CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20983

ADMINISTRATIVE DOCUMENTS

Division Director's Memorandum

Date:	Thursday, April 19, 2001
NDA:	20-983
Sponsor:	Glaxo Wellcome
Proprietary Name:	Ventolin HFA (albuterol sulfate) Inhalation Aerosol

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Introduction: This is the third review cycle for this NDA for the alternatively propelled replacement for Ventolin. The primary deficiencies in the previous cycles were CMC related, including a lack of __ testing and no acceptable interim plan for testing until such time that adequate and validated __ testing could be done.

CMC: All CMC deficiencies have been addressed, including a satisfactory plan for interim testing in lieu of __ testing and a commitment to validate __ testing and to submit a PA supplement to institute the testing in the 4th Quarter of 2001.

Pharmacology/toxicology: No new issues this cycle.

Biopharmaceutics: No new issues this cycle.

Clinical / Stastical No new safety concerns have been reported (note that this last cycle, which was primarily CMC did not include a safety update, since the last action was quite proximate and no substantive new safety data have been generated). The labeling as amended is deemed acceptable from a safety standpoint. No phase 4 commitments are made, though the expectation is that the company will report on clinical acceptability of this product in the post-marketing setting with US data, as outlined in the proposed rulemaking on the CFC phaseout.

Site inspections/EERs: There is in place an overall acceptable recommendation issued on Feb-26-01.

Pediatrics: The sponsor argues that this application does not even invoke the Pediatric Rule. However, I am not sure I am in agreement with their argument, particularly since the Division has cited albuterol as a molecule needing more pediatric information down to birth. While such studies might not be appropriate for this dosage form, the sponsor makes albuterol inhalation solution and could study that down to birth. Since Glaxo already did a pediatric supplement of their nebulization formulation down to 2, we will waive this age group, but only defer on the 0 – 23 month olds.

Conclusions: This NDA will be approved, with some CMC commitments and agreements.

Robert J. Meyer, MD
Director, Division of Pulmonary and Allergy Drug Products.

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

/s/

Robert Meyer
4/19/01 05:37:52 PM
MEDICAL OFFICER

Division Director's Memorandum

Date:	Thursday, July 01, 1999
NDA:	20-983
Sponsor:	Glaxo Wellcome
Proprietary Name:	Ventolin HFA (albuterol sulfate) Inhalation Aerosol

Introduction: This is an NDA for the alternatively propelled replacement for Ventolin – a CFC-based MDI for the delivery of albuterol to the airways in asthma and other bronchospastic conditions. Unlike Proventil HFA, this product uses only drug substance (albuterol sulfate) and propellant (HFA-134a) in the formulation without any surfactant or co-solvents (Proventil HFA contains oleic acid and ethanol). This product was intended to be a 1:1 substitute for the current CFC-driven albuterol inhaler, both in terms of its pharmaceutical development and its clinical development.

CMC: Dr. Bertha was the primary CMC reviewer and the CMC aspects of the application have already undergone several cycles of information requests and answers to those requests from the sponsor. One notable fact with this application, in addition to the lack of surfactants/co-solvents is that the sponsor has elected to utilize an overwrap for this product, due to moisture sensitivity. A remaining issue to resolve with this product has to do with dose-content uniformity testing, since the product will not meet the current DPDP standards applied to modern MDIs (including Proventil HFA). Note that since this product is even more moisture sensitive than most, a statement should be placed in labeling to **not** perform the "float test" is warranted.

Pharmacology/toxicology: Due to their non-participation in IPACT-1 (the consortium of pharmaceutical manufacturers formed to study the toxicology of HFA-134a), the sponsor did their own complete pre-clinical testing of the propellant, as well as a bridging program of the drug formulation to support its development. There appears to be no outstanding major issues with the Pharm./Tox. portion of the application. The formulation appears qualitatively similar to the existing CFC formulation of albuterol.

Biopharmaceutics: As a part of the "switch" programs for the replacement MDIs, the division has generally been seeking comparative PK data for the new product versus the "reference" CFC-based MDI. For albuterol inhalers, little information can be gleaned from standard dosing, however, due to the resultant low systemic exposures. Single dose exposures to 1200 mcg (i.e., 12 puffs) showed a somewhat lower resultant systemic exposure from the HFA product compared to Ventolin CFC. This presents no clinical concerns directly, but does hint at some possibility of lower delivery to the necessary biospace by the HFA product.

Clinical / Stastical: The sponsor conducted a program based primarily on the Division's Points to Consider document of Sept. 1994, along with further input from the Division. The review for the NDA was Dr. Trontell, with the secondary review being handled by Dr. Jenkins. The Medical Officer review is quite complete, and therefore the reader is referred to the review for details. However, it appears that the sponsor has well supported the safety and efficacy of this product in its use as a regularly scheduled

bronchodilator. However, in terms of its comparability to the marketed Ventolin product, there is a consistent signal (in the adults and adolescent studies – SALA 3002, 3005 and SALB-2001) that the dose delivery from this device is less than from the CFC product it is intended to replace. This difference appears quite small, but is quite consistent. A statement in the labeling reflecting that the effects of this product are comparable to Ventolin CFC but cannot be assumed to be fully equivalent in individual patients is warranted.

The pediatric dose-ranging and safety information shows this product reasonably comparable in effect and safety to the Ventolin CFC in this population. The signal of somewhat diminished effect seen in older children and adults is not apparent in this data set, suggesting a different patient-device interaction in younger children compared to adults (something seen with other devices / products as well).

Auditing / Data Checking: The medical officer did limit data checking of line listings and CRFs from the four pivotal studies without identifying significant issues. DSI was asked to audit two study sites, one for SALA 3002 and one from 3006. Neither study site was found to have deficiencies from good clinical practices that would suggest a significant individual or systemic issue for interpreting the resultant data. However, two investigators were later identified by the sponsor as having problems with data integrity (Dr. Edwards and Casale, the former of which DSI has investigated). These data were not used in the efficacy analyses.

EERs were sent for the Zebulon NC site, the Ware UK sites, the Scotland facility, the Evreux stie and the Barnard Castle, UK site. All sites were found acceptable, with an overall acceptable recommendation issued on Jun-25-99.

Labeling: Overall, the proposed labeling is largely acceptable. Some labeling comments regarding all aspects of the NDA review will be forwarded as preliminary comments to the sponsor.

Conclusions: This NDA will be given an approvable action, since there are significant remaining CMC issues that preclude approval at this time. Apart from these issues, the application is mostly acceptable, though final labeling will not be arrived at with the sponsor until such time that the CMC issues are resolved.

/S/

Robert J. Meyer, MD
Acting Director,
Division of Pulmonary Drug Products.

JUL 1 1999

Patent Information for
VENTOLIN® HFA Inhalation Aerosol
NDA 20-983

Active Ingredient:	albuterol sulfate
Strength of Drug Product:	120 micrograms per inhalation
Dosage Form:	inhalation aerosol
Route of Administration:	oral inhalation
Applicant Firm Name:	Glaxo Wellcome Inc.
Patent Number:	**5,674,471**
Coverage:	albuterol and salts or solvates thereof and 1,1,1,2-tetrafloroethane, compositions and formulations thereof and various methods of use
Issue Date:	7 October, 1997
Expiration Date:	19 August, 2014
Patent Number:	**5,676,929**
Coverage:	a canister containing albuterol and salts or solvates thereof and 1,1,1,2-tetrafloroethane, compositions and formulations thereof

Issue Date: 14 October, 1997

Expiration Date: 14 October, 2014

The Undersigned certifies to the best of his knowledge and belief that the above listed patents are valid patents claiming formulations of albuterol sulfate, methods of use and/or its administration system, the subject of a New Drug Application.

18 March, 1998
Date

Charles E. Dadswell
Registered Patent Attorney
United States Registration No. 35,851

EXCLUSIVITY SUMMARY FOR NDA # 20-983 SUPPL #_____

Trade Name: Ventolin HFA Inhalation Aerosol
Generic Name: albuterol sulfate HFA Inhalation Aerosol
Applicant Name: GlaxoSmithKline HFD # 570

Approval Date If Known: April 19, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X__/

   If yes, what type? (SE1, SE2, etc.)_____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /_X__/ NO /_ __/

If yes, NDA # 20-503____. Drug Name _Proventil HFA Inhalation Aerosol

(Note: The major portion of the formulation for this inhalation product is the propellant. The sponsor is required to conduct clinical trials of such formulation to determine the safety and efficacy of the product with the new propellant.)

