=1.1-33.3% and for hydroureter is 4.85%; range = 0.7-26.7% in Principles and Methods of Toxicology/ Edited by Wallace Hayes, Raven press 1994). In addition, no such effects were evident in the pilot study wherein F0 rats received comparable treatment. Thus, these latter findings are of doubtful toxicological significance.

Table 10. Summary of the Incidence of Fetal Skeletal Malformations and Variations in Rats

Dose groups (mg/kg)	Air Cont.	Placebo	BDP/HFA (mg/kg) 0.24	1.15	2.83
		No. of Fetuses (No. of litters)			
Number Examined:(# Litters):	137(24)	141(23)	153(23)	144(24)	146(24)
Skeletal Malformations:	0(0)	0(0)	0(0)	0(0)	0(0)
Skeletal Variations:					
Sternebra					
Delayed ossification	12(10)	5(5)	17(8)	25(14)	36(18)
% affected	9(42)	4(22)	11(35)	17(58)	25(75)
Skull (IO)					
Any Variations	8(7)	8(7)	8(5)	7(6)	14(9)
% affected	6(29)	6(30)	5(22)	5(25)	10(38)
Frontals (IO)	2(2)	0(0)	1(1)	1(1)	2(2)
Parietals (IO)	4(4)	1(1)	2(1)	2(2)	10(7)
Interparietals (IO)	4(3)	4(4)	5(4)	4(4)	1(1)
Superoccipital (IO)	0(0)	5(4)	5(3)	1(1)	0(0)
Sutura/Frontals Enlarged	2(2)	1(1)	1(1)	4(3)	8(7)
Body of Hyoid (IO)					
IO/Reduced	1(1)	0(0)	1(1)	0(0)	0(0)
Thoracic Centrae					
Combined Observations	31(15)	28(13)	36(16)	38(20)	45(20)
% affected	23(63)	20(57)	24(70)	26(83)	31(83)
Dumbell Shaped	25(14)	21(11)	28(15)	30(17)	32(17)
Bipartite/IO/A	10(7)	8(5)	10(6)	18(12)	20(10)
Lumbar Centrae					
Dumbbell Shaped	0(0)	1(1)	1(1)	1(1)	0(0)
Dumbbell/bipartite	0(0)	0(0)	0(0)	0(0)	2(2)
Ribs:					
Wavy/bulbous	1(1)	0(0)	0(0)	4(2)	0(0)
Rudimentary 14th	16(11)	18(8)	8(7)	22(11)	11(9)
Cervical	0(0)	0(0)	3(2)	0(0)	0(0)
Pelvic Girdle (IO)	1(1)	0(0)	0(0)	1(1)	0(0)
Sacral Vertebrae (IO)	8(6)	7(3)	10(5)	19(7)	12(8)

IO Incomplete ossification; A = Unossified (possibly absent)
Note: Variations which occurred only in the air control or placebo group are not included.

Review of the data in The data in Table 10 above show that there was no treatment-related increase in the incidence of skeletal malformations in any of the groups treated with Beclomethasone Dipropionate, However the incidence of sternebral variations (reduced ossification) were significantly increased at the high dose relative to that in the air controls. These effects were probably related to reduced fetal weights seen in this group.

In conclusion, Beclomethatasone Dipropionate/HFA exposure via inhalation during the period of organogenesis produced slight initial reductions in maternal body weights, reduced fetal weights and increased incidence of sternebrae variations (delayed ossification) at the mid and high doses (daily doses of 1.15 and 2.83 mg/kg/day, respectively). These effects are consistent with the known effects of beclomethasone and other corticosteroids in rats. There was no increases in the incidence of external visceral, or skeletal malformations at any dose tested. However, treatment-related effects of increased incidence of red/red foci in the adrenals of F1 fetuses were observed at the mid and high doses. The toxicological significance of this finding in regard to the normal physiology and development of F1 fetuses should be addressed by the Sponsor.

SUMMARY AND EVALUATION:

Currently the Sponsor has submitted a 90-day inhalation toxicity study in rats, a 1year inhalation study in dogs and a Segment II inhalation Reproductive toxicity study in rats in support for developing a Beclomethasone dipropionate (BDP) in an HFA-134a propellant formulation for the treatment of asthma.

In the 3-month inhalation toxicity study in rats, inhalation of beclomethasone dipropionate/HFA at pulmonary doses of 4.8, 24.0, and 125.0 µg/kg for 90 days was well tolerated, with no mortality or drug-related clinical signs of toxicity observed. Treatment related effects were limited to mild reductions in body weight gains (3-14% in males and 9-18% in females in all drug-treated groups) and reduced white blood cells due mainly to lymphocyte depletion were seen in both sexes at the high dose. The thymus was identified as the target organ of toxicity with dose-dependent reductions in thymic organ weights and thymic lymphoid depletion observed histologically at the mid and high doses. All effects were reversible after 8 weeks of recovery. The 4.8 µg/kg pulmonary dose (including estimated deposition factors) was the NOAEL for the study.

In dogs, BDP/HFA was administered by inhalation at estimated inhaled doses (excluding deposition factors) of 0.05, 0.16, and 0.5 mg/kg/day for 52 weeks. Likewise, a separate group of dogs were administered BDP formulated with CFC at an estimated inhaled dose of 0.5 mg/kg/day. Both high dose formulations resulted in exacerbation of demodectic mange, necessitating the premature sacrifice of several dogs/sex in each group. Treatment-related effects observed with both formulations included: clinical signs of distended abdomen, skin thickening, excess body fat, hair loss, skin reddening and increased incidence of skin lesions; Target organs of toxicity included: adrenals, liver, lymphoid tissue (lymph nodes, spleen, and Peyer's patches), skin, bone marrow (slight hypoplasticity), and exocrine pancreas (atrophy). In addition, evidence of reproductive organ toxicity was observed in both sexes. Male dogs dosed with the high dose HFA formulation showed an increased incidence of focal prostatitis, which was not observed in the high dose BDP/CFC males. In general the toxicity observed with the HFA

formulation, including effects on reproductive organs, were consistent with that expected with chronic administration of corticosteroids in dogs. However, unexpected findings of focal prostatitis were observed in the high dose BDP/HFA males, with no such findings in the high dose CFC group males. Toxicokinetic data showed that the HFA formulation was also associated with increased systemic exposure (AUC values) compared to the BDP/CFC formulation. Since a major cause of prostatitis in dogs is bacterial infection, the increased systemic exposure in the high dose HFA group may have contributed to increased immunosupression, thus leading to a greater susceptibility to prostatic infection. The 0.16 mg/kg mid dose of BDP/HFA showed no incidence of prostatitis and resulted in systemic exposures which were comparable to those observed in the high dose (0.5 mg/kg) CFC group. The Sponsor should address the toxicological significance of the observed prostatitis in dogs, relative to the clinical development of the BDP/HFA formulation. The 0.05 mg/kg dose of BDP/HFA was the NOAEL for the study.

Originally, the 1-year study in immature dogs was requested by the Division to examine possible tracheal deformities which had been reported in mature dogs following chronic administration of beclomethasone. However, the standard gross and histological examinations of the pulmonary system employed in the 1-year dog study reviewed herein, were inadequate to detect possible morphometric, macroscopic, and/or microscopic changes in the trachea. At a pre NDA meeting held September 8, 1997, the Sponsor was asked to perform a more detailed examination of the trachea and lung tissues, if available, in order to address this particular concern. In this regard, other chronic toxicity studies in dogs have not established clear evidence of corticosteroid-induced effects on tracheal development.

