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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-911

Approvable Letter (S)

NDA 20-911

MAY 11 2000

3M Pharmaceuticals
Building 270-3A-08, 3M Center
St. Paul, MN 55144-1000

Attention: David M. Markoe, Jr.
Senior Regulatory Specialist

Dear Mr. Markoe:

Please refer to your May 11, 1998, new drug application for QVAR (beclomethasone dipropionate HFA) Inhalation Aerosol.

We also refer to your submissions dated February 28, and April 10, 14, and 20, 2000.

We are reviewing the Chemistry, Manufacturing and Controls section of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

Comments are cross-referenced in parentheses to our letter of February 18, 2000.

1. As previously indicated, tighten your specification for [redacted] in the drug substance to be the same as that of your supplier, or alternatively, qualify the impurity. (Comment 4.)
2. Tighten the specification limits for [redacted] to conform with the drug substance supplier's proposed limits in DMF [redacted]
3. Additional comments pertaining to impurities and degradation products may be forthcoming, pending a pharmacological/toxicological review.
4. Provide the validation information and data which provide the basis for [redacted] conditions to be employed as part of the manufacturing operations [redacted]. This should include information such as the [redacted] attained, and their usual variability from canister to canister. (Comment 8.)
5. You are reminded of your commitment to develop a method that might have better ability to distinguish between suitable and unsuitable mouthpieces, in order

to meet the requirements for QC testing in addition to dimensional controls. An example of a method that may meet these requirements may be a spray pattern test on incoming mouthpieces, using — rather than the drug product for improved visualization. Provide a target date of July 31, 2000, for fulfillment of this commitment. (Comment 11.)

6. Provide an updated monograph for the — gasket to DMF [] which contains a statement in the specification sheet for the — gaskets describing the agreements with the respective fabricators to notify you in advance of any changes in manufacturing procedure, raw materials or specifications. You have indicated that this would appear in the updated amendment to DMF [] however it does not appear to be present in the April 10, 2000, amendment to that DMF. (Comment 15.a.)
7. The following comments pertain to our previous comment 16:
 - a. Clarify if the — placebo data provided in Tables 12, 13 and 14 (vol. 9.1, pp. 35-36 of the February 28, 2000, amendment) were obtained with the modified method involving light irradiation, or with the previously described method 3523. If these data were not obtained by use of Method 3523, provide the alternate method and its complete validation data.
 - b. The limit of quantitation (LOQ) for the placebo — assay is most recently described as "about — ng/can for — and — " (vol. 9.1 of the February 28, 2000, amendment, page 34). This is discrepant with the LOQ values provided in the validation of Method 3523 (vol. 7 of the August 17, 1999, amendment, page 99), which are listed as — and — ng/canister, respectively. Rectify and explain these discrepancies.
 - c. The — placebo data provided in Tables 12, 13 and 14 (vol. 1 of the February 28, 2000, amendment), are listed for each — as "below the limit of detection" (LOD). Clarify that the LOD's referred to are those described on page 99, vol. 7 of the August 17, 1999 amendment for Method 3523 — ng/canister).
 - d. Clarify whether recoveries of — leachables in the current placebo study are represented by the validation data on page 101, vol. 7 of the August 17, 1999, amendment for Method 3523.
8. Tighten the specification limit for the drug substance process impurity —

[redacted] in the drug product to agree with that proposed by [redacted] in their DMF [redacted] (Comment 18.c.)

9.

[redacted] description section of the package insert. This proposal is still under consideration and there may be additional comments in the future. Correct the following: [redacted]

Include in this statement information about [redacted]

In addition, provide the conditions under which the MMAD was measured [redacted]

[redacted] When this response is provided, it will be evaluated to determine the acceptability or the unacceptability of the indicated statement in the package insert. (Comment 26.d.)

10. Modify the immediate container labels in accordance with 21 CFR 201.10(g)(2), which requires that the established name have a prominence commensurate with the prominence of the proprietary name. (Comment 26.e.(1))
11. Correct the immediate container labels for the 80 mcg products (as provided in the April 10, 2000, and April 20, 2000, submissions). These labels state that each actuation delivers — mcg of the drug. (Comment 26.e.(1))
12. You are reminded of your agreement to add the product strength to the established name in the labeling. (Comment 26.f. (4))
13. Explain the purpose of wiping the mouthpiece/actuator with a tissue or cloth. Indicate whether any drug buildup with use has been observed in the orifice. Indicate whether running hot water from a tap has been evaluated as a means to clean the mouthpiece/actuator. (Comment 26.g.)
14. Provide at this time, copies of the certificates of analysis for the specific batches of drug samples and drug reference standards to be provided to FDA laboratories. Provide an additional copy of the methods validation package. (Comment 27.)
15. DMF [redacted] remains deficient; the DMF holder was notified of deficiencies on February 4, 2000, and a response has not yet been received. Their agent indicated on March 1, 2000, that they were working on a response and would respond shortly. (Comment 29.)
16. Any deficiencies pertaining to DMF [redacted] will be sent directly to the DMF holder

when our review is completed. (Comment 29.)

17. It is noted that in the Proventil HFA labeling, each actuation delivers 120 mcg of drug from the valve, and 108 mcg of drug from the mouthpiece, which represents a 12 mcg or 10% retention of the drug in the mouthpiece. QVAR Inhalation Aerosol, which has a very similar if not identical mouthpiece, delivers 100 mcg from the valve, and 80 mcg from the mouthpiece, which represents 20 mcg or 20% retention of the drug in the mouthpiece. Explain the different drug retention capabilities of the mouthpieces for QVAR Inhalation Aerosol and Proventil HFA Inhalation Aerosol.
18. The first page of each manufacturing order for the Loughborough facility indicates that if manufacturing time is longer than _____ it must be fully explained in the "Occurrences During Filling/Finishing" section. Clarify this statement. Such long manufacturing times are unacceptable. Revise and resubmit master batch records accordingly.

If you have any questions, call Mrs. Sandy Barnes, Project Manager, at (301) 827-1075.

Sincerely,

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Guirag Poochikian, Ph.D.
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DNDC II, Office of New Drug Chemistry
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FEB 18 2000

3M Pharmaceuticals
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St. Paul, MN 55144

Attention: David M. Markoe, Jr.
Regulatory Specialist

Dear Mr. Markoe:

Please refer to your new drug application (NDA) dated May 11, 1998, received May 12, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for QVAR (beclomethasone dipropionate) inhalation aerosol.

We acknowledge receipt of your submissions dated August 11, and 17, November 10, and December 2, 1999, and January 10, 2000. Your submission of August 17, 1999, constituted a complete response to our May 12, 1999, 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 comments.

1. The data submitted are not sufficient to support a statement between QVAR and CFC-beclomethasone, such as
Replace the sentences regarding the relative potency issue in the DOSAGE AND ADMINISTRATION section of the package insert with the following.

L

J

2. Submit a full, final study report, along with the primary data, for study 1366-BRON. This study is critical to a determination of the proportionality of the 40 and 80 mcg dosage strengths of QVAR. While it appears that a conclusion of proportionality of the two strength products is reasonable, based on the study summary for 1366-BRON and on the other data contained in your NDA, a final determination cannot be reached without a full review of study 1366-BRON.
3. Delete any specific reference to

While you have presented adequate data to support the recommended starting dose and the highest dose in patients previously on bronchodilators, and inhaled corticosteroids, there are insufficient data to

Deficiencies listed below are followed by a comment number in parentheses, which corresponds to the related comment in our letter dated May 12, 1999.