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a

complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDAs# __ 20-503, 19-489, 19-243, 19-773, 19-269, 18-062, 17-853, 19-112, 19-383, 19-604

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-291__

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies SALA 3002, SALA 3005, SALA 3006, SALB 2001

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 Study SALA 3002 YES /___/ NO /__X_/

Investigation #2 Study SALA 3005 YES /___/ NO /_X_/

Investigation #3 Study SALA 3006 YES /___/ NO /__X_/

Investigation #4 Study SALB 2001 YES /___/ NO /__X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 Study SALA 3002 YES /___/ NO /__X_/

Investigation #2 Study SALA 3005 YES /___/ NO /_X_/

Investigation #3 Study SALA 3006 YES /___/ NO /__X_/

Investigation #4 Study SALB 2001 YES /___/ NO /__X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

SALA 3002____ _____SALA 3005___

SALA 3006____ _____SALB 2001___

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #[_1_ YES /_X_/ NO /___/

Explain:_____

Investigation #2

IND # [_____1_ YES /_X_/ NO /___/

Explain:_____

Investigation #3

IND #[_____1_ YES /_X_/ NO /___/

Explain: _____

Investigation #4

IND #1 ___1___ YES /_X_/ NO /___/

Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

/S/ 4.19.01

Signature/Title/Date

/S/ 4/19/01

Signature of Office/Division Director/Date

III. Marketing Exclusivity

NDA 20-983

Ventolin® HFA (albuterol sulfate, USP inhalation aerosol)

Request for Marketing Exclusivity

Pursuant to Section 505(c)(3)(D)(iii) and 505(j)(4)(D)(iii) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.108(b)(4), Glaxo Wellcome Inc. requests three years of exclusivity from the date of approval Ventolin® HFA (albuterol sulfate, USP inhalation aerosol) for the treatment or prevention and relief of bronchospasm in patients 4 years of age or older with reversible obstructive airway disease and the for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

We hereby certify as to the following:

Section 8, Item VIII.D. of this application contains a list of non-Glaxo Wellcome published studies or publicly available reports of clinical investigations known to Glaxo Wellcome through a literature search that are relevant to the use of Ventolin HFA for the prevention and relief of bronchospasm in patients 4 years of age or older with reversible obstructive airway disease and the for the treatment or prevention of exercise-induced bronchospasm in patients 4 years of age and older. This search is comprehensive in that it includes data for the use albuterol in 1,1,1,2-tetrafluoroethane (HFA-134a or GR106642X) in adolescent and adult patients (≥ 12 years of age), and pediatric patients (4 to 11 years of age).

Glaxo Wellcome has thoroughly searched the literature and to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of Ventolin HFA for such use.

Thus, Glaxo Wellcome Inc. is entitled to exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and sponsored by Glaxo Wellcome Inc. The following investigations are "essential to the approval of the application" in that there are no other data available that could support FDA approval of the application.

Indication – Treatment or prevention and relief of bronchospasm in patients 4 years of age or older with reversible obstructive airway disease and the for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

GM1998/00123/00. A single-center, randomized, double-blind, placebo-controlled, crossover study to compare the protective effect of single doses of salbutamol administrered by pressurized inhaler propelled by a mixture of propellants 11 and 12 or by an alternative propellant GR106642X against exercise-induced bronchospasm in patients with reversible airways obstruction (Protocol No. SALB2001)

RM1997/00651/00. A randomized, double-blind, parallel-group, 12-week study to evaluate the safety and efficacy of switching from albuterol 200mcg (180mcg ex-actuator) in CFC propellant 11 and 12 administered QID to albuterol 200mcg (180mcg ex-actuator) in GR106642X propellant administered QID and to albuterol 200mcg (180mcg ex-actuator) in GR106642X in propellant administered as needed in adolescent and adult subjects with asthma (Protocol No. SALA3002)

RM1997/00761/00. A randomized, double-blind, parallel-group, 12-week study to compare the safety and efficacy of albuterol 200mcg (180mcg ex-actuator) in CFC propellant 11 and 12 administered QID versus albuterol 200mcg (180mcg ex-actuator) in GR106642X propellant administered QID versus placebo in adolescent and adult subjects with asthma (Protocol No. SALA3005)

RM1997/00818/00. A randomized, double-blind, parallel-group, clinical trial assessing the safety and efficacy of albuterol 200mcg (180mcg ex-actuator) QID in CFC propellant 11/12 versus albuterol 200mcg (180mcg ex-actuator) QID in GR106642X propellant versus placebo in GR106642X in paediatric subjects aged 4-11 years with asthma (Protocol No. SALA3006)

The clinical investigations are defined as "new" as they have not been relied on by the FDA to demonstrate substantial evidence of effectiveness of previously approved drug products for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug application.

The investigations were "conducted or sponsored by Glaxo Wellcome" in that Glaxo Wellcome Inc. was the sponsor of the investigational new drug application (IND) under which these investigations were conducted.

/S/

C. Elaine Jones, Ph.D
Product Director, Regulatory Affairs

NDA 20-983

Ventolin HFA
(albuterol sulfate, USP inhalation aerosol)

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

25 SEP 98

Charles E. Mueller
Head, US Clinical Compliance
World Wide Compliance

Date

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The list of Glaxo Wellcome Principal Investigators for the above titled submission has been compared with the 12Nov97 Food and Drug Administration Debarment List and the 27Apr98 Disqualified, Restricted, and Given Assurances lists.

Jeanne Kistler

29 Sep 98

Jeanne Kistler
Compliance Standards & Information Administrator
World Wide Compliance

Date

Memorandum of Telephone Facsimile Correspondence

Date: April 18, 2001

To: Michael Golden
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Guirag Poochikian, Ph.D.
Chemistry Team Leader

Subject: NDA 20-983/Ventolin HFA/CMC comments

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

We have reviewed your March 30, 2001, and April 12, 2001, amendments and we have the following comments.

1. Update and submit revised drug product specifications.

2. Provide a commitment to submit by May 2001 validation information (e.g., methods, results), comparative data, and results of the investigation for resolution of the discrepant data obtained by the two laboratories testing for

3. The following comments pertain to the 44 page master batch record supplied in appendix 1 of the April 12, 2001, amendment.

   a. Provide clarification of the lot size, i.e., inhalers (see p. 1 versus p. 6).

   b. The master batch record should be assigned a revision number and item description on each page, and should include all of the necessary signatures and dates (see p. 1).

4. The following comments pertain to the revised stability commitment and protocol as they appeared on pp. 10 and 11, respectively, of the April 12, 2001, amendment."

   a. Revise the commitment to state that the *first* three production-scale commercial batches will be placed on stability.

   b. Add to the third paragraph of the commitment that out-of-specification results or the deterioration in the product will be reported as per 21 CFR 314.81(b)(1)(ii).

   c. Clarify in footnote "**" to table F6.1 that the expiration dating period is calculated from the date of formulation suspension preparation.

Memorandum of Telephone Facsimile Correspondence

Date: March 2, 2001

To: Michael Golden
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Guirag Poochikian, Ph.D.
Chemistry Team Leader

Subject: CMC comments/NDA 20-983

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

1. Tighten the AQL and the limit on the number of acceptable non-conforming units before batch rejection for the interim testing procedure. With reference to our previous request in the telephone facsimile of January 26, 2001, regarding the interim testing procedure and sampling, the current AQL for true defectives in a batch of % for fill weights outside of the range (g) after quarantine (21 days) is considered lenient. In addition, the number of allowable non-conforming units in stressed samples is not acceptable since your assessment that % low weight canisters are possible" (February 26, 2001 amendment) appears inflated based on the limited data provided for unstressed post-quarantine canisters on p. 9 of your December 6, 2000, amendment (units or % found non-conforming after 15 days, no additional after 21 days).