Collectively the observed effects with the BDP/HFA formulation in the 90-day inhalation toxicity study in rats and the 1-year inhalation toxicity study in dogs, including effects on reproductive organs in dogs, are consistent with those expected with chronic administration of corticosteroids. There was no unexpected toxicity observed in either species, with the exception of an increased incidence of prostatitis in dogs treated with the high dose BDP/HFA formulation. The toxicological significance of the observed prostatitis in dogs as it relates to the clinical development of the BDP/HFA formulation should be addressed by the sponsor.

In the segment II inhalation reproductive toxicity study in rats, administration beclomethasone dipropionate/HFA-134a at estimated pulmonary doses (considering deposition factors) of 0.24, 1.15, and 2.83 mg/kg/day during the period of organogenesis produced slight, yet reversible, suppression of maternal body weight gains. Beclomethasone did not increase the incidence of external, visceral, or skeletal malformations in F1 offspring in rats. However, it was associated with delayed development at the mid and high doses, including reduced fetal weights and increased incidence of sternebrae variations (delayed ossification). These effects are consistent with the known effects of beclomethasone and other corticosteroids on fetal

development. F1 fetuses also showed an increased incidence of red/red foci in the adrenals. The toxicological significance of this finding in regard to the normal physiology and development of F1 fetuses should be addressed by the Sponsor.

RECOMMENDATIONS:

1. The Sponsor should address the toxicological significance of the observed increased incidence of prostatitis in the one year study in dogs (3M study No. 0793CD0401) in the high dose BDP/HFA group.

2. In the Segment II inhalation developmental toxicity study of beclomethasone in rats, treatment related findings of red/redden adrenals were observed in F1 fetuses from F0 females given the mid and high doses. The toxicological significance of this finding in regard to the normal physiology and development of F1 fetuses should be addressed by the Sponsor.

/S/ 2/23/98
Shannon P. Williams, Ph.D.

Original IND
c.c. HFD-570
HFD-570/C.J.Sun
HFD-570/Nicklas
HFD-570/S. Williams
HFD-570/S. Barnes

/S/ Feb 23, 1998

LETTER TO THE SPONSOR:

We have reviewed your submission to IND —— dated 6/17/97 and have the following comments:

1. In the 1-year oral toxicology study in dogs (3M study No. 0793CD0401), males given the high dose beclomethasone dipropionate HFA formulation showed an increased incidence of focal prostatitis, which was not observed in the high dose CFC control group. The toxicological significance of this finding in relation to the clinical development of the BDP/HFA formulation should be addressed.

2. In the Segment II inhalation developmental toxicity study (Report N0. L08398) of beclomethasone in rats, treatment-related findings of red/redden adrenals were observed in F1 fetuses from F0 female rats given the mid and high doses. The toxicological significance of this finding in regard to the normal physiology and development of F1 fetuses should be addressed.

HFD-570 : DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Labeling Review

NDA No. 20-911 **Submission Date:** 12 MAY 1998

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 14 SEP 2000

Information to be Conveyed to Sponsor: Yes (✔), No ( )

Sponsor: 3M Pharmaceutical Division

Drug Name: *Generic:* Beclomethasone dipropionate *Commercial:* QVAR™

Drug Class: Steroid

Route of Administration: Oral inhalation

Background: Revisions to the sponsor's proposed label were communicated via fax to the sponsor as described in the Labeling Review for NDA 20-911 (dated September 12, 2000). The sponsor resubmitted a draft label which incorporates most of the recommended changes on September 13, 2000. The sponsor's revised draft labeling to the NDA is evaluated below. In addition, the sponsor was asked to address a discrepancy related to the maximum dose tested in the Segment II reproductive toxicity study performed in rats using the QVAR formulation (Study number L08398). The available information suggested a maximum inhaled dose of 28.3 mg/kg/day was tested while the sponsor refers to a maximum dose of 15 mg/kg in the proposed label.

The following sections of the proposed label should be revised as follows:

In the "**Carcinogenesis, Mutagenesis, Impairment of Fertility:**" section, the first sentence of the first paragraph should read "The carcinogenicity of beclomethasone dipropionate was evaluated in rats which were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day."

The first sentence of the second paragraph of this section should read "Beclomethasone dipropionate did not induce gene mutation in bacterial cells or mammalian Chinese Hamster ovary (CHO) cells in vitro."

The second and third sentences of the third paragraph of this section should read "Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 20 times the maximum recommended daily inhalation dose). No inhibition of the estrous cycle

in dogs was seen following 12 months of exposure to beclomethasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mg/kg (approximately 15 times the maximum recommended — daily inhalation dose ——

In the "**Pregnancy**" section, the last sentence of the paragraph subtitled "**Teratogenic Effects**" should read "Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

The Sponsor addressed the dose discrepancy in the Segment II reproductive toxicity study in rats by indicating that the assumptions used in calculating the actual dose to the animal were different from those used by the Division. Specifically, the sponsor assumed a gestation Day 20 body weight of 348 g and a minute volume average of 0.15 l/min. The assumptions used by the Division at the time of review were a body weight of 250 g and a minute volume average 0.2 l/min. The Sponsor stated that they find either set of assumptions to be acceptable. However, the more conservative values were used in other submissions outside of the US.

The Sponsor's originally proposed dose of 15 mg/kg/day in the QVAR label is acceptable since their assumptions in calculating the animal dose are valid and produce a more conservative dose estimate. In addition, it is worthwhile to provide consistency among the various submissions for this drug product.

Based upon the above comments, the following sections of the sponsor's proposed label should read as follows with the additions and deletions marked accordingly:

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenicity of beclomethasone dipropionate was evaluated in rats which were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. There was no evidence of carcinogenicity in this study at the highest dose, which is approximately 30 times the maximum recommended — daily inhalation dose

Beclomethasone dipropionate did not induce gene mutation in ~~the~~ bacterial cells or mammalian Chinese Hamster ovary (CHO) cells in vitro. No significant clastogenic effect was seen in cultured CHO cells in vitro or in the mouse micronucleus test in vivo.

In rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg/day (approximately 200 times the maximum recommended — daily inhalation dose —). Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 20 times the maximum recommended — daily inhalation dose —

— No inhibition of the estrous cycle in dogs was seen following 12 months of exposure to beclomethasone dipropionate by the inhalation route at an

estimated daily dose of 0.33 mg/kg (approximately 15 times the maximum recommended daily inhalation dose).

Pregnancy: Teratogenic Effects: Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) beclomethasone dipropionate was teratogenic and embryocidal in the mouse and rabbit when given at a dose of 0.1 mg/kg/day in mice and or at a dose of 0.025 mg/kg/day in rabbits. These doses in mice and rabbits were approximately one-half the maximum recommended human daily inhalation dose on a mg/m^2 basis. No teratogenicity or embryocidal effects were seen in rats when exposed to an inhalation dose of 15 mg/kg/day (approximately 190 times the maximum recommended daily inhalation dose). There are no adequate and well controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

RECOMMENDATIONS

1. The proposed labeling submitted by the sponsor is acceptable, with incorporation of the suggested revisions for the labeling sections entitled: Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy as indicated above.

2. The Sponsor's comments regarding the dose discrepancy in the Segment II reproductive toxicity study performed in rats using the QVAR formulation (Study number L08398) are acceptable and the originally proposed dose of 15 mg/kg should be used in the label.