4. Tighten the acceptance criterion for _____ in the drug substance as indicated in our letter to the drug substance supplier's DMF _____ or, alternatively, qualify the impurity. (Comment 6a)
5. Address our previous comments, which are still pending, concerning specifications for drug substance impurities and residual solvents. These previous comments should not be applied to _____ which should be limited to less than 0.1%, or adequately qualified, as indicated in 18.b below. (Comments 6b(1)-(4), and 7b).
6. The minimum proposed fill weight shelf life specifications of _____ for _____ actuation products, respectively, are not acceptable unless it can be demonstrated that particle size distribution and dose uniformity are met for product containing these minimum amounts of formulation. Otherwise, increase and tighten the proposed labeled net contents weight and fill weight specifications.

This issue was previously raised in our letter of May 12, 1999(Comment 8a), and discussed at the meeting between FDA and 3M on August 26, 1999, and subsequently in a teleconference with 3M on September 17, 1999.

7. Specify in the batch records a maximum and a minimum lag time (equilibration period), as previously requested (comment 11g), in order to adequately cull out canisters that are grossly leaking. After this equilibration period, the drug product should be 100% tested for canister weight, and at this time the quality control release

tests for particle (droplet) size distribution and content uniformity should be performed to insure that the product has the same performance as when used by the patient.

8. Establish 100% validated — testing of the drug product during manufacture, as indicated in our letter dated May 12, 1999 (Comment 11h), and discussed in the meeting on August 26, 1999. Alternatives to — testing may be proposed. Incorporate the test in the master batch record.
9. Comment 13e in our letter dated May 12, 1999, which pertains to the drug product specification for medication delivery/through life, still applies. In addition, reference is made to our meeting on August 26, 1999, concerning this issue, and you are reminded of FDA's proposal of the following alternatives. Provide stability data for separate means.
 - a. You may propose a modified test procedure with separate means at beginning (n=5) and end (n=5) of the canister.
 - b. Alternatively, at first level testing for means at the beginning, middle and end, the number of canisters tested for each mean may be increased, to address your concern that separate means may reflect a tightening of the specification.
10. Limit the percent recovery in methods 3157 and 3158 for particle size distribution (PSD) to a percentage of label claim as previously requested, without additional adjustment based on valve delivery. Mass balance of the drug should be demonstrated to be within appropriate specifications as part of the system suitability test, before the analyses on the drug product samples are performed. (Comment 13f(2))
11. The following comments pertain to the spray pattern test for the drug product (method 2049). It is not clear that — is sufficient distance from the mouthpiece to the paper in this test to allow discrimination between suitable and unsuitable mouthpieces. Provide adequate data to demonstrate that the proposed test gives sufficient discrimination to detect unsuitable mouthpieces. Any "unsuitable mouthpieces" used in the comparison should not be obvious extremes, but rather should show more typical failures within the normal production batch. Indicate whether this test is adequate to control various different anticipated types of orifice defects. (Comment 13k(1))
12. Final comments on the appropriateness of the drug product acceptance criterion for spray pattern is deferred, pending satisfactory resolution of the test method issues (see comment 11 above). (Comment 13k(3))

13. Provide the complete chemical composition of the — gasket, including any and all additives used by the gasket fabricators, as requested previously. (Comment 14a)
14. We note that — notified you in October 1996, of an additional O-ring manufacturing plant in — Provide comparative acceptance test data for O-rings from both the old and new manufacturing sites. (Comment 14c)
15. The following comments pertain to the actuator:
 - a. Provide a copy of an agreement with each of your suppliers for the actuator/mouthpiece and the — gasket, to notify you in advance of any changes in manufacturing procedure, raw materials or specifications, since a DMF was not referenced for the mouthpiece/actuator and — gasket fabricators. Include a statement in the specification sheets for the mouthpiece/actuator and for the — gaskets describing the agreements with the respective fabricators. (Comment 14c)
 - b. The following comments pertain to demonstration of equivalence of the mouthpieces obtained from various suppliers. (Comment 14d(5))
 - (1) Provide comparative plume geometry data for actuators from all sources, as previously requested in our letter dated May 12, 1999.
 - (2) When the method for the spray pattern is improved, as discussed elsewhere in this letter, use it to provide updated comparative data for mouthpieces from all suppliers.
 - c. Clarify whether the actuator fabricators add any additional raw materials to the — in manufacturing the actuator, other than — in — carrier. If so, provide the complete composition of the actuator. (Comment 14d(6))
 - d. Clarify which actuators were manufactured with — (as mentioned in your original NDA, vol. 1.8, page 191), and provide information about its composition, and references to the indirect food additive regulations for its components. (Comment 14d(6))
 - e. The following comments pertain to actuator extractables.
 - (1) To better control actuator extractables, modify the specification to require that all significant recurring peaks must be present at minimum specified individual levels, and propose separate specifications for — actuator extractables for actuators manufactured using each — source. (Comment 14d(9)(c))

(2) Your response to comment 14d(9)(d) in our May 12, 1999, letter indicates that a proposal has been made to control significant new peaks with an individual _____ limit. Such a limit is not found in your specifications for the actuator (August 17, 1999, amendment, volume 2.6, pages 217 and 223). Modify and resubmit the specifications as indicated to include an appropriate limit _____) for _____ and the other changes indicated above

(3) Clarify the meaning of _____ in your specification. Express the limits relative to concentration of each extractable in the actuator (w/w), as well as by _____ values. Further comments on the new proposed specifications are withheld pending additional information. (Comment 14d(9)(d))

also
recovered
NDMA.

16. Comments on the proposed _____ extractable specifications are withheld at this time due to the following issues. Investigate the reasons that the placebo _____ data from aged placebo are higher than the sum of all _____ component _____ extractable data, including the O-ring. Provide reasonable assurance that the proposed _____ component _____ extractable specifications will limit _____ in the drug product to those levels that are observed in either drug product or placebo. Provide a commitment to identify new approaches to greatly reduce or eliminate _____ from your MDI drug products in the long term, and to implement these approaches in a timely manner. This comment is based on data provided in your amendment dated August 17, 1999, volume 2.2, page 157. (Comment 15d)

→ 17. The stability data have not been evaluated at this time for the proposed expiration dating period, pending final agreement on drug product specifications. See comments elsewhere in this letter. (Comments 17c, 17d(1), 17d(2) and 17d(3), and others)

18. The following comments pertain to specifications for drug related impurities in the drug product, based on your data. (Comment 17i(2) and others, as indicated)

- a. Reduce the 21BMP limit from _____ % maximum to _____ % maximum.
- b. Either qualify _____ in terms of mutagenicity potential or limit it to less than 0.1% in the drug product, as previously indicated in comment 13o in our letter dated May 12, 1999.
- c. When the limits for impurities in the drug substance are tightened, also tighten limits for the drug product for _____ (these are process impurities only), as previously requested for the drug substance (Comments 17i(2) and 17i(3)). Comment 6b(2) of our May 12, 1999, letter still applies, relative to

limitation and qualification of the — and — impurities in the drug substance. (See comment 5 of this letter.)