2. Revise and resubmit the "commitment to ongoing stability studies" section of the stability protocol to reflect the previous version presented in your December 18, 1998, amendment. In spite of the earlier agreement, the language regarding the withdrawal of non-compliant lots of drug product from the market has been significantly changed. The commitment should also clearly indicate that the batches placed on stability annually will be of production scale.

3. The following comments pertain to the overage proposed for this drug product formulation.

   a. Revise the application to set a particular target for the drug substance overage used in the manufacturing formula and include supporting data. The application currently describes the overage of the drug substance to be used for the drug product as "up to %." Your December 18, 1998, amendment provided ex-actuator and ex-valve dose delivery data on batches of drug product prepared with overages of %. The manufacturing formula listed on p. 6 of 47 of the master batch record in your December 6, 2000, amendment indicates that the manufacturing overage is %. The description of "up to %" for an overage of drug substance is not specific. The necessity to change the overage in the range of %, as would appear to be allowed by your description of "up to %," is not acceptable.

   b. Provide data demonstrating that the overage for the drug product formulation is needed to account for manufacturing losses and not from product instability, e.g., adsorption of the drug substance on the inside portions of the container/closure components such as the valve and canister wall, absorption into valve gaskets.

4. Revise and submit the master batch record (MBR) to clearly indicate an upper quarantine time for the bulk production batches. In addition, the MBR should reflect other modifications resulting from the above comments.

We remind you of the following commitments.

1. We remind you of your commitment to submit the yield data for the interim testing of the drug product as discussed during the November 27, 2000, telephone

conference by March of 2001. Data should be presented in terms of the yield after filling, (for the applicable samples), 3 week quarantine, checkweighing/ testing, and application of protective packaging. The comparison data from the interim program on the yield of acceptable product (in terms of performance and leakage) from the same batch subjected to *and* not subjected to the validated conditions are necessary to gauge the adequacy of the conditions in being able to detect and cull out grossly leaking canisters *and* those with marginal seal strength that may present a leakage problem once exposed to higher than normal temperature conditions.

2. We remind you of the commitment to implement the final testing of each batch of drug product by the 4th quarter of 2001. This will be done using a prior-approval supplement and a summary of the information to be included is provided.

3. As for your upcoming Advair Inhalation Aerosol drug product application, GlaxoSmithKline should commit to provide complete supporting information for periodic validation of the (or their contract laboratories') testing results for the valve gasket extractables testing by March 2001.

4. We remind you of your commitment to provide, by March 2001, to the application and the Agency laboratories, the necessary samples, standards and associated certificates of analysis so that the assessment of your drug substance and drug product methodology can be carried out.

We remind you of the following agreements.

1. GSK states that any future proposals for testing of extractables from incoming canisters will be submitted as a prior-approval supplement.

2. The future addition of alternate actuator suppliers/manufacturing sites will be supported via a prior-approval supplement.

Memorandum of Telephone Facsimile Correspondence

Date: January 25, 2001

To: Michael Golden
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Guirag Poochikian, Ph.D.
Chemistry Team Leader

Subject: Comments for NDA 20-983

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

1. With reference to our previous comment 6.a. of the January 2, 2001 letter, the number of annual commercial batches placed on stability each year should be determined relative to the number produced and testing of *all* parameters should be performed. It is noted that the size of each batch was estimated to be K units each as per your Dec. 6, 2000 response to the Agency comment 3.e of the Aug. 17, 2000 letter, and based on your current estimates for the number of batches to be produced annually, you are proposing to place % of the production batches on stability in the first three years of production. The stability protocol and commitment for annual batches should be revised to account for increased production, e.g., three batches for the first year, and one batch for the following years with a minimum of % of the batches each year, whichever is larger. Submit the revised stability protocol and commitment to the application.

2. Revise the three types (sample, trade, and refill) canister labels to be consistent with the cartons and package insert in terms of the recommended storage position, i.e., "store canister with mouthpiece down."

3. Confirm that in terms of the interbatch quality imparted by your application of the currently proposed 95% confidence level for the interim test samples with an acceptable quality limit (AQL) of %, if 4 of the samples were found to have a fill weight outside of the range of g after the 21 day quarantine period, the associated batch would be rejected. See related comment below.

4. The current AQL for true defectives in a batch of % for fill weights outside of the range (g) after quarantine (21 days) is considered too lenient, particularly when considering the data presented in table 3.1 of your response to comment 3 of the Oct. 31, 2000 letter. This AQL should be tightened significantly. Consideration of an increased level of confidence should also be given.

Memorandum of Telephone Facsimile Correspondence

Date: November 21, 2000

To: Sara Nelson
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Robert Meyer, M.D. /S/ 11/22/00
Director, DPADP

Subject: Labeling comments for NDA 20-983/Ventolin HFA Inhalation Aerosol

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

The following changes to the label should be made [line numbers refer to the non-strike-out version of the revised package insert in the 6/29/00 submission]:

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

Labeling Changes

Memorandum of Telephone Facsimile Correspondence

Date: October 31, 2000

To: Michael Golden
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Guirag Poochikian, Ph.D.
Chemistry Team Leader

Subject: CMC Comments for NDA 20-983

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

Our review of the Chemistry, Manufacturing and Controls (CMC) section of your submission is complete, and we have identified the following deficiencies. Comment numbers in parentheses refer to the August 17, 2000, "information request" letter.

5. Revise the HOW SUPPLIED section of the labeling (June 29, 2000) to be consistent with the revised version (Sept. 29, 2000) of the patient's instructions to indicate that the canister should be stored with the "mouthpiece" end down. (comment 6)

6. As for your approved NDA 18-473, Ventolin Inhalation Aerosol, add the priming and repriming instructions to the carton for the HFA product.

7. The dose content uniformity specification acceptance criteria for both mean and individual determinations currently proposed in the September 29, 2000, amendment are not acceptable. We refer to your agreement at the December 11, 1997, meeting and your application through your June 29, 2000, amendment of the specification acceptance criterion of __% of label claim (LC) to both the means of the minimum dose at beginning and end determinations separately at release and for stability samples. We refer you to the dose content uniformity specification

acceptance criteria included in attachment 2 in your submission dated August 25, 2000, as well as the telephone conference of September 18, 2000, where it was indicated that the following additional amendments to these specifications should be made:

8. Revise and provide an updated copy to the application of the valve specification acceptance criteria that includes the frequency of periodic testing of individual and mean weight per actuation. (comment 9)

If you have any questions, call Ms. Parinda Jani, Project Manager, at (301) 827-1064.

APPEARS THIS WAY
ON ORIGINAL

Memorandum of Telephone Facsimile Correspondence

Date: October 4, 2000

To: Michael Golden
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Robin Huff, Ph.D. 10-4-00
Supervisory Pharmacologist

Subject: Comment for NDA 20-983

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

Your contention that preclinical studies performed with Ventolin HFA inhalers qualify the leachables presumes that at the time the canisters were used they contained a substantial proportion of the levels of leachables measured in stability batches. In order to support this assertion, identify the age of canisters at the time of use in the preclinical studies and demonstrate that their age allows for the above assumption to be reasonable. Alternatively, study WPT/96/075, which was performed for IND and in which you measured total leachables, can be relied upon for qualification of the leachables, if the following two criteria are met. First, verify that the 500 µg/inhaler level you report reflects the level at the start, as opposed to the end, of the study. Second, demonstrate that the gaskets and composition of all components of the valve are identical in the salmeterol/fluticasone inhalers used for this study and Ventolin inhalers.

JAN I

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 26, 2000

TO: N 20-983 File, Ventolin HFA (albuterol sulfate inhalation aerosol)

THROUGH: Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary Drug Products (HFD-570)

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
Division of Pulmonary Drug Products (HFD-570)

SUBJECT: Call from field inspector Lisa Hornback (Consumer Safety Officer/Inspector from DHHS/FDA/ORA/CE-FO/CHI-DO) on 9/25/00 regarding the inspection of in the United Kingdom

BACKGROUND: An inspection request was submitted via the EES on July 20, 2000, for which is responsible for the testing of the levels of in the gaskets for the valves for Glaxo's drug product Ventolin (albuterol sulfate HFA inhalation aerosol)

CONTENT: Ms. Hornback called from the United Kingdom from the analytical testing firm She wanted to inquire as to whether or not we thought it necessary for the firm to have a system suitability check for the precision of the quantitation of the method. I said that I thought this would typically be required for such a method for the determination of extractables/leachables. She also indicated that all of the levels of the that were seen in the sample chromatograms provided by the firm were below the supposed detection limit of the method. I explained that that was understandable since the gasket material does not include the historical source of the in MDI valve gaskets. I suggested that they could, for validation purposes, spike the sample with standards (these standards are available from the EPA). The inspector indicated that Glaxo had stated that they had discussed the validation issue with the CDER CMC team. I informed her that our Sept. 18, 2000 telephone conversation with Glaxo covered the issue of the

verification of the reproducibility of the results by a second laboratory and that Glaxo had agreed to provide us an update on this issue early in November before the December action date.

