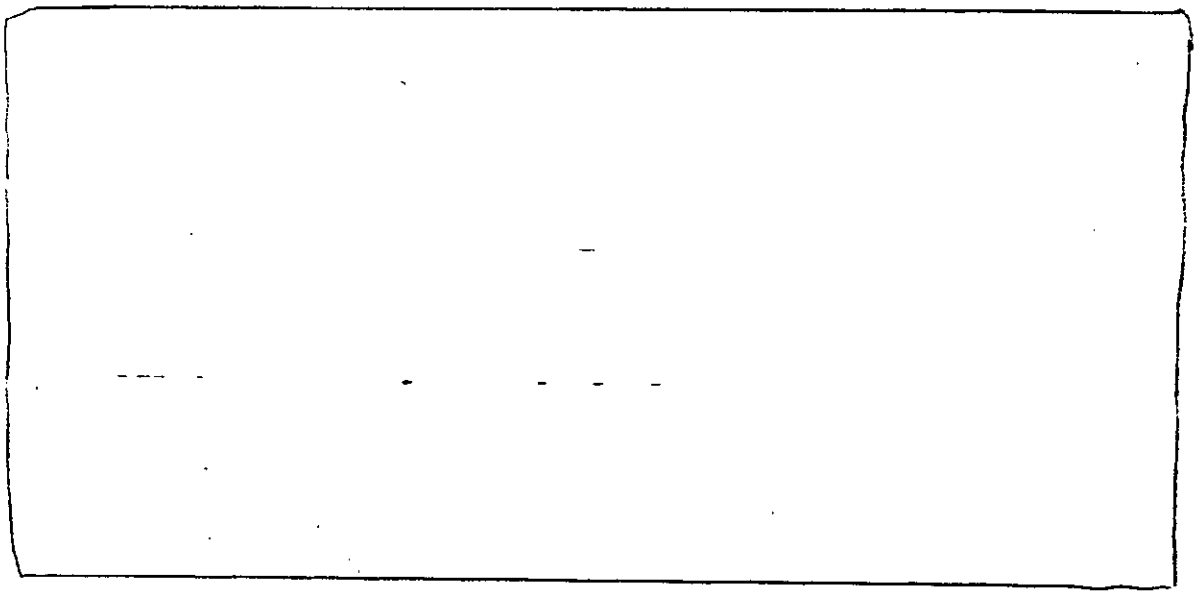
We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

APPEARS THIS WAY
ON ORIGINAL

We have completed our review of the Clinical Pharmacology and Biopharmaceutics section of this application, and we have the following comments.

The analytical methods used for the pharmacokinetic studies submitted under this NDA are less than satisfactory. The analytical methods had been submitted and reviewed previously under NDAs 20-233 and 20-441. Review of those applications also determined that the analytical methods used for the pharmacokinetic studies were less than satisfactory and the deficiencies were sent to you. No improvement on the analytical methods have been made. Therefore, it is important to again summarize the deficiencies below for future improvement.



If you have any questions with regard to these comments, please contact Ms. Gretchen Trout, at (301) 827-1058.

APPEARS THIS WAY
ON ORIGINAL

Memorandum of Telephone Facsimile Correspondence

Date: March 18, 1997

To: Dennis Bucceri
FAX # 508-836-8390

From: Gretchen Trout
CSO, Division of Pulmonary Drug Products

Subject: Rhinocort Aqua, NDA 20-746

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

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

Thank you.

APPEARS THIS WAY
ON ORIGINAL

Reference is made to your New Drug Application (NDA) dated July 29, 1996 for Rhinocort Aqua (budesonide) Nasal Spray. The submission was reviewed for microbiology aspects of the drug product, and we have the following comment and request for additional information.

Non-sterile topical drugs should be free from pathogenic indicator organisms such as those listed in USP <61>. Microbial limits test method [redacted] only provides for the enumeration of total aerobic bacteria and molds/yeasts in the drug product. Please provide the method used to determine the presence/absence of pathogenic indicator organisms in the drug product.

