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RESEARCH**

APPLICATION NUMBER:

21-457

APPROVABLE LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-457

Ivax Research, Inc.
4400 Biscayne Boulevard
Miami FL 33137

Attention: Steve Viti, Ph.D.
Director, Regulatory Affairs

Dear Dr. Viti:

Please refer to your new drug application (NDA) dated January 30, 2003, received January 31, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Volare HFA (albuterol sulfate, USP) Inhalation Aerosol.

We acknowledge receipt of your submissions dated April 1, May 5 and 15, June 6, 19, 26, July 15 and 18, August 5, 7, 15, and 29, September 19, October 10, 15, 20 (2) and 30, and November 17, 2003.

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

1. The following comments pertain to the drug substance.
 - a. The following comments pertain to the controls for particle size distribution and the micronization process.
 - (1) Provide an appropriate particle size specification (acceptance criteria and test method) _____ in order to assure consistent and reproducible particle size distribution across all batches of *micronized* albuterol sulfate. The acceptance criteria may include, at a minimum, _____
 - (2) Revise the acceptance criteria for *micronized* drug substance to include _____. The currently proposed acceptance criteria for particle size are inadequate to ensure reproducible particle size distribution across lots.
 - b. Provide data validating the sensitivity of the _____ methods for the quantification (% w/w) of _____.
_____ Pending the submission of these data and our evaluation, comments pertaining

to control of [REDACTED] are withheld.

c. Revise the drug substance specifications to include a test or combination of tests with associated acceptance criteria to control the [REDACTED] thereby ensuring consistent batch-to-batch quality of *micronized* drug substance. Provide data to support the proposed acceptance criteria.

d. The following comments pertain to the drug substance specifications.

- (1) Tighten the acceptance criteria proposed for *total specified*, *total unspecified* and *total impurities* in *micronized* albuterol sulfate to be reflective of the data, e.g., *total specified* NMT [REDACTED], *total unspecified* NMT [REDACTED], *total impurities* NMT [REDACTED]
- (2) Revise the acceptance criteria proposed for *any unspecified* to NMT [REDACTED]
- (3) Limit the levels of [REDACTED] in the drug substance to [REDACTED] or provide qualification data to support the current proposed specifications (e.g., a toxicology study of at least 90 days duration which demonstrates an adequate safety margin at a inhaled dose producing no adverse effects). The toxicological information, which is referred to DMF [REDACTED] for [REDACTED] impurities, could not be found in this DMF. In consultation with the DMF holder, provide the location of this information either by page number, and/or date of amendment to the DMF [REDACTED]
- (4) Revise the acceptance criteria for microbial limits for the drug substance to include " [REDACTED] Provide data supporting the proposed acceptance criteria for microbial limits in the *micronized* albuterol sulfate.
- (5) Tighten the limit for the acceptance criterion proposed for [REDACTED] residual solvent in *micronized* albuterol sulfate to reflect the data provided, e.g., NMT [REDACTED] Refer to comment 2.a below.
- (6) Revise the proposed acceptance criterion for *Identification by IR spectrum* to read " [REDACTED]
- (7) Confirm that future Certificates of Analysis (COA) for the *micronized* drug substance will report data and present the acceptance limits as reflected in the revised drug substance specification sheet.
- (8) Revise the specification document [REDACTED] to indicate that it applies to the [REDACTED]

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- (9) Revise the specification document [REDACTED], to clearly identify the test attributes that are performed during routine and non-routine testing. Include the testing schedule proposed (p 300346, 3.2.S.4) for annual batches of *micronized* albuterol sulfate in the specification document.
 - (10) The proposal to accept the COA test results for [REDACTED] for non-routine testing is acceptable provided that these test results are verified periodically by you as per the testing schedule specified for annual batches in the drug substance specification document. Refer to comments 1.d. (5) above and 2.a below.
 - (11) Revise the drug substance specification document to specify the type of test methodology used for each of the test attributes (e.g., [REDACTED]). Additionally, in order to manage and track any change(s) made to a method, assign a unique identification number to each method which will change sequentially with every change. This comment is equally applicable to the drug product specifications.
 - (12) Provide a description of the testing protocol for the drug substance in terms of sampling (per container vs. per batch), and number of batches to be tested per year after full testing of the first three commercial batches of *micronized* albuterol sulfate. The frequency of reduced testing, if proposed for an attribute or attributes, must be supported with adequate data.
 - (13) For attributes that are measured quantitatively, both for the drug substance and the drug product, report their test results in numerical values, rather than reporting as "complies or passes" wherever applicable (e.g., batch analysis, COA etc).
 - (14) Provide a periodic testing schedule to verify the specific optical rotation results from [REDACTED] and include it into drug substance specification.
 - (15) Resubmit the updated drug substance specification accordingly based on the above comments.

e. The following comments pertain to the drug substance test methods.

