CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-911

Administrative Documents

Ted K. Ringsred
Intellectual Property Counsel

Office of Intellectual
Property Counsel

3M

May 6, 1998

Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: **PATENT INFORMATION**

To Whom It May Concern:

This information is submitted in compliance with FDCA § 505(b) and 21 CFR §314.53(c) in support of 3M Pharmaceuticals' new drug application for its HFA-134a beclomethasone dipropionate metered dose inhaler product.

The undersigned declares that U.S. Patent No. 5,605,674 covers the formulation, composition, and/or method of use of the HFA-134a beclomethasone dipropionate metered dose inhaler product. This product is the subject of this application for which approval is being sought.

The undersigned declares that U.S. Patent No. 5,695,743 covers the formulation, composition, and/or method of use of the HFA-134a beclomethasone dipropionate metered dose inhaler product. This product is the subject of this application for which approval is being sought.

The undersigned declares that U.S. Patent No. 5,683,677 covers the formulation, composition, and/or method of use of the HFA-134a beclomethasone dipropionate metered dose inhaler product. This product is the subject of this application for which approval is being sought.

Sincerely,

Ted Ringsred

Ted K. Ringsred
Office of Intellectual Property Counsel
Intellectual Property Counsel

Minnesota Mining and
Manufacturing Company

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PARAGRAPH IV CERTIFICATION

3M Pharmaceuticals certifies that Patent No. 4,364,923 is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the HFA-134a beclomethasone metered dose inhaler product for which this application is submitted. 3M Pharmaceuticals will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under § 314.52(c) with respect to the content of the notice.

Ted Ringsred May 6, 1998

Ted K. Ringsred Date
Office of Intellectual Property Counsel
Intellectual Property Counsel

CLAIMED EXCLUSIVITY

3M claims exclusivity, in accordance with 21 CFR 314.50(j) and with reference to 21 CFR 314.108(b)(4). 3M Pharmaceuticals certifies that this application contains new clinical investigations as set forth in to 21 CFR 314.108(a), that are essential to approval of the application and were conducted or sponsored by 3M.

May 6, 98

Florence Wong Date

Director Regulatory Affairs

PATENT STATEMENT

In accordance with FDCA 505(b), the following information is provided:

U.S. Patent No. 5,605,674 is owned by 3M Pharmaceuticals and expires on February 25, 2014. This patent claims the drug product for which approval is sought. A claim of patent infringement could reasonably be asserted under this patent if a person not licensed by 3M engaged in the manufacture, use or sale of the drug product for which approval is sought.

U.S. Patent No. 5,695,743 is owned by 3M Pharmaceuticals and expires on July 6, 2010. This patent claims the drug product for which approval is sought. A claim of patent infringement could reasonably be asserted under this patent if a person not licensed by 3M engaged in the manufacture, use or sale of the drug product for which approval is sought.

U.S. Patent No. 5,683,677 is owned by 3M Pharmaceuticals and expires on November 4, 2014. This patent claims the drug product for which approval is sought. A claim of patent infringement could reasonably be asserted under this patent if a person not licensed by 3M engaged in the manufacture, use or sale of the drug product for which approval is sought.

Ted Ringsred May 6, 1998

Ted K. Ringsred Date
Office of Intellectual Property Counsel
Intellectual Property Counsel

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	020911	**Trade Name:**	QVAR(BECLOMETHASONE DIPROPIONATE)80/40MG
Supplement Number:	000	**Generic Name:**	BECLOMETHASONE DIPROPIONATE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	AE	**COMIS Indication:**	QVAR IS INDICATED FOR MAINTENANCE TREATMENT OF ASTHMA AS PROPHYLACTIC THERAPY/AND IS ALSO INDICATED FOR ASTHMA PATIENTS WHO REQUIRED SYSTEM CORTICOSTERIOD TREAT
Action Date:	5/12/99		

Indication # 1 in maintenance treatment of asthma as prophylactic therapy. QVAR is also indicated for asthma patients who require systemic corticosteroid administration, where adding QVAR may reduce or eliminate the need for the systemic corticosteroids.

Label Adequacy: Adequate for SOME pediatric age groups

Forumulation Needed: Other

Comments (if any):

Lower Range	Upper Range	Status	Date
12 years	Adult		

Comments:

This page was last edited on 9/15/00

Signature - /S/

Date 9/15/00

3M May, 1998

GENERIC DRUG ENFORCEMENT ACT OF 1992

DEBARMENT CERTIFICATION

This information is submitted in accordance with Section 306(k)(1) of the Act [21 U.S.C. 335a (k)(1)].

I certify that 3M Pharmaceuticals did not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with this new drug application (NDA 20-911) for QVAR™ inhalation aerosol.

Marie D. Kuker
Manager, Regulatory Affairs
North America

TEAM LEADER MEMORANDUM

DATE: February 15, 2000

TO: NDA 20-911 QVAR (beclomethasone dipropionate HFA) Inhalation Aerosol

FROM: /S/
Badrul A. Chowdhury, MD, PhD
Acting Medical Team Leader,
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Secondary medical review of QVAR (beclomethasone dipropionate HFA) Inhalation Aerosol response to approvable letter

CC: HFD-570: Meyer, Nicklas, Barnes

Administrative

NDA 20-911 for QVAR Inhalation Aerosol was submitted by 3M Pharmaceuticals to the Agency on May 11, 1998. An approvable letter was sent to the sponsor on May 12, 1999. Three clinical and biopharmaceutics deficiencies, and about 20 CMC deficiencies were identified in the approvable letter. The Agency met with the sponsor on June 24, 1999, to discuss the deficiencies particularly the CMC deficiencies. On August 17, 1999, the sponsor submitted an amendment to the NDA responding to the deficiencies, and on January 10, 2000, submitted revised proposed labeling for QVAR to be consistent with our comments sent on the May 12, 1999, action letter. The user fee goal date for completion of this response review is February 18, 2000. The response to the clinical comments are discussed in Dr. Nicklas's primary medical review dated February 11, 2000, and signed February 14, 2000. In subsequent sections the sponsor's responses to the deficiencies and our positions on the issues are briefly discussed. Detailed reviews on these issues can be found in the primary reviews referred to above.

CMC

The outstanding CMC deficiencies are discussed in Dr. Schroeder's review dated February 10, 2000. One CMC concern with this product is the presence of foreign particulates in QVAR presumably coming from the components of the canister, valve assembly, and perhaps the materials used to wash them during manufacturing. These are discussed in Dr. Schroeder's review in pages 97 through 100.

The

specification for limiting [redacted] is [redacted] ppm, which is acceptable from CMC perspective. The worst case assessment for [redacted] in [redacted] micrograms per actuation, and high individual value of [redacted] microgram per actuation. From a clinical standpoint there is no reason to believe that small particulates are of concern. These particles are present at very low levels in QVAR and during normal breathing they are likely to be quickly exhaled out. Furthermore, these particulates were presumably present in clinical trial batches without giving any safety signals; and possibly other drugs in similar canisters out in the market has these particulates in them. Therefore, batch to batch monitoring to limit [redacted] will not be necessary for QVAR.

Review of the sponsor's response to clinical deficiencies

The approvable letter identified three major clinical deficiencies. In the following sections the sponsor's responses to these deficiencies and our view on the responses are discussed.

Comparability of QVAR and beclomethasone CFC

In the approvable letter we indicated that the sponsor has not demonstrated comparability between QVAR and beclomethasone dipropionate CFC (BDP-CFC) to a degree that was sufficient to allow labeling that [redacted] On our review, we concluded that the ratio between QVAR and BDP-CFC varied depending on outcome measures. For example, for FEV_1 the ratio was 2-2.5:1, for $FEF_{25-75\%}$ the ratio was 4:1, and for lung deposition the ratio was as high as 10:1. QVAR is expected to have a higher lung deposition and perhaps a larger effect size compared to BDP-CFCs for the same ex-actuator dose because QVAR is a solution as opposed to BDP-CFCs which are suspensions, resulting in a smaller mean particle size compared to BDP-CFCs. The sponsor in principle agrees with our position, but maintains that without explicit dosing information in the label physicians may incorrectly assume that they two are comparable and switch at a 1:1 ratio resulting in unnecessary overdosing of patients. While this is true if one concludes that physician will make such mistakes, the [redacted] Furthermore, QVAR is a stand alone product and should have its own dosing recommendation and does not have to be tied to other BDP products. Therefore, [redacted] must be removed from the label. A modification of the sponsor's proposed label in this regard removing any reference to a ratio between QVAR and BDP-CFC should be included in the label to incorporate the findings from the available studies and address the concerns raised by the sponsor.

The sponsor's proposed lines in the DOSAGE AND ADMINISTRATION section of the label should be modified to read as follows:

Proportionality of QVAR 40 mcg and QVAR 80 mcg dose strengths

In the approvable letter we indicated that the dose proportionately and clinical comparability of the 40 mcg and 80 mcg dose strengths of QVAR was not established. The 80 mcg dose strength was only studied in one study (study 1083) and only at one dose level (320 mcg/day). The sponsor therefore had not established safety and effectiveness of the 80 mcg dose strength across the range of doses proposed in the labeling, nor linked the 80 mcg dose strength to the 40 mcg dose strength by other studies. During the June 24, 1999, meeting with the sponsor we indicated that new data, particularly convincing PK data, might support the 80 mcg dose strength.

The sponsor responded by giving the reasoning that since QVAR is a solution and therefore the aerosol is homogenous, the concentration of each droplet is proportional to the amount of drug in the formulation. The sponsor provided in-vitro cascade impactor data to support the CMC in-vitro equivalence of the two strengths when administered at the same nominal dose. The sponsor also provided results from a PK study (study 1194-BRON) using total-BOH assay. Total-BOOH was validated by the sponsor to represent the active metabolite 17-BMP. Using the total-BOOH assay, the sponsor demonstrated in study 1194-BRON that a single dose of 400 mcg of QVAR using the 40 mcg/puff formulation was proportional to 800 mcg of QVAR using the 80 mcg/puff formulation. The major shortcoming of the study was that the sponsor did not study 400 mcg and 800 mcg doses delivered by both the formulation strengths.

The sponsor also provided data from clinical studies 1083, 1163, 1115, and 1267 to support dose proportionality. The latter two studies were new and were designed to compared QVAR with fluticasone at comparable dose levels. While the data from these studies are supportive, which is not acceptable.

In a submission dated November 10, 1999, the sponsor submitted results from another PK study (1366-BRON) that addresses the concerns raised above. The study was a 4-period crossover study in 32 patients with asthma. Patients received each of the following QVAR treatments: 100 mcg ex-valve from the 50 mcg/actuation strength inhaler, 100 mcg from the 100 mcg/actuation strength inhaler, 400 mcg from the 50 mcg/actuation strength inhaler, and 400 mcg from the 100 mcg/actuation strength inhaler. That study came in later in the review cycle and has not been fully reviewed by the biopharmaceutic reviewer. Therefore a final decision on proportionately of the two dose strengths cannot be rendered at this time. On my preliminary review of the summary data it appears that this study shows comparability of the 40 mcg and 80 mcg dose strengths of QVAR. If so, this would sufficiently support the dosage proportionality, taken together with the CMC data and the other clinical information.

