CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75313

CHEMISTRY REVIEW(S)

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-313

FIRM: Zenith Goldline Pharmaceuticals
Attention: Jason A. Gross
140 Legrand Avenue
Northvale, NJ 07647
Tel# (210) 767-1700.
FAX# (800) 631-1583

US authorized agent for:
Steripak Limited, UK
(wholly owned subsidiaries of *IVAX Corp*)

DOSAGE FORM: Inhalation Solution

STRENGTH: 0.02%

DRUG: Ipratropium Bromide

CGMP STATEMENT/EIR UPDATED STATUS: The EER is pending for
All other firms listed as per the EER Summary report dated 11/19/99 are satisfactory at this time.

Manufacturing and processing will be performed at:

Steripak Ltd.
Goddard Road Astmoor Ind. Es.
Runcorn, Cheshire, U.K.

Packaging and labeling and testing of the referenced drug product will be performed at:

Steripak Ltd.
4 Pembroke Court Manor Park
Runcorn, Cheshire, U.K.

The firm at the above sites will perform all manufacturing, testing, packaging and stability testing (except sterility testing of the drug product).

EER STATUS: Acceptable on for the Steripak Goddard Road and the 4 Pembroke Court sites, respectively, as per J.D. Ambrogio. All other sites except have acceptable EER. The inspection is pending.

The Drug Substance; Ipratropium Bromide, is manufactured by
Manufacturer: Supplier/Distributor:

Drug Master File:

has been added as a contract packager to perform the pouching operation at their facility at:

The following contract laboratories are utilized:

Steripak states they **do not** use services of any contract laboratories in the manufacturing, processing, or labeling.

BIOEQUIVALENCY STATUS: The firm requested a waiver from performing a bioavailability /bioequivalence study due to the quantitative and qualitative similarity of their product with Boehringer Ingelheim's Atrovent® Inhalation Solution (Ipratropium Bromide Inhalation Solution 0.02% w/v). The Division of Bioequivalence recommended that the bio waiver be granted on 5/14/98.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Method validation by the District Laboratory was performed by the Philadelphia District laboratory, and was found adequate for regulatory purposes. Refer to the MV report dated 9/29/99 in the ANDA Vol. 2.1 and MV follow-up report dated 11/9/99 in Vol. 3.1). The drug substance and drug product have a Ph.Eur. monograph.

Steripak provided information and data to support an in-house Method for the determination of impurities and degradants in Ipratropium Bromide drug product. The Method is applicable for release and stability testing. Validation of the method was performed and was found adequate (accuracy, precision, recovery, resolution, linearity, specificity, limit of Quantitation and ruggedness over the stability period were performed). The information is satisfactory.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? The Drug Product (Ipratropium Bromide Inhalation Solution, 0.02% w/v)) will be packaged in mL polyethylene blow/fill/seal containers (strips of 5) with a fill volume of mL. The container is manufactured low density polyethylene (LDPE) polymer. Strips of 5 ampoules will be placed into a foil pouch consisting of laminate , , with as the contact surface. The foil pouch contact surface is the same resin as the ampoule).

The foil overwrap demonstrated to be adequate to protect, while not contaminate, the drug product, was not utilized with the exhibit batches. The above-described c/c system will be utilized for production batches.

LABELING: SATISFACTORY. Labeling was found satisfactory as per the 12/7/99 labeling approval summary of Theresa Watkins (see Vol. 4.1).

STERILIZATION VALIDATION (IF APPLICABLE): Acceptable. The drug product The product is was recommended for approval on the basis of sterility assurance on 1/5/00 as per Lynn Ensor, Ph.D.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
An exhibit batch #7B4001 of L (theoretical yield of ampules) was manufactured on 9/17/96. The entire bulk batch was filled into ampoules. The exhibit batch production records were submitted (refer to Vol. 1.2, pp. 236-365 of the Original 2/6/98 ANDA submission. Steripak also submitted a blank batch record for a Liter proposed production batch.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS exhibit batch manufactured to support this application was made from the same process as the proposed production batches. A Liter exhibit batch was utilized for the stability studies. A Liter proposed production batch size will be utilized.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?: **The proposed production batches will be manufactured utilizing the same manufacturing process as the exhibit batch.**

cc: ANDA #75-313
HFD-600/Reading File
Endorsements:
HFD-625/K.Furnkranz/1/24/00 /S/ 1/28/00
HFD-625/M.Smela/1/27/00 /S/ 1/31/00
V:\firmsam\steripak\ltrs&rev\75313appsum.fkf.doc
F/T by: gp/1/27/00
Approve

38. **Chemistry Comments to be Provided to the Applicant:**

ANDA: 75-313 APPLICANT: Steripak Limited

DRUG PRODUCT: Ipratropium Bromide Inhalation Solution; 0.02%.