Trou

MAR 12 1997

NDA 20-746

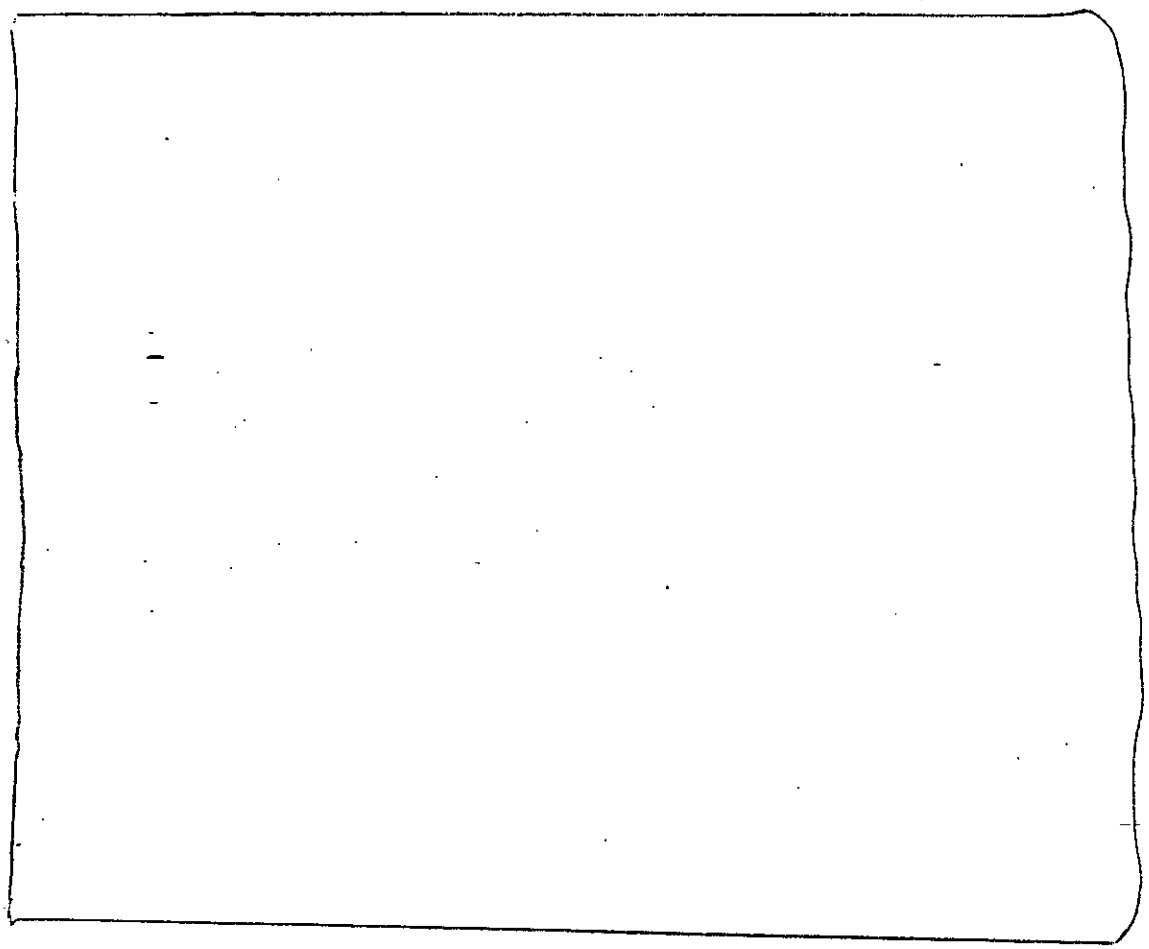
Astra USA, Inc.
P.O. Box 4500
Westborough, MA 01581-4500

Attention: Dennis Bucceri
Vice President, Regulatory Affairs

Dear Mr. Bucceri:

Please refer to your pending July 29, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhinocort (budesonide) Aqua Nasal Spray.