In the approvable letter we indicated that there were inadequate data to allow for a claim that QVAR is and that such claims be deleted from the label. The

sponsor has such claims in the "
subsection in CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION sections of the proposed label.

The sponsor agrees that studies have not been performed with QVAR and agrees to remove any statements in the labeling that implies this claim. In an apparent contradiction, the sponsor states that since QVAR can be used at a dose lower than BDP-CFC, similar statement to the BDP-CFC labeling regarding recommendation to allow dosing in patients who require systemic corticosteroids can be applied to QVAR. The sponsor proposes to suggesting the recommended dose and highest dose of QVAR based on severity of patient's asthma as reflected by previous therapy. The ' subsection in DOSAGE AND ADMINISRATION section of the label begins with a statement that "

Such dosing recommendations and statements implies of QVAR and are not supported by the available data.

As regards the the sponsor can include in the labeling the class statement for inhaled corticosteroids dealing with this issue, but remove any specific reference to a of QVAR from all sections of the label. should be removed from the table in the DOSAGE AND RECOMMENDATION section of the label. While the sponsor has adequate data to support the recommended starting dose and the highest dose in patients previously on bronchodilators, and inhaled corticosteroids, there is insufficient data evaluating

Recommendations

NDA 20-911 QVAR (beclomethasone dipropionate HFA) Inhalation Aerosol is recommended an approvable action because of CMC deficiencies noted in Dr. Schroeder's review and clinical deficiencies discussed above and in Dr. Nicklas's review.

The sponsor has not demonstrated

While it is clear that for the same nominal dose, efficacy is higher for QVAR compared to BDP-CFC, there is no data to support a label statement that . Therefore, such statement should be removed from the label and replaced with a general statement on comparability. Proposed wording to that effect is included above in the section dealing with this issue. Determination of proportionality of 40 mcg and 80 mcg dose strengths, and therefore approvability of the 80 mcg dose strength is pending review of the new PK study 1366-BRON. Although the data looks convincing, final judgement on dose proportionality between of the two dose strengths cannot be rendered before the study is fully reviewed. On the issue of : of QVAR, the sponsor has no data to support such a specific claim; therefore, all such claims from the label must be removed.

Director's Memorandum (addendum to 5/99 memo)

Memorandum to:	NDA 20-911
Product:	QVAR (beclomethasone dipropionate HFA) inhalation aerosol
Memo date:	9-14-00
Memo from:	Robert J. Meyer, MD Director, DPADP

ADMINISTRATIVE

THIS MEMORANDUM IS TO DOCUMENT THE DECISIONAL CONCLUSIONS FOR NDA 20-911 – QVAR (BLECOMETHASONE DIPROPIONATE HFA) INHALATION AEROSOL, AN HFA-REFORMULATED BECLOMETHASONE (BDP) METERED-DOSE INHALER. UNLIKE THE CFC-MDI, THIS IS A SOLUTION-BASED FORMULATION WITH A SUBSTANTIAL DIFFERENCE IN DELIVERY CHARACTERISTICS. IT HAS BEEN THROUGH 3 REVIEW CYCLES (THIS BEING THE THIRD – DUE DATE 9/15/00), MOSTLY DUE TO CMC DEFICIENCIES. THIS MEMO IS INTENDED TO SUPPLEMENT DR. JENKINS' MEMO OF MAY 1999, AS WELL AS THE COMPLETED DISCIPLINE REVIEWS FOR THIS NDA AS AMENDED. IT SHOULD BE NOTED THAT ALTHOUGH THE RESUBMISSION WAS DATED 2-18-00, WE DID NOT CONSIDER THIS A COMPLETE RESPONSE BECAUSE A MAJOR DEFICIENCY WAS IN A DMF, TO WHICH THE SUBMISSION RESPONDING TO OUR LAST DEFICIENCY LETTER WAS RECEIVED ON MARCH 15, 2000.

CLINICAL:

THERE WERE NO NEW CLINICAL ISSUES ARISING FROM THIS REVIEW CYCLE, ALTHOUGH FROM THE FIRST CYCLE, THE SPONSOR PROVIDED GOOD PK DATA TO RELATE THE TWO DOSAGE STRENGTHS (THEY ARE SYSTEMICALLY BIOEQUIVALENT). FOR A SOLUTION MDI, WE CAN TAKE THIS AS SUPPORTIVE OF RELATIVE PROPORTIONALITY FOR CLINICAL EFFECT OF THE TWO STRENGTHS (E.G., 360 MCG PROVIDED AS 8 PUFFS OF THE 40 MCG STRENGTH SHOULD PROVIDE COMPARABLE RESULTS TO 4 PUFFS OF THE 80 MCG STRENGTH). THIS HELPED RELATE SOME OF THE DATA FROM DIFFERING TRIALS, SINCE THE SPONSOR DID NOT PROVIDE CLINICAL DATA TO RELATE THE TWO DOSAGE STRENGTHS IN ANY MEANINGFUL WAY (I.E., OVER A RANGE OF OVERLAPPING DOSES IN THE SAME TRIAL(S)). NOTE THAT CMC HAD CONSULTED THE CLINICAL TEAM WITH A QUESTION OF ANY SIGNALS OF CLOGGING, SINCE THIS HAS BEEN AN ISSUE WITH PROVENTIL HFA. AFTER REVIEWING THE CLINICAL DATABASE, THE CLINICAL TEAM DID NOT FEEL THAT THERE WAS ANY DATA TO RAISE CONCERNS OVER CLOGGING WITH THIS PRODUCT.

CMC {SEE F.O.I NOTE BELOW'}

MOST CMC ISSUES WERE RESOLVED SATISFACTORILY IN THIS RESUBMISSION.

[redacted]

BIOPHARM/BIOMETRICS/PHARM-TOX:

NO ISSUES APART FROM LABELING AND THOSE DESCRIBED ABOVE.

RECOMMENDATION:

BASED ON THE ORIGINAL NDA AND THE ADDITIONAL DATA PROVIDED THROUGH THE RESUBMISSIONS, THIS PRODUCT WILL BE APPROVED WITH AN 18-MONTH EXPIRATION DATING PERIOD. THERE WILL BE A PHASE 4 COMMITMENT TO SUPPORT ANY LENGTHENING OF THE EXPIRATION DATING PERIOD WITH FULL DATA AMENABLE AND ANALYZED STATISTICALLY AND THAT ANY SUCH SUBMISSION WILL BE VIA A PRIOR APPROVAL SUPPLEMENT.

/S/

9/14/00

ROBERT J. MEYER, MD
DIRECTOR, DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

CC: Chowdhury/Medical Team Leader/HFD-570
Barnes/Project Manager/HFD-570
Poochikian/Chemistry Team Leader/HFD-570
Division File/HFD-570
NDA #20-911

MEMORANDUM

DATE: May 12, 1999

TO: NDA 20-911

FROM: John K. Jenkins, M.D. /S/ 5/12/99
Acting Director, Division of Pulmonary Drug Products, HFD-570

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 20-911 for QVAR (beclomethasone diproprionate) Inhalation Aerosol was submitted by 3M Pharmaceuticals on May 12, 1998. QVAR contains HFA-134a as the propellant and is designed to serve as a non-CFC replacement for the currently available CFC MDIs containing beclomethasone (Beclovent and Vanceril 42 mcg and 84 mcg). The NDA was designated by the division to receive a standard review. The user fee goal date for NDA 20-911 is May 12, 1999.

Clinical

The clinical development program for QVAR was discussed with the sponsor at numerous time points over the past several years. The Division made numerous recommendations to the sponsor with regard to the approach taken on the following points; 1) evaluation of the comparability of QVAR to existing CFC-based MDIs containing beclomethasone, 2) evaluation of the dose proportionality of the two proposed strengths of QVAR (40 and 80 mcg delivered per actuation from the mouthpiece), 3) the duration of the placebo-controlled clinical trials, and 4) the evaluation of the systemic safety of QVAR as well as other issues. 3M Pharmaceuticals chose not to follow much of the Division's advice in the conduct of their program. Instead, they have presented a number of studies for review that are a cross between studies to evaluate the comparability of QVAR to a CFC MDI as recommended by the Division's 1994 Points to Consider Document and studies that are designed to evaluate QVAR as a "stand-alone" new product. Unfortunately, as detailed in the Medical Officer Review prepared by Dr. Nicklas and in the comments noted below, the overall adequacy of the clinical development program is marginal and does not adequately support much of the labeling proposed by the sponsor.

The clinical development program for QVAR included four adequate and well-controlled studies that are the primary basis of the sponsor's application (Studies 1081, 1083, 1129, and 1192). For a more detailed analysis of each of these studies, please refer to the Medical Officer Review prepared by Dr. Nicklas. I will summarize these four studies briefly here and discuss the conclusions that can be drawn from the studies individually and collectively.

Study 1081 was a 6-week, randomized, blinded, placebo-controlled study of QVAR 80 mcg and 160 mcg/day (delivered as divided doses twice daily using the QVAR 40 mcg ex-actuator strength) in mild-to-moderate asthmatics who were not receiving inhaled corticosteroids. Both

doses of QVAR were superior to placebo for the primary endpoint, FEV_1, and for most of the secondary endpoints. There was also a slight dose ordering of the magnitude of response for most of the primary and secondary endpoints. No unexpected safety concerns were raised by the results of this study. Overall, this study supports the safety and effectiveness of doses of 80 and 160 mcg/day of QVAR 40 mcg in patients with mild-to-moderate asthma.

Study 1083 was a 6-week, randomized, blinded, placebo-controlled study of QVAR at a daily dose of 320 mcg versus placebo in patients with mild-to-moderate asthma who were not receiving inhaled corticosteroids. QVAR 40 mcg or QVAR 80 mcg were used to deliver the same nominal daily dose in this study. Note that this is the only adequate and well-controlled study in the sponsor's application that directly compares the two QVAR strengths. Both doses of QVAR were superior to placebo for the primary endpoint, FEV_1, as well as for most of the secondary endpoints. For the primary endpoint and for many of the secondary endpoints, QVAR 40 mcg produced slightly greater degrees of improvement than QVAR 80 mcg at the same nominal daily dose. The sponsor performed "equivalence" analyses in an attempt to show that the two strengths of QVAR produced the same clinical response in these studies. These analyses are not interpretable given the study design that only included one dose of each strength of QVAR rather than the multiple doses of each strength that the Division would recommend. Without such a comparison of doses, it is impossible to determine the difference detecting ability of the clinical trial and therefore impossible to evaluate the "equivalence" of the two dosage strengths. There were no unexpected safety concerns based on the results of this study. Overall, this study demonstrated the safety and effectiveness of QVAR 40 mcg and QVAR 80 mcg versus placebo when dosed at a total daily dose of 320 mcg in patients with mild-to-moderate asthma. Due to the study design, no definitive conclusions can be reached regarding the dose proportionality of the two strengths of QVAR. In fact, for many of the analyses, QVAR 40 mcg appeared to be slightly better than QVAR 80 mcg.