There are no deficiencies remaining.

cc: ANDA 75-313
DUP JACKET
Division File
FIELD COPY

/S/ 1/28/00 1/31/00

/S/ 1/27/00

Approve

MAR 10 1999

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-313 **APPLICANT:** Steripak Limited

DRUG PRODUCT: Ipratropium Bromide Inhalation Solution, 0.02%

The deficiency presented below represent MAJOR deficiency.

A. Deficiency:

Container:

Your response to the Agency's deficiency letter dated November 5, 1998 for the inhalation product packaged in LDPE containers for which you are seeking approval concerning the need to employ a secondary overwrap such as a laminated foil or a pouch to ensure the identity, strength, quality, and purity of the product is not satisfactory.

Please provide the previously requested comparative data for at least 3 months of storage at accelerated conditions (40°C), if you intend to market this product without an overwrap. Also, provide the comparative studies data using analytical methods appropriate to detect possible contaminants at sensitivities in the 100 ppb range. These comparative studies should be performed using other sensitive analytical methods in addition to those methods previously used. The vials that do not have a protective overwrap must be packaged identically as proposed for market (same inks, same adhesive, same labels, same cartons).

The foil overwrap that you used in your comparative study led to contamination of the product. If you choose to use an overwrap to market the product, select one and perform the validation to show that it does not cause contamination in the product.

In addition to responding to the deficiency presented above, please note and acknowledge the following comments in your response:

1. Method Validation from the FDA district laboratory has been requested for the drug substance and the finished dosage form.

2. The microbiological section is pending review. After the completion of review, comments, if any, will be communicated separately.

3. The labeling section is pending review due to its delayed submission. In the future, please make a statement in your cover letter for the delayed response.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-313 APPLICANT: Zenith Goldline Pharmaceuticals

DRUG PRODUCT: Ipratropium Bromide Inhalation Solution, 0.02%

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

Manufacturing and Processing:

9.

Container/Closure System:

12. Please verify if Biological Test Center will be the future testing sites for Biocompatability and Ames Test.

Laboratory Controls - Finished Drug Product and Validation Data:

13. Please provide a copy of a typical chromatogram of Ipratropium Bromide Inhalation Solution drug product.

14. Please revise your drug product release specification to include testing, limits and specification for impurities/degradation products (known, unknown, and total).

15. Please provide the Content Uniformity Testing Data for the submission lot.

16. As indicated in section XV, assay of the packaged drug product has been performed by . Please provide an explanation of your "NOTE" included in section XVI (page 481).

17. Please provide the experimental data on stability of standard and sample preparation (drug product) which support the degree of reproducibility of ipratropium bromide method validation.

18. Please tighten percent RSD value of content uniformity based on your validation data for product release and stability samples.

19. Please provide the identity of the ipratropium bromide lot which was qualified for use as an in-house standard.

20. Please tighten percent RSD value of replicate injections of degradants based on your instrument precision data.

Stability:

21. Please revise your stability protocol to include accelerated storage conditions.

22. Test intervals of room temperature stability data provided on page 909 do not comply with your stability protocol. Please explain.

23. Orientation of samples provided in the accelerated and room temperature data is different from your stability protocol. Please provide the correct orientation in your stability protocol.

24. The protocol number provided in stability data is different from your stability protocol. Please correct.

25. The method used for the determination of ipratropium bromide content in your stability protocol (R015) is different from your finished product test specification methods Please explain.

26. Please explain the following based on the standard ipratropium bromide solution chromatogram provided in stability test specifications (page 898).

    (a) The method for the determination of assay and degradant/impurities is not acceptable in that the major peak is not base line separated from the impurity peak.

    (b) The solvent front is labeled as bromide, sodium chloride, and hydrochloride. Please explain where the bromide is originating from.

    (c) The major peak is labeled as ipratropium. Please explain if that is the coeluted degradant coming from the drug product.

27. Please provide the actual test data in numbers for the degradation products (known, unknown and total) for the stability samples. Also, tighten the limits for total degradants from % .

28. Please provide all available room temperature stability data of your exhibit batch.

29. Accelerated stability data for the ANDA lot (7B4001) shows a trend in ipratropium bromide content. Please explain.

30. Please provide limits and specification of weight loss of product for stability samples.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Methods Validation for the drug product by one of FDA's laboratories will be requested after validation and testing issues are resolved.

2. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with CGMP at the time of approval.

3. The microbiological section is pending review. After the completion of review, comments, if any, will be communicated separately.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research