

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-784

APPROVABLE LETTER(S)



DEPARTMENT OF HEALTH & HUMAN
SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-784

Aventis Pharmaceuticals
200 Crossing Boulevard
P.O. Box 6890
Bridgewater, NJ 08807-0890

Attention: Dr. Eric Floyd
Senior Director, US Regulatory Affairs

Dear Dr. Floyd:

Please refer to your new drug application (NDA) dated December 16, 1996, received December 17, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nasacort (triamcinolone acetonide) HFA Nasal Inhaler.

We acknowledge receipt of your submissions dated March 21, and May 5, 2003. Your submission of March 21, 2003, constituted a complete response to our May 31, 2002, action letter.

We also acknowledge receipt of your submissions dated August 7, and September 2, 2003. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this 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 address the following:

1. The following comments pertain to the triamcinolone acetonide (TAA) drug substance.
 - a. DMF — was reviewed and was found to be inadequate for support of your application. Comments have been forwarded to the holder.
 - b. Provide confirmation that the annual testing frequency for drug substance impurities will include the _____ and the total of these is limited to *less than (<)* . —
 - c.



2. The following comments pertain to the drug product.
 - a. The current revised acceptance criteria for the Unit Spray Content are not adequate and are reflective of the unacceptable variability of this important product performance parameter. Take measures to improve the product performance for this parameter and revise the acceptance criteria to reflect those proposed in your November 30, 2001, amendment and agreed upon with the Agency.
 - b. Because _____ are structural alert groups for mutagenicity, revise the drug product release and stability impurities acceptance criteria (4:v002:p0139 and 143) to limit the *total* of the _____ to "less than _____ or _____ qualify the impurity / _____) by conducting genotoxicity testing. In order to qualify the impurity, test the _____ in the microbial mutation assay and either a mammalian chromosomal aberration assay or the mouse lymphoma tk assay. Also revise the specifications listed in the stability protocol (4:v004:p032).
 - c. Clarify the meaning of the phrase " _____ top of 4:v005:p275) for the method for determination of foreign particulates in the drug product (Method _____, i.e., _____). Revise the method for clarity on this point.
 - d. Provide the identity and toxicological assessment information associated with the foreign particulate findings for Can 2 of batch 02AC0528 (4:v002:p036). Furthermore, the inclusion of the two outlying foreign particulate size profiles for the above batch and batch 02AC0531 in the determination and justification of the acceptance criteria is not appropriate. Make the necessary revisions to the acceptance criteria.
 - e. Provide tightened acceptance criteria for the incoming drug product components (i.e., drug substance, excipients, valve, canister, etc.) as well as tightened in-process controls applied during the drug product manufacture to effect a general decrease in the overall drug product

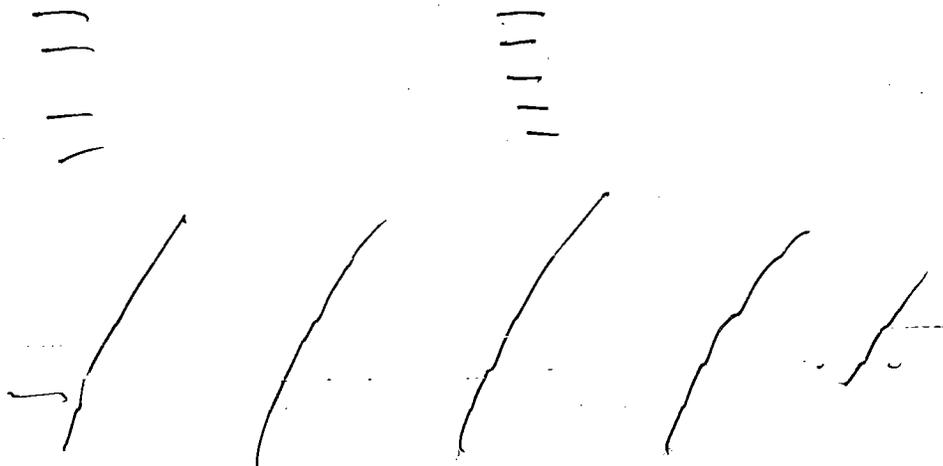
variability, particularly in terms of the particle size distribution as currently measured both by the _____ cascade impactor and _____ equipment.

f. The following comments pertain to the particle size distribution and associated controls for the drug product.

(i) Tighten the acceptance criteria for the particle size distribution as determined by the _____ cascade impaction methodology. As indicated at the February 10, 2003, telephone conference, the current drug product particle size distribution acceptance criteria proposed are not acceptable and would allow a high level of product variability. The Agency recognizes that the tightening of the _____ CI acceptance criteria may result in a higher batch rejection rate but must apply current Agency standards consistently to aerosol products. Reference is also made to the comment 1.c above.

(ii) Tighten the acceptance criteria for the control of the particle size distribution by the _____ methodology. Basing your release specifications on the _____ is not appropriate

Consideration has been given to the fact that figure 11 (4:v002:p054) appears to demonstrate reasonable consistency of the API particle size _____ used for manufacture of the new Holmes Chapel Stability batches manufactured under the conditions proposed for commercial manufacture (refer to comment 1.c above). And although no _____ PSD data are available from the time of release for these three stability batches from Holmes Chapel, data after storage under long term conditions of 25°C/60%RH for only _____ is suspected to be reasonably representative. Based on the standard deviations observed from the new Holmes Chapel stability data (both with and without overwrap) the following release acceptance criteria are appropriate:



(iii) Provide assurance that the _____ for the Method _____ will be fixed (4:v005:p291).