Study 1192 was a 6-week, randomized, blinded study of daily doses of QVAR 40 mcg and CFC BDP MDI (42 mcg ex-actuator) at total daily doses of 100, 400, and 800 mcg in patients who were receiving inhaled corticosteroids at baseline. In order to simplify reporting of doses, this study will be discussed based on the nominal ex-valve dose of QVAR and CFC BDP rather than the ex-actuator dose generally preferred by the Division (i.e., for both formulations the ex-valve dose is 50 mcg). Also note, that this study did not include a placebo control as generally recommended by the Division for this type of study. The results of this study revealed a slight dose ordering of response for both QVAR and CFC BDP for FEV_1. At each dose level, the numerical response to QVAR was slightly greater than the numerical response to CFC BDP. No consistent pattern of the ratio of response of QVAR to CFC BDP was seen for FEV_1. For example, the QVAR response at 100 mcg was generally slightly greater than or comparable to the CFC BDP response at 400 mcg, suggesting a 4:1 or greater relationship. Conversely, the QVAR response at 400 mg was generally comparable to or slightly less than the CFC BDP response at 800 mcg, suggesting a 2:1 or less relationship. For most of the secondary endpoints, similar dose ordering of response for both QVAR and CFC BDP as well as a generally greater response for a given nominal daily dose with QVAR was seen. The inconsistency of the ratio of response between the two products at different nominal doses was also observed for many of the secondary endpoints. There were no unexpected safety findings from this study relative to the comparison of QVAR to CFC BDP. This study was the only adequate and well-controlled study

that included a dose response comparison of QVAR to CFC BDP. The study design failed to include a placebo arm. Thus, interpretation of the efficacy of the 100 mcg dose is this patient population (i.e., patients previously receiving inhaled corticosteroids) is difficult. Overall the study supports the safety and effectiveness of the 400 and 800 mcg daily doses of QVAR and suggests that the clinical response to QVAR at a given nominal dose is somewhat greater than the response to CFC BDP. Unfortunately, the study does not support the clinical comparability of the response of QVAR to CFC BDP since no consistent ratio of response between QVAR and CFC BDP was seen. In other words, it is not possible to state from the results of this study that

as proposed by the sponsor.

Study 1129 was a 12-week, randomized, blinded, placebo-controlled study of QVAR 40 mcg at a dose of 400 mcg/day versus CFC BDP (42 mcg ex-actuator) at a dose of 800 mcg/day in asthmatics, most of whom were on inhaled corticosteroids at baseline. In order to simplify reporting of doses, this study will be discussed based on the nominal ex-valve dose of QVAR and CFC BDP rather than the ex-actuator dose generally preferred by the Division. This study design differed from the other four studies in that patients underwent a run-in period of oral corticosteroid therapy (prednisone 30 mg/day) to maximize control of their asthma prior to randomization instead of the single-blind placebo inhaled corticosteroid washout used in the other studies. This study design may provide greater power to detect differences between doses of inhaled corticosteroids, particularly in situations where patients are randomized to doses of inhaled corticosteroids less than the dose required to maintain their optimized asthma control. Unfortunately, the sponsor included only one dose each of QVAR and CFC BDP. Such as study design severely limits the conclusions that can be drawn regarding the two actives unless one of the active arms is significantly better than the other; a finding that was not observed in this study.

For the primary endpoint, AM PEFR, both actives were significantly better than placebo in maintaining the optimized levels of asthma control obtained during the oral corticosteroid run-in period. At all time points over the 12-week trial, the QVAR response was numerically superior (i.e., a lesser fall in AM PEFR) to the CFC BDP response though these differences were not statistically significant. For FEV_1, a similar pattern of slightly greater numerical responses was seen with QVAR than with CFC BDP. This pattern generally held true for other secondary endpoints with the exception of rescue beta-agonist use where the results for QVAR and CFC BDP were reversed; i.e., beta-agonist use decreased slightly in the CFC BDP group while beta-agonist use increased slightly in the QVAR group. No unexpected safety findings were noted from the study and generally the QVAR and CFC BDP groups reported similar numbers and severity of adverse events. Overall, this study supports the safety and effectiveness of QVAR 40 mcg at a total daily dose of 400 mcg versus placebo. The study design and the results preclude any definitive assessment of However, numerical trends consistently favored QVAR at a dose of 400 mcg/day as being slightly more effective than CFC BDP at a dose of 800 mcg/day. These data would suggest a ratio of clinical response of greater than the 2:1 proposed by the sponsor.

Turning to safety issues, please refer to Dr. Nicklas's review for a more detailed overview of the safety profile for QVAR, particularly with regard to the ISS. I will focus on only one important safety issue, the systemic adrenal response to QVAR at the doses recommended by the sponsor

in the proposed labeling. This issue is important since the proposed dosing range of up to 640 mcg/day for QVAR is suggested by the sponsor to
— , based on the sponsor's proposed 2:1 ratio for clinical response to QVAR and CFC BDP. The maximum recommended dose of CFC BDP in currently approved labeling in the US is 672 mcg which means that the local and systemic safety of QVAR at the upper end of the proposed dose range must be carefully examined.

The best study that addressed this issue was Study 1162, a 2-week, randomized, blinded, placebo-controlled study in mild asthmatics who were not receiving corticosteroids at baseline. The study evaluated doses of QVAR 40 mcg of 200, 400, and 800 mcg/day and CFC BDP of 800 mcg/day. In order to simplify reporting of doses, this study will be discussed based on the nominal ex-valve dose of QVAR and CFC BDP rather than the ex-actuator dose generally preferred by the Division. Patients were required to have normal adrenal function at baseline and were sequestered and monitored closely throughout the study. Adrenal function was evaluated by means of AM cortisol levels, 24-hour urinary free cortisol, and ACTH stimulation (short test) at baseline and after two weeks of treatment. The 24-hour urinary free cortisol results, probably the most sensitive test of systemic corticosteroid activity included in this study, showed a dose dependent decrease in QVAR treated patients that was statistically significant versus placebo at the 400 and 800 mcg/day doses. Curiously, the response to 800 mcg/day CFC BDP was greater than the response to QVAR 800 mcg/day despite the reported greater systemic exposure to beclomethasone following administration of QVAR at the same nominal dose of CFC BDP. The results obtained from the AM plasma cortisol levels and the ACTH stimulation tests were not as conclusive of a systemic effect of QVAR as the 24-hour urinary free cortisol levels. This is not unexpected given the relative insensitivity of these two measures to detect changes in adrenal function compared to 24-hour urinary free cortisol levels. These results will need to be accurately reflected in the QVAR labeling. Note that the QVAR 80 mcg strength was not included in this study and data for 24-hour urinary free cortisol levels following administration of the doses proposed in the labeling are not available.

Overall, the clinical conclusions regarding QVAR can be summarized as follows:

1. The sponsor has demonstrated the safety and effectiveness of QVAR 40 mcg in patients not previously on inhaled corticosteroids and in patients previously on inhaled corticosteroids across the proposed dose range of 80-640 mcg/day.
2. The only data from an adequate and well-controlled study to establish the safety and effectiveness of QVAR 80 mcg comes from Study 1083. That study demonstrated the safety and effectiveness of QVAR 80 mcg at a total daily dose of 320 mcg versus placebo in patients not previously receiving inhaled corticosteroids. Unfortunately, the study was not adequately designed to allow a conclusion regarding the dose proportionality of QVAR 40 mcg and QVAR 80 mcg. Therefore the safety and effectiveness data for QVAR 40 mcg cannot be extrapolated to QVAR 80 mcg. This means that the sponsor has not adequately demonstrated the safety and effectiveness of QVAR 80 mcg across the range of asthma severity and doses proposed in the labeling. Additional clinical data will be needed to support approval of QVAR 80 mcg in the form of additional adequate and well-controlled studies to establish the safety and effectiveness across the recommended dosing range and in various asthmatic populations. Alternatively, the sponsor should submit data to adequately establish the dose proportionality of clinical response of QVAR

40 mcg and QVAR 80 mcg to allow extrapolation of safety and effectiveness findings and dosing recommendations from QVAR 40 mcg to QVAR 80 mcg.

3. The has not been adequately established to

While the clinical response to QVAR is generally greater than that of CFC BDP when administered at the same nominal daily dose, the sponsor has failed to convincingly establish the clinical response ratio for QVAR versus CFC BDP. For some endpoints and analyses, the sponsor's proposed ratio of 2:1 appears reasonable, however for other endpoints and analyses the ratio appears to be 1:1 or 4:1 or greater. It is worthwhile to note that the clinical response ratio for QVAR versus CFC BDP does not come close to the ratio the sponsor claims based on in vivo lung deposition studies. In those studies, the amount beclomethasone deposited in the "airways" following QVAR was approximately 10 fold greater than the amount deposited in the "airways" following the same nominal dose of CFC BDP. These data demonstrate the lack of clinical correlation of and clinical findings and underscores the Division's refusal to accept in vivo deposition studies as a substitute for adequate and well-controlled clinical trials with traditional endpoints.

4. QVAR has been shown to be generally safe and well tolerated across the proposed dosage range with no apparent signal of significant new toxicity as compared to CFC BDP. QVAR is systemically active as evidenced by a dose ordered significant suppression of 24-hour urinary free cortisol levels in Study 1162. These data will need to be accurately reflected in the QVAR labeling.

5. [

Thus, QVAR 40 mcg is approvable from a clinical standpoint for the range of doses proposed by the sponsor. The labeling will need to be dramatically altered to more accurately reflect the data available and to remove [ ] QVAR 80 mcg is not clinically approvable at this time. The sponsor will be given general labeling comments based on the above conclusions; final labeling review will be deferred pending the submission of any additional clinical data to address the deficiencies noted above.

Pharmacology/Toxicology

Beclomethasone is currently approved for inhalation use, therefore the preclinical toxicology program was primarily focused on evaluating the local and systemic toxicity of the new formulation of BDP in HFA-134a. Note that the safety of the new propellant, HFA-134a, was extensively evaluated by IPAC and the data from these studies has been previously found to be adequate to support approval for chronic inhalation administration (i.e., Proventil HFA). The bridging toxicology studies in rats and dogs revealed typical systemic effects of corticosteroids

and no worrisome local airway toxicity.