On a related issue, for the overall method validation package Ms. Hornback indicated that she would not evaluate in detail the package being provided by Glaxo for the associated application. I stated that we would review the package and determine if it was suitable for submission to our laboratories for method validation.

With regard to the [ ] inspection, I asked that she include me on the courtesy copy list for her report and I stated that we had discussed with Glaxo.

/S/

Craig M. Bertha, Ph.D.
Chemistry Reviewer

cc:
Orig. NDA 20-983
HFD-570/Div. Files
HFD-570/CBertha 9/27/00
HFD-570/GPoochikian
HFD-570/PJani

Memorandum of Telephone Facsimile Correspondence

Date: May 3, 1999

To: Elaine Jones
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Cathie Schumaker
Supervisory Project Manager

Subject: Comments for NDA 20-983/Ventolin HFA

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

STUDY	Problem Canisters/# returned	Comments
SALA3002	3 or 4/6	Leakage
SALA3005	15/31	9 clogged, 6 empty
SALA3003	1/1	Clogged
SALA3006	0	
SALB2001	0	
SALA3009	?	
SALB2003	?	
SALB1003	?	

Questions for Glaxo:

1. Pertaining to the products used in the clinical trials, is the US commercial container closure system (USCCCS) identical to the to-be-marketed US formulation?

2. Calculate the overall rate of device performance problems with the HFA and CFC albuterol products based upon the number of canisters dispensed during the clinical trial(s). For example, if 15 albuterol HFA canisters were determined to have malfunctioned out of 1000 dispensed, the overall rate of malfunction would be 1.5%.

   - Calculate this overall rate for all trials (combined and individually) using the to-be-marketed US device and formulation.
   - Calculate this overall rate for all trials > single dose using the to-be-marketed US device and formulation.
   - If differences are noted in the type or rates of undesirable drug product behavior between trials, it would be appropriate to explore the reasons for this and report the results. Examples include trials performed under differing environmental conditions, presence or absence of specific patient instructions for cleaning and/or inhaler maintenance, etc.

3. In addition to the overall device malfunction rates above, provide rates for all appropriate subcategories of device problems. For example, specify rates of leakage and clogging per total canisters dispensed. Analyses by trial type and conditions as in the bullets of item 2 above should be done if appropriate.

4. You have indicated that study SALA 3009 (the methacholine challenge) was done with the US to-be-marketed formulation. This study was done with varying water content in the canister. Which of the doses/water content products is the same as the to-be-marketed US formulation?

5. Was trial SALA3002 done using the US commercial container-closure system and/or to-be-marketed formulation? One summary table in the NDA indicates otherwise. (Vol 1, page 215)

Attachment

MEMORANDUM OF TELECON

DATE: December 14, 2000

APPLICATION NUMBER: NDA 20-983

BETWEEN:

Name: Michael Golden,
Tom Gerding,
Phone: 919-483-3692
Representing: GlaxoWelcome

AND

Name: Ladan Jafari, Regulatory Project Manager
Craig Bertha, Chemistry Reviewer
Guirag Poochikian, Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Methods Validation Package

Background: The Division of Pulmonary and Allergy Drug Products contacted Dr. Michael Golden of GlaxoWelcome to request that four copies of updated methods validation package for Ventolin HFA be submitted for review as soon as possible. The Division also requested that this package include composition of the drug product formulation, acceptance criteria and methods for the drug substance, acceptance criteria and methods for the drug product, supporting validation data for drug substance and drug product methods, list of available samples with their respective sample numbers, and analytical results for available samples (i.e., Certificate of Analysis). Dr. Golden indicated that they would provide all of the above items, except for the list of available samples and their respective sample numbers, and analytical results. This telecon was arranged to discuss whether GlaxoWelcome could submit the methods validation package without the list of samples and their respective sample numbers, and their analytical results.

Discussion: GlaxoWelcome indicated that the original samples, bridging samples as well as experimental batches are all out of expiry, and inquired if they could provide us with updated samples after the new batches are manufactured. GlaxoWelcome indicated that the new batches will be manufactured late January or early February of 2001,and the samples would be ready in March of 2001.

The Division inquired about the number of manufacturing facilities for this NDA , and GlaxoWelcome responded that there are manufacturing facilities in France, United Kingdom, and Spain, as well as [redacted] in the United States. However, the only facility submitted in this pending application for approval, would be the [redacted] facility. The Division reminded GlaxoWelcome that a prior approval chemistry supplement must be submitted with supportive data for use of any other manufacturing site, e.g., the three European facilities.

The Division inquired about the number of batches that were produced previously, and GlaxoWelcome indicated that they thought that they had produced a batch of units, divided into three different sub-batches for both valves and cans. GlaxoWelcome also indicated that they had done some stability testing on these batches. GlaxoWelcome stated that they could submit the stability test results of the experimental batches identified as in their recent submission dated December 6, 2000, if this is going to be an approvability issue. However, they were not sure how quickly they could get all the data to us, considering that the Holidays are upon us.

The Division indicated that leakage is a major concern, and that the Agency would want assurances in minimizing leak rate with appropriate controls, e.g., crimp settings. The Division reminded GlaxoWelcome that the concerns for leakage and associated controls are very important and should be addressed before the drug is introduced to the market, thus eliminating the potential of a recall as a result of leakage. The Division stated that high number of complaints would cause a serious reliability concern for all HFA products. GlaxoWelcome stated that the only assurance that they can give the Agency at this point is the fact that they have data from batches prepared with the revised crimp parameters from their European facilities and that they would incorporate those revised parameters in manufacturing the new batches. GlaxoWelcome also stated that there was no gross leakage problem from their European batches, and therefore, they do not expect to see any difference in the facility either. With regard to the "rest of the world data complaint rates" provided in the December 6, 2000, submission in response to our comment 3 of the October 31, 2000, CMC telephone facsimile, the Division inquired as to how GlaxoWelcome relates complaint rates from other parts of the world to future complaints on the drug product manufactured at facility for US marketing. GlaxoWelcome responded that they are using equivalent manufacturing processes in all location, and therefore, do not foresee any major differences in the data produced in different facilities nor the resulting leakage and subsequent complaint rate.

GlaxoWelcome inquired if the Division had reviewed the recent submission dated December 6, 2000, and the Division responded that it was still under review. GlaxoWelcome also asked if they should submit the methods validation package without all the samples at this point, and provide the rest of the information in March 2001, when the new batches are manufactured and fully tested. The Division indicated that they would respond to that question after they had a chance to discuss it further internally, but GlaxoWelcome should hold off for the time being on submission of the methods validation packages.

Ladan Jafari
Regulatory Project Manager

/s/

Ladan Jafari
12/19/00 04:11:15 PM
CSO

Jan

MINUTES OF TELECONFERENCE

NDA: 20-983
Sponsor: Glaxo Wellcome
Product: Ventolin HFA Inhalation Aerosol
Date: September 18, 2000
IMTS: 6298
GW Attendees: Adolfo, Bonsingnore, Creasey, Golden, Pisculli, Santana, Schulz, Strickland
FDA Attendees: Bertha, Jani, Poochikian

Background: See the "information request" letter dated August 17, 2000. This teleconference was schedule to provide further clarification of the August 17, 2000, letter (See the See the submission dated August 25, 2000).

Comment 2: In order to ensure reproducibility of both the micronization and testing of the particle size distribution for the drug substance, tighten the acceptance criteria ranges for the median particle size (MPS) and the % µm.

Agency's response - GW's interpretation of this comment is correct. It is related to conditioned albuterol sulfate.