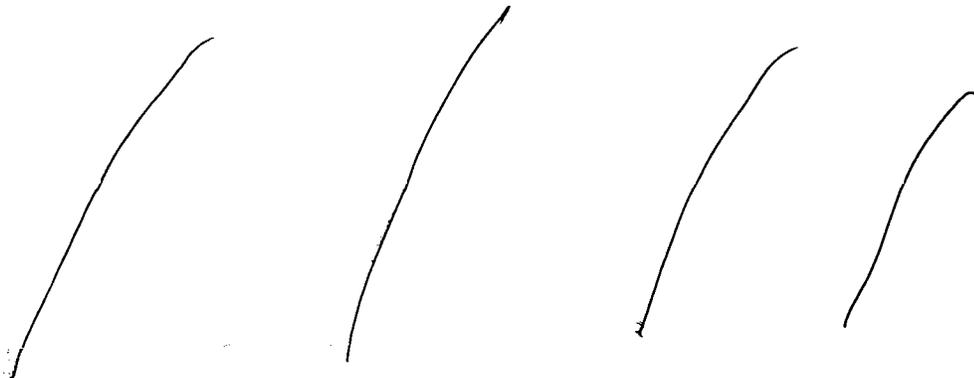
(iv) Provide a date by which the method and the associated validation data for the new aerodynamic particle size distribution methodology for the drug product will be submitted

to the Agency.

- g. Provide the results of the investigation of the _____ extractable level of _____ from the _____
- h. Further comments on the appropriate expiration dating period for the product may be forthcoming once Aventis and the Agency agree upon the appropriate specifications for the drug product (e.g., aerodynamic particle size distribution, dose delivery uniformity) and the available associated stability data can be analyzed by our biometrics team in association with these acceptance criteria.
- i. Revise the stability protocol (4:v004:p026-038) to:
- (i) Include a commitment to submit cumulative stability results for the first three commercial batches prepared at Holmes Chapel, UK and stability data for the _____ of batches placed on stability annually in the annual reports for the application.
 - (ii) Revise the specifications for Unit Spray Content, Particle Size Distribution, and Impurities accordingly.
- j. Provide _____ leachable data for samples of batches PM/066/02, PM/067/02, and PM/073/02, after storage at 25°C/60%RH for comparison to data collected for the NDA stability batches graphically presented in figure 16 (4:v002:p071). The data collected after storage at 25°C/60%RH presented in figure 16, when compared to those in table 20, do not support your assumption that storage of product "for _____ at 40°C/75%RH is considered to be representative of storage for _____ at 25°C/60%RH." Furthermore, initial levels of _____ in the new batches at timepoint zero already exceed the highest levels observed in the stability studies on earlier NDA stability batches stored at 25°C/60%RH. Therefore, acceptance criteria based on this assumption is not appropriate and room temperature data will be needed for evaluation of any revision to the current limit of _____ canister. The limits for _____ as an extractable from the _____ (total of _____) also support a much lower limit than the proposed _____ assuming that the extraction conditions were reasonably representative of the extracting potential of the formulation over shelf life and the extractables acceptance criterion for the _____ are reflective of the data.
- k. The following comments pertain to the foil laminate overwrap.
- (i) _____
 - (ii) Provide _____ data for the incoming foil laminate such that your acceptance criteria for these parameters (4:v003:p364) can be evaluated. In addition provide the corresponding acceptance criteria that are applied for _____ testing of the overwrapped drug product.

1. Once drug product specifications are finalized, submit four copies of the methods validation package for the drug substance and drug product methods that each include the following: 1) tabular list of samples with lot number, identity, package size and type, date of manufacture and quantity indicated; 2) descriptions of the drug substance and drug product analytical procedures with sufficient detail to allow FDA analysts to perform them; 3) validation data supporting the individual analytical procedures including raw data and data from stress studies where necessary; 4) analytical results for the submitted samples, if feasible, using the methods included in the validation package with associated dates when determinations were made; 5) the components and composition of the drug product; 6) specifications for the drug substance and drug product; 7) material safety data sheets (MSDSs) for all samples, standards, and reagents.

m. The following preliminary comments pertain to the labels and labeling submitted.



3. Provide data demonstrating that the following three potential _____ leachables are not present in the formulation of the product during shelf life: _____
_____. If so, set the acceptance criteria at the validated limit of detection levels. If any of these leachables are present, provide appropriate qualification and corresponding acceptance criteria. For _____ additional qualification data are not needed if it is shown that the concentration of this potential leachable would not exceed _____/canister during product shelf life.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

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.

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, call Colette Jackson, Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

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

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this page is the manifestation of the electronic signature.**

/s/

Badrul Chowdhury
9/23/03 05:13:02 PM

5.

[Redacted]

6.

[Redacted]

7. Remove the ' [Redacted] for the Content Uniformity USP test for canister assay (method [Redacted] Limits of [Redacted] of target are not supported by data.

8. The current control of foreign particles by the [Redacted] method [Redacted] is not satisfactory. Revise the method accordingly or establish new methodology to control of foreign particles less than [Redacted] in size, those greater than [Redacted], and those greater than [Redacted]. Controls should be applied at both the time of release and during the testing of stability samples of the drug product.