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



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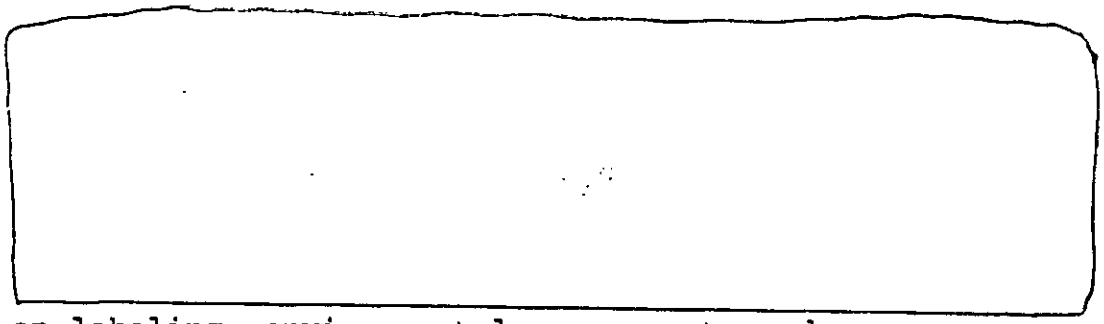
confidential

commercial

information



Comments on labeling, environmental assessment, and microbiology will be forwarded when available.

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

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

Sincerely yours,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Memorandum of Telephone Facsimile Correspondence

Date: March 6, 1997

To: Dennis Bucceri
FAX # 508-836-8390

From: Gretchen Trout
CSO, Division of Pulmonary Drug Products

Subject: Labeling Guidance

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

Thank you.

Dennis - the attached document was prepared by the Office of Clinical Pharmacology and Biopharmaceutics to provide guidance to sponsors with regard to the design of the *Pharmacokinetics* section of package inserts. We are providing it to you as a FYI.

APPEARS THIS WAY
ON ORIGINAL

DIVISION INTERNAL GUIDELINE FOR THE PREPARATION OF THE PHARMACOKINETIC SECTION OF THE LABELING

Currently, the FDA is attempting to standardize the content and presentation of the information that is to be given in the ***Pharmacokinetics*** portion of the ***Clinical Pharmacology*** section of the package insert. The ***Pharmacokinetics*** portion should present information as appropriate under the subheadings of ***Absorption, Distribution, Metabolism, and Excretion***. Following this, there should be a section with the heading of ***Special Populations***, where pharmacokinetic information under the subheadings of ***Geriatric, Pediatric, Gender, Race, Renal Insufficiency, Hepatic Insufficiency, and Drug-Drug Interactions*** should be included. Where relevant information is lacking it should be so stated.

Lastly, a table(s) with mean (±SD) pharmacokinetic parameters determined under single and steady state conditions should be prepared. This table(s) should include bioavailability, peak concentration, time to peak, clearance, volume of distribution, half-life, and renal clearance for healthy subjects, and each special population including the drug's intended target population. Also, if appropriate a plot that illustrates drug plasma/serum concentration vs. time (i.e., different dosage strengths. comparison to a reference product, etc.) may be included.

Memorandum of Telephone Facsimile Correspondence

Date: January 24, 1997

To: Dennis Bucceri
FAX # 508-836-8390

From: Gretchen Trout
CSO, Division of Pulmonary Drug Products

Subject: NDA 20-746 Rhinocort Aqua

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

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Thank you.