Comment 3b: Indicate the validated pressure range that is obtained when canisters are heated to an internal temperature ranging from °C.

GW's comment – GW has done some preliminary work with pressure measurement of the canister, but is not sure of the final methodology. GW would like to know whether it is necessary to characterize the internal pressure/internal temperature relationship.

Agency's response - The Agency stated that GW should characterize the internal pressure of the canister. The Agency can not rule out that the internal pressure needs to be validated as the process is unknown. Additionally, the Agency asked that for both the interim testing, data should be provided for the numbers of canisters being as well as the yields at subsequent stages (e.g., first check-weigh, check weigh after quarantine, after protective packaging applied).

Comment 3e: Provide a copy of the master batch record and flag the specific parts that provide detail on the interim testing methodology.

GW's comment - GW is working to finalize the interim testing methodology, which will be completed and incorporated into the master batch record by November 2000. GW would like to know whether it would be acceptable to provide a copy of the updated master batch record separately at a later date.

Agency's response - The Agency agrees with this approach, and would like to receive and review the master batch record document before an action is taken on this application.

GW agreed to provide a copy of the master batch record at the beginning of November 2000.

Comment 4 - We remind you of your agreement, as outlined in the response to comment 8 of the July 1, 1999, approvable letter, to implement by the 4th quarter of 2001, an in-process test with an appropriate subsequent equilibration period for 100% of each batch of product. The final testing should be implemented by a prior-approval supplement.

GW's comment –In a prior approval supplement post-approval, GW would provide; 1) a complete description of the testing process controls and updated master batch records; 2) batch release data for 3 batches of drug product that have been and quarantined for 21 days; and 3) a commitment to submit stability data on these batches via annual report. GW would like to know whether this proposal is acceptable.

Agency's response – The Agency stated that in addition, GW should provide description of the process and color photographs of the equipment. With regard to validation of the process, GW should include the theoretical yield, i.e., number of canisters filled/rejected, at various time points (e.g, first check-weigh, check weigh after quarantine, after protective packaging applied).It was agreed that this yield data would be provided as soon as possible to enable the Agency to continue the review of the CMC section. The supplement should contain 3 months of accelerated stability data from a 6-month study and the proposal to submit updated accelerated and long-term stability data via annual report is acceptable.

Comment 6 - Replace the word "nozzle" with "valve" in the label and labeling statement "store canister with the nozzle end down."

GW's comment - GW would like to know whether it is necessary to revise the label statement to include the word "valve."

Agency's response – The Agency stated that it is better to use the word "mouthpiece" rather than valve or nozzle. In the Patient's Instruction for Use leaflet, the storage position should be illustrated in a picture.

Comment 7 – Mean and individual dose content uniformity specification

GW's comment - GW has made the proposal for the testing, and testing as follows. GW will test 10 inhalers at the beginning and end of use, yielding 20 results. It would be considered that the requirements are met if 18 of the 20 results are less than or equal to μg) of the label claim (90 μg/actuation), and 20 of the 20 results are less than or equal to μg) of the label claim. The mean result at the beginning of use and the mean result at the end of use for the 10 inhalers must both be less than or equal to g) of the label claim.

testing: If one result at is greater than % but not greater than μg) of the label claim, it will be investigated by testing two further consecutive doses from the inhaler under investigation per the Content Uniformity method. If both of the additional test results from the inhaler under investigation are less than or equal to %, the additional tests results will be used in place of the original result and will be subject to the criteria described under the provision for using the testing.

Provision for using testing: If up to 6 of the 20 results (or 21 results, if testing is performed at from the 10 inhalers at are greater than % of the label claim, with no more than one of these being greater than % of the label claim and none greater than % of the label claim, and the mean result at the beginning of use and the mean result at the end of use for the 10 inhalers is less than or equal to % of the label claim than the product will be tested for

testing: GW will test an additional 20 inhalers at both beginning and end of use, yielding a total of 60 results (61 results if testing is performed).

It would be considered that the requirements are met if 54 of the 60 results (or 55 of the 61 results, if testing is performed) are less than or equal to % of the label claim, and 58 of the 60 results (or 59 of the 61 results, if testing is performed) are less than or equal to % and 60 of the 60 results (or 61 of the 61 results, if testing is performed) are less than or equal to % of the label claim. The mean result at the beginning of use and the mean result at the end of use for the 30 inhalers must both be less than or equal to % of the label claim.

testing: Provided the testing was not performed at if one result at is greater than % but not greater than µg) of the label claim, it will be investigated by testing two further consecutive doses from the inhaler under investigation per the Content Uniformity method. If both of the additional test results from the inhaler under investigation are less than or equal to %, the additional tests results will be used in place of the original result and will be subject to the acceptance criteria of

Agency's response –The Agency made three points of clarification:

- In terms of the numbers of results in that are allowed to be outside of % LC and within % LC, these should be revised to 59 of 60 (or 60 of 61) as opposed to the interpreted quantity of 58 of 60 (or 59 of 61).

- The Agency asked that the testing" section be revised with the addition of two clarifying statements:

  - "If either of the additional test determinations are outside of % of LC, the requirements are not met."

  - "If the overall determinations meet the 'Provisions for using proceed to testing.

Comment 9 - In terms of the periodic verification of the supplier results for valve delivery testing performed on incoming valve lots, the interval for the performance of this testing by Glaxo-Wellcome should be indicated in the application, and because individual (as opposed to mean) valve delivery is not being controlled at release of the drug product, the frequency of your periodic evaluation should be higher than what may be typical.

GW's comment - GW would like to know whether the proposed frequency of testing the incoming valves batches, i.e., every 50th batch or 1 batch every 4 months, is acceptable.

Agency's response - The Agency would like GW to test every 10th batch, or, at least 1 batch of the incoming valves per month.

Comment 12 - Although the performance of duplicate analyses for by the contract laboratories does provide a measure of intermediate precision, it does not provide the necessary validation of their results (reproducibility). Provide such data and revise the methods to indicate the frequency of the periodic verification of the results of extractables testing of incoming valve components.

GW's comment – GW would like to know whether it would be acceptable to continue to use sample blinding and the same contract laboratory , until work is completed to establish an independent laboratory.

Agency's response - The Agency would like GW to identify another contract laboratory to validate the results. In the interim, the proposal to continue using the sample blinding is acceptable. The extractables procedures should be same for both laboratories. The analytical methods could be different, however, in case they are different, they should be related to each other . Appropriate validation of the methods would be required. The Agency asked for an update on progress by early November 2000.

GW's response – GW will identify another contract laboratory and submit the information to the Agency by mid November.

Comment 14 - Propose an acceptance criterion for the size of the for incoming actuators from

GW's comment – GW is proposing to include only a specification in the acceptance criteria.

Agency's response – The proposal to include a specification in the acceptance criteria is acceptable.

/S/

Parinda Jani
Project Manager

CC:
Orig NDA 20-983
Div File/HFD-570
HFD 570/Bertha/10-13-00
HFD-570/Poochikian/10-13-00
HFD-570/Jani

Teleconference minutes

MINUTES OF TELECONFERENCE

NDA: 20-983 September 24, 1999
Sponsor: Glaxo Wellcome
Product: Ventolin HFA Inhalation Aerosol
GW Attendees: Golden, Morgan, Riebe, Wilson
FDA Attendees: Bertha, Jani, Poochikian, Rogers

Background: See the "approvable" letter dated July 1, 1999, and the minutes of the August 23, 1999, industry meeting. This teleconference was schedule to provide further clarification of the August 23, 1999, meeting (See the attached facsimile transmission of September 21, 1999).

Comment 5: Identification test for the racemic property of the drug substance

Discussion - As stated during the meeting of August 23, 1999, the Agency would like GW to include in the drug substance specifications, acceptance criteria for racemic albuterol. The Agency is requiring this testing because of the availability of levalbuterol both as drug substance and as drug product. The Agency does not agree with the "would comply if tested" approach. The proposed testing discussed during the August 23, 1999, meeting, i.e., first three commercial batches and then every 10th batch, is acceptable.