9. The current proposed acceptance criteria for the aerodynamic particle size distribution, as determined by [Redacted] cascade impaction, are not adequate and are reflective of the unacceptable variability of this important product performance parameter, e.g., [Redacted]

- a. Take corrective measures, where appropriate, to the [Redacted] [Redacted] to decrease this variability. Once the variability in this parameter is lessened, tighten the associated acceptance criteria for cascade impactor testing of the product to reflect the improvements and to ensure intra-can, intra- and inter-batch consistency.
- b. Provide an explanation of the phenomenon behind the large difference in the emitted dose that is obtained from the drug product when tested by the cascade impactor test methodology as opposed to the Unit Spray Content (USC) test methodology. Data for your development batches indicate that upon cascade impactor testing the emitted dosing is [Redacted] than that expected by the target [Redacted] from USC data.

- c. Future control of aerodynamic particle size distribution for this and related products should adopt cascade impaction methodology

Please investigate other options.

10. Provide data, or provide a reference to data already submitted, on the extracted levels of _____ (method SOP _____ that support the proposed acceptance criterion of _____
11. Further comments on the appropriate expiration dating period for the product are withheld until the drug product specifications, with respect to the aerodynamic particle size distribution, are updated, submitted and can be statistically analyzed versus the available associated stability data with 95% confidence limits.
12. Regarding the previous comments 18.a and 18.b of the February 4, 2000, Agency letter, additional comments may be forthcoming that are pertinent to the expiration dating period and a statistical analysis of the stability data for all parameters, pending review of data submitted in response to this letter.
13. Revise the stability protocol to increase the number of annual batches placed on stability per year relative to the _____ proposed in the response on p. 4-1-56 of the November 30, 2001, amendment, e.g., _____ of the product batches produced per annum.
14. Revise the stability protocol to include testing for all leachables of the drug product, not just for the levels of _____
15. Revise the stability protocol with regard to the withdrawal of batches of product failing specification to the following:
16. Once drug product specifications are finalized, submit four copies of the methods validation package for the drug substance and drug product methods that each include the following: 1) tabular list of samples with lot number, identity, package size and type, date of manufacture and quantity indicated; 2) descriptions of the drug substance and drug product analytical procedures with sufficient detail to allow FDA analysts to perform them; 3) validation data supporting the individual analytical procedures including raw data and data from stress studies where necessary; 4) analytical results for the submitted samples using the methods included in the validation package with associated dates when determinations were made; 5) the components and composition of the drug product; 6) specifications for the drug substance and drug product; 7) material safety data sheets (MSDSs) for all samples, standards, and reagents.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

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.

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, call Ms. Colette Jackson, Project Manager, at 301-827-5580.

Sincerely,

{See appended electronic signature page}

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

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/s/

Robert Meyer

5/31/02 12:00:28 PM



NDA 20-784

Aventis Pharmaceuticals
C/O Quintiles, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708

Attention: Wayne Vallee
Director, Regulatory and Technical Services

Dear Mr. Vallee:

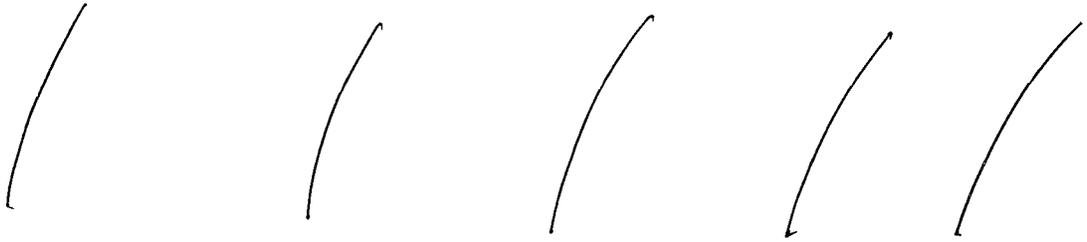
Please refer to your new drug application (NDA) dated December 16, 1996, received December 17, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NASACORT (triamcinolone acetonide) HFA Nasal Aerosol.

We acknowledge receipt of your submissions dated November 30, 2001, February 28, and April 30, 2002. Your submission of November 30, 2001, constituted a complete response to our December 16, 1997, action letter.

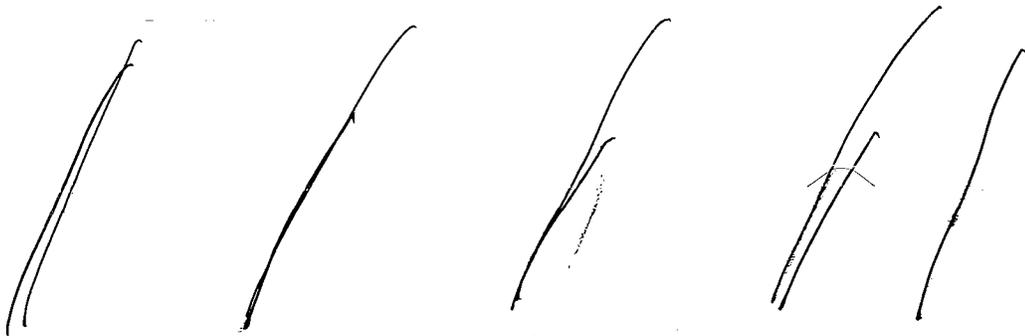
We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Tighten the acceptance criteria of _____ (currently proposed as NMT _____) to reflect the data as provided in your _____, e.g., to less than _____.
2. A deficiency letter was forwarded to _____ regarding the _____ Refer to your response in the November 30, 2001, amendment to comment 2.b of the Agency's February 4, 2001, approvable letter.
3. Provide a detailed description of the _____ including the parameters controlled and the allowable validated ranges for these _____.
4. Because the _____ is a structural alert, revise the acceptance criterion for the level of _____ in the drug substance and drug product to "less than _____ or qualify the impurity by conducting genotoxicity testing. In order to qualify the impurity, test the _____ in the microbial mutation assay and either a mammalian chromosomal aberration assay or the mouse lymphoma tk assay.