/S/

Timothy J. McGovern, Ph.D., Pharmacologist

Original NDA 20-911
CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/S. Barnes
HFD-570/R. Nicklas
HFD-570/T.J. McGovern

CENTER FOR DRUG EVALUATION AND RESEARCH

PILOT DRUG EVALUATION STAFF

Pharmacology Review

IND: [redacted]

SPONSOR: 3M, Minnesota

DATE SUBMITTED: April 28, 1993

DATE RECEIVED BY CDER: April 28, 1993
DATE RECEIVED BY HFD-007: April 29, 1993
DATE RECEIVED BY REVIEWER: May 7, 1993
DATE OF REVIEW: May 24, 1993

DRUG: Beclomethasone oral MDI inhaler

CATEGORY: Anti-inflammatory steroid

INDICATION: Bronchial asthma

Beclomethasone dipropionate (BDP) is [redacted] metered-dose inhaler in the presence of [redacted] surfactant and CFC 11 and 12. It forms clathrate with trichloromonofluoroethane (TCMFE). This CFC accounts for 25-50% of the total drug substance and propellants in each canister. Each actuation delivers 42 ug of BDP, maximal daily dose is 840 ug/day in adults. Upon inhalation delivery, BDP is available in systemic circulation and may produce HPA suppression if higher than recommended dose is used. HPA suppression assay was done after 28 day dosing. Partial suppression was observed at about 1600 ug/day dose. The package insert of BDP oral inhaler also refers to the fact that effect of the steroid on the developmental or immunologic processes in the mouth, pharynx, trachea and lung is unknown. 3M company marketed CFC containing BDP at 50, 100 and 250 ug per actuation (ex-valve) in UK.

The present IND has been submitted with a view to develop BDP aerosol formulated with HFA-134a, a non-CFC propellant.

Several clinical studies with MDI were initiated to investigate the systemic delivery of BDP using HPA suppression as a clinical end point. Doses used were 1200, 2000 or 2800 ug for 10 days.

In another study 200 ug/actuation BDP formulation with HFA-134a, HFA-134a placebo and propellant 11/12 BDP and placebo were compared in asthmatic patients. Total of 8 consecutive inhalations were given to compare cough response between formulations. However, the study report is not available yet.

HFA-134a blood levels were also determined after 8 inhalations from a formulation designed to deliver albuterol. The blood concentration reached 0.2-0.7 ug/ml within 1-3 minutes after dosing which reduced to one third after 15 minutes. Level of HFA-134a from chronic exposures of 16 inhalations per day for 14 days was between 0.33 to 1.22 ug/ml within two minutes after 4 inhalations on Day 14. Doubling the size of the dose increased HFA-134a levels to 0.55-2.36 ug/ml. The blood levels were reduced to 10% within 15 minutes after inhalations of propellants. These studies were done to show the kinetics of the propellant.

In the present IND, the effect of BDP at 200, 800, and 1600 ug/day for 14 days will be evaluated among steroid naive asthmatics. HPA sup-

pression will be assessed using inhalation doses of BDP vs. 10 mg prednisone. Kinetics of BDP will be developed among asthmatics if an assay methods is available.

BDP has higher topical potency than oral form (3 times) because first pass metabolism generates beclomethasone which has very little glucocorticoid activity.

Pharmacology and toxicity of BDP have been established to some extent except carcinogenicity, mutagenic potential of BDP have not been reported to today's standard. Carcinogenicity data to the inhaled steroid for 95 weeks in rats have been done according to this IND write-up. Although the current package insert has a class warning suitable for Pregnancy Category C, the effect of the steroid during maturation is not known. A two-year carcinogenicity study in rats conducted by —— revealed that HFA-134a has potential to induce leydig cell tumor probably by inducing peroxisomal proliferation.

Actually, the safety profile of HFA-134a is under review at HFD-155 (Pulmonary Drug Products). Therefore, safety factors initiated by the above review should be addressed there. Among the issues, peroxisomal proliferation to HFA-134a via formulation of trifluoroacetic acid (TFA) and leydig cell tumor are of important consideration. Whether BDP increases these events in combination with HFA-134a is an important issue which should be resolved. Page 43, Vol. 1 of the IND states that HFA-134a metabolized to trifluoroacetic acid which has been referred to as a peroxisomal proliferator and rodent carcinogen (*Hepatology* 9:570, 1989) in the literature. *In vitro*, HFA-134a is metabolized by cytochrome P450IIEI, induced by pyridine and ethanol.

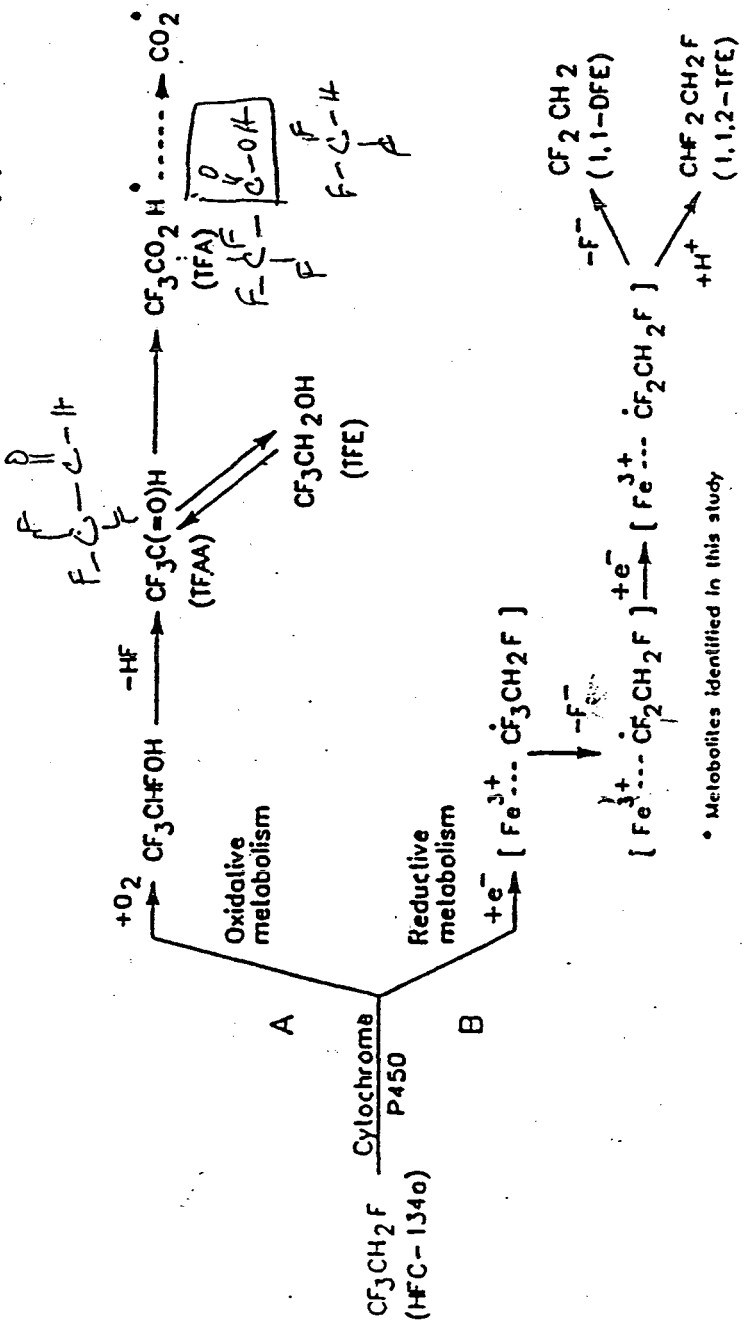
In a clinical study using HFA-134a inhalation up to 8 inhalations, HFA-134a levels were 200-700 ng/ml in blood immediately after inhalation which disappeared within 10-15 minutes after dosing. On chronic administration for 14 days as 4 inhalations per day to another 14 days as 8 inhalations per day, HFA-134a level was within 331-1222 ng/ml blood on 14th day within one minute after 4th inhalation. Similarly, within one minute after 8 inhalations, blood levels were 546-2357 ng/ml which reduced to 10% of this level within 15 minutes. Therefore, blood levels of HFA-134a were dose-dependent and HFA-134a did not accumulate in the blood. Soon after dosing HFA-134a was metabolized to trifluoroacetic acid. The amount of HFA-134a inhaled in

these experiments corresponded to placebo formulations, however, at this stage it is not known whether it will correspond to the amount delivered from beclomethasone MDI.