There are no outstanding pharmacology/toxicology issues and the application is approvable from a preclinical standpoint with appropriate labeling. Comments regarding the preclinical section of the labeling will be included in the action letter.

Biopharmaceutics/Clinical Pharmacology

The systemic exposure, as measured by total BOH, of QVAR 40 mcg has been shown to be approximately twice as great as CFC BDP when administered as a single dose at the same nominal dose. This 2:1 ratio of systemic exposure was also observed following multiple dosing. The interpretation of these and other PK data, however, are severely restricted due to the failure of the sponsor to develop a sensitive assay to measure serum levels of BDP and its various metabolites. Other sponsors have developed such a sensitive assay. The sponsor has also not provided PK data that can be considered definitive with regard to the dose proportionality of QVAR 40 mcg and QVAR 80 mcg. A dose proportionality study of QVAR 40 mcg and QVAR 80 mcg will be needed to support approval of QVAR 80 mcg.

The data submitted for the PK of QVAR cannot be considered definitive due to the limitations imposed by the use of an insensitive assay. QVAR 40 mcg is approvable from a biopharmaceutics/clinical pharmacology standpoint with appropriate labeling. A dose proportionality study of QVAR 40 mcg and QVAR 80 mg should be performed using a sensitive assay to support approval of QVAR 80 mcg (along with other studies).

CMC

The sponsor proposes to market two strengths of QVAR to correspond to the two strengths of CFC BDP currently marketed in the US. QVAR 40 mcg delivers 50 mcg BDP from the valve and 40 mcg from the actuator. QVAR 80 mcg delivers 100 mcg from the valve and 80 mcg from the actuator. QVAR is formulated as a solution. This differs from CFC BDP, which is formulated as a suspension. The sponsor has attempted to make an issue of the particle size distribution of QVAR relative to CFC BDP as an indicator that QVAR will be more efficiently delivered to the lung and therefore more effective at the same nominal dose. To a certain extent, the in vitro data are supported by the data from the clinical trials, however, the sponsor has not established a firm link between the in vitro performance differences and the clinical performance of QVAR. Please see the review prepared by Dr. Schroeder for a complete analysis of the CMC information submitted by the sponsor. As noted by Dr. Schroeder, there are numerous outstanding deficiencies that must be adequately addressed before this NDA can be approved.

The application is not approvable from a CMC standpoint. Numerous deficiencies will be communicated to the sponsor in the action letter.

Data Integrity

The Division did not request that the Division of Scientific Investigations conduct audits of clinical sites involved in the clinical trials submitted in support of approval of QVAR. This decision was made based on the fact that BDP has been approved for many years for inhalation use and Division policy to limit our requests for audits to NDAs and ES where we believe these limited resources are best utilized. Based on the limited auditing of the database conducted by the medical officer and other reviewers, there is no reason to question the integrity of the database.

Labeling

The proposed tradename, QVAR, was consulted to the CDER Labeling and Nomenclature Committee and was found to be acceptable. The name is also acceptable to the Division, however, inclusion of the word ——— in the established name is not acceptable. Consistent with Division policy, the ex-actuator delivered dose will need to be included in the tradename for each dosage strength (assuming that more than one strength is approved). Since the product will not be marketed using an existing tradename that has not been linked to CFC BDP, the use of the suffix HFA to distinguish the product from CFC BDP will not be required. There are numerous deficiencies with the draft labeling as submitted by the sponsor. Given the extent and potential impact of the clinical deficiencies identified above on the final labeling, only general comments regarding the labeling will be provided to the sponsor at this time.

Conclusion

Overall this application is approvable with regard to the QVAR 40 mcg strength. There are numerous CMC and labeling issues related to this strength that must be adequately addressed by the sponsor prior to approval. QVAR 80 mcg is not approvable due to serious clinical concerns regarding demonstration of safety and effectiveness across the proposed dosing range and due to numerous CMC deficiencies. The sponsor should receive an APPROVABLE letter stating all deficiencies identified during the review of the application. Labeling comments will be limited to general comments at this stage.

cc:
NDA 20-911
HFD-570 Division File
HFD-570/Jenkins
HFD-570/Barnes

Printed by Sandra Barnes

Electronic Mail Message

ivity: COMPANY CONFIDENTIAL

Date: 06-May-1999 12:19pm
From: John Jenkins
JENKINSJ
Dept: HFD-570 PKLN 10B45
Tel No: 301-827-1050 FAX 301-827-1271

TO: Richard Nicklas (NICKLAS)
TO: Sandra Barnes (BARNES)

CC: John Jenkins (JENKINSJ)
Subject: Proposed clinical comments to sponsor

Dick and Sandy

Here is some suggested wording for clinical comments to be included in the action letter for QVAR. These are modified from the comments that Dick gave me last week and are open for comment.

1. The safety and effectiveness of QVAR have not been adequately demonstrated to be clinically comparable to a currently marketed chlorfluorocarbon-based (CFC) beclomethasone diproprionate metered dose inhaler (MDI). In particular, your claim

is not supported by the available data. Therefore, delete all references to from the labeling and delete the proposed chart contained in the Dosasge and Administration section of the ing.

2. The dose proportionality and the clinical comparability of the safety and effectiveness of the two proposed strengths of QVAR (i.e., 40 mcg ex-actuator and 80 mg ex-actuator) have not been adequately established by the available data. Since the 80 mcg ex-actuator stength of QVAR was only studied in one adequate and well controlled clinical trial (i.e., Study 1083) and only at a dose of 320 mcg/day, the safety and effectiveness of the 80 mcg ex-actuator strength of QVAR have not been established across the range of doses proposed in the draft labeling. Therefore, the 80 mcg ex-actuator strengh of QVAR is not approvable. Delete all references to the 80 mcg ex-actuator dose from the labeling or submit any new data that establish the safety and effectiveness of the 80 mcg ex-actuator strength of QVAR across the entire range of doses proposed in the draft labeling.

3. Since the clinical comparability of QVAR to an approved CFC-based beclomethasone diproprionate MDI have not been established and since QVAR has not been studied in adequate and well controlled clinical trials to evaluate the safety and effectiveness of QVAR for the proposed indication to has not been established. Delete reference to this indication from the proposed labeling or submit new data that support the safety and effectiveness of QVAR for this indication.

I also need a copy of the draft labeling so I can follow Dick's proposed ents and add my own.

/s/

Memorandum of Telephone Facsimile Correspondence

Date: August 11, 2000

To: David M. Markoe, Jr.
Senior Regulatory Specialist
3M Pharmaceuticals
Fax number: 651-737-0465

From: Alan C. Schroeder, Ph.D.

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

Subject: Comments pertaining to NDA 20-911 (QVAR Inhalation Aerosol)

Please find attached the draft comments which I mentioned in our telephone conversation this afternoon.

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. As indicated, because of the limited time left in this review cycle, kindly respond by Wednesday, August 16, 2000.

Total number of pages in this transmission: 3 (including cover sheet)

Thank you.

/s/

Alan C. Schroeder, Ph.D.
Review Chemist
Division of Pulmonary and Allergy Drug Products

cc: HFD-570/Division files
NDA 20-911
HFD-570/Poochikian
Schroeder
Barnes

The comments listed below are cross-referenced (in parentheses) to comments in our letter of August 1, 2000.

1. You are reminded that DMF [redacted] is deficient and a letter, dated July 27, 2000, was sent to the DMF holder. (Comment 1)

2. As previously requested, modify the [redacted] test in the manufacturing process for the drug product to achieve a target of 3 minutes of immersion, which is based on your data. The allowed range around 3 minutes should also be tightened ([redacted] or alternatively, 3 minutes should be the minimum permitted immersion time. (Comment 2)

3. Provide the same limit on total manufacturing time [redacted] for the drug product at the Northridge, CA manufacturing site as for the Loughborough, UK site, unless you can provide other data to justify an alternative limit. Provide appropriately updated master batch records for the Northridge site. (Comment 3)

4. You are reminded of the following commitments which you have made.

   a. [redacted]

   b. A commitment to submit a more reliable method to monitor [redacted] in placebo by March 31, 2001. (Comment 8b)

5. Samples picked up by the Minneapolis District Office on April 25, 2000 were not intended to be used for methods validation by the FDA. Set aside the required reference standards, drug substance samples and drug product samples to be submitted to FDA laboratories upon their request, for methods validation/verification for this NDA. If information pertaining to these samples and reference standards already provided needs to be updated, provide such updates as an amendment to the method validation package with appropriate identification and Certificates of Analysis. (Comment 5)

6. Comments are withheld pertaining to the proposed expiration dating period, pending the results of a Biometrics review of the stability data. (Comment 6)

7. Comments are withheld pertaining to safety of impurities and leachables, pending the results of a pharmacology review of your responses in the August 4, 2000 amendment. (Comments 9 and 10).

8. The following comments pertain to labeling.

   a. As previously requested, modify the immediate container labels, as well as the carton labels, to increase the prominence and conspicuousness of the entire established name. This may be done, for example, by making the letters bold and increasing the space between the letters. Also as previously requested, improve the overall legibility of the immediate container label so that it will be easier for the patient to read. Additional space on the label to achieve these goals may be obtained for example, by removal of the duplicate "3M Pharmaceuticals" under the net contents statement, and by reducing the size of the trade name. (Comment 7b)

   b. Additional labeling comments may be forthcoming, including comments related to your proposal for a statement in the package insert, pertaining to particle size of the emitted aerosol spray. (Comment 7a)

9. You have indicated that dimensional controls for the actuator are a more sensitive measure than the spray pattern test, for ensuring consistent product performance. Provide a description of the methods used, and their validation, for control of the mouthpiece orifice, ——— according to the 8/17/99 amendment, vol. 2.6, page 215. This information should include the data to demonstrate that these methods can distinguish typical defects in the orifice and stem socket, and are appropriate to identify suitable and unsuitable mouthpieces. The best of the two methods for control of the orifice should be used as an acceptance test, or a combination of the two, as appropriate. (Comment 8a)

****
*** TX REPORT ***
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SUB-ADDRESS	
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PGS.	3
RESULT	OK

Memorandum of Telephone Facsimile Correspondence

Date: August 11, 2000

To: David M. Markoe, Jr.
Senior Regulatory Specialist
3M Pharmaceuticals
Fax number: 651-737-0465

From: Alan C. Schroeder, Ph.D.

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

Subject: Comments pertaining to NDA 20-911 (QVAR Inhalation Aerosol)

Please find attached the draft comments which I mentioned in our telephone conversation this afternoon.

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. As indicated, because of the limited time left in this review cycle, kindly respond by Wednesday, August 16, 2000.