- d. Limit total impurities to an amount that better reflects the — data
 - e. The — stability data that you have provided appear to show the — (an impurity/degradant of some potential safety concern) is reduced significantly with storage in the upright orientation. Therefore, upright storage may allow reduction in the proposed specifications for the — impurity (as requested above). Alternatively, the — impurity may be qualified to support the proposed specifications. Upright storage was suggested previously in our letter dated May 12, 1999 (Comment 17i(4)), and in our meeting with you on August 26, 1999.
19. The following comments pertain to proposed specifications for particle size distribution using the cascade impactor, based on your data. (Comment 17m(2))
- a. Tighten mean specifications for the 40 mcg drug products (100 and 200 actuations) to be within — µg/actuation for the plate grouping 4-6.
 - b. Establish a lower limit for the plate 7 and — specification grouping for 40 mcg drug products (100 and 200 actuations), e.g., NLT — and — µg for individuals (outer and inner limits, respectively), and NLT — µg for the mean.
 - c. Tighten the lower specification limits for 80 mcg drug products (100 and 200 actuations) for the —, e.g., — mcg/actuation for the inner individual limit, — mcg/actuation for the outer individual limit (August 17, 1999, amendment, vol. 2.2, pg. 247), and — mcg/actuation for the mean.
 - d. Tighten mean specifications for 80 mcg drug products (100 and 200 actuations) to be within — µg/actuation for the plate grouping 4-6.
 - e. Establish a lower limit for 80 mcg drug products (100 and 200 actuations) for the plate 7 and — grouping, e.g., NLT — and — microns for individuals (outer and inner limits, respectively), and NLT — microns for the mean.
20. Modify the stability protocol and stability commitment to include fill weight as a test parameter at each stability test interval. (Comment 18c)
21. The data submitted do not support the proposed — repriming interval. Reduce the repriming interval based upon the data provided and modify labeling accordingly. (Comments 19a, 23d(3), and 23y(3)).

22. The proposed statement about adjustment of experimental equipment and conditions (e.g., in method 3131, August 17, 1999, amendment, volume 2.6, page 40) implies that laboratory SOPs may take precedence over conditions established by method validation; delete the phrase " _____ " and correct this in all methods in which this statement is used. Submit all pertinent revised documents. (Comment 5e)
23. Clarify the contradictory statements pertaining to the _____ which _____ (August 17, 1999, amendment, vol. 2.2, page 20, paragraph 1, sentences 3 and 4). (Comment 10e)
24. Reflect any change in the fill weight release specifications for drug product in the acceptable weight range for the QA samples. (Comments 11e(1)-(2))
25. Provide Table 99, mentioned in your response to comment 19g (August 17, 1999, amendment, vol. 2.2, page 289).
26. The following are preliminary comments on the labeling. Modify and submit the draft package insert and carton and container labels to reflect the comments and the revisions listed below. Further labeling comments will be provided once the deficiencies noted in this letter are adequately addressed.
- a. The language used in the second last sentence of the description section of the package insert pertaining to _____ should also be used in the dosage and administration section and in the patient's package insert, rather than using the term _____ " (Comment 23u(1))
- b. Modify the statement in the package insert that _____ as well as the related statement in the patient's instructions for use. Modify the statement as follows.
- _____ Move the statement from the
DOSAGE AND ADMINISTRATION to the HOW SUPPLIED section of the
package insert. (Comment 23x(5))
- c. Clarify why the package insert does not refer to the proposed 200-actuation canisters for both product strengths.
- d. Remove the statement in the description section of the package insert pertaining to the _____

e. The following comments, pertaining to immediate container labels, apply to proposed labels from both 3M Pharmaceuticals and Hoechst Marion Roussel (HMR), unless otherwise indicated.

- (1) Where space permits, by reorganizing information on the labels, indicate the amount of drug delivered per actuation through the mouthpiece.
- (2) The phrase "Inhalation Aerosol" should be part of the established name (HMR).
- (3) Modify the overprinted phrase "Professional Sample Not For Sale" as it makes it difficult to read the labeling underneath (3M sample).

f. The following comments, pertaining to carton labels, apply to proposed labels from both 3M Pharmaceuticals and Hoechst Marion Roussel (HMR), unless otherwise indicated.

- (1) Add the following statement to the labels: "For optimal results, the canister should be at room temperature when used."
- (2) An NDC code is recommended; it is noted that the sample cartons do not have an NDC code (HMR).
- (3) In the sample carton labels, the phrase "Inhalation Aerosol" should come after the phrase "beclomethasone dipropionate HFA 80 mcg" and should be at least the same in size and prominence as "beclomethasone dipropionate HFA 80 mcg." (HMR)
- (4) Include the strength of the drug product (40 mcg or 80 mcg) as part of the established name in both the immediate container labels and the carton labels, including the sample cartons. (3M)
- (5) Replace the fanciful — ' of "QVAR" in the places where it appears in the carton and immediate container labels with a more conventional — ' to reduce the chances of misidentification by the patient.

g. We note that the labeling instructions for Proventil HFA Inhalation Aerosol call for washing the mouthpiece/actuator weekly under warm running water. The labeling instructions for QVAR Inhalation Aerosol, however, only call for the mouthpiece to be cleaned weekly with a clean, dry tissue or cloth. Since the mouthpieces from both Proventil HFA and QVAR have essentially the same size orifices, the cleaning instructions in the labeling for QVAR should be made consistent with those for Proventil HFA, to insure that patients do not have problems with clogged orifices, or you should provide

adequate justification for not adopting the approved cleaning instructions for Proventil HFA.

27. Provide an updated methods validation package (3 copies), with modifications in specifications and methods made in accordance with our May 12, 1999, letter and in accordance with this current letter.
28. Since there are two proposed sources of actuators, in future reports, you should always indicate which actuator source was used with which batch of drug product.
29. DMFs [redacted] and [redacted] are deficient and the DMF holders have been notified of our deficiencies. (Comments 21 and 14d(6))

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

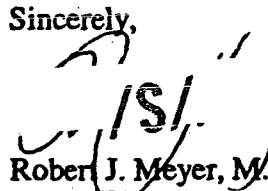
Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond 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 informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

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,


Robert J. Meyer, M.D.
Director

Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Archival NDA 20-911

HFD-570/Div. Files

HFD-570/S.Barnes

HFD-570/Reviewers and Team Leaders

HFD-002/ORM

HFD-102/ADRA

HFD-40/DDMAC (with labeling)

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: sb/February 15, 2000

Initialed by: P. Jani 2/16/00

A.Schroeder 2/17/00

G. Poochikian 2/17/00

R. Uppoor 2/17/00

R. Nicklas 2/18/00

B. Chowdhury 2/18/00

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APPROVABLE (AE)

MAY 12 1999

3M Pharmaceuticals
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Attention: David M. Markoe, Jr.
Regulatory Specialist

Dear Mr. Markoe:

Please refer to your new drug application (NDA) dated May 11, 1998, received May 12, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for QVAR (beclomethasone dipropionate) inhalation aerosol.

We acknowledge receipt of your submissions dated September 8, 10, 11 and 23 and October 23, 1998, and January 8, 13, March 22, and April 9, 1999.

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 comments.

1. The safety and effectiveness of QVAR have not been adequately demonstrated to be clinically comparable to a currently marketed chlorfluorocarbon-based (CFC) beclomethasone dipropionate metered dose inhaler (MDI). In particular, your claim that _____ is not supported by the available data. Therefore, delete all references to _____ the labeling and delete the proposed chart for _____ contained in the DOSAGE AND ADMINISTRATION section of the draft labeling.
2. The dose proportionality and the clinical comparability of the safety and effectiveness of the two proposed strengths of QVAR (i.e., 40 mcg ex-actuator and 80 mg ex-actuator) have not been adequately established by the available data. Since the 80 mcg ex-actuator strength of QVAR was only studied in one adequate and well controlled clinical trial (i.e., Study 1083) and only at a dose of 320 mcg/day, the safety and effectiveness of the 80 mcg ex-actuator strength of QVAR have not been established across the range of doses proposed in the draft labeling. Therefore, the 80 mcg ex-actuator strength of QVAR is not approvable. Delete all references to the

80 mcg ex-actuator strength from the labeling or submit new data that establish the safety and effectiveness of the 80 mcg ex-actuator strength of QVAR across the entire range of doses proposed in the draft labeling. Any additional pharmacokinetic studies would be expected to include a more specific assay than the one used in prior studies.