HYDROFLUOROCARBON 134a: PHARMACOKINETICS AND METABOLISM IN RATS FOLLOWING A SINGLE EXPOSURE BY INHALATION

FIGURE 1

POSTULATED OXIDATIVE (A) AND REDUCTIVE (B) ROUTES OF METABOLISM OF HFC134a [4]



Clinical Protocol:

#1064 Bron

This study is designed for comparison of BDP-HFA-134a with placebo in asthma patients. Doses chosen are 200, 800 and 1600 ug per day for 2 weeks. Patients will have asthma and are between the ages of 18 - 65 years. Female patients will be screened for pregnancy. Female patients eligible for participation are post-menopausal, surgically sterilized, or are using birth control measures. Patients should be capable of with-holding asthma medications. Therefore, these patients may have mild symptoms of airway hyperreactivity.

FORMULATIONS			
	MG/ACTUATION	G/VIAL	% W/W
BDP	0.050, 0.200	0.012, 0.048	0.084, 0.337
ALCOHOL	4.74, 4.728	1.135, 1.132	7.993, 7.973
HFA-134a	54.51, 54.372	13.053, 13.020	91.923, 91.690
TOTAL	59.3, 59.3	14.2, 14.2	100, 100

According to the protocol at 800 ug/day dose of BDP, 216 mg of HFA-134a will be delivered to the lungs; at 1600 ug/day dose of BDP, about 432 mg of HFA will be delivered to the lungs. Each canister will deliver 200 inhalation doses.

The sponsor briefly stated the findings related to the metabolism of HFA-134a from — conducted studies. However, these studies will be reviewed separately for the — sponsored DMF by the Pulmonary Division.

Kinetics and metabolism of HFA-134a after single dose exposure by inhalation in rats:

Report #CTL/R/1090. This study was done by — during May-October, 1991.

Wister rats were exposed to 10,000 ppm of HFA-134a for one hour which was a mixture of cold and ^{14}C HFA-134a. Urine, feces and exhaled gas radioactivity was measured in metabolism cage for 5 days. About 1% of the inhaled dose was excreted in urine, feces and expired air within one hour after cessation of exposure. Urinary excretion was equal to 0.1% or less of the dose and fecal excretion was 0.05% or less of the total exposed dose, measured as total radioactivity. About 0.2% of the total dose was excreted as carbon dioxide. The major metabolite in urine was trifluoroacetic acid. The total metabolism was 0.4% of the total radioactivity in expired air, feces and urine. The sponsor stated that there was no accumulation of radioactivity. However, there was no accounting for the rest of the radioactivity.

10,000 ppm HFA-134a was allowed to flow through the exposure chamber at 12/min rate. Radioactivity and the level of HFA-134a atmosphere in the chamber was monitored by sampling air every 5 and 30 minutes using —— scintillation counter. At the end of the metabolism study, residual radioactivity in the carcass was determined. The oxidative metabolism profile suggests that HFA-134a converts into trifluoroacetic acid and then CO_2. The method for dose determination have not been discussed. However, it is assumed that the dose was determined from the minute volume over one hour and the atmospheric concentration.

Radioactivity excreted in feces, urine, exhalation and that remaining in the carcass was 1.15% of the inhaled dose after the exposure. Although it is not clear how they calculated inhaled dose, it appears that most of the HFA-134a was exhaled during the exposure period and very little was carried on in the system. Average amount of HFA-134a equivalent/g of tissues after 5 days was 13.07 for liver, 27/14 for lung, 22.65 for heart, 5.9 for testes and no detectable amount in plasma.

Acute toxicity of BDP/HFA-134a in the dog by inhalation:

One male beagle dog was given 250 inhalations in one day over a 5 hour period. This was repeated by another 400 inhalations over a 4 hour period two days later. Each actuation had 250 ug of BDP ex-valve. Therefore, total doses each day were 62.5 and 100 mg of BDP. The amount of HFA-134a delivered in each day was not calculated. If we calculate HFA-134a dose considering 54 mg/actuation, the total HFA-

134a given by inhalation per day would be 13.5 g in Day 1 and 21.6 g in Day 2. The schematic of dog inhalation apparatus has been presented. It appears that an inhalation tube was placed in the mouth covered with a mask. The aerosol generated from MDI was inhaled through the tube by regular breathing. This procedure will deposit some of the aerosol in the mouth and GI tract. The sponsor has not measured the percent of the delivered dose deposited in the lung. However, an article presented by the sponsor (*Am Rev Resp Dis* 141:S-44, 1990) suggested that 75% of the delivered dose of radioactive BDP absorbed through the lung by 30 minutes. However, the deposition may vary depending on the particle size.

Clinical signs were unchanged, however, food intake was reduced after the first days of exposure.

7-Day nose only inhalation exposure to BDP-134a for mutation in rats:

Study #TF1-1. This study was done by ——— ——— in August, 1991, according to GLP.

The nose only exposures were given for 1 hour per day for 7 days to 5 rats/group (SD rats, 8-9 weeks of age at the time of exposure). The groups were: air control group and vehicle group (which contained propellant and surfactant corresponding to the highest test article concentration, 0.01, 0.1 and 1 mg/liter atmosphere in the chamber, measured as active + inactive substances). The test article was delivered into the chamber from MDI formulations. For the toxicity study, formulations contained ——— alcohol, and HFA-134a. The formulation for human trial had alcohol and HFA-134a only, no surfactant was added to it.

Rats were exposed using multiport nose only exposure chamber. One exposure chamber was used for each of the three levels of exposure. Each exposure was for one hour for 7 days. Aerosol mass concentration was determined through a glass fiber filter twice during 1 hour exposure. The mass concentration will represent both active and inactive ingredients. Therefore, the active ingredient was chemically analyzed by ——— Aerosol particle size was measured by impactor.

Gravimetric analyses showed that total mass (mg/L) at low, mid, and high dose groups were: 0.01, 0.109 and 1.069, respectively, which

were similar to the targeted mass. The placebo mass was 0.441, about half of the high dose group. The chemical analyses for BDP in the chamber showed the following results:

EXPOSURE GROUP	TARGET TOTAL CONCENTRATION MG/L	BDP CONCENTRATION MG/L
1		
2	Placebo	--
3	0.01	0.009
4	0.10	0.058
5	1.0	0.463

Therefore, rats were exposed to nose only inhalation from an atmosphere containing 9, 58 and 463 ug/L of BDP. Chamber concentrations of HFA-134a cannot be calculated because the data were presented in IR absorbance units which cannot be converted into particle weight. The particle size (mass median aerodynamic diameter) of aerosols was around 2 Um to allow nasal inhalation into the lungs.

There were no mortalities associated with these exposures. Body weight gain was unaffected. No obvious clinical signs were reported in the study. Liver lesions, increased liver weight, and small thymus weight were seen on gross observation which is expected for steroids. Weight of adrenals was not affected in this study.