5.



6.



7. Remove the _____ or the Content Uniformity USP test for canister assay (method _____). Limits of _____ of target are not supported by data.

8. The current control of foreign particles by the _____ method _____ is not satisfactory. Revise the method accordingly or establish new methodology to control of foreign particles less than _____ in size, those greater than _____, and those greater than _____. Controls should be applied at both the time of release and during the testing of stability samples of the drug product.

9. The current proposed acceptance criteria for the aerodynamic particle size distribution, as determined by _____ cascade impaction, are not adequate and are reflective of the unacceptable variability of this important product performance parameter, e.g., _____

- a. Take corrective measures, where appropriate, to the _____
_____ to decrease this variability. Once the variability in this parameter is lessened, tighten the associated acceptance criteria for cascade impactor testing of the product to reflect the improvements and to ensure intra-can, intra- and inter-batch consistency.
- b. Provide an explanation of the phenomenon behind the large difference in the emitted dose that is obtained from the drug product when tested by the cascade impactor test methodology as opposed to the Unit Spray Content (USC) test methodology. Data for your development batches indicate that upon cascade impactor testing the emitted dosing is _____ than that expected by the target _____; from USC data.

- c. Future control of aerodynamic particle size distribution for this and related products should adopt cascade impaction methodology that _____

Please investigate other options.

10. Provide data, or provide a reference to data already submitted, on the extracted levels of _____, (method SOP _____) that support the proposed acceptance criterion of _____
11. Further comments on the appropriate expiration dating period for the product are withheld until the drug product specifications, with respect to the aerodynamic particle size distribution, are updated, submitted and can be statistically analyzed versus the available associated stability data with 95% confidence limits.
12. Regarding the previous comments 18.a and 18.b of the February 4, 2000, Agency letter, additional comments may be forthcoming that are pertinent to the expiration dating period and a statistical analysis of the stability data for all parameters, pending review of data submitted in response to this letter.
13. Revise the stability protocol to increase the number of annual batches placed on stability per year relative to the _____ proposed in the response on p. 4-1-56 of the November 30, 2001, amendment, e.g., _____ of the product batches produced per annum.
14. Revise the stability protocol to include testing for all leachables of the drug product, not just for the levels of _____
15. Revise the stability protocol with regard to the withdrawal of batches of product failing specification to the following: _____

16. Once drug product specifications are finalized, submit four copies of the methods validation package for the drug substance and drug product methods that each include the following: 1) tabular list of samples with lot number, identity, package size and type, date of manufacture and quantity indicated; 2) descriptions of the drug substance and drug product analytical procedures with sufficient detail to allow FDA analysts to perform them; 3) validation data supporting the individual analytical procedures including raw data and data from stress studies where necessary; 4) analytical results for the submitted samples using the methods included in the validation package with associated dates when determinations were made; 5) the components and composition of the drug product; 6) specifications for the drug substance and drug product; 7) material safety data sheets (MSDSs) for all samples, standards, and reagents.

When your respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

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.

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, call Ms. Colette Jackson, Project Manager, at 301-827-5580.

Sincerely,

{See appended electronic signature page}

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

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this page is the manifestation of the electronic signature.**

/s/

Robert Meyer
5/31/02 12:00:28 PM



NDA 20-784

Food and Drug Administration
Rockville MD 20857

FEB 4 2000

Aventis Pharmaceuticals Products, Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Attention: Judith R. Plon
Director, Regulatory Affairs

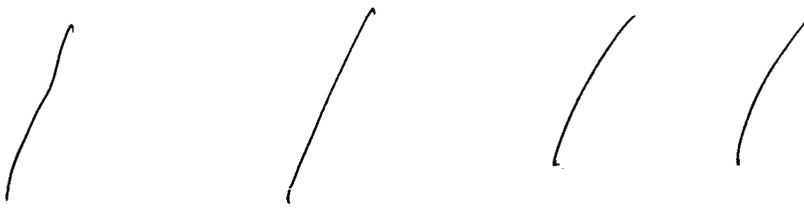
Dear Ms. Plon:

Please refer to your new drug application (NDA) dated December 16, 1996, received December 17, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nasacort HFA (triamcinolone acetonide) Nasal —

We acknowledge receipt of your submissions dated July 30, and December 9 and 20, 1999. Your submission of July 30, 1999, constituted a complete response to our December 17, 1997, 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 address the following comments. Note, numbers in the parentheses following the comments refer to previous comments as contained in the December 17, 1997, action letter.

1. Upon resolution of the pending issues pertaining to the acceptance criteria provided for all incoming materials, including drug substance, dehydrated alcohol, and the container closure system (valve, actuator and aluminum canister), submit updated specifications. (Comment 1)
2. The following comments pertain to the drug substance, triamcinolone acetonide (TAA).
 - a. Specify the frequency of testing for the attributes of incoming drug substance and periodic retest date validating the supplier's test results as a footnote in the drug substance specification document. (Comment 1)

b. 

3. The following comments pertain to dehydrated alcohol. (Comment 39)

a. Tighten the specification proposed for _____ (NMT _____) to reflect the data as provided in _____

b. Adopt the USP compendial specification for the UV absorption specification, as provided for dehydrated alcohol, USP.

4.

5.