3. Since the clinical comparability of QVAR to an approved CFC-based beclomethasone dipropionate MDI has not been established and since QVAR has not been studied in adequate and well-controlled clinical trials to evaluate

for this indication are not appropriate. Delete all references to this indication from the DOSAGE AND ADMINISTRATION section of the draft labeling or submit new data that adequately support this indication.

4. Submit analyses of the safety data from study 1163 subsetted based on patient use during the first 8 weeks of either the 40 mcg/inhalation or the 80 mcg/inhalation strength of QVAR.

5. The following comments pertain to the method for purity of the drug substance, Method 3313.

- a. Add a resolution requirement to the system suitability tests for separation of [] and [] peaks, which are the closest peaks in the chromatogram.
- b. Use at least five replicate injections for the system precision test, and tighten the RSD limit.
- c. Add a test for tailing factor to the system suitability tests.
- d. Implement a quantitative system suitability specification to insure the sensitivity of the method to detect and quantify low level impurities.

- e. Delete the following sentence (v. 1.6, page 13): _____

_____ Whereas minor adjustments may be made to obtain acceptable operation, significant changes should not be made without prior approval as well as validation. This comment also applies for all other appropriate drug substance and drug product methods. Revise all pertinent documents and resubmit them.

- f. High variability for _____ was observed in the comparison of three different _____ systems and in precision data for the drug substance in Tables 15 and 16 (v.1.6, pp. 50, 52, 53). Determine whether there may be a problem with the analytical method for BDP, or if there may be a stability problem for BDP during analysis, in terms of variable _____ degradation product formation. Provide the results of your findings and make any appropriate corrections.

- g. Tighten limits for resolution factors (v. 1.6, pg. 44), based on the data provided.

6. The following comments pertain to the specifications for purity of the drug substance.

- a. Unknown impurities should be identified, qualified and individually limited when present at or above the level of _____ % relative to drug substance.

- b. The following comments are based on data provided in certificates of analysis.

(1) Tighten the specifications as follows: beclomethasone (_____ %), beclomethasone 21-monopropionate (NMT _____ %), beclomethasone 17-propionate, _____ (NMT _____ %), and _____ (NMT _____ %).

(2) Individually limit the levels of the _____ and _____ of beclomethasone dipropionate to less than or equal to _____ % in the drug substance, or adequately qualify the compounds.

(3) Tighten specifications for beclomethasone 17-propionate, and

beclomethasone 21 —

- (4) Tighten the specification for total impurities in the drug substance, based on more recent lots of drug substance.
 - (5) For additional information, contact the drug substance supplier.
7. The following comments pertain to method 3131, and proposed specifications, for residual solvents in drug substance.
 - a. Modify the method to warn the analyst not to set the initial temperature lower than —, since the data show that the method may not work properly below this temperature.
 - b. Tighten specifications for residual solvents, based on the data. Submit the modified test procedure and acceptance criteria.
8. The following comments pertain to the fill weight of the drug product.
 - a. Tighten specifications for fill weight, considering the tight in-process controls on fill weight and the relatively low leakage rates for this product. Increase the labeled fill weight appropriately.
 - b. Provide the density of the formulation at 25°C.
 - c. Provide the amount of "undeliverable fill" at the end of the canister life.
9. The following comments pertain to analytical methods and proposed specifications for acceptance of the excipient, HFA-134a.
 - a. It is noted that the methods for acceptance of propellant HFA-134a have been updated since the approval of Proventil HFA Inhalation Aerosol (NDA 20-503). Provide a list of updated changes made to each method since it was first approved.
 - b. It is noted that for certain impurities — and — each co-elutes with one or more other potential impurities in both methods 3105 and 3106. Indicate how these specific impurities are identified and quantitated.

- c. The proposed specification limit for impurity _____ is _____ ppm, yet the limit of quantitation for _____ in method 3105 is _____ ppm (vol. 1.8, pg. 74). Indicate how _____ is limited below the level of quantitation.
 - d. Develop and implement appropriate quantitative system suitability tests for the chromatographic methods utilized for analysis of HFA-134a, to insure appropriate method performance.
 - e. Clarify specifically which impurities are the target analytes for method 3106.
10. The following comments pertain to the manufacturing procedures for the drug product.
- a. Describe the materials comprising the surfaces of the manufacturing equipment which are or may be in contact with components of the drug formulation during the manufacturing process at each manufacturing site.
 - b. Describe the _____ mentioned in the master manufacturing orders for the Northridge facility and the _____ at the Loughborough facility (e.g., vol. 1.7, pp. 106 and 227). Describe how the _____ is purified at each site.
 - c. Explain _____ of the manufacturing procedure set up for filling at the Northridge site (e.g., vol. 1.7, pg. 106). Describe the _____ and the _____.
 - d. Provide a diagram and an explanation of the formulation and filling equipment at each site. Indicate whether the filling lines and filling head are refrigerated, and whether the formulation tank is open to atmospheric pressure.
 - e. The following comments pertain to filling target ranges. At the Northridge site, control limits are listed as _____ g of the _____ g target (for 200 actuations), yet the target listed for the filling process at the Loughborough site is _____ g. Tighten the range around the target at the Loughborough facility (_____ g) to match that at the Northridge facility. Modify the batch records to reflect this change.

11. The following comments pertain to in-process controls and tests during drug product manufacture.

- a. Clarify how many canisters are in a —
- b. Describe the spray test procedure, and describe the — " (v. 1.7, pg. 113).
- c. Provide an executed record of drug product batch number PD3798.
- d. Describe the "general tests" listed in vol. 1.7, pg. 110.
- e. The following comments pertain to the instructions in the master manufacturing orders for " — " (e.g., vol. 1.7, pg. 110). It is stated that for vials selected for certain in-process tests, the weight of each vial must fall between — (100 actuation size) or between — and — (200 actuation size). "If a vial sample falls outside this range then re-sample until a vial of the correct weight is sampled."
 - (1) Tighten the proposed weight range.
 - (2) \
 - (3) Provide the in-process specifications for each test performed, —
—).
- f. There appear to be fewer in-process tests and controls performed at the Loughborough site, and little description of sampling procedures. Provide a comprehensive comparative side by side summary of the in-process checks and controls at each of the two manufacturing sites, which are expected to be very similar.
- g. Indicate the length of time that the drug product is stored under quarantine before testing (see vol. 1.7, page 19).
- h. Implement — testing for the drug product to cull out future potential leakers under conditions of use.