- (1) Revise the method for identification of the drug substance by infrared spectroscopy to include [REDACTED]. Refer to comment 1.d.(6) above.
- (2) Include representative chromatograms for all standard, system suitability, limit of detection (LOD), and limit of quantitation (LOQ) solutions as well as a typical drug substance sample, as part of the HPLC method for quantitative determination of impurities/degradation products in *micronized* albuterol sulfate. Additionally provide chemical structures of all known impurities within this

Note that the valve down storage orientation proposed for routine post-approval stability testing may or may not be appropriate, pending our evaluation of these data.

- (2) Revise the post-approval stability commitment to place batches in to the stability program based on the annual production rate, e.g., for ~~_____~~
~~_____~~
- (3) Include leachable testing as one of the stability test attributes. If an acceptable correlation between the container closure extractables and drug product leachables is established, the routine testing for leachables may not be necessary. Additionally, revise the drug product specification to include testing for leachables.
- (4) In addition to the proposed test frequency, include an ~~_____~~ test point for related substances in the stability protocol.
- (5) To provide greater assurance of representative sampling, increase the number of inhalers to ~~_____~~ that are tested by the multistage cascade impactor methodology for both release and each stability time point. Continue testing each inhaler at both the beginning and end. See comment 2.e above.
- (6) Include similar details for stability testing of post-approval batches to that of the ~~_____~~ batches (NW-SP-098, Attachment 1, pp. 300008 – 300028) as a part of post-approval stability protocol.
- (7) Revise and resubmit the updated stability protocol addressing the above comments 2.f(1-6).
- (8) As committed to in the submission (p 300002, Sec. 3.2.P.8, v 1.7), provide a full and comprehensive statistical comparison and evaluation for the critical performance attributes [*Dose Content Uniformity* (inter and intra-inhaler through life), *APSD* (for each stage and revised groupings), *Drug content per inhaler* (Assay), *Leakage rate*, *Spray Pattern* and *Plume Geometry* ~~_____~~] of the drug product on the basis of all available release and stability data for ~~_____~~ ~~_____~~ .ches of Albuterol sulfate HFA MDI. As applicable, include statistical parameters such as *Min*, *Max*, *Range*, *Mean*, *Std. Dev*, and *% RSD* for side-by-side comparison of attributes within and across batches for all storage conditions (temperature/humidity, orientation). As appropriate provide graphical representation(s) of the stability data to identify trends. In order to facilitate our review provide these data in SAS data files if available.
- (9) The following comments pertain to the APSD mass deposition data for the drug product.
 - (a) Investigate and explain the causative factors (~~_____~~)

- ~~_____~~
- (b) For consistent and reproducible performance of the drug product, take corrective measures to ~~_____~~

- (c) Provide updated APSD data for ~~_____~~ ~~_____~~ batches for beginning and end of inhaler. At each testing interval, we strongly recommend to test the same ~~_____~~ inhalers each for beginning and end as compared to the current testing ~~_____~~ ~~_____~~ (see comment 2.e. and 2.f. (5) above).

- (d) As applicable, analyze the data for all proposed stage groups with appropriate statistical parameters (Mean, Standard deviation, % RSD, min, max etc.) and provide a side by-side comparison of these data within and across batches for all storage conditions (temperature, orientation). As appropriate provide graphical presentation(s) of these data to identify trends, if any, while comparing within a batch and across batches with time and storage (condition and orientation). Additionally, identify significant shifts (~~_____~~) in mass deposition profile for any of these groups if observed with time and storage conditions. In order to facilitate our review provide these data in SAS data files if available. See comment 2.f. (8) above.

- (10) The following comments pertain to the dose content uniformity (DCU) of the drug product.

- (a) Provide an explanation for the observation of ~~_____~~

- (b)
- ~~_____~~

(11) Note that comments regarding your proposed expiration dating period may be forthcoming pending your submission of updated stability data for _____

g. The following comment pertains to the Drug Product Characterization/labeling: Revise the *Patient's Instructions for Use* to indicate the need to prime and reprime (greater than 2 weeks) the inhaler with three (3) "test sprays", based on the data presented in your drug product characterization studies (section 3.2.P.5.7). Additional comments regarding the labeling may be forthcoming pending our review of your response to the comments herein.

h. Note that deficiency letters have been forwarded to the holders of the following DMFs: _____

3.

4. The CLINICAL TRIALS section of the proposed product label includes _____

product label to remove this information.

Revise the proposed

5. Reformat your proposed package insert to meet the requirements of 21 CFR 201.56.

When you respond to the above deficiencies, include a safety update as described in 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.

Inspections of the _____ sites for _____
_____ have not been completed. A satisfactory inspection of all manufacturing facilities referenced in the application will be required prior to approval of this application.

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 this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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), you may request an informal meeting or telephone conference with this division to discuss what 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 approved.

If you have any questions, call Akilah Green, Regulatory Project Manager, at (301) 827-5585.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D. Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Badrul Chowdhury
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