Comment 8: **testing**

Discussion - GW asked whether there was any flexibility to perform the testing as either an test and the extent of detail necessary to consider a response adequate. The issues related to the filling process, quarantine time after filling, identifying the available technology for the testing, purchasing and validating the equipment and the test, were discussed. The Agency is willing to accept an interim approach (with statistical sampling and discarding of tested samples). The time-line for the final implementation of the testing should be submitted with the response. The interim approach should be in place at the time of the approval.

Comment 11 – Mean and Individual Dose Content Uniformity

Discussion – GW proposed several alternative approaches for content uniformity/mean content per actuation specification. The Agency made several proposals for dealing with an out of specification result for individual dose content uniformity; GW may be able to replace the result with two or more individual results and treat the retest results individually applying the same acceptance criteria (21 determinations for the instead of 20). GW may be able to replace the value with the additional value and average in the value with others.

GW should propose an upper limit on the values that are outside of ___ % that will require retesting. Instead of retesting just with one additional dose from the suspect canister, it may be prudent to test two or more consecutive doses from the suspect canister. GW can evaluate the alternatives to address the issue of dose content uniformity and make a proposal in the submission.

Comment 12 – Valve delivery at release

Discussion - The Agency is in agreement with the proposal as long as testing is done on every incoming valve (component) batch with the mean and individual specification limits of ± 10% and ± 15%, respectively.

Comment 18 – ___ testing at release

Discussion –The Agency does not agree with "would comply if tested" concept. As previously discussed at the August 23, 1999, meeting, if the ___ tests and specifications for the incoming components are adequate and a correlation to the drug product ___ is made, it may be possible to dispense with the latter after approval.

Comment 30 - Acceptance of actuators from two suppliers and their comparability

Discussion - GW stated that both suppliers for the actuators would be used simultaneously. The Agency stated that it is not comfortable with interchangeability of the actuators. Very strong comparative analytical data would be required to assure the comparability of both actuator sources.

In terms of the extractables comparability, it is not clear how sensitive the current routine acceptance testing for actuator extractables with examination is in terms of the composition and potential changes (i.e., a change in a mold release reagent, changes in polymer, changes in fabrication conditions) in the composition of actuators. The proposed method may not be sensitive enough to determine the extractables. GW may need to develop a routine chromatographic extractables profiling method that would be applied to each batch of incoming actuators from each source instead of the method. The chromatographic profiling is an ideal way to demonstrate that the composition remains the same for each source.

The method was approved for Serevent Inhalation Aerosol (NDA 20-236/S-006) with a commitment to investigate and resolve any problems if unusual FT-IR spectral changes occur, even if they are not sufficient to fail the proposed specifications. A similar commitment would be required for this NDA

A one time qualification study for particle size would be required to demonstrate comparability between the actuators from both sources. testing with acceptance criteria for the size and shape of the should be performed for every incoming actuator batch.

GW will provide a proposal for acceptance criteria for the comparability of actuators from different sources.

Comment 35 a/d – In-use period

Discussion – The data presented so far do not necessarily support the proposed 3-month in-use period. As discussed at the August 23, 1999, meeting, the Agency would like to know what additional data would be obtained to determine the in-use period for product with overwrap removed near the expiry.

Parinda Jani
Project Manager

CC:
Orig NDA 20-983
Div File/HFD-570
HFD 570/Bertha
HFD-570/Jani

Meeting Date: August 23, 1999 **Time:** 10:00-11.30 AM
Location: Conference Room "C" **IMTS #:** 4699
Sponsor: Glaxo Wellcome, Inc.
NDA: 20-983
Product: Ventolin-HFA (albuterol sulfate) Inhalation Aerosol
Type of Meeting: CMC

FDA Attendees:

Craig Bertha, Ph.D.	Chemistry Reviewer
Badrul Chowdhury, M.D.	Acting Medical team Leader
Parinda Jani	Project Manager
Steve Koepke, Ph.D.	Deputy Director, Division of New Drug Chemistry II
Robert Meyer, M.D.	Acting Director, DPADP
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Brian Rogers, Ph.D.	Chemistry Reviewer
Vibhakar Shah, Ph.D.	Chemistry Reviewer
Eugene Sullivan, M.D.	Medical officer

Glaxo Attendees:

Alan Cripps, B.Pharm. Ph.D.	Sr. Project Team Leader, Inhalation Product Development
Michael Golden	Assistant Director, Regulatory Affairs
Elaine Jones, Ph.D.	Product Director, Regulatory Affairs
Ramona Krailler, Ph.D.	Product Director
John Morgan, Ph.D.	Director, Regulatory Affairs
Steve Plating, Ph.D.	Vice president, Quality Assurance
Sue Rider, M.Sc.	Senior Scientist, Inhalation Product Development
Michael Riebe, Ph.D.	Department Head, Inhalation Product Development
Mark Schulze, Ph.D.	Research Investigator, Inhalation Product Development
Keith Truman, B.Sc.	Manager, DPI Group, Inhalation Product Development

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Background: See the "approvable" letter dated July 1, 1999, and the submissions dated July 29, and August 13, 1999. This meeting was scheduled to provide clarification for the following issues in the AE letter that may have direct impact on the approvability of the product (The comment # listed are from the AE letter dated July 1, 1999).

Comment 3.a. - The cross-validation and particle size distribution (PSD) data for common batches of drug substance (DS) analyzed by the control sites

FDA comment - The PSD data for the twenty batches of DS that were commonly analyzed at both the control departments were examined (tables A3 and A4, pp. 40-43, February 26, 1999, amendment).

Analysis (n = 20 batches)	Analysis				Analysis			
PSD	MPS (µm)	% <1 µm	% <5 µm	% < 10 µm	MPS (µm)	% <1 µm	% <5 µm	% < 10 µm
Average	1.96	21.61	94.26	99.93	2.19	17.96	92.00	99.53
SD	0.14	2.70	2.07	0.10	0.15	2.24	2.04	0.26

These data reflect that there is an 11% difference in the average (n = 20) median particle size and an 18% difference in the % <1 µm particle size averages when comparing the [ ] results.

GW comment - GW asserts these differences are due to instrumentation differences at the sites, rather than real differences in the DS. Similar magnitude of differences in PSD is seen from both sites for fluticasone.

FDA response - Comparative data runs on the same standards at both sites, particularly for the finer particles (1- 5 microns) should be submitted in the complete response.

Comment 4 - The acceptance criteria limit of not greater than (NGT) % for the [ ] albuterol impurity in the drug substance

GW comment - GW proposes to limit this impurity in the drug substance and drug product to %.

FDA response - The proposed limit of % is acceptable from a CMC perspective, however, from pharmacology/toxicology perspective, any impurity at or above the threshold of % must be qualified.

Comment 5 - Identification test to ensure that the conditioned albuterol is racemic

GW comment - GW will update the specifications for drug substance to include an acceptance criteria for racemic albuterol. GW further proposes [ ] testing (i.e., first three commercial batches, then every 10th batch) to control this parameter. The testing will be done at the albuterol sulfate stage prior to micronization or conditioning.

FDA response - The Agency concurs with the proposed approach.

Comment 7 - Testing methodology for validation of all propellant supplier's test results reported on certificates of analysis (COA)

GW comment - The testing methodologies for the validation provided in the original NDA submission are actual methods (not just description) that will be used by the contract laboratory. The transferring of the supplier's testing methods to the contract laboratory has not been completed yet. GW proposes to provide comparative data for the first three commercial batches in an annual report.

FDA response - Representative comparative data obtained with these methods and the corresponding COAs must be submitted before approval. The Agency does not concur with the approach of providing comparative data in the first annual report.

Comment 8 - Institute testing

GW comment - GW uses % check weighing following the quarantine period to control gross leakage for currently marketed CFC product and to-be-marketed HFA product. Because of the moisture sensitivity of HFAs, immersing the canisters in would be detrimental, similarly, exposing the canisters to high temperatures would be unacceptable for safety concerns for line operators as there is potential that canisters could explode (the process stopped for the CFC product). If lack of testing by will have any impact on the approval of this product, GW would like to know that now. GW can commit to develop such method in future and propose a time line for implementation.

FDA response - The Agency believes that there should be testing of the product followed by 3-4 week lag period to single out those units with marginal seal strength or defective valves. By the check-weighing method in place to control "gross leakage", it is possible that a canister found to containing g of total fill after filling could leak mg within the 2 week holding period and still be packaged and released with a total remaining fill of g., yet this would correspond to a leak rate of %/year.