6. The proposed specification, _____ for the drug content uniformity assay ($n = ______$ is not acceptable. Modify the manufacturing process and institute adequate in-process controls to ensure _____ of the target for drug content uniformity assay per canister (i.e., _____). Revise the drug product specification and associated test method to reflect the above changes and resubmit an updated drug product specification. (Comment 7)

7. Specify the limits for *Net fill weight* or *Net content* for the drug product as agreed on the specification documents, _____ . Also, clearly indicate the target fill weight of the drug product per canister. Rectify this discrepancy and resubmit the revised drug product specifications. (Comment 11)

8. The individual shot weight for the drug product should not be different from the valve performance acceptance criterion (_____), that is NMT _____ of the target. Revise the _____ proposed for individual shot weight acceptance criteria. Additionally, explain the basis for the target shot weight being mg/spray as opposed to the theoretical shot weight being _____ ug/spray. (Comment 13)

9. The proposed *unit spray content* (USC) specifications for _____ are not adequate. You may propose a reasonable number of true outliers (that fail

_____ with definitive upper and lower limits for individual testing at each stage, and justify with appropriate data. Additionally, the means of each of the beginning and end determinations for each canister at each stage should remain within _____ of the label claim. (Comment 15)

10. The following comments pertain to particle size distribution (PSD) of the drug product.

a. The data are inconclusive to support the equivalence between two types of valves (old vs. modified). Either provide additional data to support the equivalence or withdraw one of the valves. Additionally, establish an upper mass limit in the PSD test for particles greater than _____ (Comment 32)

b. Provide a summary of the attempts that have been made to lessen the variability observed with PSD (as requested earlier - comment 32.e., letter dated December 17, 1997). Revise the proposed acceptance criteria to ensure intra-can, intra- and inter-batch consistency with regard to particle size distribution.

11. The individual PSD data provided from the lots using one _____ actuator _____ differs from that of the other _____, showing significant variability in the

_____ The submitted data are inconclusive to support the equivalence between two _____ actuators. Either provide data to definitively support the equivalence of the actuators, or withdraw one actuator from the NDA. Establish an upper mass limit in the PSD for particles greater than _____ and tighten the overall acceptance criteria proposed for PSD to reflect the data. (Comment 17)

12. Tighten _____ acceptance criteria to better reflect the data and _____

13. Institute _____, or alternatively, shorten the repriming interval (e.g., to 3 days without use the product should be reprimed, rather than the currently proposed _____ (Comment 28)

14. The results of USC stability data, based on an ANOVA, _____ are not sufficient. _____

15. The following comments pertain to extractables and leachables.

- a. Establish acceptance criteria for _____ as extractable(s) in their _____ in the NDA in order to assure consistent quality of _____. Alternatively, this information could be provided by the supplier of the _____.
- b. The acceptance criteria provided for _____ in attachment 14 (v8.3, p 3-43, p 3-48) and in the _____ amendment (04/16/99) differ from the specification provided for _____ (1-21) in comment 24. Rectify this discrepancy and resubmit corrected documents.
- c. Tighten the specifications proposed for _____ as leachables in the drug product to reflect the data.
- d. Identify in the specifications the _____ used _____.

16. Confirm the supplier(s) and ingredients of the _____ since the information provided in this regard in attachment 12 in the current submission differ from the information provided in the previous submission (Attachment 19, amendment dated August 13, 1997). Provide quantitative composition of the _____ (e.g., in terms of weight/weight or weight/volume for a production scale batch). (Comment 16)

17. The following comments pertain to the container-closure of the drug product.

a. The following comments pertain to _____ actuators:

(1)

.....
/ / / /

b.

/ / /

c.

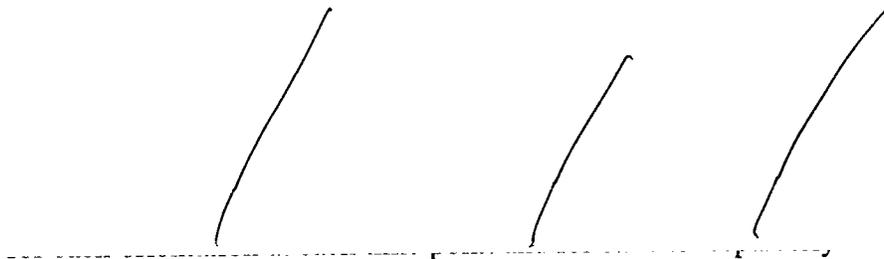
/ / /

d. Note that DMFs _____ have been found inadequate to support your application. The holders of these DMFs have been recently notified of several comments for their respective products. You are encouraged to work with each one of them to resolve the pending issues with their respective products. As appropriate, revise the necessary documents in the NDA to reflect any changes that may occur in each DMF in response to the agency's comments. (Comment 24)

18. Revise the proposed expiration dating period of _____, taking into account the following comments. (Comment 29)

a. The regression analysis of TAA assay for lot 15-34A-1 shows that it will fail to meet the assay specification (—), beyond (—)

b.



c. Submit updated stability data for all three lots of the drug product using the new valve.

d. Further comments on the appropriate expiration period, (—) are withheld until the drug product specifications are finalized, particularly those of a quantitative nature [TAA content uniformity, USC, and PSD], and until the updated stability data of individual dose can be statistically analyzed for all quantitative parameters with 95% confidence limits. (Comment 29)

19. The following comments pertain to the stability protocol as provided in attachment 20 (p 4-83) of the current submission. (Comment 38)

a. Revise the stability protocol to include additional time points for testing of (—) between the initial time point and the expiry dating period in order to assure that level of (—) does not exceed the approved specification. See comment 15 above.

b. Revise the stability protocol so that the number of batches placed on "routine room temperature study" better reflects the number of batches manufactured annually for each strength of the drug product. This comment is applicable to lots manufactured with both valves.