Total number of pages in this transmission: 3 (including cover sheet)

BARNES

Record of Telephone Conversation

Date:	August 11, 2000
Subject:	NDA 20-911
Initiated by:	FDA
Product Name:	Qvar Inhalation Aerosol
Firm Name:	3M Pharmaceuticals
Contact:	David Markoe
Telephone Number:	(651) 736-5015

I called Mr. Markoe to tell him that we would send comments (by fax), pertaining to their last amendment (dated 8/4/2000), this afternoon and that he could call me when he receives them if he has any questions. I said we would like a response by Wednesday, August 16 in view of the limited time left in the review cycle. I said that this may be the last opportunity to resolve the CMC issues. He asked about the subject areas of the comments and I briefly listed them.

He called me back later in the day to say that he had received my fax and that he had one question. — (holder of Type II DMF — is shut down until August 28, and probably won't be able to respond to our deficiency letter until September. Before they shut down, they gave verbal assurances to 3M that they would agree to a U.S. only specification for the drug substance, in which they would accept the tightened specification for the — impurity (i.e., its limit would be NMT 0.1%, as requested by our pharmacologist in lieu of qualification). I asked what would happen to batches of drug substance which failed specifications and he said that they would probably go into European products. He said that 11 of the last 18 batches produced could meet the proposed specification. He also said that — indicated that they would address the issue of the — being an intermediate (rather than starting material). On the basis of this verbal assurance from — 3M changed their NDA specifications for the drug substance to NMT — %. He asked if, in view of this information, we could accept the DMF at this time for the NDA. I said that this would have to be discussed internally.

He thanked me.

/S/ 8/11/2000

cc: Orig. NDA #20-911 HFD-570/Division files HFD-570/ACSchroeder/8-11-2000 HFD-570/GPoochikian HFD-570/CSO SBarnes /S/ 8/11/00	R/D init. by: F/T by: ACSchroeder/8-11-2000 ACSfile: N2000_08_11_tel.doc

Memorandum of Telephone Facsimile Correspondence

Date: May 4, 2000

To: Dave Markoe
651-737-0465

From: Sandy Barnes
Project Manager

Subject: NDA 20-911

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Thank you.

Here is the Information Requst Letter I mentioned to you earlier this week.

Sandy Barnes
Project Manager
Division of Pulmonary and Allergy Drug Products Drug Products

Record of Telephone Conversation

Date:	August 20, 1998
Subject:	NDA 20-911
Initiated by:	FDA
Product Name:	Qvar HFA Inhalation Aerosol
Firm Name:	3M Pharmaceuticals
Contact:	David Markoe (regulatory affairs)
Telephone Number:	(612) 736-5015

August 19, 1998 telecon:

This was to clarify contract testing facilities (drug product) and their responsibilities so that we could submit an EES request.

See vol. 1.7 pg. 7 (original NDA).

The following is information for the commercial drug product. The 3M Northridge (CA) and Loughborough (UK) manufacturing facilities are the primary testing sites for drug product release. Northridge is a main lab for stability testing of drug product manufactured at Northridge, whereas drug product manufactured at Loughborough is mainly stability tested at

The other laboratories perform specialty testing. David said that he was at the airport, and that Mark Morken would call me to provide additional information.

August 20, 1998 telecon:

This call was with Mr. Mark Morken (who works for David Markoe). He provided the following information about the contract test laboratories:

only

perform the method for the drug product.

3M R&D Laboratories (St. Paul, MN) will provide back up testing for all tests.

provides

Laboratories 3M Sante (Pithiviers, FR) and 3M R&D

(St. Paul, MN) perform release testing on components.

, provides

Alan C. Schroeder, Ph.D.

cc: Orig. NDA #20911 HFD-570/Division file HFD-570/ACSchroeder/8-20-98 HFD-570/GPoochikian HFD-570/CSO SBarnes	R/D init. by: /S/ 8/20/98 F/T by: ACSchroeder/8-20-98 ACSfile: N20911_98-08-19_tel.doc

Memorandum of Telephone Facsimile Correspondence

Date: August 23, 2000

To: Dave Markoe
651-737-0465

From: Sandy Barnes
Project Manager

Subject: NDA 20-911

Thank you.

Attached and below are the labeling comments from the Medical Officer. Additional comments from CMC, Pharm/tox and Clinical Pharmacology will be sent when they are available.

We have the following comments in addition to those shown on the attached marked-up package insert and patient's instructions for use.

1. Thoughout the labeling, including the legend on the graphs, revised the dose of Qvar from daily dose to the dose given twice daily.

2. The heading on page 5 that reads " " is inconsistent with the first sentence that reads another clinical trial, 347 patients with symptomatic " .." Resolve this inconsistency.

3. Add a Geriatric Use subsection to the labeling according to 21 CFR part 201.

4. Revise the table on page 12 to indicate that the doses given are daily doses and that these are events that occurred significantly more frequently in the Qvar group than in the placebo group. In addition, annotation 23 refers to the table on page 148 of volume 271, but the data in the table on page 148 is different than the data in the table in the package insert. Address this inconsistency.

/S/

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products

cc: Orig NDA
Div File
HFD570 Barnes
HFD570 Nicklas

17 pages redacted from this section of the approval package consisted of draft labeling

Memorandum of Pre-NDA Meeting

Date: September 8, 1997

IND [redacted]

Sponsor: 3M Pharmaceuticals, Inc.

Drug: beclomethasone dipropionate HFA

FDA Representatives

Sandy Barnes, Project Manager
Dale Conner, Team Leader, Pharm.D., Clinical Pharmacology and Biopharmaceutics
James Gebert, Ph.D., Biometrics Reviewer
Bradley K. Gillespie, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
David Hilfiker, Project Manager
Peter Honig, M.D., Clinical Team Leader
John Jenkins, M.D., Division Director
John Leak, Ph.D., Review Chemist
Richard Nicklas, M.D., Medical Officer
C. Joseph Sun, Ph.D., Pharmacology Team Leader
Shannon Williams, Ph.D., Pharmacology Reviewer
Hilary Sheever, Ph.D., Pharmacology Team Leader
Shan Chu, Medical Officer

3M Pharmaceuticals' Representatives

Gene Colice, M.D., Associate Director
Jennie Vanden Burgt, US Clinical Project Leader
Les Harrison, Senior Research Specialist, Drug Metabolism
Chet Leach, Division Scientist, inhalation toxicology
Sujata Hannon, Senior Biostatistician, Statistical Data Services
Patti Stampone, Biostatistical Specialist, Statistical Data Services
Danna Ross, Research Specialist, Inhalation Drug Delivery
Kathy Ledoux, Research Specialist, Analytical Research & Development
Dave Markoe, Regulatory Specialist, Regulatory Affairs
Florence Wong, Director, Regulatory Affairs

The background package for this meeting is dated June 10, 1997.

Agenda

Introduction - 3M
Chemistry - FDA - Dr. Leak
Pre-clinical - FDA - Dr. Williams
Clinical Pharmacology - FDA - Dr. Gillespie
Clinical - FDA - Dr. Nicklas
Discussion
Conclusions

Following introductions, 3M Pharmaceuticals presented an introduction consisting of timelines for the submission of their data. 3M expects to submit the NDA in February of 1998. The data from the long term safety study will be submitted in the 4 month safety update.

The meeting then followed the agenda listed above.

The CMC issues raised during the review of albuteral also apply to this application, the FDA recommended that 3M address these issues in the upcoming NDA. The data presented in the June 10, 1997 submission was reviewed and the following comments were conveyed.

1. The following comments pertain to the Foreign Particulate testing.

   a. Although figure 1 as presented indicates there is a proportional number of —— to —— particulates determined by microscopic method for the samples used, there is no assurance that this ratio will hold for future batches of the drug product. In addition, foreign particulate matter amounts are under-reported using —— values since foreign particles between —— and —— are not included.

   b. Data reported is based on mutiple activations. There is no information provided as to whether most or all of the foreign particles are in one activation.

   c. Data in tables 1 and 2 indicate a large batch to batch variability in both total canister —— assay and microscopic —— —— assay and there is an increase with storage time. The NDA should address what has been done to stop —— formation, which is a contaminant, in the drug product.

d. Since —— particles increase with time and is a measure of product contamination, incorporating the —— —— test method at release only, rather throughout the full stability test period, is not recommended.

e. In the specification for —— in the drug product, information should be included as to the detection limit and the quantitation limit.

2. The following comments pertain to the Meeting Minutes of December 10, 1996 and the sponsor discussion of meeting issues.

Although the numbered items in the meting minutes have been addressed in the discussion beginning on page 94 and most details will be included in the NDA, several items need comment.

a. Item 12c on page 97 only indicates that extractables will be determined in the placebo. Data should also be included on the extractables from each component of the system that comes in contact with the drug product. Extraction should continue for a sufficient time and a suitable temperature to reach a constant value and provide a good profile of extractables. Proper solvents should be used for the extraction. Extractables in the placebo should continue past the proposed —— and results reported in the NDA.

b. Item 13 on page 97 indicates that —— will only be covered in the Development Pharmaceutics report. This storage condition should also be included in the stability protocol for the supportive data. This storage condition need not be used for stability studies of annual batches, but incorporated in stability studies if changes are made (valve, etc.)

c. Information should be provided as to the length of time the O-ring will be available, what is currently underway to use the —— —— O-rings, what pre-extraction procedures are currently being used and what procedures will be used in the future and be available when the NDA is submitted.

d. It is stated on page 98 that "those lots of drug product in the formal stability study program which were not used in clinical studies will have at least one determination of individual impurities using the method submitted in the NDA." The NDA should include an explanation as to why this determination is not to be performed at all pull points in stability studies.

3. The strengths are expressed in the draft labeling as — or — they should be expressed as ex-actuator.

4. The following comments pertain to the Table of Contents.

   a. Item 3.3.2, should include names and addresses of all parties involved in the manufacturing, including — contractors, testers, packagers, etc. This should also apply to drug substance manufacturers.

   b. Item 3.5.5, Development stability should include stability protocols and all data from all batches obtained under the protocols.

5. More information is needed on the changes in the valve and actuator parts of the container closure system during Phase 3 clinical trials and the NDA stability program as indicated in the table on page 176 and included in statements in item 2.1 on page 177.

6. Item 5.25, the following modification should be made to the Current Stability Protocol.

   a. There should be a separate test method and specification for the appearance of the valve components and the inside of the container.

   b. There should be a specification and method for extractables.

   c. The Number of Activations should be the Number of Medication Dose Activations.

   d. Particle Size Distribution should be presented as a complete distribution at each point between the valve and the filter.

The following Pharmacology/Toxicology issues were identified.

7. 3M was asked to determined if tissue from the 1-year dog study are still available, to reexamine the lungs and trachea. 3M indicated that the lungs were not fixed in a manner that would permit meaningful examination of alveolar size, but it might be possible to examine tracheal rings for any implications of growth abnormalities.