12. Describe the sampling plan(s) utilized for drug product testing, and include the number of canisters utilized for each test in the specification sheets.
13. The following comments pertain to analytical methods and specifications used for the drug product.
 - a. Modify the specification for appearance to provide examples of physical changes that would cause failure of the specification. The stability results reported in the future should describe the components of the drug product, rather than stating "conforms."
 - b. The following comments pertain to method 3267 for foreign particulates.
 - (1) Clarify, in the method, whether the entire sample is counted, and whether the specification limit refers to the number of particles in one actuation or ten actuations.
 - (2) Control foreign particulates less than _____ microns in size, using an appropriate method, since _____ below _____ microns are more likely to be inhaled into the lungs.
 - (3) Provide validation data to show whether _____ foreign particles may be distinguished _____
 - (4) Reconsider the specification, based on batches with complete data at all time points (e.g., 0, 3, 6, 9, 12, 18, 24 months).
 - c. The following comments pertain to the specifications for fill weight.
 - (1) Tighten the specifications.
 - (2) _____ Indicate the undeliverable fill for each canister size at the end of the canister life (i.e., the amount of formulation held up in the canister at the end of its life), and the amount of the formulation used in manufacturing (_____)
 - d. The following comment pertains to methods #3189 and 3190 (for medication delivery/content uniformity) and related methods. Tighten the system suitability test criteria for system precision, since _____ % appears to be too high a limit, based on data provided.

- e. Modify the specification for medication delivery/through life as follows. The phrase _____ should be replaced by the following phrase, _____ of label claim.
- f. The following comments pertain to methods #3157 and #3158 for particle size distribution. Update the methods accordingly.
- (1) It is noted that the lowest values of the linearity ranges studied are considerably higher than the limit of quantitation. Indicate whether the drug concentrations used in the linearity study are sufficient to insure proper quantitation of the stage or system component(s) with the lowest amount(s) of deposited drug. Since the standards used in the analytical method are single concentration standards, provide linearity data to include all anticipated concentrations.
 - (2) For valid results, limit the percent recovery, based on data, to a percentage of the labeled claim.
 - (3) Provide information as to how a new cascade impactor will be qualified, and what steps are taken to reduce variability between cascade impactors.
- g. The following comments pertain to method #3285 for ethanol content. Update the method accordingly.
- (1) Specify the validated — used in the method, rather than listing it as an example.
 - (2) The comparison data in report AIR 70-97 (vol. 1.5, page 333) should be augmented by individual data and a relative standard deviation for each batch.
 - (3) Explain why the standard solution for ethanol is prepared as an MDI. Use standards more simply prepared with ethanol at an appropriate concentration in a suitable solvent, to improve accuracy and to eliminate the effects of potential leakage from a standard MDI.

- h. The following comments pertain to methods #3269-3272 for drug-related impurities. Update the methods accordingly.
- (1) Include an appropriate test and limit for _____ in system suitability tests.
 - (2) It is a concern that the value of the retention time standard may be diminished if the components of that standard are optional. Require the use of sufficient standards to ensure that the method is suitable.
 - (3) Implement a more appropriate quantitative specification to insure the sensitivity of the method to detect and quantify low level impurities.
 - (4) Demonstrate that no impurities co-elute with the drug substance peak.
 - (5) The _____ impurity is poorly resolved from the large drug substance peak (v. 1.9, pg. 246) in the sample chromatogram provided, and even though good linearity has been demonstrated in a drug matrix, improve the chromatography to insure accurate quantitation of this peak.
 - (6) Clarify, on each specification sheet, whether drug substance impurities (process impurities) are included in the drug product specification for total impurities.
 - (7) Indicate whether the _____ degradant may degrade further in the drug product due to reaction with ethanol or water, for example.
 - (8) Reduce the expiration dating period of the retention time standard (v. 1.9, pg. 336) to _____ based on data provided.
 - (9) Provide data pertaining to recovery of the analytes from the formulation, to provide information about the accuracy of quantitation of individual impurities in the drug product matrix.
 - (10) In your report AIR-234-97 (v. 1.5, pg. 252), in which _____ and _____ impurities methods are compared, a number of the impurities are listed as below the quantitation limit. Provide comparative data, where possible, to demonstrate that both methods give the same results for all impurities; analysis of _____ drug product may be performed to obtain this information.

- (11) Provide validation data for — methods #3201-3204, since these methods were used to obtain some of your primary NDA stability data.
- i. The following comment pertains to method #3289 for — content. Clarify what is meant, for example, by a system suitability sample prepared at — % of the calibration range of — mcg/mL. It is not clear how one sample can be prepared relative to a range. Update the method accordingly.
- j. The following comment pertains to your method #2073 for microbial limits. Limit
Modify the method to include this restriction.
- k. The following comments pertain to your method #2049 for spray pattern. Update the method accordingly.
- (1) Generate data for spray patterns at multiple distances from the actuator, to establish the optimum distance for this test in terms of discriminating ability.
- (2) Provide photographs of representative spray patterns.
- (3) Tighten the allowed ranges for — based on your data.
- l. Develop and implement a method for canister pressure and a specification (at release).
- m. Provide a sampling plan for all analytical methods for drug substance and drug product.
- n. The drug product specification sheets should specify the number of drug product units tested for each parameter.
- o. Limit the level of the — to less than or equal to — % in the drug product, or provide adequate qualification for this degradation product. Additional comments on drug-related impurity specifications are withheld pending further information.
- p. Additional comments pertaining to drug product specifications are withheld, pending a response to comment 17 in this letter.

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

- a. Provide part numbers, source and fabricator for each valve component, O-ring and gasket that comprise the _____ alternatively, provide a DMF reference to where this information may be found. Provide or reference the composition of each valve component (_____)
- b. Modify canister specifications to include control of canister residues.
- c. Provide letters of authorization, including submission dates and page numbers, for the appropriate DMFs for the _____ O-ring, for the _____ valve, for the mouthpiece/actuators and for the _____ and other _____ used to manufacture the mouthpiece.
- d. The following comments pertain to the actuator/mouthpiece.
 - (1) The range around the target dimension for the orifice _____ is large and should be justified at both extremes with data, or tightened, to insure consistency of the drug product's performance (e.g., particle/droplet size distribution, plume geometry and velocity, spray pattern.)
 - (2) Provide the orifice diameters for actuators used in clinical and NDA stability studies.
 - (3) Provide representative photographs of plume geometry at various time points over the life of the plume using the drug product.
 - (4) Perform IR identification testing on the molded actuator, not on the _____ prior to molding.
 - (5) Provide comparative individual data for actuators of both colors from all sources _____; include those used in clinical/stability studies, and those intended for marketing. These data should include chemical composition, extractable profile, critical dimensional measurements, schematic drawings, performance data _____

(i.e. individual and mean

data)). Schematic drawings (e.g., vol. 1.8, pp. 205 and 210) should include additional dimensions and permitted ranges (e.g., mouthpiece diameter and length, sleeve diameter, etc.), including all suppliers. Some or all of this information may be referenced to an appropriate DMF.

- (6) Provide information pertaining to the composition and acceptance controls for each raw material used to manufacture each actuator. Include citations to the FDA indirect food additive regulations for each chemical component used to manufacture the actuator/mouthpieces.
- (7) In the specification for the visual inspection of the mouthpiece/actuator, discovery of contamination on the mouthpiece _____ or on the product after assembly _____ should be cause for rejection, rather than be allowed at low levels (_____).
- (8) Significantly tighten the proposed spray pattern specification for actuator acceptance for average diameter _____, based on the data provided.
- (9) The following comments pertain to method 3286 for determination of _____ extractables from the actuator.
 - (a) Expand the chromatograms on pages 253, 255 and 256 of vol. _____ to improve legibility.
 - (b) The method should be able to detect changes in composition of the mouthpiece.
 - (c) Explain significant differences between the chromatograms of the extracts of the two sources of inhalers _____ in view of the fact that there is a single set of extractable specifications, and that the only difference between the two actuators is color (vol. 1.3, page 11). The purpose of this test and specification is to detect any changes in composition. Justify this discrepancy with adequate data or rectify it.
 - (d) Include a statement in the specification for _____ extractables in the actuator, to the effect that if there are

noticeable changes in the chromatogram, even if the specification is passed, there will be an internal investigation to insure that the composition has not changed.