This study indicated that at 0.058-0.463 mg/L atmosphere exposure to rats for 1 hour daily for 7 days showed systemic glucocorticoid effect based on the thymus weight reduction. Amount of propellant in the exposure chamber was not quantified.

7-day inhalation toxicity to BDP/HFA-134a formulation in dogs:

Report #7658. This study was done at —— in March, 1991.

Beagle dogs, 5-6 months of age, 9.5-11.5 kg at procurement, 2/sex/group, were allotted for placebo control, 6.25 mg BDP/dog/day, 62.5 mg BDP/dog/day were given as 250 actuations for each group. Animals were exposed to BDP or placebo after 10 weeks of acclimatization. Animals were dosed daily in five sessions 1 hour apart for 7 days. Dosing procedure was similar to that shown in the acute experiment done previously. The inspiration of air into the lung opened an inlet flap valve and expiration opened an outlet flap valve positioned at right angles to the horizontal plane. Each flap valve opened in one direction only. Opening of the valve could monitor the breathing. MDI was actuated during inspiration and continued to actuate in alternate breathing cycle. After every 20 actuations the face mask was removed. In each session 50 actuations were made. (See the following page.) Blood samples were taken on predose, Day 1 after the first and last session, and on Day 8 prior to necropsy.

Ophthalmologic changes, ECG, clinical condition, food intake and body weight were determined during the experiment.

Drug related clinical signs and weight changes were not observed in the 7 day exposure. Ophthalmological examinations did not reveal any treatment-related changes in this study.

ECG was examined at pre exposure and after the last dose on Day 7. At preexposure one high dose female (#12) showed shorter Q-T interval. Sinus arrhythmias were also seen in mid and high dose groups and also in the control group. Abnormalities in the ST wave (negative T-wave, coving, elevation and depression) was associated with all four dogs in the high dose group. WBC were increased in treated groups although corticosteroids should have shown the opposite effect.

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Liver weights at high dose were increased which was associated with an increase in the transaminase level. Adrenal and thymus weights were reduced at low and high doses. No tracheal change was observed in the study.

Histological data confirms that liver at high dose group had swollen hepatocytes with no glycogen accumulation (edematous swelling). Thymus and adrenal atrophy were present at low and high doses. Although pneumonitis was seen in all dogs in placebo and BDP groups, tracheal abnormalities were not observed.

Data from this experiment suggest that 6.25 and 62.5 mg BDP/day (measured as amount generated ex-valve not the dose delivered into the lungs) induced systemic glucocorticoid activity. Pneumonitis was observed in all dogs in the placebo and BDP treated groups. No tracheal changes observed in the study which could develop as a consequence of the steroid. However, at the high dose abnormal S-T wave in the ECG was observed at the end of 7 days dosing which could result from propellant and steroid combination. One should see whether similar adverse effects were seen in the long term studies in dogs. The propellant dose in the study has not been mentioned. Also the particle size and deposition characteristics have not been evaluated in this study.

28-day inhalation toxicity to BDP/HFA-134a formulation in rats:

Study #TF1-2 dated January, 1993, conducted at ——— according to GLP.

This study was conducted using BDP-HFA-134a formulation containing surfactant and BDP propellant 11/12 formulation containing surfactant. The BDP-HFA-134a formulation by % W/W was as follows:

	BDP-HFA-134a	Placebo	BDP/P11-12
BDP	0.43% W/W	--	0.32%
Alcohol	14.86%	14.92%	--
—	0.50%	0.5%	0.08%
HFA-134a	84.21%	84.58%	--
P11	0	0	26.11%
P12	0	0	73.49%
	100%	100%	100%

It is not clear how much BDP and propellant was delivered per actuation ex-valve. Perhaps it was not necessary because animals did not inhale directly.

Inhalation exposure system was similar to that for 7-day toxicity study in rats. Aerosols were diluted with compressed air to obtain a specific concentration in the exposure chamber. The schematic of the aerosol generating system is shown on the next page. The following groups and doses were designed for the experiment:

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Group	Formulation	Weight Dose mg/L	BDP Dose mg/L	Particle Size Um	Rats Per Box
1	Air control	--	--	--	20
2	Placebo HFA-134a	0.067	--	—	20
3	BDP/HFA-134a	0.005	0.003	—	20
4	BDP/HFA-134a	0.052	0.025	—	20
5	BDP/HFA-134a	0.101	0.047	—	20
6	BDP/P11-12	0.064	0.049	—	20

The weight dose expressed total mass per liter, which includes BDP, propellant, ethanol and —— for the drug under investigation.

The MDI generates aerosols on actuation by a pneumatic actuator. Continuous supply of aerosol is obtained by repeated actuation and diluted by compressed air to the desired concentration. The particle size was similar to the 7-day study. However, as stated before, the absolute amount of propellant in the chamber was not determined.

Rats (SD-TAC:N:) were 8-9 weeks of age at the beginning of exposure and weighed about 260 g.

Exposures were made for one hour per day for 28 days.

No deaths were reported in this study. No significantly untoward effects were noted as clinical signs.

Loss of body weight gain (-30%) was observed only in male Group 5 (BDP/HFA-134a at 0.1 g/L), female rats in the same dose lost 12.5% body weight gain which was not statistically significant. BDP exposure caused reduction in the weight of the thymus at 0.025 (Group 4), 0.047 (Group 5) and 0.049 (Group 6) g/L doses, which is the sign of typical corticosteroid-like effect. However, no obvious changes in the liver with respect to morphology, chemistry, and histology was observed. In the opinion of the reviewer, the higher dose would have been necessary to show the effect on the liver. Thymus atrophy was observed histologically, which was dose-dependent and observed in the

BDP/P11/12 group also. The pathology report suggested that hepatotoxicity was not severe enough compared to the placebo. Nasal changes and changes in the lung were observed in placebo and filtered air groups and, therefore, considered to be unrelated to treatment.

It can be concluded that systemic glucocorticoid effect was seen in rats exposed to inhalation of BDP at 0.003, 025, 0.047 g/L from HFA-134a and propellant 11/12 formulations. However, considering severity, the exposures should be given at higher doses that the minimum chosen. The sponsor also has not calculated the dose deposited into the lung for both BDP and the propellant.

28-day inhalation study in beagle dogs:

Report #7700. Study conducted at ——— in June, 1991. The study was done according to GLP.

Beclomethasone (HFA-134a formulation containing BDP, ——— ethanol, and propellant 134a was used. Each actuation generated 250 ug pf BDP ex-valve. Placebo formulation was used for comparison. The particle size of the aerosols have not been mentioned. Minimum temperature of housing was 62.6°F and maximum was 69.8°F. Dogs weighed about 10 kg and were 6 months of age at the start of the experiment.

Group	Dose	#/Sex	BDP Dose mg/day
1	Air Control	4	--
2	Placebo	4	--
3	Low BDP	4	2.5
4	Mid BDP	4	7.5
5	High BDP	4	25

Animals in Groups 2-5 received the same amount of HFA-134a and other excipients per day.

Dogs were dosed in two sessions, two hours apart, at each session they received 50 actuations. All dogs except air control group received the same number of actuations per day. Exposure system was similar to that described in the previous study.

Clinical signs, body weight, food consumption, ophthalmoscopy, ECG was taken pretrial on Days 27/28, respiratory parameters. Blood samples were collected for BDP assay on Day 1 at preexposure and immediately after the second dosing, after the second dosing on Day 28, and in the morning of Day 29. At necropsy, organ weights were determined and tissues were fixed for histological staining.