8. 3M was reminded of the need for qualification of impurities for the supplies used in the toxicology program. Based on the earlier discussion of — it would be appropriate to include — in the impurity profile comparison.

The following Clinical Pharmacology comment was made.

9. The information outlined in the Human Pharmacokinetics section of the submission appears adequate to support filing of an NDA. 3M was encouraged to continue attempts to develop a sensitive and specific assay to measure ——.

The following clinical issues were identified and should be addressed in the NDA.

10. Although there were a large number of studies perform, the data may not be sufficient to support the 100 mcg strength and the 800 mcg per day dose.

11. —— are not acceptable for demonstrating ——.

12. The —— data is not acceptable for labeling or advertising.

The purpose of today's meeting was to identify issues from the June 10, 1997 package that should be addressed in the NDA when it is submitted.

This concluded the meeting.

/S/

Sandy Barnes
Consumer Safety Officer

cc
Original IND ——
Div File
S. Barnes/3-14-98
FDA meeting attendees

MEETING MINUTES

Date: December 10, 1996

IND: [redacted] beclomethasone dipropionate in HFA-134a

Sponsor: 3M Pharmaceuticals

Representing FDA:

Sandy Barnes, Project Manager
Lindsay Cobbs, Project Manager
Peter Honig, M.D., Medical team Leader
John Leak, Ph.D., Review Chemist
Guirag Poochikian, Ph.D., Chemistry Team Leader
Brian Rogers, Ph.D., Review Chemist
Alan Schroeder, Ph.D., Review Chemist
C. Joseph Sun, Ph.D. Pharmacology Team Leader
Shannon Williams, Ph.D., Pharmacologist

Representing 3M Pharmaceuticals:

Kerri Ann Arnott, Manager, Regulatory Affairs
Gene Colice, M.D., Associate Director, Clinical Research
Jim Elvecrog, Manager Inhalation Drug Delivery
Chet Leach, Ph.D., Division Scientist, Pathology/Toxicology
[illegible]thy Ledoux, Section Leader, Analytical
[illegible]rk Markoe, Regulatory Specialist
Jeff Patrick, Analytical Research & Development
Danna Ross, Ph.D., Section Leader, Inhalation Technology
Maria Westfall, U.S. and Internal Program Manager

Background:

On October 11, 1996 3M requested a meeting to discuss aspects of the Chemistry, Manufacturing and Control (CMC) section of IND [redacted] 3M followed the initial request with a complete meeting package on November 21, 1996.

Agenda:

Introductions

Introduction - 3M

Discussion of questions from November 21, 1996 submission

2. The NDA should contain data collected on individual plates.

3. A descriptive appearance of the valve components and canister should also be added to the specifications. In addition the term "[redacted]" is not acceptable, "[redacted]" should be deleted and a more quantitative approach be if the content is not colorless.

4. Validation of valve delivery over a number of batches and time should be provided to confirm that the target value and average is correct.

5. The NDA should include an additional test for identification of beclomethasone dipropionate for a total of two tests for identification.

6. Medication delivery specifications should include sampling at the beginning, middle and end of the labeled content. In addition, studies should be performed to show the profile of medication delivery from the end of the labeled contents to the end of the canister.

7. The specification for beclomethasone content should not be two tier, if there is failure in the first tier, the batch fails. 3M should consider increasing the number of vials tested.

8. As stated previously impurities should be identified $\geq$ 0.1 percent.

9. A profile of impurities should be established to insure that changes that may occur can be investigated.

10. The [redacted] data should include a profile, i.e. each accessory and stage from the valve to the final filter in order to establish specifications. No comment can be made as to the proposed groupings.

11. The total combined molds and yeast count should be reduced (
The organism Enterobactiaceae should also be included in the specifications.

12. The following tests should be added:

    a. The suspension should be examined, at least initially, by microscope for

    b. An appropriate test and specification for spray pattern should be included in the drug product specification.

    c. The DMF should include data on valve extractables.

13. In addition, 3M should address temperature cycling, priming, and effect of cold temperature.

14. It was strongly recommended that 3M pre-extract O-rings.

In response to the sponsor's question # 2 regarding a change of methods during stability, the FDA indicated that a side by side comparison of the old and new method should be provided.

In response to the sponsor's question # 3 regarding electronic submissions FDA advised the sponsor that at this time disks are preferable to CD-ROM however the sponsor should reconfirm this prior to the submission of the NDA. The sponsor was advised that the FDA would appreciate receiving the stability data in Excel. Other area of the CMC section that would be useful in an electronic format include Drug Substance and Drug Product Specification, statement of composition and the stability protocol. The FDA would also be interest in receiving the preclinical and clinical data in electronic form.

In response to the sponsor's question regarding development pharmaceutics report the FDA responded that a single report that covers the product and changes made throughout development is useful, however the changes should be cross reference and also be identified in the appropriate sections.

3M was advised to insure that all question raised in IND are addressed when the NDA is submitted.

This concluded the meeting.

/S/

Sandy Barnes
Project Manager
Division of Pulmonary Drug Products

Attachment: Copy of Transparencies

cc: Orig IND —
Div File
FDA Meeting Attendees
R/D initialed by S. Williams 2/19/97
C. J. Sun 2/19/97
J. Leak 2/20/97
G. Poochikian 2/23/97

N:\IND — \96-12-10.min

Minutes of End of Phase II Meeting

April 12, 1995

IND —— Beclomethasone Dipropionate MDI HFA 134a

3M Pharmaceuticals

Meeting Attendees

FDA - Robert Temple, John Jenkins, Martin Himmel, Richard Nicklas, Joseph DeGeorge, Soo Choi, Gretchen Strange, Sandy Barnes

3M - Bert Slade, Florence Wong, Maria Westfall, David Donnell, Jennifer VandenBurgt, Patti Stampone, Les Harrison, Chet Leach, Dave June, Kerri-Ann Arnott, Barbara Moore, Corinne Bouchire

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Background packages dated July 5 and December 2, 1994 and January 4 and April 6, 1995

After introductions, 3M proceeded to give a presentation following the agenda outlined in their April 6, 1995 submission. Copies of the agenda and transparencies used during the presentation are attached.

3M clarified that the only difference between the 50mcg, 100mcg and 200 mcg dosages is the concentration of beclomethasone. The valves are identical in composition and size.

Preclinical/toxicology

3M outlined the toxicology studies performed (page 11 of the attachment) and gave a brief overview of the results of each study.

The FDA agreed that the preclinical studies are the type needed for an NDA. We could not comment on the adequacy of the studies for approval until the are submitted with the NDA for review.

The issue of the 1 year juvenile dog study remains unresolved. 3M understood the focus of the study to be the development of the Endocrine system and had designed their study to address that issue. HFD 150 had understood the purpose of the 1 year juvenile dog study was to investigate the development of the lung and trachea.

This issue should be resolved prior to submission of the NDA.

Clinical

3M has developed a bioanalytical assay for Beclomethasone which is able to assay in the range of 10-300pg/mL. This method will be published in May 1995, 3M will provide the FDA with a copy of the abstract which was published last year and a copy of the complete publication when it is available.

3M outlined the Pharmacokinetics, and Phase I, II and III studies which they have completed or are ongoing, the following specific deficiencies and problems were noted by the FDA:

1. Study 1129-Bron used only one dosage of each product, 400mcg 3M HFA-134a and 800mcg Beclovent 50.

2. Study 1163-Bron had no placebo arm and did not use the approved U.S. beclomethasone, therefore cannot be used for approvability.

3. Study 1183-Bron used only one dosage of each drug, 400mcg.

4. Studies 1129-Bron and 1130-Bron contained no ACTH stimulation testing and no 24 hour UFC collection.

These issues may not affect the approvability of the 3M beclomethasone HFA-134a NDA however they will make it difficult to label the new product. The new labeling should contain information informing the clinician how to substitute the new HFA-134a beclomethasone for the previously approved products. The 3M development program as outlined does not provide the information needed 3M had proposed two additional clinical trials 1163-Bron 12 month Safety & Efficacy and 1162-Bron Dose Ranging safety to complete their clinical development program. The FDA recommended the following changes to these protocols.

1163-Bron

1. Patients should be kept on the same dose for the first 2 months of the trial; the sponsor should ensure adequate representation of patients at the highest dose proposed for marketing. After 2 months the individual patient doses may be titrated based on clinical response.

2. ACTH should be measured at 1d, 2m, 4,m, 8m and 12m.

1162-Bron

1. This study should be revised to include efficacy in addition to the dose ranging and should include

   It would also serve to support the approval of the 800 ug dose, which is higher than the currently approved CFC product.

2. The trial may need to be expanded beyond 28 days depending on the sensitivity of FEV_1 and peak expiratory flow rate to detect a dose response.

3. We do not feel the patients need to be housed as 3M proposed and in fact have some concern regarding the artificial environment, although if as difference were shown from placebo this tril would support approval.

4. In order to strengthen the 100mcg program, we recommend using overlapping doses of 50mcg and 100mcg to link these dosages. Although 3M claims to have shown pharmacokinetically that two 50mcg doses equal one 100mcg dose we are not sure this can be interpreted to clinical use. /It was agreed that the Division would further consider this issue and get bacm to 3M.

5. Severe asthmatic could be added to the study if adequate rescue medications were offered.

3M will revise the protocols for 1162-Bron and 1163-Bron and submit them to the IND for our review.

The NDA is planned for submission during the second quarter of 1997.

This concluded the meeting.

/S/

Sandy Barnes
Consumer Safety Officer

Attachments - Agenda
Copy of Transparencies presented

ccIND
Div File
HFD-155SBarnes
HFD-155M.Himmelrevised 6/7/95
edited 7/13/95
HFD-155R. Nicklas/no comments
HFD-155J. Jenkins/revised6/27/95
HFD-155SChoi
HFD-155G. Strange

Proposed Agenda :

1.	Introduction of Participants and purpose/goal of the meeting	.... K.A. Arnott (5 min.)
2.	Brief Overview of Pharmaceutical Product Performance	..... D. June (5 min.)
3.	Brief Overview of Preclinical Program	..... C. Leach (5 min.)
4.	Review of Clinical Program	..... D. Donnell (20 min.)
5.	Comments and Discussion	..... All
6.	Conclusion	..... K.A. Arnott

We look forward to seeing you on the 12th of April and if you have any questions or comments, please contact the undersigned at (612) 733-2296.