- (e) Include a limit on total unspecified peaks present.
- (f) Modify specifications as indicated, and provide representative data to justify the proposed specifications.

e. The following comments pertain to the valve.

- (1) Each batch of valves received should be accompanied by a certificate of analysis (COA). Evaluate the COA to verify that each valve component complies with its dimensional specifications.
- (2) Provide comparative individual data to support the change from valve _____ Include individual cascade stage data and content uniformity through life data.
- (3) Provide comparative data to support the final valve change during drug development (_____)

_____. Evaluate for occlusion additional batches of the higher strength drug product manufactured with the improved _____ using a simulated clinical-use test protocol, and include in this test an older batch of drug product. Perform this test using a protocol similar to that used for Proventil HFA Inhalation Aerosol: after actuating the drug product under a clinical-use protocol, the drug product is allowed to remain unused for variable periods, then the next actuation is be tested for medication delivery.

- (4) In your study of partially occluded drug product (v. 1.3, pg. 61), provide information about the drug products which gave abnormal plumes and/or firing, but were found to be _____ % or less occluded, and therefore, not counted as malfunctioning devices.

- f. The following comments pertain to your simulated use testing study (v. 1.3, pg. 63).
- (1) Provide a comparative analysis of differences between beginning, middle and end of the canister. Provide information on the cause of such differences, where they exist.
 - (2) Mention is made of _____ that were dislodged and collected in the cascade impactor (and in the apparatus used for medication delivery collection). Provide information on the origin and characterization of these drug _____ especially in light of the improved valve stem manufacturing procedure.
- g. Certain drug product samples were returned by patients in clinical trials for fit problems between stem and actuator, taste issues, and inconsistent dosing (v. 1.3, pg. 53). Provide additional information about the investigation of these problems, and actions taken to resolve them.
- h. Provide a sample of the drug product (or placebo), including an assembled and disassembled valve, gasket and O-ring.
- i. Provide comparative valve function data, including stability data, for the drug product, for valves containing _____ components extracted with _____ and those extracted with ethanol. These valve function data should include the following parameters: actuation force required (with aging), leakage, and medication delivery/through life.
- j. Provide the manufacturing site for the test article (the actuator) for the following toxicological studies: 0396EB0302, 0396EB0303, 0396EB0304, and 0396AM0305 (vol. 1.4, pp. 178-252).
15. The following comments pertain to the stability study pertaining to leachables in the placebo.
- a. Provide or reference test methods used for analysis of leachables in placebo drug product.
 - b. Provide complete chemical names for the _____ extractables which were target analytes in the placebo study, for any names listed that are not complete (e.g., see v. 1.4, pg. 66).

- c. Update leachable data for placebo product on stability.
 - d. Compare the _____ extractable specifications and data with the placebo data pertaining to leachables.
 - e. There are _____ /gasket specifications for a number of specified extractables that do not seem to have been analytes in the placebo study. Indicate if these extractables were ever target analytes in the placebo extractable (leachable) study (e.g., _____ other _____ extractables from the O-ring, valve _____ components, and the _____ component; _____ extractables, etc.). If not, these other leachables need to be studied on stability in placebo.
16. The following comments pertain to your discussion of planned future changes in _____
- a. Confirm that all stability data and other information supplied to NDA 20-911 have been generated using drug product manufactured with valves containing only diaphragms and tank seals made from _____ material, and only _____ O-rings.
 - b. If proposed changes in _____ composition and source are to be made, refer to our teleconference with your firm on April 23, 1998. Marketed product must use the _____ A change will require a pre-approved supplement with submission of appropriate supporting data.
17. The following comments pertain to the drug product stability data.
- a. Update the _____ stability data. Proposed specifications, including stage and component groupings in the PSD specifications, will be further evaluated based on individual stage data, when stability data are updated.
 - b. Update the stability data for drug related impurities and degradation products in the drug product, obtained with the _____ methods.
 - c. Update drug product stability data obtained with the one actuation method, for medication delivery through-life.
 - d. The proposed expiration dating period, based on the limited data provided, is not adequately supported. Data for the stability batches are incomplete, since data using the final methods are not available for all pull points for individual

batches. Provide additional stability data. Submit appropriate analyses of the stability data based on revised proposed specifications, evaluated with the proposed analytical methods.

- (1) Evaluate medication delivery through life and cascade impactor particle size distribution based on individual specifications as well as mean specifications.
- (2) Include the following additional parameters in a statistical analysis of data for determination of the expiration dating period: valve delivery, drug-related impurities, leakage rate, ethanol content, water content, content and foreign particulates.
- (3) Identify which data have been used for each analysis of the expiration dating period.
- (4) Describe stability failures based on updated, proposed specifications in the NDA, rather than based on in-house specifications in place at the time of analysis, to give a more complete analysis.

e. The following comments pertain to the test for foreign particulates.

- (1) Clarify the basis for the difference in storage orientation based on storage orientation.
- (2) Clarify whether the valve is known to be a significant source of foreign particulates over time.
- (3) Identify the intended shipping/storage orientation of drug product. It may be appropriate to store the drug product in the upright position, due to the differences in number of foreign particles with storage orientation.

f. Analyze medication delivery through-life data for potential trends from beginning to end-of-canister life. Provide medication delivery data (including separate means for beginning, middle and end) for beginning, middle and end of canister.

g. Provide a comparison of medication delivery data between the two strengths of drug product at the beginning and end of canister, to show appropriate dose proportionality.

- h. Demonstrate dose proportionality in terms of comparative particle size distribution of the two strengths of drug product. These data should include individual stage cascade impactor data, and beginning versus end of canister data for the two drug product strengths.
- i. The following comments pertain to drug related impurities.
- (1) Update the stability data section to include tabular and graphical stability data () grouped by each individual impurity (and total impurities) for drug-related impurities to facilitate assessment of specifications. Data for each individual impurity (and total) should be sub-grouped according to storage orientation.
 - (2) Tighten proposed drug-related impurity specifications based on lot data which include all pull points () including specific impurities as well as total impurities. Similarly, revise specifications for other test parameters, based on all pull points. Perform a statistical analysis of the expiration dating period for total impurities, and for any specified impurity for which there is sufficient data above the quantitation limit.
 - (3) Tighten drug product specifications for drug substance impurities, which are not also degradation products, when drug substance impurity specifications are tightened. Contact your drug substance supplier for more information.
 - (4) In view of the observed differences in levels of foreign particulates and drug related impurities (degradation products), on stability storage of the drug product at different orientations, consider storing the drug product in the upright position, to minimize such impurities. Investigate the reason for such differences, and base the specifications on the preferred storage position.
 - (5) It is noted that the () total drug-related impurities data for Lot PD3798, stored inverted at () (vol. 1.11, page 268, and vol. 1.13 page 68) do not exactly match the () data in the stability update (amendment dated 1-8-99, page 119). Similarly, the data for the individual impurity designated as () for this same lot, storage conditions and storage orientation is discrepant at the () pull point (see January 8, 1999 amendment, page 117

and vol. 1.3, page 173). Although these discrepancies are not large, rectify the discrepancies. Identify and rectify any other discrepant data between the stability update of January 8, 1999, and the original NDA.