APPEARS THIS WAY
ON ORIGINAL

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. and sizes, pump delivery (µg/spray), 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 in the pivotal PK studies should represent [redacted] 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 ?

cc: Orig. NDA 20-746
Div. File
HFD-870/Chen
HFD-870/Conner
HFD-570/Trout
HFD-570/Anthracite

CORRESPONDENCE

INDUSTRY TELECONFERENCE MINUTES

AstraZenecaZeneca
NDA 20-746
Rhinocort Aqua (budesonide) Nasal Spray
September 30, 1999

FDA REPRESENTATIVES

Ray Anthracite, Medical Reviewer
Bob Meyer, Division Director
Gretchen Trout, Project Manager

SPONSOR REPRESENTATIVES

Elliott Berger, VP – Regulatory Affairs
Frank Casty, Global Medical Leader
Eric Couture, Regulatory Liaison Director
Donna Dea, Respiratory Therapeutic Area Regulatory Leader
Robert Monaghan, Regulatory Project Manager
Carolyn Russello-Callahan, Regulatory Labeling Manager

BACKGROUND: The Division requested this teleconference to discuss including pediatric data in the labeling for Rhinocort Aqua.

The Division pointed out that although the growth study conducted by AstraZeneca (05-3046) was not ideal, it was active controlled and reasonably well-designed, and showed a growth effect. However, 3046 studied a dose in excess of that which the FDA has determined is approvable (256 mcg/day studied, vs. 128 mcg/day highest recommended dose). The Division and AstraZeneca discussed either including the data from this study in the label, or having AstraZeneca commit to conducting another long-term pediatric study and including the results of that study in the label. AstraZeneca pointed out that they have already submitted a protocol for [redacted] which they intend to start in [redacted] AstraZeneca agreed to send a commitment in writing that they will conduct this study and will revise the labeling according to the results of the study. The commitment will include a specific timeframe for submitting the final study report. The Division agreed to this commitment, and therefore will not include the results of study 05-3046 in the label at this time.

The Division also pointed out an error in the package insert in the DOSAGE AND ADMINISTRATION section, where a reference to 64 mcg was omitted. AstraZeneca agreed to fix this error.

/S/
Gretchen Trout, Project Manager

Trout

SEP 26 1999

INDUSTRY TELECONFERENCE MINUTES

AstraZeneca
NDA 20-746
Rhinocort Aqua (budesonide) Nasal Spray
August 25 & 26, 1999

FDA REPRESENTATIVES

Jean Nashed, Chemistry Reviewer
Gretchen Trout, Project Manager

SPONSOR REPRESENTATIVES

Michael Elia, Director Regulatory Affairs
Cheryl Larrivee-Elkins, Director of Pharmaceutical Technology
Pontus Lilliehorn, Pharmaceutical and Analytical R&D
Robert Monaghan, Regulatory Project Manager
Per Niklasson, Manager Regulatory Affairs
Ann Smith, Manager Product Operations
Ziggy Waraszkiewicz, Director of Analytical Development

BACKGROUND: The Division requested this teleconference to obtain clarification on several points from Astra's submissions dated July 20 and August 13, 1999 (see attachment which was sent to Astra via facsimile identifying specific topics).

1. The Division emphasized that "regulatory specifications" refers to the compilation of tests along with the method and acceptance criteria. We would also like the testing site, but this can be presented in a separate tabular format. Astra should submit specification numbers and identify which specifications was superseded by the current specifications. Astra must submit all method numbers, method numbers should not change everytime the specification number is changed (it makes it impossible to track). All changes to methods and specifications should be clearly identifiable and traceable.

   Conclusion: The Division and Astra agreed that Astra would submit a table in the form of attachment 2 from the July 20, 1999, submission and add the sentence "these are specifications effective XX (date), and supersede specifications of XX (date)." This will be acceptable for drug substance and drug product release and stability specifications for approval of the NDA, if Astra wants to change it in the future it will require a supplement.

   In addition, Astra needs a stability testing protocol for the drug substance. If Astra wants to skip testing of certain points, they still need to attach the drug substance specification and state that this test is only performed on release. Astra's proposed [redacted] month expiry, [redacted] months test period is acceptable. Astra needs to clarify that manufacturing is by [redacted]

2. The Division accepts Astra's tightening of the acceptance criteria for [redacted] For total specified and total impurities, even taking into account [redacted] the acceptance criteria needs to be tightened further. The Division understands that Astra has limited data with [redacted] but the specification they are proposing is in excess of what is supported the current data.