Due to the July 29, 1997, Federal Register Notice on environmental assessment, we recommend that you submit a request for a categorical exclusion in accordance with 21 CFR 25.31(b).

During recent inspections of your Manati, PR manufacturing facility, a number of deficiencies were noted and conveyed to you by the inspector. Satisfactory inspections for all sites will be required before this application may be approved.

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.

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, call Mrs. Sandy Barnes, Project Manager, at (301) 827-1075.

Sincerely,

A handwritten signature in black ink, appearing to read "Robert J. Meyer, M.D.", written over a faint, illegible typed name.

Robert J. Meyer, M.D.

Director

Division of Pulmonary and Allergy Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Food and Drug Administration
Rockville MD 20857

NDA 20-784

DEC 17 1997

- Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
P.O. Box 1200
Collegetown, PA 19426-0107

Attention: Judith R. Plon
Director, Regulatory Affairs

Dear Ms. Plon:

Please refer to your new drug application dated December 16, 1996, received December 17, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nasacort HFA (triamcinolone acetonide) Nasal

We acknowledge receipt of your submissions dated February 28, March 4, 14, and 21, April 4 and 7, May 1 and 22, August 13, September 5, October 1 and 24, and November 21, 1997. The user fee goal date for this application is December 17, 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 information requested below. Please note that the numbers in parentheses following the comments provided below refer to the comments of the May 19, 1997, information request letter.

1. For all materials used as part of the drug product (e.g., drug substance, excipients, valve, canister, actuator, etc.), all acceptance test methods and specifications, and pertinent data, should be part of the application. For container-closure components in particular, the specifications and test methods should be included for physicochemical and dimensional properties, extractables, and pertinent performance characteristics. For any of the materials used as part of the drug product that are accepted from a supplier based on a certificate of analysis, the analysis of several initial incoming batches of these materials should be performed by you

with methods that are part of the application and the resulting data provided to the application. If comparability of results is determined, future validation of the supplier's results may be proposed for appropriate predefined intervals. The above mentioned information for all materials used as part of the drug product should be included in a single amendment to the application. Also refer to comments 2., 16., 17., 19. - 27., 41. - 43. below.

2. The incoming drug substance should be tested by _____ at appropriate predefined intervals in order to validate the supplier's assessment of the _____ triamcinolone acetonide. (comment 1.c.)

3.

4. Provide a copy of the Master Production Record (master batch record) amended to include _____

If possible, please flag the amended sections in the record to expedite our review. (comments 3.d.(3). and 4.a.)

5.

Additionally, it is important that the record contain specific and detailed directions in terms of the method of identification and quarantine of potentially defective units (e.g., since last acceptable test results). Submit the amended master batch record (not necessarily completed) and flag the revisions if possible. (comment 3.f.)

6. The _____ procedure _____ which is used for testing of the stability samples, should include

_____ / _____ / _____ / _____ /
The revised method should be included in the amendment. (comment 5.f.)

7. Your proposed specifications for drug content assay of individual canisters are not acceptable. Each individual unit (not composite of three) should be controlled to within _____ of the target for canister assay. Make the appropriate revisions to the drug product material specifications and test methods. (comment 5.h.)

8. The regression analyses of the three-canister composite TAA assay results provided (attachment 29, pp. 2-211 and 212 of the August 13, 1997, amendment) indicate an apparent increase with time on stability and high variability of the canister TAA content. Provide an explanation for these observations and outline the corrective action(s) that have been/will be taken. (comment 5.h.)

9. / / / /

10. In order to evaluate the specifications for minimum and maximum diameters for the spray pattern, it is necessary that you provide the data upon which these were based. (comment 5.s.)

11. The drug product material specifications _____ should include limits for fill weight or net content. _____
12. The stability data indicate that _____ Therefore, a specification for _____ in the drug product should be proposed that will control this parameter to levels that are reflective of those observed for the pivotal clinical and stability batches. (comment 5.u.)
13. Since shot weight is normally not dependent on the formulation, as opposed to the unit spray content (USC), we recommend that specifications for individual and mean valve delivery (shot weights as described in methods _____ be proposed which will complement USC testing and specifications and provide additional quality control for the product. (comments 5.v. and 7.g.)
14. The following comments relate to the _____ particle sizing methods for the drug product on stability _____
- a. Specifications for the drug substance particle size in the formulation should be instituted that control the number of particles above and below the _____ cut-off. These specifications should be reflective of data from the relevant batches of drug product. In addition, the specifications should include a qualitative description of the typical TAA morphology.
 - b. Specifications should be included which limit the number of foreign particles (non-TAA morphology) that are observed in typical samples.
 - c. For the above, provide supporting data to aid in the evaluation of the proposed specifications. (comment 5.w.)

15. The current proposed unit spray content (USC) specifications do not provide adequate control of the dose content uniformity and are not reflective of the stability data. These specifications should be modified accordingly. (comment 5.z.)
16. The complete *chemical* composition (qualitative and quantitative) of the _____ should be provided or referenced. The information can be provided directly from the supplier to the Agency if desired. _____
17. In order to justify the use of multiple suppliers with _____ for the components of the actuators, provide comparative data for actuators prepared by each manufacturer _____ to demonstrate close equivalence, i.e., dimensional properties (e.g. orifice dimensions), extractives profiles, and performance characteristics (unit spray content, spray pattern/plume geometry, aerodynamic PSD by e.g., cascade impaction, by mass on each stage, accessory, etc.). (comment 6.c.(4).)
18. The change protocol, as provided on p. 2 - 5 of attachment 22 (August 13, 1997, response), is not appropriate for critical components of the container-closure system. Changes in the critical components of the drug product container-closure system (which are defined as those device components that contact either the patient or the formulation, components that impact the mechanics of the overall performance of the device, any necessary secondary packaging, any changes in _____ or supplier, manufacturer or manufacturing, etc.) should be reported in a prior approval supplement and be accompanied with the appropriate supporting data. In the absence of data to support the ability of the above mentioned protocol to determine the equivalency in terms of the container-closure system for the many potential change combinations that could take place, the protocol should be withdrawn from the application. (comment 6.e.)