- j. The following comments pertain to _____ content.
- (1) Update and analyze data in the last ten stability lots, and propose a reasonable specification _____
 - (2) Rectify the following discrepancy. _____ content stability data for drug product stored inverted at _____ for lot # PD3991, reported for the _____ pull point in vol. 1.11, page 306, appear as the data for the _____ pull point in the stability update dated January 8, 1999 (page 207), and the specific _____ data in volume 1.11 do not appear in the stability update. The _____ data have been completely changed in the stability update. Identify and correct any other discrepancies between the data previously reported and that reported in the update.
- k. Update and analyze the data for ethanol content and reevaluate the proposed specification. Further comments are deferred pending receipt and evaluation of a response to this deficiency.
- l. Tighten the proposed specifications for water content, based on the data provided, since the expiry (based on other test parameters) is to be limited to less than _____ months at this time.
- m. The following comments pertain to particle size distribution obtained with the cascade impactor.
- (1) Comments on the stability specifications (and their tiered nature) are withheld pending receipt of additional information.
 - (2) Data used to develop the cascade impactor particle size distribution specification, according to vol. 1.3, page 210, are too limited, and do not include complete sets of data for each lot (_____. Repeat this evaluation based on updated stability data.
 - (3) Update and analyze five actuation stability data, and compare with 20-actuation stability data. Five actuation data should include individual

stage and component data for each canister, as well as mean values and standard deviations for each group of 5 cans tested.

- (4) Provide a more thorough analysis of individual cascade impactor stages and components based on the stability data, to justify the stage and component groupings chosen for the PSD specification.
- (5) Provide or reference drug product characterization data, to demonstrate the effect of storage on the particle size distribution at the labeled number of actuations for each presentation of the drug product.
- (6) Provide or reference drug product characterization data to establish the amount of drug deposited per actuation on the mouthpiece.

18. The following comments pertain to your commercial stability commitment and stability protocol. Submit a revised protocol, in accordance with the following comments.

- a. Include accelerated storage conditions _____ in the stability protocol for the first three production lots, because the NDA stability lots were approximately _____ production scale. A proposal may be made to eliminate certain test parameters, to reduce the amount of effort for this accelerated data.
- b. Include leakage rate as a stability parameter.
- c. The stability protocol should list the specifications that will apply to the stability testing, or else it should specifically make reference to the drug product specifications. It should also include, for completeness, the following information: normal container storage & shipping orientation, sampling plans, and content and format of stability data for the stability report.
- d. The proposed ~~3~~ month expiration dating period is not acceptable, based on the data and analysis provided.
- e. It may be advantageous to package, store, ship and handle drug product in an upright position, based on the stability data provided.

f. ☐

Therefore,
provide complete test intervals in the protocol at this time.

- g. Modify the stability commitment for monitoring annual batches of drug product, after the completion of the stability requirement for first three sets of production batches, to reflect the annual production rate of the drug product.

19. The following comments pertain to your developmental studies of the drug product.

- a. Repriming data provided (vol. 3, pp. 227-239) are not conclusive. Provide more definitive data for one presentation of the product (e.g., drug product unprimed for 1, 3, 5, 7 day time points, with a separate set of canisters for each time point). The data provided support repriming after more than 24 hours of non-use, and using two actuations to reprime.
- b. Several instances of discrepancies are reported between valve delivery and medication delivery as part of your repriming studies. For example, compare the mean medication delivery for actuation 11, upright, with that for actuation 12, inverted (vol. 1.3, page 229). The difference is — of label claim, whereas the corresponding valve deliveries are virtually identical. In addition, we note the more extreme discrepancy discussed on page 230 and the aberrant medication deliveries discussed on page 232. It would be expected that medication delivery should be directly related to valve delivery for a solution formulation. Determine whether these examples reflect formulation/device problems or alternatively, problems with the variability of the analytical method.
- c. Provide individual stage data for your study of the profile of actuations near canister exhaustion (vol. 1.3, page 242).
- d. The study of the performance of the drug product after storage at cold temperatures doesn't support the use of cold product. Significant changes in dose delivered and particle size distribution resulted from operation after — storage, compared to storage at 25°C.
- e. Provide adequate information to support the conclusions reached in your study of the measurement of MDI spray dynamics (vol. 1.3, pg. 266). The information and data provided in this study are not sufficient to support a labeling or promotional claim relative to the — in the event

that the you are considering such a claim. To support the conclusions reached, pertaining to _____ e, additional information would need to be provided.

- f. Provide individual data for each test parameter, as well as individual stage and component data for cascade impactor testing, for your study on the effect of water content on product performance (vol. 1.3, page 270).
 - g. Describe the storage conditions for the lots of drug product used in clinical studies, for which comparison data between the clinical lots and the toxicological lot are reported in Table 2 (volume 1.5, page 272). Provide comparison data for other significant peaks that have not been reported, e.g., _____ impurity - and any other identified peaks that were present. Pharmacological evaluation of all of these data will be withheld until a response is provided.
20. Additional comments pertaining to stability data and proposed specifications are withheld pending an update of the data.
21. DMFs _____ are deficient and the DMF holders have been notified of the deficiencies.
22. Provide further qualification for the following drug product extractables: _____
23. Submit revised draft package insert, carton and container labeling that incorporate the following preliminary comments.
- a. Include the strength in mcg in the name, in all labels and labeling, e.g., QVAR 40 mcg (beclomethasone dipropionate HFA 40 mcg) Inhalation Aerosol.
 - b. Delete the modifier _____ " from the proposed tradename.
 - c. The typeface size in the package insert is too small to be readily legible. Revise it to be larger, and more prominent and legible.
 - d. The following comments pertain to the DESCRIPTION section of the package insert.

(1) _____

- (2) Indicate the number of actuations per container for each fill size.
 - (3) Include a statement pertaining to the number of priming actuations needed before using the MDI for the first time and in cases where the aerosol has not been used for more than a specified period of time.
(See comments elsewhere in this letter on this issue.)
- e. Delete all references throughout the labeling to QVAR 80 mcg unless you submit new data from clinical trials that support the safety and effectiveness of that strength across the entire recommended dosing range.
- f. Insert the class labeling text for inhaled corticosteroids with regard to the potential for suppression of linear growth in children.
- g. Delete all references throughout the labeling to [REDACTED]
all references throughout the labeling to [REDACTED]. The clinical significance of these observations has not been demonstrated, therefore, delete all inferences drawn from such data throughout the labeling including, but not limited to, the speculation that [REDACTED]
- h. Replace all occurrences of the word '[REDACTED]' with "corticosteroid."
- i. Delete all references throughout the labeling to [REDACTED]
- j. Rewrite the Pharmacodynamic subsection of the CLINICAL PHARMACOLOGY section to more accurately reflect the significant dose dependent decrease in urinary free cortisol levels observed in response to QVAR in Study 1162.
- k. Rewrite the Clinical Trials subsection of the CLINICAL PHARMACOLOGY section to more accurately reflect the data from the adequate and well controlled clinical trials (i.e., Studies 1081, 1083, 1129, and 1192) that support the safety and effectiveness of QVAR 40 mcg. Delete all references throughout the labeling to [REDACTED] and delete all speculation regarding [REDACTED]

- l. Delete all references throughout the labeling to the use of QVAR with

- m. The PK data submitted based on serum BOH and/or total BOH levels can only be viewed as supportive data.

Revise the Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section as follows.

- (1) Replace the second sentence in the first paragraph with the following sentence.

"Bioavailability information on beclomethasone dipropionate after inhaled administration is not available".

- (2) Replace the second paragraph with the following paragraph.

- o. Revise the first sentence in the Pharmacodynamics subsection of the CLINICAL PHARMACOLOGY section as follows.