Yours sincerely,

Corinne Bouchire
Senior Regulatory Officer

Redacted 29

pages of trade secret and/or confidential commercial information

K1.1

K1.1

N20911

N20911

Rec. 11/29/00 8:37 AM

ICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-911 /SE____ - _____

Drug QVAR Applicant 3M

RPM Barnes Phone 7-1055

☐ 505(b)(1)
☒ ~~505(b)(2)~~ Reference listed drug Bedovent

☐ Fast Track ☐ Rolling Review Review priority: ☒ S ☐ P

Pivotal IND(s) IND ~~00,038~~ —

Application classifications:
Chem Class 3
Other (e.g., orphan, OTC) ____

PDUFA Goal Dates:
Primary 9/15/00
~~Secondary~~ _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☒ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☒ AP ☐ AE ☐ NA

- Labeling & Labels
  FDA revised labeling and reviews..... _____
  Original proposed labeling (package insert, patient package insert) ..... _____
  Other labeling in class (most recent 3) or class labeling..... _____
  Has DDMAC reviewed the labeling? Not for mail Rev..... ☐ Yes (include review) ☐ No
  Immediate container and carton labels ..... _____
  Nomenclature review X

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.
  Exception for review (Center Director's memo)..... N/A
  OC Clearance for approval..... N/A

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) Material Submitted to DDMAC ☐ Materials requested in AP letter

- Post-marketing Commitments
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....

- Was Press Office notified of action (for approval action only)?..... ☐ Yes ☒ No
  - Copy of Press Release or Talk Paper..... N/A

- Patent
  - Information [505(b)(1)] ..... N/A
  - Patent Certification [505(b)(2)]..... X
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....

- Exclusivity Summary .....

- Debarment Statement X

- Financial Disclosure
  - No disclosable information ..... Not Need Submitted N/A
  - Disclosable information – indicate where review is located ..... N/A

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings X
  - Date of EOP2 Meeting Dec 10, 1996
  - Date of pre NDA Meeting Sept 8, 1997
  - Date of pre-AP Safety Conference N/A

- Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) .....

- Clinical review(s) and memoranda X

Continued ⇨

- Safety Update review(s) ..... X in Mo Rev

- Pediatric Information
  - ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☒ Deferred
  - Pediatric Page X
  - ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable

- Statistical review(s) and memoranda X

- Biopharmaceutical review(s) and memoranda X

- Abuse Liability review(s) ..... N/A
  - Recommendation for scheduling ..... N/A

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits ..... See DD Memo Dated 5/12/99 ..... Not Requested
  - ☐ Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda X

- Statistics review(s) and memoranda regarding dissolution and/or stability X

- ~~DMF review(s)~~ ..... —

- Environmental Assessment review/FONSI/Categorical exemption X

- Micro (validation of sterilization) review(s) and memoranda ..... N/A

- Facilities Inspection (include EES report)
  - Date completed Sept 14, 2000 ..... ☒ Acceptable ☐ Not Acceptable

- Methods Validation ..... ☐ Completed ☒ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda X

- Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 13, 1998

FROM: Alan C. Schroeder, Ph.D. 7/13/98

SUBJECT: 45 Day Filing Meeting for NDA 20-911 (QVAR HFA Inhalation Aerosol)

TO: NDA 20-911 File

The following information was collected from the NDA, and from faxes from the applicant in response to our questions (refer to faxes dated 6/12/98 and 7/1/98; see attachments). It formed the basis of the CMC discussion at the 45 day filing meeting.

Background:

DRUG PRODUCT: Beclomethasone Dipropionate HFA-134a Inhalation Aerosol - solution MDI (ethanol present; no other excipients). Intended dose is *one actuation* (40 or 80 mcg, depending on strength) twice a day. Repriming interval is proposed as once every 2 weeks. A expiration dating period is proposed for both strengths.

The canister is a 10 mL canister (fitted with a 50 µL metered dose valve (Neotechnic: valve contains 3 components: diaphragm and tank seal made of , and a gasket made of . Also, a O-ring is used as an additional seal when the valve is crimped onto the canister. are said to be identical to those used in Proventil HFA MDI. Actuator/dust cap are made from Actuators are either dark mauve or beige, and the dust cap is grey.)

80 mcg drug delivered ex-actuator is equivalent to 100 mcg delivered for the proposed drug product. (See vol. 1.2, pg. 14. Note that method 3191 for through-life medication delivery does describe actuations made through the mouthpiece into the collection apparatus: see vol. 1.9 pg. 79.)

The drug product is supplied in two sizes: 200 actuations and 100 actuations per canister, and two strengths for each size, 80 mcg and 40 mcg per actuation (ex-actuator).

3M and Hoechst Marion Roussel "have agreed to co-promote this product in the U.S. under the same tradename of QVAR™."

Drug Substance (NDA vs. pivotal IND clinical studies)

Manufacturer(s)/Site(s)

NDA site: [redacted] - DMF [redacted] (according to the 6/12/98 fax, [redacted] is indicated to be the manufacturer for all drug substance lots - and [redacted] DMF [redacted] is referenced).

Method of Synthesis/Scale - method of synthesis is referenced to the NDA, vol. 1.6, Section 4.2. (No changes in synthesis over the drug development process are specified.). Scale of batches is said to be described in [redacted] DMF [redacted]

Purity profile of drug substance - see NDA vol. 1.2 (pages 22 and 27), and vol. 1.6 (pp. 207-212).

Drug Product

Formulation (IND vs. NDA) -
Investigational formulations: see pp. 19-21 (v. 1.2) and compare NDA formulation (v. 1.7, pp. 2-3): they are the same for each strength and vial fill.

Note however that changes are indicated in early formulations in the Pharmacology/Toxicology section: v. 1.2, pg. 22. It is stated that early toxicology studies used a formulation that contained [redacted] and up to [redacted] ethanol. This is the case for toxicology studies 0791AD0137, 0791RR0511, 0791AD0138, 0791SR0512); however the "subsequent and more pivotal longer term toxicology studies (i.e., 0792SR0390, 0791SD0139, 0793CD0401) used no [redacted] and [redacted] ethanol in the formulation in order to match the proposed marketed product." This was discussed with the pharmacology reviewer (Dr. Tim McGovern) and found not to be a problem.

Manufacturer(s)/Site(s)

[redacted]
3M Health Care Ltd.
Derby Road
Loughborough,
Leics, LE11 1EP
UK

DMF [redacted]

or

3M Pharmaceuticals
19901 Nordhoff St.
Northridge, CA 91324-3298

Product release and stability testing: various sites (see application).

It is noted that stability data have been provided from both manufacturing sites (above), and that clinical supplies for the six "pivotal clinical trials" were manufactured at both sites.

Batch numbers (used in clinical studies): see NDA vol. 1.2, pg. 21. Note that the 6 "pivotal clinical trials" as per. vol. 1.2, pg. 96, used clinical supplies manufactured at both Loughborough, UK and at Northridge, CA (see vol. 1.2, pg. 21 and vol. 1.11, pp. 3-8). Both 50 mcg/puff and 100 mcg/puff strengths used in clinical studies have been manufactured at both manufacturing sites (almost all of the drug product used in clinical studies were the 200-actuation size, rather than the 100 actuation size).

Container/closure system (IND vs. NDA) - see vol. 1.3 pp. 7-12.

There have been changes over the drug development program in the valve (and to a lesser degree, the actuator), see below.

Valve:

Original valve (— components for gasket seal and diaphragm. (Problem: inadequate sealing at diaphragm-stem interface on stability).

First change (IND amendment 5/5/94, replacement of diaphragm with) was used for all phase 2 and 3 studies and contains the configuration intended for marketing.

Second change (: change in valve design from moving bottle emptier to fixed bottle emptier.) Purpose of change: to reduce variability at the end of product life. This change occurred late in Phase 3 (amendment dated 8/28/97). Study #1163 (12 month safety trial) was conducted with this modification (but no previous studies). Applicant claims data to demonstrate that there is no difference in performance between this and the previous valve, except at the end of product life. (Graphical summary of data, see v. 1.3, pp. 24-26).

Third change: improvement of manufacturing method for in the valve stem ( ) This occurred only after Phase 3 clinical trials. (It will be clarified with the applicant whether there are comparative data to support this change).

Actuator:

For clinical trials, actuator was produced from a single cavity mold (manufacturer: [redacted]

For to be marketed product, two suppliers of actuators are proposed [redacted] - same design, only differences in external markings, color and slight sleeve design changes (apparently to hold canister more securely).

Stability (quality and adequacy of data)

batch numbers (and other identifying information) of drug product on stability - vol. 1.11, pp. 3-8 (clinical lots identified on stability).

PROBLEMS: Note that earlier methods were later found to be inadequate, and therefore, much stability data cannot be used in the statistical determination of expiration dating period (e.g., for impurities: this affects all but one clinical lot; see vol. 1.11, pg. 242, and as an example for all test parameters, see vol. 1.12, pg. 201 and following. For impurities, it appears that there is a maximum of 6 months of data for batches to be used for stability analysis, and there are no comparisons for individual impurities because of method inadequacies (v.1.11, pg. 242).

As another example, note medication delivery data (v. 1.11, pg. 130). Much of the data available used a two actuation method, which was later changed to a one actuation method (one actuation dose is intended). It is claimed that there is no statistical difference between the two methods. Both two actuation data and one actuation data were combined and analyzed together for estimation of expiration dating period.

As another example (see v.1.12, pg. 1 & following) - The cascade impactor method for most studies used a [redacted] method. This was determined not to be representative of recommended dosing, and a [redacted] method was developed to more closely reflect actual patient use. Later stability samples were switched to the [redacted] method. It was found that the two methods do NOT produce [redacted] The stability report only analyzes the [redacted] data.

manufacturing site - either Northridge, CA or Loughborough, UK (see vol. 1.11, pp. 3-8)

batch size(s) vs. proposed production batch size - NDA stability lots (see vol. 1.11 pp. 4-7), which include clinical lots were compared to batch records ("examples" of master manufacturing orders):

> NDA stability lots had batch sizes of [redacted] (Northridge facility) and [redacted] (also [redacted] (Loughborough facility).

To-be-marketed lots (from examples of master manufacturing orders, e.g., v. 1.7, pg. 193): batch size —— for all Northridge batches and —— (for 100 vs. 200 actuation canisters, respectively) for Loughborough batches.

Therefore, it appears that NDA stability batches were manufactured to approximately one-third the scale of the intended production batches, using "production scale" equipment (v. 1.11, pg. 3).

method of manufacturing - "same for all lots" (per 6/12/98 fax) as described in vol. 1.7, beginning with page 14. Note *that differences between the two manufacturing sites* are described in vol.1.7, pp. 20-23.

extent of data in CCS proposed as market package - (see vol. 1.11 - 1.14 for stability data). See above under "batch numbers." Note that four parameters were analyzed for determination of an expiration dating period: i.e., beclomethasone dipropionate content, drug-related impurities, medication delivery/through life, and particle size distribution, —— impactor. (Other parameters which could have been analyzed, but were not, include for example, valve delivery, fill weight, content.")

Because of impurity assay problems (see above), the impurity data were not subject to regression analysis and determination of 95% confidence interval. Total drug related impurities are said to be within specification (data are available for various lots, from 12 to 36 months - see pg. 25, vol. 1.11).