23. The following comments pertain to leachables in the drug product.

- a. Compounds leaching into the drug product formulation during shelf life are typically controlled with appropriate tests (on stability batches) and drug product materials specifications. The preliminary extractables/leachables data indicate that it may be possible to utilize the proposed extractables protocols, test and specifications for the various container-closure components as a surrogate for control of leachables for some of the compounds leaching into the formulation. However, due to the pending results from the studies outlined in the amendment dated October 24, 1997, we may have additional comments.
- b. It is stated on p. 14 of the October 24, 1997, amendment that the _____ leachables data are consistent with extractables data. However, the extractive testing of the _____ did not result in detection of any _____ by the method whereas some of this _____ was detected, albeit not quantified (_____ , as a leachable in some of the _____ samples of drug product. The solvents and conditions used for the extraction of the incoming _____ should be sufficiently aggressive to, at a minimum, mimic the levels found in leachables studies. (comment 6.o.(1).)

24. We acknowledge that extractables profile protocols and test methods are still under development for some of the incoming container-closure components for demonstration of potential indirect control leachables in the formulation of aged product. Please be aware that in terms of the extractables profiling of incoming components, the extractables protocols (e.g.,

_____, test methods, and limits on extractives should become part of the acceptance specifications for each component and these should be submitted in the subsequent amendment to the

application (refer to comment 1. above). If extractables testing is performed by the supplier(s) of a component, the supplier(s) should have release specifications for the extractables profile and provide the results on the corresponding certificate of analysis (COA). The results on the COA should be validated and the results submitted in the subsequent amendment. Once the reliability of the supplier(s) COA has been established, the testing frequency for these incoming container-closure components may be reduced to a predefined schedule. It would expedite the review if the results of the extractables profiling were provided in a tabular format for each appropriate container-closure component along with the limits that become part of the acceptance specifications. In addition, the complete profile of leachables found in the aged samples should be provided in tabular form for ease of comparison with the corresponding extractables data. Please note a safety evaluation for the complete extractables/leachables profile for the drug product should be provided for review by pharmacology/toxicology.

25. It was not clear from the preliminary results presented (p. 23 of the October 24, 1997, amendment) that extractables and leachables originating from the _____ were being studied as for the _____ Extractables profiling for determination of maximum amount of extractables for this component, routine acceptance extractable profile testing, and examination for leachables from this component should be performed with as much rigor as used for the _____ (comment 6.o.(1).)
26. In order to provide control over the physicochemical parameters for the actuator bodies and inserts as tested using the USP <661> tests, corresponding specifications should be proposed that are reflective of the data. (comment 6.p.)
27. In addition to the current acceptance specifications for critical dimensions for each lot of incoming actuator components from each supplier, there should be acceptance specifications and testing in terms of the extractives profile (not just nonvolatile residue by weight as per USP <661>). Once the reliability of the suppliers is established based on data from multiple batches, reduced testing may be considered. Testing and specifications

should be implemented to control key performance parameters such as spray pattern for the incoming actuators. Please also refer to the comment resulting from review of the response to 6.c.(4). above. (comment 6.p.)

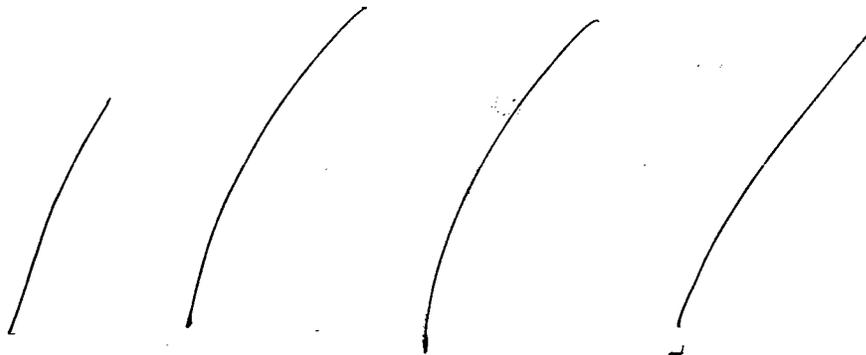
28. From the USC data presented thus far for the primary stability batches, there appear to be differences in the amount of USC variability

_____ Please address the observations outlined in comment 7.h. of our May 19, 1997, letter. Additionally, the _____ period allowed before repriming is not supported by data for containers stored in the upright position. As you have indicated in the original submission, :



29. Comments on the proposed expiration period of _____ will be withheld until the drug product specifications, particularly those of a quantitative nature, have been finalized and the updated stability data can be statistically analyzed for all quantitative parameters with 95% confidence limits. Please note that our review may be expedited if this analysis is provided. Please also refer to comments related to our earlier comments 5.s, 5.u, 5.v, and 7.g, as well as 5.w. (May 19, 1997, letter). (comment 7.a.)

- 30.