   Conclusion: Astra will discuss with their chemists, and will consider tightening the specification for total specified and total impurities to [redacted] at release for both strengths, [redacted] for 64 mcg and [redacted] for 32 mcg during shelf-life. The Division agreed that this would be reasonable.

   For [redacted] Astra's proposed specification is too high. Astra stated that they need data from additional batches in order to tighten the specification.

   Conclusion: Astra will submit a Phase 4 commitment to look at the first 20 batches of drug product and tighten the specifications based on the data (post approval).

   For [redacted] from the pump, Astra's proposed specifications are too loose. The Division informed Astra that we are dealing with the supplier [redacted] separately because their response deals with more than just this one pump.

   Conclusion: Astra will look at their data and try to tighten the specifications, in addition their committed to working with [redacted] Astra will submit final acceptance criteria for the pump.

3. The Division requested that Astra resubmit all of their Phase 4 commitments (including the pharm/tox commitment) in one submission.

4. Modification of analytical method for measurement of color in drug product.

   Astra stated that initial studies indicate that preparing a sample of filtrate is difficult and they have not been successful. The Division replied that they should submit a protocol outlining what they have tried and what the results were, and include a commitment to work on it further.

   Conclusion: Astra will provide a Phase 4 commitment to study color measurement on the first 20 batches and will fsubmit final method and specifications within 9 months post-approval.

5. With regard to the environmental assessment, the Division informed Astra that what they submitted was acceptable prior to the change in the regulations, however we could not locate a submission where they provided data on all budesonide containing products combined. Astra explained that they submitted it previously, but they will resubmit it.

In addition, the Division requested the methods validation package for all methods.

FOLLOW-UP TELECONFERENCE

August 26, 1999

FDA REPRESENTATIVES

Jean Nashed
Gretchen Trout

ASTRA REPRESENTATIVES

Michael Elia
Cheryl Larrivee-Elkins
Robert Monaghan
Ann Smith

BACKGROUND: Astra requested this teleconference to clarify several of the Division's requests from August 25, 1999.

Astra explained that they have separate specifications for budesonide and micronized budesonide, each with its own expiry and re-test period. Astra wanted to discuss the Division's request for one specification for micronized budesonide. The Division explained that time 0 is the date the drug substance is manufactured. Astra replied that when the drug substance is micronized it changes the surface criteria and the date of micronization should be day 0. This is what they would test at release, 12 and 24 months. The Division stated that it is confusing to have two expiry dating periods for one drug substance. Normally we propose one set of specifications with all test parameters, then they can indicate that some parameters are performed at release only and some are performed after micronization only.

The Division questioned what is the average time from manufacture of the drug substance to micronization. Astra replied that they will have to ask their colleagues. With regard to length of time from micronization to being used in the drug product, Astra stated it is within the [redacted] year shelf-life. The Division suggested that a [redacted] year shelf-life after micronization is too long and should be tightened. Astra questioned if this was regardless to the stability data which show the micronized substance is stable for [redacted] years. The Division replied that the stability data Astra provided proves that they followed certain parameters, but they still need one set of specifications.

The Division questioned if Astra always tests the drug substance before using in the drug product. Astra replied that they do not, the drug substance is released as acceptable micronized material and stored as per the current protocol. They only retest it if it reaches the testing period. Anything left after [redacted] months is discarded. The Division stated if they always test it before use this is probably acceptable, otherwise the testing period should be shortened, normally we see 3-6 months retest period for micronized drug substances.

Conclusion: Astra needs to submit one set of specifications, however they can indicate that they test for different parameters at different times (e.g., before and after micronization). Astra will clarify how they trace batches of drug substance from [redacted] through micronization, and they will consider shortening the retest and overall expiry period.