In the interim, the Agency may accept some form of testing on a statistical sample (samples tested discarded from batch) but GW should come up with methods for testing of % of the product in the future and propose a for instituting % testing, particularly since more HFA based products are under development.

Comment 9 - Include in the labels and labeling as to the most appropriate storage position(s) for the product based on data

GW comment - GW acknowledged that there appeared to be an effect of storage orientation upon stability testing at 40°C/75%RH, but the effects of orientation are not significant, and the highly stressed condition of 40°C/75%RH is not indicative of what would be expected under non-stressed long-term storage. GW believes that the long-term storage data for inhalers stored at 25°C/60%RH, 25°C/75%RH and 30°C/60%RH for various orientations, protected and unprotected, do not show any clear trends, and therefore, it is not necessary to include storage orientation in the labeling. As for mail order delivery, the drug would still be overwrapped where this phenomenon is not observed.

FDA response - For conditions of 40°C/75%RH for 6 months, all of the differential loss seen when stored upright vs. inverted occurred between 3 to 6 months. The loss in the first three months was about the same. The length of the in-use period agreed upon will impact on whether or not there should be information on recommended storage position in the labeling since the 40°C/75%RH data indicate that the difference in behavior under the two storage positions do not manifest itself until the second 3 months. The data presented for the

7ZX027 sub-batches for product stored unprotected both inverted and upright under conditions of 25°C/75%RH are inconclusive in showing an effect of position.

Since the same trend towards larger losses of finer particles was observed for unprotected product under each storage condition with upright versus inverted storage, it would make sense to indicate the most favorable storage position in the labeling so that the patient will receive product behaving as best as possible.

The Agency questioned whether GW had 24-month data for the lower temperature conditions for unprotected product and whether or not an increased loss resulting from storage orientation was seen.

GW response - GW will submit the data for unprotected product at 25°C/60%RH for the primary stability batches at 24 months with the complete response. There are no data available beyond 12 months for 30°C/60%RH conditions.

FDA response – The Agency can not make a judgement at this time, whether or not a labeling statement will be required until the updated stability data for the unwrapped product are reviewed.

Comment 10.a. - The dosing variability issues associated with testing methodology

GW response - GW uses three different waste-firing techniques to evaluate content per dose: semi-automated, fully-manual, and fully-automated. The PSD through life data were collected with manual wasting and manual collection (MW-MC). The dose content uniformity (DCU) through life data were collected either by automated wasting with automated collection (AW-AC) or with MW-MC. The phenomenon observed is that with the automated wasting, there is a buildup of DS somewhere inside the device. When the product is removed from the automation apparatus, jarring causes this material to become dislodged and to become part of the dose obtained during collection. The phenomenon is strictly related to the quick wasting technique, the simulated use testing (with a normal dosing time schedule) did not result in this phenomenon.

FDA response – The Division is interested in the work on determining what is the cause of the analyst-to-analyst differences when MW-MC is done for DCU through life and would like to have a summary of what type of wasting and collection techniques were used for collection of all of the data presented in the application.

GW response – GW would supply the requested data in the complete response. GW would provide references to the appropriate sections, if the data and/or explanation were submitted previously.

Comment 11: Content Uniformity Specifications (See submission dated August 23, 1999)

GW response - GW believes that the dose through use trend for this product is typified by a slight increase in mean dose over the first few actuations from the can, with occasional individual results outside the range of __ % of the target. This trend is reproducible batch-to-batch and does not change significantly with storage. GW proposes several potential options for control of the individual and mean doses (August 23, 1999, submission, Tables 1 and 2).

FDA response - In terms of the testing and specifications for DCU, the number of units __ tested in the should be doubled (i.e., 20). The numbers of (currently __ %) proposed by GW is high. Data for batch 6ZX013 indicate that only % of the determinations are between __ % and/or __ % of labeled claim (LC), excluding the aberrant end-of-use values. The limit for the __ of (% of LC) is wider than what the Agency may be willing to accept. An __ limit of __ % of LC may be considered by the Agency.

In terms of the DCU mean, the Agency acknowledges that a more defined trend from the beginning to end is seen with this HFA product. If GW's proposal to control the beginning and the end DCU means separately with limits wider than __ % of LC is considered then the Agency would like to have an additional specification to control the combined mean to a tighter level, e.g., __ % of LC.

A third option provided (retesting of the same units that delivered aberrant results to see if the following doses were adequate and then throwing out the initial test results) will need to be discussed internally before further comment.

GW response - GW may decide to submit a __ proposal for the Agency's review before the official response comes in. The __ will probably consist of some retesting approach (as the third approach in table 5 of the August 23, 1999, correspondence, and the first approach in table 5).

FDA response - Any agreement reached for DCU, should be very clearly indicated on the specification sheet and the methods so that it can be interpreted clearly by the Agency (compliance and reviewer).

Also discussed was the availability of the data for the thick-wall canisters. GW stated that there are data available for the thick-wall canisters for the European batches, but the methodology used and the specifications are different (based on single actuation instead of single dose). GW has preliminary data available for the drug product with valves manufactured with resins, which GW believes, are very encouraging (not yet submitted to the Agency). The value of DCU testing on stability protocol was discussed. The Agency stated that it is premature to discuss the value of DCU on stability, GW could propose changes to the stability protocol, once adequate database is developed.

Comment 12 - Valve delivery testing for the drug product at release

GW response – GW believes that the control of valve delivery (i.e., shot weight) is best achieved at the component level. Because of the difficulties encountered (i.e., sporadic dose variability) with removal of the units from the automation dosing apparatus during use and weighing, GW does not wish to perform this testing on the DP. Alternatively, GW could test another group of MDI units from the same batch for valve delivery.

FDA response - Data presented in the application indicate that valve delivery %RSDs ranged from about % and the dose delivery from these same units ranged from %. It may be that part of the increased variability is due to analytical error in determining the amounts of albuterol but it seems very unlikely that all of it is due to this. The formulation properties and characteristics may be playing a role in adding to this variability.

GW should establish the relationship of the valve delivery with DCU and then may drop testing on the DP with a supplement after approval and to replace it with testing at the component stage. This test and specification should not be dropped for the drug product when future MDI applications come in.

GW response – GW has established correlation at the development stage and will provide the data. GW has data from fully automated testing that is used for the product marketed in Europe and worldwide. GW will submit the proposal prior to submitting the complete response.

Comment 17 - Acceptance criterion from not greater than (NGT) % to NGT % for the albuterol impurity (GW472080)

See discussion under comment 4.

Comment 18 - Revised specifications for release of the drug product to include a test for

GW response - GW believes that the control of is best achieved at the component level.

FDA response – The Agency prefers the testing of the drug product for with associated specifications for control of the at the NDA stage. If there is a validated method for testing of at the component level that can produce data that can be correlated to data for the drug product then it would be reasonable to control this parameter at the component stage. If this correlation is shown and control is done at the component stage, then the actuator specification sheet should have acceptance criteria for this parameter (size and shape), should reference the method, and the acceptance testing method should be provided. The Agency typically would like to see this test done on the drug product in the early phase of its life, particularly with these HFA formulations that have proven to be less predictable in their performance than seen in MDI

formulations historically (dosing variability, potential for clogging, particle sizing profile shifts, etc.).

Once a correlation of the testing at the component level is made to the obtained on the DP, GW may delete the test for the DP through a supplement. The Agency routinely wants to see testing of MDI drug products at release with controls on the size and shape of obtained.

Comment 25 - Validation data of the supplier results for extractable from the various components

GW response - GW proposed to submit the validation data of the supplier's results for extractables from various components in the first annual report.

FDA response – The Agency does not agree with the proposed approach. GW needs to submit the validation data prior approval.

Comment 26 - Tighten the acceptance criteria for the levels of emanating from the components of the valve and the from the gathering ring

GW response – The proposed specification is based on the tolerance interval. This approach is taken over a process capability approach due to limited data set. GW believes that a minimum of 20 batches is needed to calculate the specifications based on process capability, data for which will be available post approval. GW proposes to provide updated acceptance criteria for based on process capability analysis within 12 months post approval via a "changes being effected" supplement.