Medication delivery data were analyzed by combining two actuation data with one actuation data (applicant refers to a study in the Development Pharmaceutics section which claims no statistical difference between the two sets of data: see vol. 1.3, pg. 79). Medication delivery (v. 1.11, pg. 130) - there are two actuation data for 11 lots through 24 months, one lot through 36 months (6 lots to 36 months with a switch from two to one actuation methods after 24 months). Other lots are provided with smaller amounts of stability data. (95% confidence limits do not seem to be provided graphically: see v. 1.11, pp. 143-144 and 166-167, for example, although they were mentioned previously: see vol. 1.11, pg. 21).

Calculated expiration dating periods for various product configurations and various test parameters are given in vol. 1.11, pg. 24 (impurities are not included in the statistical estimate, as indicated above). Calculations are for the following parameters: content, medication delivery, —— particle size distribution (for each of 4 sets of combined stages).

Particle size distribution: (statistical treatment is only based on the 20-actuation method data). Data are available for up through 36 months (7 lots of data) and for an additional 12 lots of data (through 24 months).

Other lots of data (with shorter time frames) are available. Figures start at vol.1.12, pg. 104.

test methods (e.g., protocol, stability-indicating assay method, etc.)

Stability protocol: see pg. 8-20, vol. 1.11. Storage conditions were 25°C/60%RH and 40°C/75%RH (except for the first 9 months of the first NDA stability lot, #PD3511, initiated at [redacted] then switched to 25°C/60%RH for the remainder of the study). All lots were stored inverted, some lots were stored also in an upright and/or a horizontal position. Test intervals were standard. In some cases additional test intervals were also added. Test parameters studied appear to be typical for MDIs, with the exception that specifications for net content weight and pressure were missing. Data have been analyzed for overall trend analysis, and comparisons of storage conditions, storage orientations, manufacturing sites, product configurations and clinical/non-clinical lots. The method for drug related impurities (see v. 1.9, pg. 315 & following) is said to monitor – known process impurities and – identified degradation products (in the drug product formulation).

Environmental assessment. A categorical exclusion is claimed under 21 CFR 25.31(b). [vol. 1.14, pg. 282]

Conclusions: The Division agreed to file this application (refer to 45-day filing meeting on 7/7/98).

cc:	Orig. NDA #20-911 HFD-570/Division File HFD-570/ACSchroeder/7-13-98 HFD-570/GPoochikian HFD-570/CSO SBarnes	R/D init. by: /S/ 7/14/98 F/T by: ACSchroeder/7-13-98 ACSfile: N20911_45day_memo.doc **ATTACHMENTS**

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Expiration Date: November 30, 1996.

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

3M Pharmaceuticals
Bldg. 260-6A-22, 3M Center
St. Paul, MN 55144-1000

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

3M Pharmaceuticals
Bldg. 260-6A-22, 3M Center
St. Paul, MN 55144-1000

Attn: Dave Markoe

3. TELEPHONE NUMBER *(Include Area Code)*
612-736-5015

4. PRODUCT NAME
QVAR (beclomethasone dipropionate, USP) Inhalation Aerosol

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER
3457

7. LICENSE NUMBER/NDA NUMBER
NDA 20-911

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES ☒ NO *(See reverse if answered YES)*

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse if answered YES)*

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
D. M. Markoe, Jr.	Regulatory Specialist	6 May 98

FORM FDA 3397 (12/93)

APPLICANT NAME 3M PHARMS

PRODUCT NAME QVAR (BECLOMETHASONE DIPROPIONATE) 80/40MG.

FORM MUST BE COMPLETED ASAP

1. YES User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMIS DATA ELEMENTS

2. (YES) NO CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE *CROSS REFERENCED* IN ANOTHER SUBMISSION?

3. YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION		
N_____	_____	FEE	NO FEE
N_____	_____	FEE	NO FEE

4. (YES) NO BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N_____	_____	N_____	_____

5. P (S) PRIORITY OR STANDARD?

/S/ 5/21/98

6. CSO SIGNATURE/DATE SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 1133	HFD# 570	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION: Sandy Barnes		Qvar	beclomethasone dipropionate HFA, inhalation a

A. Look-alike/Sound-alike

	Potential for confusion:		
Kwell	XXX Low	____ Medium	____ High
Quiebar	XXX Low	____ Medium	____ High
Quarzan	XXX Low	____ Medium	____ High
Cutar	XXX Low	____ Medium	____ High
	____ Low	____ Medium	____ High

B. Misleading Aspects:

C. Other Concerns:

There may be some pronunciation problems

D. Established Name

XXX Satisfactory

____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 4/6/99

ATTACHMENTS
7/13/98 Memo to file

3M Pharmaceuticals
Regulatory Affairs 260-6A-22, 3M Center, St. Paul, MN 55144

FAX

Date: 12/June/98
Number of pages including cover sheet: 3

To:
Sandy Barnes
HFD-570
Phone: *8 301 827 1075
Fax phone: *8 301 827 1271
CC:

From:
David Markoe
3M Pharmaceuticals
Phone: (612) 736-5015
Fax phone: (612) 737-0465

REMARKS: ☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Sandy,

As we discussed....location of CMC information for Dr. Schroeder. The lot number of drug substance used in the 12 month dog study is expected from Loughborough on Monday. I'll call when it is available.

- Dave

Clarification of CMC information for NDA 20-911 (requested by Dr. Schroeder).

Drug Substance

Batch # 's and purity profiles of drug substance that were used in pre-clinical, clinical and NDA stability along with the manufacturer, method of synthesis and batch scale size

The batch numbers and purity profiles of drug substance used in clinical studies and NDA stability can be found in **Volume 1.6 (Section 4.2 – Drug Substance) in the tables beginning on page 207**. These lots can be linked to the *drug product* produced from the drug substance in tables provided in **Volume 1.11 (Section 4.7 – NDA Stability) beginning on p. 3**.

Batch numbers of drug substance used in pre-clinical studies are tabulated below:

3M Toxicology Report Number	Drug Product Lot	Drug Substance Lot
0791AD0137	CT910532	3686/M1 (
0791AD0138	CT910532	3686/M1 (
0791RR0511	FN5880	3782/M1 (
0791SR0512	FN5882 & FN 5884	3782/M1 (
0791SD0139	CT910532	3686/M1 (
0792SR0390	FN6036 & FN6037	3782/M1
0793CD0401	93I01	Awaiting Response from Loughborough

Purity profile of the drug substance used in pre-clinical studies is discussed in the **Application Summary – Volume 1.2 (pages 22 and 27).** See also vol. 1.5 pg. 265 & 280-282, 279 (d product)

The method of synthesis is noted in **Volume 1.6 (Section 4.2 – Drug Substance) beginning on p.3**. The manufacturer for all drug substance lots is — and their DMF — is referenced. The actual scale size of batches is found in — 's DMF.

Drug Product

Batch # 's used in clinicals, the manufacturer of the batches used in clinicals along with the container-closure system and method of manufacture used in relationship to pre-clinical, clinical and NDA stability

The batch numbers of drug product used in clinical studies can be found on **p. 21 of the Application Summary – Volume 1.2**. The manufacturer of these batches is identified on the tables provided in **Volume 1.11 (Section 4.7 – NDA Stability) beginning on p. 3**. In addition, all NDA stability lots can be found in this section. The drug product is manufactured at one of two sites: Northridge, CA or Loughborough, UK.

purity profile of d.p. - see v. 1.11 - 1.14

The method of manufacture is the same for all lots and this method can be found in **Volume 1.7 (Section 4.3 – Drug Product) beginning on page 14**.

The development and changes to the container-closure system as compared with the to-be-marketed product are described in **Volume 1.3 (Section 4.1 - Development Pharmaceutics) beginning on p.** 7.

Drug product lots used in pre-clinical studies can be found in the tabulation above. CT910532 and 93I01 were produced in Loughborough and "FN" lots are laboratory lots produced in the St. Paul laboratory or Northridge production facility.

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 20911/000
Priority: 3S
Org Code: 570
Stamp: 12-MAY-1998 Regulatory Due: 31-AUG-2000
Action Goal:
District Goal: 20-DEC-1999
Applicant: 3M PHARMS
3M CENTER BLDG 260 6A 22
ST PAUL, MN 551441000
Brand Name: QVAR(BECLOMETHASONE DIPROPIONATE)80/40MG
Established Name:
Generic Name: BECLOMETHASONE DIPROPIONATE
Dosage Form: AER (AEROSOL)
Strength: 80 AND 40 MCG/ACTUATION

FDA Contacts:
S. BARNES (HFD-570) 301-827-1050 , Project Manager
A. SCHROEDER (HFD-570) 301-827-1068 , Review Chemist
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation:

ACCEPTABLE on 14-SEP-2000 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 21-DEC-1999 by S. FERGUSON (HFD-324) 301-827-0062
WITHHOLD on 07-MAY-1999 by M. GARCIA (HFD-322) 301-594-0095

Establishment: 9610441
3M HEALTH CARE LTD
LE11152
LOUGHBOROUGH, LEICESTERSHIR
DMF No:
AADA No:

Profile: ADM
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-MAR-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment: 2010441
3M PHARMACEUTICALS INC
19901 NORDHOFF ST
NORTHRIDGE, CA 91328
DMF No:
AADA No:

Profile: ADM
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-MAR-2000
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

Responsibilities:
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment: 2126770
3M PHARMACEUTICALS INC
3M CENTER BLDG 270-3A-01
DMF No:
AADA No:

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

SAINT PAUL, MN 551441000

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **18-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE RELEASE TESTER**
FINISHED DOSAGE STABILITY TESTER

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **27-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **18-APR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-APR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

Establishment:

DMF No:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: DMF No:
AADA No:

Profile: **CRU** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**

Establishment: DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **27-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: DMF No:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **27-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Printed by Sandra Barnes

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 07-May-1999 08:25am
From: John Jenkins
JENKINSJ
Dept: HFD-570 PKLN 10B45
Tel No: 301-827-1050 FAX 301-827-1271

TO: Richard Nicklas (NICKLAS)
TO: Sandra Barnes (BARNES)

CC: John Jenkins (JENKINSJ)
Subject: Labeling Comments for QVAR

Dick and Sandy

Here are my proposed labeling comments for the QVAR letter. Most of these track along with Dick's review recommendations. There are so many problematic areas that I don't think we should try to send them marked up labeling, we should send comments in the letter only. Feel free to comment on these if you feel they should be modified or that other comments should be added.

DRAFT

1 pages redacted from this section of the approval package consisted of draft labeling

There may be other comments from other disciplines such as biopharm and pharm/tox since I have not made reference to these sections above other than the comment about removing the references regarding comparable systemic exposure of QVAR and CFC BDP.

John