31. For the drug product, any impurity occurring at \geq _____ will need to be specified. Therefore, your specification for "Other Individual Impurities" for the drug product for both release and stability should limit these to less than ($<$) _____ Make the appropriate changes to your specifications. (comment 7.d.)

32. The following comments pertain to the particle size profile testing and specifications for the drug product.
- a. As stated in comment 7.1. of our May 19, 1997, letter, the specifications for particle size distribution should also be given in terms of the mass amount of drug substance found on each accessory and the various stages of the cascade impactor. The specification should clearly indicate the units (mcg per 10 actuations).
 - b. Specifications for the amount of drug substance found on stages 2, 3, and 4 should have lower limits in addition to the upper limits proposed.
 - c. Both upper and lower limit specifications should be proposed for the amount of drug substance obtained on stage 1 + IP, since this comprises a substantial amount of the delivered drug substance.
 - d. A specification range should be proposed for the amount of drug substance (by weight) that is < _____ μ m in size, i.e., that found on stages 5, 6, and the filter.
 - e. Although the average particle size profiles for the primary stability batches _____ appear to be similar, the underlying intra-batch variability evident from the data appears to be quite high. For example, for all stability data collected for the _____ primary stability batches stored under the _____ inverted position at 25°C/60%RH, the average quantity of TAA found on _____ with a standard deviation of _____. Variability of this large magnitude is apparent throughout the particle size profiles. Provide a summary of the attempts that have been made to lessen this variation and what further action will be taken in this regard. Currently, the proposed specifications need significant revision in order to ensure intra- and inter-batch consistency of the particle size profile. (comment 7.1.)

33. The following comments pertain to the ethanol content in the drug product.

a. The 25°C/60%RH stability data presented in the August 13, 1997, amendment indicate ethanol concentrations ranging from about _____ w/w% for time-points of up to _____. Provide adequate data to justify the proposed specification range of _____ w/w % which would give assurance that the performance characteristics (USC, particle size distribution) of the drug product will not be adversely impacted with ethanol concentrations at the extremes of the proposed specification range. Alternately, the specification should be tightened to more closely reflect the data.

b.

/// | | |

34. As previously suggested in comment 7.o. of our May 19, 1997, letter, in order to control spray pattern variability for future batches of drug product to that observed for the current batches, the _____ specification should be tightened, _____ . (comment 7.o.)

35. The data for _____ for the _____ primary stability batches of product indicate that the _____ There should be _____ specifications at both release and stability that are reflective of the data.

/// | | |

36. We acknowledge your response in the August 13, 1997, amendment to comment 7.r. of our May 19, 1997, letter. Please outline the exact differences (e.g., materials, dimensions, etc.) between the _____ valve and the _____ valve and explain why the shot weight is higher for the latter. (comment 7.r.)

37. (

38.

39. We remind you of your commitment to develop a test method to monitor the _____ in the Dehydrated Alcohol, USP used in this drug product. Once the method is developed, you should set specifications based on data from a number of lots of this excipient. The method, data, and specifications should be submitted with the amendment. (comment 2.a.)

40. We remind you to propose specifications for _____ for the excipient Dehydrated Alcohol, USP by December 1997. Please submit the data supporting the proposed specifications with the amendment. (comment 2.b.)

41. We remind you of your commitment to confirm, at appropriate intervals, the supplier's results for all parameters on the certificate of analysis for incoming HFA-134a propellant. Your amendment should identify the testing site and supply the method. Data demonstrating the ability of the alternate site to obtain comparable results should also be provided. (comment 2.d.)

42. The following comments pertain to Drug Master Files (DMFs) referenced in your application.

a. Please be aware that DMF _____ remains inadequate to support your application. (comment 6.a.)

b. It is noted that DMF _____ remains inadequate to support this application and comments have been forwarded to the holder. Comments have also been forwarded to the holder of a supportive DMF referenced in DMF _____ (comment 6.a and 6.b.)

- c. As per your response to comment 6.c.(1), reference was made to the _____ submission of March 27, 1997, in DMF _____ authorized by their letter of the same date, for information on the _____ We wish to inform you that the _____ DMF is deficient with regard to our comment. (comment 6.c.(1).)
- d. In terms of information on _____ requested in comment 6.c.(3) of the May, 19, 1997, letter, please be aware that DMF _____ has been found to be deficient in support of your application. (comment 6.c.(3).)
- e. Please be aware that DMF _____ does not adequately support your application and we are awaiting the response of the holder to our March 7, 1997, letter. (comment 6.a. and 6.h.)
43. We have the following preliminary comments regarding the labeling.



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

Due to the July 29, 1997, Federal Register Notice on environmental assessment, we recommend that you submit a request for a categorical exclusion in accordance with 21 CFR 25.31(b).

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with current good manufacturing practices (CGMP) is required before this application may be approved. We have been notified by our compliance branch that the facility at 500 Arcola Road, Collegetown, PA 19426 is not performing extractable and leachable testing for the component and container/closures.

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.

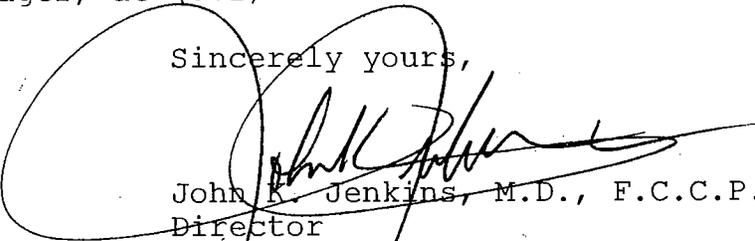
Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

Any amendments 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.

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. Sandy Barnes, Project Manager, at (301) 827-1075.

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