FDA response - The specifications should be tightened based on the currently available data. If future data on a "minimum of 20 batches" supports a widening of the limits, then a "prior approval" supplement should be submitted to change the limits after approval of the application. If the updated data supports tightening of the acceptance limits, a "changes being effected" supplement can be submitted.

Comment 30.c. - Acceptance of actuators from the two suppliers

GW comment – GW proposes to use to demonstrate the comparability of performance characteristics of actuators from different suppliers.

FDA response - Comparative performance characteristics should include an examination of the PSD of the emitted dose in addition to the generated. As the product has a greater potential for clogging and this is possibly related to the performance characteristics of the actuator, a good comparison would be to look at the PSD data. Testing of the PSD of the emitted dose would be the ultimate test to assure that the patient will be receiving the

correct amount of fine particles regardless of the source of the actuator. In order to eliminate some of the variability, GW may wish to provide comparative PSD data (and other data) from actuators sourced from both suppliers utilizing the same group of canisters.

GW response – GW indicated that this was undesirable since the results from this test are usually rather variable. GW questioned whether this PSD testing was a one-time test for initial qualification of the suppliers .

There was no agreement reached on what performance test would ultimately be done and whether the PSD testing would be a one-time test for initial qualification of the actuator supplier.

Comment 33 - Revise the stability protocol to indicate that the annual batches of drug product will be stored under conditions of 25°C/75%RH and tested for one-third of the expiration dating period

GW response – GW proposes to list the testing at 25°C/75%RH protected as optional on the ongoing stability protocol and not invoke testing for annual batches unless a difference is seen in the profiles between the development data at 40°C/75%RH protected and the first three batches stored at 25°C/75%RH protected. GW does not see a need to set up another stability protocol for this condition for the annual batches. Testing of the incoming laminate and other protective materials (desiccant) and some testing of the seal integrity, would provide enough assurance that the protective packaging is doing its job.

FDA response - If protective packaging is used for an inhalation product, the annual batches should be stored under the conditions of 25°C/75%RH to provide continued assurance that the protective packaging is still doing its job (no changes in the laminate, sealing is adequate, etc.). The Agency does not inspect the suppliers of packaging materials such as laminates and desiccants and if the suppliers have made changes (or materials supplied to them may change, e.g., aluminum foil may come from a new source) that GW would not know about or these may not be detectable with acceptance testing proposed. Testing of the DP in the final marketing packaging is the best way to provide assurance that the patient is getting a DP that is protected adequately and that the key parameters of PSD and dosing are within established specifications. Alternatively, GW could make a proposal to address this prior to the formal response.

Comment 35.a. and 35.d. - In-use period of 6 months proposed for the drug product once the protective packaging is removed

GW response – For the dry powder inhalers, GW has used compliance with specification limits over a given amount of time approach. GW requested clarification why such an approach is not suitable for the HFA products. In reference to perform in-use studies with more testing points, GW proposed to modify the stability protocol for the first three production batches with more frequent testing during the first three months (i.e., every 4 weeks) and provide the data in the first annual report.

FDA response - The specification limits for the particle size groupings were based on data for the drug product stored with protective packaging under conditions of 25°C/60%RH. The ranges allowed took into consideration the manufacturing capability and the typical variability (batch to batch, analytical, etc.). If drug product is released on the low end of this specification range, and then the patient uses it and the drop in fine particles of the magnitude seen for unprotected product stored under conditions of 25°C/75%RH, i.e., %, the product during use would not be delivering fine particles within the specification range. Just because the results remain within specification at one point doesn't give adequate assurance that future batches will follow the same pattern.

GW response - The in-use period is usually determined based on whether or not the PSD remained in specification after the overwrap was removed. A statistical analysis of the data with confidence intervals is difficult because of the limited number of points and the variable nature of the PSD data.

FDA response – The Agency acknowledged the difficulty but the concern is that batches of DP released with PSD profile data at the low end of the range in terms of the fine particles could be expected to experience the % drop in fine particles observed once the protective packaging is removed (as seen with product unprotected stored at 25°C/75%RH) which would mean that the patient would no longer be getting the amount of fine particles specified. In addition, the Agency would like to see the in-use study at 25°C/75%RH (protective overwrap removed) run on product near its expiry. In terms of the frequency of the in-use test points, The Agency recommends 2-week intervals so that the curve or trends are fully defined.

GW response - GW acknowledged that the in-use curve would be more defined if additional points had been obtained in the beginning. GW proposed that instead of manufacturing new batches, they could remove the overwrap from older product already stored on stability for some time.

There was no agreement reached whether the recommended additional data for in-use period testing will be required prior–approval, and/or whether GW could conduct the testing on the older product already stored on stability.

Parinda Jani
Project Manager

CC:
ORIG NDA 20-983
DIV FILE/HFD-570
HFD-570/BERTHA/9-8-99
HFD-570/POOCHIKAIN/9-8-99
HFD-570/SULLIVAN
HFD-570/CHOWDHURY
HFD-570/MEYER/9-3-99

MEETING MINUTES

Ventolin HFA
NDA 20983
Memo of phone conversation

Representing Glaxo: Elaine Jones
Mark Schultz

Representing DPDP: Anne Trontell

The phone conversation was in response to Anne Trontell's request for clarification of the May 13, 1999 response to FDA request/comment: Clinical, CMC. In the 1998 product return data there was a table of substantiated complaints, which included "actuators cleaning" for 235 canisters. The questions and replies were as follows:

1. Do the substantiated complaints refer to a subset of the 391 Ventolin HFA complaints? Mark Schultz indicated that the substantiated complaints were encompassed in the preceding table of Ventolin HFA complaints, and did NOT represent an 260 additional problems to the 391 presented in the Ventolin HFA complaints.
2. What does the substantiated complaint "Acuators cleaning" mean? Mark Schultz indicated that this refers to products that were found to be clogged with drug when returned, but which functioned normally after washing according to patient instructions.

The instructions for the HFA product distributed in [redacted] are similar to those for the US product. The instructions recommend washing at least weekly, thorough drying, and to test fire the product if drying was incomplete.

Elaine Jones of Glaxo indicated that there appears to be a greater clogging problem with the HFA than the CFC product. Glaxo also indicated that they have not been able to reproduce actuator clogging in a laboratory setting, despite manipulations of temperature and humidity.

Anne Trontell expressed her thanks for the clarification.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20983	**Trade Name:**	VENTOLIN HFA (ALBUTEROL SULFATE USP INHA
Supplement Number:		**Generic Name:**	ALBUTEROL SULFATE USP INHALATION AEROSOL
Supplement Type:		**Dosage Form:**	Aerosol, Metered; Inhalation
Regulatory Action:	AE	**Proposed Indication:**	for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, PARINDA JANI

/S/ 6/29/99

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 020983
Trade Name: VENTOLIN HFA (ALBUTEROL SULFATE USP INHA
Generic Name: ALBUTEROL SULFATE USP INHALATION AEROSOL
Supplement Number. 000 **Supplement Type:** N
Dosage Form:
Regulatory Action: AP **Action Date:** 4/19/01
COMIS Indication: TREATMENT OR PREVENTION OF BRONCHSPASM IN PATIENTS 4 YEARS OF AGE AND OLDER WITH REVERSIBLE OBSTRUCTIVE AIRWAY DISEASE AND FOR THE PREVENTION OF EXERCISE-INDUCB

Indication #1: for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease.
Label Adequacy: Adequate for some pediatric age groups
Formulation Needed: Other
Comments (if any) Ventolin Inhalation Solution is approved for patients 2 years of age and above. Waiver is granted for 2 - years of age. Deferral is granted for children below 2 years of age.

Lower Range	Upper Range	Status	Date
0 months	2 years	Deferred	12/31/02

Comments: Ventolin Inhalation Solution is approved for patients 2 years of age and above. Waiver is granted for 2 – 4 years of age. Deferral is granted for children below 2 years of age.

Indication #2: for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.
Label Adequacy: Adequate for all pediatric age groups
Formulation Needed: No new formulation is needed
Comments (if any)

Lower Range	Upper Range	Status	Date
0 months	4 years	Waived	

This page was last edited on 4/20/01

/S/ 4.20.01

Signature Date