Dosed animals showed salivation at higher incidences than placebo group. Average body weight gain was reduced at mid dose by about 18% compared to air control. Dogs at high dose group actually lost weight from the preexposure period, which was unrelated to food consumption. Ophthalmological findings were not drug-related except corneal opacity in the left eye for one dog at high dose, which is expected with BDP for prolonged exposure.

ECG findings: No change was observed for placebo and BDP treatment groups. 7-day toxicity study showed prolongation of S-T segment at the high dose, which could be unrelated to the treatment.

Respiratory parameters were not changed significantly due to placebo or BDP treatments.

Blood chemistry was related to liver changes, e.g., higher alkaline phosphatase activity, higher protein levels in blood.

Organ weights at necropsy suggested increase in the weight of liver and a reduction in the weight of the thymus and adrenals which were due to the systemic glucocorticoid activity.

Histological findings suggested inflammation of hepatocytes at mid and high dose groups.

Atrophy of the adrenals (zona fasciculata) and thymus was present. Hypocellularity of bone marrow was present in the mid and high dose groups. Placebo group did not show histological changes in the liver, adrenals, thymus, and testes.

Although dogs enrolled in the study did not show pneumonitis with the exception of one female in Group II, alveolitis and bronchiolitis were present in treated, placebo, and air control groups. There were no changes to tracheal airways.

To conclude, the study revealed that BDP/HFA-134a treatment produced systemic glucocorticoid effects; however, placebo aerosol did not show systemic toxicity. However, particle size of the aerosols, dose of BDP and HFA-134a deposited in the lung and concentrations in systemic circulation were not mentioned. Although highest dose group showed systemic glucocorticoid-like toxicity, the highest doses selected should have been higher.

The study confirms that 100 actuations per day for 28 days in beagle dogs did not show toxicity other than that expected of BDP. 100 actuations of placebo also did not show toxicity. Cardiac abnormality seen in the 7-day study was incidental and could not be repeated in the 28-day study.

Summary:

BDP/HFA-134a formulation has been developed to examine safety and efficacy in bronchial asthma. HFA-134a inhalation showed dose-dependent levels of HFA-134a in blood within 2 minutes after inhalation, which was reduced to about 10% of the previously observed value within 10-15 minutes post inhalation. HFA-134a is metabolized to trifluoroacetic acid (TFA) which has the potential to induce peroxisomal proliferation and related toxicities in rodents. Therefore, it is necessary that the kinetics of TFA in humans at the maximum recommended dose be compared with TFA at toxic doses in dogs and rodents. Radiotracer studies of inhaled HFA-134a showed that most of the hydrocarbon is exhaled during exposure. Similarly in acute and subacute toxicity studies ppm of HFA-134a and BDP delivered was not calculated. Both dog and rat toxicity studies showed systemic glucocorticoid-like toxic effects on liver, adrenal and thymus. However, cardiovascular abnormality due to the new propellant was not evident.

The dog toxicity study was more reliable study because the dose was delivered directly into the mouth for inhalation. It was suggested to the company that they conduct a one-year toxicity study with the formulation using immature beagle dogs for evaluating the local effect of inhaled steroid upon respiratory airways. The sponsor agreed to run the experiment in the future and the reviewer should help the sponsor on the design of the experiment.

In my view, the proposed clinical trial may be initiated; however, the following recommendations should be made to the sponsor:

Recommendations:

1. The proposed clinical study on BDP/HFA-134a formulation may be initiated. However, the sponsor should determine ppm of HFA-134a and BDP inhaled per day for each dose. Plasma/blood level of trifluoroacetic acid over time should be determined also.

2. For the inhalation study report #CTL/R/1090 on kinetics of radiolabeled HFA-134a, the sponsor should discuss how the calculation of the inhaled dose of HFA-134a was determined.

3. The sponsor should discuss the possibility of clathrate formation between beclomethasone and HFA-134a, as well as the possibility of a complex formation between ethanol and HFA-134a.

4. Since ethanol induces P450 subset needed for the metabolism of HFA-134a, it is necessary that trifluoroacetic acid levels be determined in a special population who consumes ethanol in a regular basis. The dose of HFA-134a should correspond to the level that would be given with the maximum recommended human dose of BDP.

5. Levels of trifluoroacetic acid (TFA) in patients at therapeutic levels should be determined. Express data on ppm of HFA-134a delivered versus ng/ml of TFA in the blood/plasma in patients. Similar determinations should be done in rats and mice at doses used for carcinogenicity bioassay. Comparative differences in the ppm for HFA-134a deposited between man, mice, and rats versus TFA levels in blood/plasma should be presented. These data, along with the review and analysis of carcinogenicity data

presented by [redacted] will be used to consider whether there is any potential need for running carcinogenicity assay for BDP/HFA-134a in the future. The issue would be whether BDP would increase the sensitivity of tumors present in the carcinogenicity bioassay of HFA-134a.

6. Regarding the one year beagle dog study, if the sponsor undertakes such a study, dogs should be about 4 months of age at dosing. The sponsor should propose a protocol which would be evaluated in the division before initiation of the study.

/S/

Asoke Mukherjee, Ph.D.
Pharmacologist
Pilot Drug Evaluation Staff
Center for Drug Evaluation and Research

cc: Orig. IND
HFD-[redacted]
HFD-007/Mukherjee
HFD-007/LeSane
HFD-340
HFD-502
R/D Init. by: Conrad Chen 5/24/93
F/T by: Barbara Shekitka 6/14/93

MAY 12 1999

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Chemistry Consult #1

NDA No. 20-911 **Date of Consult:** 09 SEP 1998

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 12 MAY 1999

Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: 3M Pharmaceutical Division

Drug Name: *Generic:* Beclomethasone dipropionate *Commercial:* QVAR™

Chemical name: 9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Formula: $C_{28}H_{37}ClO_7$

Molecular Weight: 521.05

Drug Class: Steroid

Review:
Dr. Alan Schroeder requested a safety assessment of reported levels of extractables ———) and USP Biological Reactivity tests on actuator extractables.

Safety Assessment of Extractables from the Drug Product:

The following formula was used to determine the maximum possible daily dose intake of each extractable from the marketed product by a 50 kg patient:

Daily Dose Intake of Extractable (ng/kg/day) = the product of the Maximum Potentially Inhaled per breath (ng/breath) and the Maximum Recommended Actuations/day (16) divided by 50 kg.

The results in the following tables show the proposed maximum exposure to ——— extractables. Data from two types of component extraction were presented in the report (extraction). Analyses were generally conducted at initial make-up, 1, 2, 3 and 6 months at 40 degrees Celsius and 75% RH, as well as 3, 6, 9 and 12 months at 25 degrees Celsius and 60% RH. Data for total extractables is presented at initial, 1 and 3 months at 40 degrees Celsius and 75% RH. Total extractable levels were determined evaporating propellant and drying the residue at 105 degrees Celsius for one hour. The

remaining residue was weighed and total percent extractables was calculated using the weight of the formulation in the vial. These levels (ppm or µg/mg; ppb or ng/mg) were then converted to µg/breath (assuming 11.8 g of formulation in a 200 actuation canister or 59 mg formulation per actuation). It should be noted that extractable levels may need to be reassessed when data from later timepoints become available.

extractables:

Table 1 lists the — extractables, the maximum amount present in the product, the maximum potential human exposure, and the Safety Index (Time Weighted Average, State ambient air limits, state Drinking water limits). The sponsor stated that there was negligible safety concern due to the very low levels of — extractables present in the drug product. In most cases, this reviewer concurs as the maximum expected human exposure is significantly below that allowed by ACGIH Time weighted averages for inhalation exposure. In two cases, inhalation exposure limits have not been set, — In both of these cases, drinking water limits were used to determine a safety index (calculated for a 50 kg adult and based upon daily water intake of 2 L, used for EPA risk assessment). Although the route of administration for the current product is inhalation, safety indices of > 16,000 are provided by the drinking water restrictions set for the extractables. Exposure limits for — are not available. However, — is considered an essential trace nutrient and is not expected to present a health concern at the levels present in the drug product. For inhalation data, inhalation volumes of 7 and 14 m^3 were used for 8 and 24 hour exposure durations, respectively, for a 50 kg individual, based upon EPA estimates for a 70 kg individual.