- p. Revise the entire WARNINGS and PRECAUTIONS sections to be consistent with the wording included in the labeling of inhaled corticosteroid drug products recently approved by this Division (e.g., Flovent Inhalation Aerosol, Flovent Rotadisk for Diskhaler, Pulmicort Turbuhaler). Any deviations from the wording of these sections from that included in recently approved products must be justified with data or valid scientific arguments.

- q. In the PRECAUTIONS section, revise the misleading statement that "
" to more accurately reflect the documented significant decreases in urinary free cortisol observed in Study 1162 with QVAR and the potential for clinically meaningful HPA suppression in patients treated with recommended doses of QVAR.
- r. Update the Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy subsections of the PRECAUTIONS section as follows .
- (1) State the doses (mg/kg) for the referenced preclinical studies. The preclinical exposures should be compared by mg/m² dose normalization or AUC, if available.
 - (2) Restructure the label as described in 21 CFR, 201.56 and 201.57. For example, teratogenicity findings should be included in the Pregnancy subsection of the label rather than in the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection.
 - (3) Add a statement to the Pregnancy subsection of the label under "Non-teratogenic Effects" indicating that findings of drug-related adrenal toxicity in fetuses following BDP/HFA-134 administration in rats suggest that infants born of mothers receiving substantial doses of BDP/HFA-134 during pregnancy should be observed for adrenal suppression.
- s. Revise the Pediatric Use subsection of the labeling to state that "Safety and effectiveness of QVAR have not been demonstrated in pediatric patients less than 12 years of age." Include in this section a discussion of the number of patients 12 to 16 years of age included in the clinical trials program for QVAR and any valid inferences that can be made regarding the safety and effectiveness of QVAR in this age group compared to older patients. See comment 23. f. above with regard to including the class labeling text for inhaled corticosteroids and growth in children in this subsection.

- t. Revise the ADVERSE EVENT section to include data only from the adequate and well-controlled studies that support the safety and effectiveness of QVAR 40 mcg (i.e., 1081, 1083, 1129, and 1192). Revise the Adverse Event table to delete the column marked "I" and to delete all references to "I". Also, revise the Adverse Event table to list adverse events for QVAR and CFC-BDP based on the total daily dose delivered to patients instead of _____.
- u. The following comments pertain to the DOSAGE AND ADMINISTRATION section of the package insert.
- (1) Modify the priming and repriming instructions, as indicated elsewhere within this letter.
 - (2) Provide more specific guidance on the initial recommended dose and the maximum recommended dose of QVAR for patients with different severity of asthma based on prior antiasthma therapy (e.g., bronchodilators alone, inhaled corticosteroids) and specify that specific dosing recommendations for QVAR in patients who require oral corticosteroids are not available. Delete the proposed table regarding _____.
- v. Delete all references throughout the labeling regarding dose proportionality of QVAR 40 mcg and QVAR 80 mg unless you submit new data from clinical trials or other scientifically valid data that support the claimed dose proportionality of the two strengths and unless you submit new data from clinical trials to support the safety and effectiveness of QVAR 80 mcg across the entire recommended dosing range (see comment 2. above).
- w. Delete all references throughout the labeling to _____

_____ and claims that _____

Replace these statements with a statement that the consistency of dosing after the labeled number of actuations have been delivered cannot be assured and that the product should be discarded when the labeled number of actuations have been used.

x. The following comments pertain to the HOW SUPPLIED section of the package insert.

- (1) Include the color of the dust caps in the description of the drug products.
- (2) Eliminate the following statement from the package insert.

Eliminate the similar
statement from the patient package insert.
- (3) Eliminate the following statement from the package insert.
- (4) Include a statement that the QVAR Inhalation Aerosol canister should only be used with the QVAR Inhalation Aerosol mouthpiece and that the mouthpiece should not be used with any other inhalation drug product.
- (5) Include a statement that the correct amount of medication in each inhalation cannot be ensured after the labeled number of actuations from the canister, even though the canister may not be completely empty. Additionally, include a statement that the canister should be discarded when the labeled number of actuations have been dispensed.
- (6) Include a statement regarding the appropriate temperature of the MDI before use. (See comments elsewhere in this letter on this issue.)
- (7) Indicate the preferred storage orientation.

y. Add the following statements to the patient package insert:

- (1) A statement instructing the patient to confirm that the canister is fully seated in the actuator before use of the MDI.

- (2) A statement instructing the patient to confirm the absence of foreign objects in the mouthpiece before use of the MDI and after removal of the protective mouthpiece cap.
- (3) Modified instructions on initial priming and repriming of the MDI unit (see comments elsewhere in this letter on this issue).
- (4) A statement cautioning against spraying the eyes with the formulation.
- (5) A statement regarding the appropriate temperature of the MDI before use (see comments elsewhere in this letter on this issue).
- (6) A statement indicating the preferred storage orientation.
- (7) A statement indicating that the QVAR Inhalation Aerosol canister should only be used with the QVAR Inhalation Aerosol mouthpiece and that the mouthpiece should not be used with any other inhalation drug product.
- (8) A statement instructing the patient to keep track of the number of actuations used from the canister (as part of instruction number 9).

z. The following comments pertain to the immediate container labeling.

- (1) Improve the size, prominence and legibility of the established name, relative to trade name.
- (2) Include the phrase "Inhalation Aerosol" as a part of the name.
- (3) Modify the storage statement as follows: "Store at 25°C (77°F). See USP."
- (4) The warnings beginning with the following phrase, "Contents under pressure," may be removed if necessary to provide additional space, as long as they are present on the carton and other labeling.

- (5) Make reference to the package insert for directions for use.
 - (6) Add the phrase "Rx Only."
 - (7) Indicate the net content weight.
 - (8) Include the following statement: "For oral inhalation with QVAR actuator only."
- aa. The following comments pertain to the carton labeling.
- (1) Delete the amount of drug delivered from the valve.
 - (2) The prominence and legibility of the established name are poor on the carton for the physician's samples. Submit improved labeling. See comment in 22.aa.(1), above.
 - (3) Include the following phrase: " For oral inhalation with QVAR actuator only," on the front panel of the carton for the physician's sample.
 - (4) Add the following statements: "Important: read accompanying directions carefully." "Avoid spraying in eyes."
 - (5) Indicate the preferred storage orientation.
 - (6) On the trade carton, add the phrase "Inhalation Aerosol" immediately after the established name. The boxed statement, "CFC Free," should not appear in juxtaposition with the name.

Recently, our inspectors could not complete inspection of the facilities at _____ for conformance with current good manufacturing practices (cGMP) because the facilities were not ready for inspection. Satisfactory inspections of all facilities will be required before this application may be approved.

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 informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

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

Sincerely,

JS

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

cc:

Archival NDA 20-911

HFD-570/Div. Files

HFD-570/S.Barnes ✓

HFD-570/Nicklas

HFD-570/Schroeder

HFD-570/Poochikian

HFD-570/McGovern

HFD-570/Sun

HFD-570/Chen

HFD-570/Uppoor

HFD-570/Wilson

HFD-002/ORM

HFD-102/ADRA

HFD-95/DDMS

HFD-40/DDMAC (with labeling)

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: sb/May 7, 1999

Initialed by: C. Schumaker 5/12/99

T. McGovern 5/12/99

A. Schroeder 5/12/99

R. Uppoor 5/12/99

S. Wilson 5/12/99

J. Jenkins 5/12/99

final:

filename:

APPROVABLE (AE)

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA

**DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO
ENSURE ONLY CORRECT AND CURRENT INFORMATION IS
DISSEMINATED TO THE PUBLIC.**