/S/
Gretchen Trout, Project Manager

APPEARS THIS WAY
ON ORIGINAL

NDA 20-746 Rhinocort Aqua (budesonide) Nasal Spray

CMC topics for teleconference with Astra on Aug 25, 1999.

(These do not include all CMC comments, review is still pending)

1. Format of regulatory specifications – individual method numbers (drug substance and drug product, release and stability)

   RE: 1c and a, 2f

APPEARS THIS WAY
ON ORIGINAL

2. Tightening of acceptance criteria.

   RE: 2a (total specified and total), 1b, 3a

APPEARS THIS WAY
ON ORIGINAL

3. Final detailed re-write of all commitments with submission date always specified.
   RE: 2b-e, 3a, 3b (i, ii), 6 + pharm /tox

APPEARS THIS WAY
ON ORIGINAL

4. Submission of EA statement (or reference to previously submitted) with short summary data supporting the claim for categorical exclusion. Estimate should include total budesonide used in all drug products (approved and pending) based on anticipated full production rate.

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 20-746
Div. File
HFD-570/Poochikian
HFD-570/Nashed
HFD-570/Trout

Rd accepted by: Nashed/9-14-99

MINUTES

TRCOT

RECORD OF TELEPHONE CONVERSATION

NDA 20-746 **DATE:** 07/26/99
APPLICANT: AstraZeneca
DRUG: Rhinocort Aqua (budesonide)
INITIATED BY: ___APPLICANT __X__FDA

NAMES AND TITLES OF PERSONS WITH WHOM CONVERSATION WAS HELD:

FDA:	Keary L. Dunn,	Regulatory Project Manager
	Dr. Jean Nashed,	CMC Reviewer
	Dr. Guirag Poochikian,	CMC Team Leader
	Dr. Robert Meyer,	Acting Division Director
AstraZeneca	Elliott Berger	VP, Regulatory Affairs
	Eric Couture	Director, Regulatory Affairs
	Michael Elia	Director, Regulatory Affairs
	Karen Shepherd	Supply Chain Manager
	Carolyn Russello-Callahan	Regulatory Labeling Manager
	Robert Monaghan	Regulatory Project Manager

BACKGROUND

This Telecon was initiated in reference to the labeling submitted on July 20, 1999, which was the response to the approvable letter dated June 22, 1999.

TELECON

Outstanding issues regarding the carton and container labels and the immediate container labels were discussed initially.

- The container label for the 64 mcg/8.4 mL product does not have the enlarged "64 mcg", as it should.
- As discussed previously (see meeting minutes July 13, 1999, Carton and Container comment #2), the division suggests that the entire name Rhinocort Aqua (budesonide) Nasal Spray be printed in a uniform color and presentation.
- The color differentiation between strengths (32 mcg and 64 mcg) should be more pronounced as discussed previously (minutes July 13, 1999, #4). In addition, the green (32 mcg) and the blue (64 mcg) bars that appear under the name on of the immediate container label should be moved to the top of the label.
- "Nasal Spray" needs to be more prominent.

- AstraZeneca indicated that they would put forth a good faith effort to incorporate the changes that were requested.

AstraZeneca asked if, following approval, the product could be launched using the immediate container labeling submitted in the December 23, 1998, submission and the new carton labels as agreed upon above, i.e., separate color for each strength (mock-up labels to be submitted by August 2, 1999). The sponsor committed to launching only the 32 mcg product with the label as discussed and having the new container labels within 3 months of approval (the 64 mcg product will never be marketed with the unapproved label).

The division indicated that the sponsor could be assured that this approach will be acceptable following final approval of the NDA.

/S/

Keary Dunn
Regulatory Project Manager

cc:
Orig. NDA
HFD-570/Division File
HFD-570/Dunn/
Hfd-570/Trout/7-30-99
HFD-570/Nashed/7-30-99
HFD-570/Meyer/7-30-99
HFD-570/Poochikian/8-2-99