Table 1: Identified extractables.

Extractable	Max. Conc. (extraction) ppm	Expected max. human exposure µg/day	Expected max. human exposure ng/kg/day	Comments
—	0.78	0.74	14.8	TWA: 10 mg/m^3 Safety factor ~ 94,600
—	1.41	1.33	26.6	No standards set. Not considered a safety concern at these levels.
—	0.38*	0.36	7.2	TWA: 0.5 mg/m^3 for — Safety factor ~ 9,700
—	0.1	0.09	1.9	TWA: 1 mg/m^3 Safety factor ~ 77,800
—	0.51*	0.48	9.6	Ambient air standards in various states range from 10-20 $\mu g/m^3$ Safety factor = 292 (based on 10 $\mu g/m^3$)
—	0.53	0.5	10.0	No air exposure standards set for — alone. TWA: 25 $\mu g/m^3$ for — Safety Index = 350
—	0.86	0.81	16.2	No air exposure standards set. Absolute maximum of 150 mg/L in drinking water set by WHO Safety factor ~ 370,000

Extractable	Max. Conc. extraction) ppm	Expected max. human exposure µg/day	Expected max. human exposure ng/kg/day	Comments
—	0.18	0.17	3.4	TWA = 5 mg/m³ Safety factor ~ 205,900
—	2.57*	2.43	48.5	No air exposure standards set. Drinking water limits in various states range from 20-100 mg/L Safety factor ~ 16,500
—	0.06	0.06	1.13	TWA: 1 mg/mg Safety factor ~ 116,700
—	0.26*	0.25	4.91	TWA: 0.1 mg/m³ Safety factor = 2,800
—	1.76*	1.66	33.23	TWA: 10 mg/m³ Safety factor ~ 42,170
—	0.13	0.12	2.45	TWA = 2 mg/m³ for compounds Safety factor ~ 116,700
—	0.02	0.02	0.38	No info on — alone. TWA for s — 0.05 mg/m³ (due to — Safety factor = 17,500
—	0.37	0.35	6.99	No standards have been set for air exposure of — For — TWA: 10 mg/m³ total dust State guidelines for ambient air: 0.13-0.79 µg/m³ (Montana) to 300 µg/m³ (CT) Using most conservative (0.13 µg/m³): Safety factor: 5.2
—	0.45	0.42	8.5	No federal limits for air. Ambient air: 6.55–39.29 µg/m³, (Montana) Safety factor = 218
—	0.92	0.87	17.37	TWA: 5 mg/m³ Safety factor = 40,230

* Detected by extraction.

Extractables:

The only detected — compound reported to be greater than the quantitation limit of — ppb was — — concentrations of —— ppb were determined by —— extraction, respectively. The maximum potential inhaled mass was determined to be 0.64 and 0.34 ng/breath (assumes MDI with 200 actuations and 59 mg of formulation/actuation), respectively. Thus, at a maximum of 16 actuations per day, the maximum inhaled daily dose of — would be approximately 10.5 ng/day or 0.21 ng/kg/day, based upon a 50 kg individual (Table 2). The maximum acceptable inhalation dose for — is 500 ng/kg based upon the Daily Threshold Inhalation Limit (8 hour exposure, extrapolated from NIOSH TLV). Thus, the levels of — observed in the current drug product are ~ 2,380-fold less than the Threshold Limit Human Daily Workplace Inhalation Dose. Thus, the — levels reported by the sponsor are acceptable with respect to safety.

Table 2: extractable.

Extractable	Max. amt. present (extracti) ppb	Expected maximum human exposure		Comments
		ng/day	ng/kg/day	
—	10.8	10.2	0.204	Upper bound estimates of cancer potency determined from various routes of administration in animals: 3.6×10^{-6} (Based upon upper bound risk estimate by Gaylor of 17×10^{-6} per ng/kg/d)[a]. Threshold limit daily dose workplace (8 hr IH exposure): 500 ng/kg [b] Safety factor = 2,450

a: Report by Gaylor, 1993 (Attached).
b: Extrapolated from NIOSH Threshold Limit Values (TLV).

— **Extractables:**

Multiple — extractable compounds were identified and the sponsor provided risk assessment information for these compounds. The individual daily exposure levels were very low for each of the compounds (0.4 – 3.15 µg/day).

The following section lists the identified — extractables which are considered to be properly qualified and the rationale for qualification. Table 3 summarizes the exposure data and the safety factors provided at the expressed exposure levels. For inhalation data, inhalation volumes of 7 and 14 m^3 were used for 8 and 24 hour exposure durations, respectively, for a 50 kg individual, based upon EPA estimates for a 70 kg individual.

— : Based upon a TLV-TWA of 10 mg/m^3 (ACGIH), it is expected that an individual could safely inhale ~ 70 mg — per day. In the current drug product, the maximum inhaled dose (1.62 µg/day) provides a safety factor of ~ 43,210.

— A TLV-WA of 10 mg/m^3 (8 hr) and STEL of 20 mg/m^3 have been set as airborne standards by ACGIH. The TLV-TWA corresponds to an acceptable daily dose of 70 mg/day. Thus, the maximum expected inhaled daily dose of 1.97 µg/day results in a safety factor of ~ 35,530.

— No exposure limits have been set for by OSHA, NIOSH or ACGIH. However, a potency range of 244 mg has been accepted in a sustained action oral tablet as an inactive ingredient for generic drug NDA 70-618 (potassium chloride). Following the application of a 100-fold extrapolation factor for oral to inhalation dosing, a limit of 2.44 mg would be acceptable for inhalation dosing. The maximum inhaled dose of — is expected to be 1.18 µg/day (23.6 ng/kg/day) which provides a safety factor of ~ 2,068.

is commonly used in material for food wrapping and rubber materials. The OSHA Permissible Exposure Level (PEL) for 8 hr TWA is 0.2 mg/m^3, permitting up to a total of 1.4 mg/day. The levels of in the current drug product could potentially result in a human exposure of 2.93 µg/day. This level of exposure provides a safety factor of ~ 478 compared to OSHA PEL.

: There are no set federal permissible levels in air or water, and no exposure limits by ACGIH. However, a 19-month oral carcinogenicity study in rats revealed no carcinogenic activity and a NOEL of 200 mg/kg (diet) was determined (Lefaux, R. Practical Toxicology of Plastics. Cleveland: CRC Press Inc., 1968. 363). Applying a 1000-fold safety factor (10-fold for species extrapolation; 100-fold for route of administration extrapolation) for extrapolation to human inhalation exposure, 0.2 mg/kg appears to be an acceptable exposure level. The expected maximum human inhalation dose is 0.000063 mg/kg which provides a safety factor of ~ 3,175.

