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, Florida 33137

Attention: Steven M. 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 albuterol sulfate HFA Inhalation Aerosol.

We acknowledge receipt of your submissions dated April 1, May 5 and 15, June 6, 19, and 26, July 15 and 18, August 5, 7, 15, and 29, September 19, October 10, 15, 20 (2) and 30, and November 17, 2003, December 2, 2003, March 15, and 17, April 14, 19, and 29, June 14, and 17, July 20, August 25, September 9, October 6, 8, 11, 18, 19, and 25, 26, 27 (2), 28, 2004.

The April 29, 2004, submission constituted a complete response to our November 28, 2003, action letter.

This new drug application provides for the use of albuterol sulfate HFA Inhalation Aerosol for the treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to, except for including the revisions listed as agreed upon in a telephone conversation with Ms. Akilah Green, on October 29, 2004, the submitted labeling (package insert (copy enclosed)**,** patient leaflet (copy enclosed), and carton and container labeling submitted October 28, 2004).

1. Revise the beginning of the first sentence of the WARNINGS: section of the carton and container labeling submitted October 28, 2004, to "the action of [TRADE NAME] HFA Inhalation Aerosol lasts up to 4 to 6 hours."

2. Revise the last sentence of the first paragraph in parenthesis of the Carcinogenesis, Mutagenesis and Impairment to Fertility section of the Package Insert submitted October 28, 2004, to "(approximately 210 times …)."

3. Remove the graphics from the submitted carton labeling.

These revisions are terms of the NDA approval. Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-457**." Approval of this submission by FDA is not required before the labeling is used.

We have reviewed your proposal requesting that we reconsider your trade name proposal and we object to the tradename (b)(4) as outlined in our letter dated September 29, 2004.

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring pediatric studies for ages 0 to 11 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of the treatment of bronchospasm with reversible obstructive airway disease in pediatric patients ages 0 to 11.

   Final Report Submission: October 31, 2007

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We remind you of your agreements listed in your letter dated October 27, 2004, to complete the following:

1. Limit the acceptance criteria for the leachables, (b)(4) (b)(4) and provide Within two months of approval, submit supportive information for these limits and a protocol to conduct a 90-day animal toxicology study to qualify these levels if available information is not sufficient. If after review of the supportive information the Agency decides it is not sufficient and that it will be necessary to conduct the 90-day study in animals, conduct the animal study and submit the final report to the Division within 9 months after FDA feedback on the study is received.

2. Report and consult the Agency for its safety evaluation whenever a previously unspecified leachable has been identified by GC/MS.

3. Submit a validated test method to verify the reliability of the (b)(4) results reported on the manufacturer's COA within 12 months of approval.

4. Submit a correlation study(ies) between levels of leachables in the drug product (through the shelf life or until a plateau is demonstrated) and the extractables from the container closure components of the drug product to the Agency within 12 months of approval.

5. Provide validation data for the GC/MS method used for quantitative determination of leachables in the drug product within 6 months of approval. The drug product specification, (b)(4) will be revised at that time to include the test method for leachables in the drug product, including relative retention times for all identified leachables and all volatile organic compounds (VOC) that are used in the response standard preparation for GC part of the method. In addition, representative chromatograms for response standard preparation will be included at their detection and quantitation limits for a typical sample.

6. Submit a test method and acceptance criteria with supportive data to identify and quantify foreign particulate matter in the drug product to the Agency within 12 months of approval. The acceptance criteria will include limits for particles less than (b)(4) (b)(4) Any non-metallic mineral particulates will be identified and e of asbestos-origin. At that time, the finished product specification (b)(4) will be revised.

7. Provide a Prior Approval Supplement to extend the expiry dating with 24 month stability data from the manually stressed and auto stressed exhibit batches, as well as any stability data of commercial batches available at the time of submission. Data will be submitted electronically in the format previously submitted (i.e., statistical analysis in SAS data transport format).

8. Provide supportive data demonstrating the absence of discernible within-unit APSD trends from beginning to end of inhaler throughout shelf life for the Agency's evaluation prior to modifying the APSD test methodology to test only the beginning of the inhaler for the commercial batches. If needed, the Agency may revisit the appropriateness of the APSD acceptance criteria on the basis of an evaluation of the stability data provided in support of the expiration dating extension.

9. Provide a post-approval submission with supportive data for substituting (b)(4) testing at release on the drug product with (b)(4) results from the COA (b)(4) (b)(4) lots from the (b)(4)

10. Provide a post-approval submission with appropriate data to support reduced (e.g., skip-lot testing) testing schedule for (b)(4) at stability.

11. Provide particle size results and acceptance criteria on COA accompanying each batch of (b)(4) (b)(4) (b)(4) albuterol sulfate that will be received from (b)(4) (b)(4)

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

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury

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