The 1 x 10^{-6} risk dose is 2100 ng/kg/day, po (NTP, 1988). Thus, the maximum acceptable inhalation dose, applying a 100-fold safety factor for extrapolation of oral dosing to inhalation dosing, is 21 ng/kg/day. In the current drug product, the expected maximal daily human exposure is 0.96 µg/day or 19.26 ng/kg/day (assuming a 50 kg individual). Thus, a safety factor of ~ 1.09 is provided.

is approved for use as an inactive ingredient (NDA 40-034, theophylline, 1995) at up to 150 mg oral dosing. Applying a 100-fold extrapolation factor for inhalation dosing, up to 1.5 mg is acceptable by inhalation. The maximum expected human inhalation exposure is 1.05 µg/day, providing a safety factor of ~ 1,430.

These compounds have not been classified toxicologically, but structure activity relationships to other suggest that there are no significant safety concerns at the levels found in the current drug product. For example, ACGIH has set a TLV of 100 mg/m^3 (as aerosol) as a ceiling limit (ACGIH, 1998) for ethylene glycol. The maximum expected inhaled dose of per day is expected to be 1.33 µg. Using the exposure limit set by ACGIH for ethylene glycol, a safety factor of ~ 526,300 is present.

These compounds have not been characterized toxicologically but are structurally related to their parent compound NOEL doses in a 3 month toxicity study in rats were 50 mg/kg/d in males and 210 mg/kg/d in females (Material Safety Data Sheet). The maximum expected daily exposure to these compounds is 0.76 and 0.74 µg/day respectively. Compared to the NOEL doses of in rats (2,500 and 10,500 mg/day based upon 50 kg individual), a safety factor of ~ 3,300,000 to 14,200,000 is provided.

In the current drug product, the combined two forms result in 0.16 µg/breath and 2.57 µg/day (51.4 ng/kg/d) based on 16 actuations per day. Ventolin

CFC formulation contains — oleic acid which results in 10.3 µg/actuation and 123.6 µg/day (2.5 µg/kg/d) based upon a maximum recommended 12 actuations per day. Thus, the level of — in the current formulation is ~ 64-fold less than that in Ventolin and results in ~ 48-fold less — exposure at a maximum recommended daily dose. Thus, the levels of — found in the current formulation are acceptable.

Table 3: extractables qualified by permissible exposure levels.

Extractable	Max. amt. present (extraction) ppm	Expected maximum human exposure		Comments
		µg/day	ng/kg/day	
/	1.72*	1.62	32.47	TLV-TWA = 10 mg/m³ (ACGIH) Safety factor = 43,210
/	2.09	1.97	39.46	TLV-TWA = 10 mg/m³ (8 hr) (ACGIH) Safety factor = 35,530
/	1.25	1.18	23.6	Maximum acceptable IH dose = 2.44 mg (244 mg as inactive ingredient for oral tablet; NDA 70-618, potassium chloride) Safety factor: ~ 2,068
/	3.10	2.93	58.53	OSHA 8 hr TWA = 0.2 mg/m³ Correlates to daily exposure of 2 µg Safety factor = 478
/	3.34	3.15	0.000063 mg/kg	No tumors in rat carcinogenicity study NOEL dose of 200 mg/kg in diet corresponds to 0.20 mg/kg human IH dose Safety index ~ 3,175
/	1.02	0.96	19.26	Maximum IH dose = 21 ng/kg/d (1 x 10^{-6} risk dose = 2100 ng/kg/d, po; NTP, 1988) Safety factor: 1.09
/	1.11	1.05	20.96	Maximum acceptable inhalation dose = 1.5 mg (150 mg as inactive ingredient for oral tablet; NDA 40-034, theophylline) Safety factor ~ 1,430
/	1.41	1.33	26.62	TLV: 100 mg/m³ (ACGIH) for ethylene glycol Safety factor: 526,300
~ ~	0.80	0.76	15.10	3 mos. Toxicity in rat, NOEL 50 (M) – 210 (F) mg/kg/day for — (parent compound) [a] Safety index: 3,330,000 – 13,900,000
~ ~	0.78*	0.74	14.73	3 mos. Toxicity in rat, NOEL 50 (M) – 210 (F) mg/kg/day for — (parent compound)[a] Safety index: 3,394,000 – 14,256,600
~ r	2.1 0.63	1.98 0.59	39.65 11.89	Maximum expected exposure is ~ 64-fold lower than with Ventolin CFC formulation and 48-fold lower than maximum expected dose obtained with Ventolin

* Detected by extraction.

[a] Material Safety Data Sheet.

The following section lists the identified — extractables for which no permissible exposure limits have been set by applicable organizations (ACGIH, OSHA, EPA, etc.) and only acute toxicity data is available (summarized in Table 4). In addition, the sponsor did not provide information to adequately qualify these extractables through applicable toxicity studies performed in the development of the drug product. The compounds were assessed for systemic and respiratory effects, carcinogenicity/mutagenicity potential and daily exposure levels. In terms of daily exposure, no chemicals in the EPA HEAST tables with systemic target toxicity have safe human exposure limits lower than 80 ng/kg/day, based on calculated reference concentration, RfC, with large, 1,000 – 10,000 fold safety margins. Thus, since the maximum potential daily exposure for each compound was less than 100 ng/kg (5 µg/day in a 50 kg person), none of the compounds were assessed for potential systemic toxicity. Similarly, assessment for respiratory tract effects is not needed without alerts for irritation effects or reactive structures. This approach was also based on the safe exposures for respiratory tract toxins in the HEAST tables.

The first four extractables listed in Table 4 require no further qualification since maximum potential daily exposure was less than 100 ng/kg and there were no structural alerts or indication of carcinogenic/mutagenic potential. In addition, — were consulted to CDER's Regulatory Research and Analysis Staff for a Structure Activity Review since they had been classified by RTECS as tumorigens/mutagens. The three extractables were not predicted to be either trans-gender and/or trans-species rodent carcinogens, and all three were evaluated as inactive in the MCASE QSAR Rodent Carcinogenicity Test. Thus, no further qualification is needed for these compounds since the maximum daily exposure is below 100 ng/kg and the compounds were found to be inactive for carcinogenicity. The other extractables (—) will require further qualification since they have been classified as mutagenic or neoplastic (RTECS).

— APPEARS THIS WAY
ON ORIGINAL

Table 4: extractables not qualified by permissible exposure levels.

Extractable	Max. amt. present (– extraction) ppm	Expected max. human exposure µg/day	Expected max. human exposure ng/kg/day	Comments
/	0.42	0.4	7.93	LD50 (iv) = 100 mg/kg (mouse) LD50 (ip) = 25 mg/kg (mouse) No further qualification required since daily exposures < 100 ng/kg.
/	0.42	0.40	7.93	Only acute toxicity data available: LD50: 95-900 mg/kg. LDLo: 100 – 1000 mg/kg No further qualification required since daily exposures < 100 ng/kg.
/	1.0	0.94	18.88	No toxicological characterization available. No further qualification required since daily exposures < 100 ng/kg.
/	1.24	1.17	23.41	LD50 (po) = 1620 mg/kg (rat); 1231 mg/kg (mouse). LD50 (Dermal) = 2140 mg/kg (rabbit) No further qualification required since daily exposures < 100 ng/kg.
/	0.31	0.29	5.85	LDLo (iv) = 2672 mg/kg (mice) Classified as tumorigen by RTECS Inactive in CDER consult assessment.
/	0.57*	0.54	10.76	LDLo (iv) = 5800 mg/kg (mice) Classified as tumorigen by RTECS. Inactive in CDER consult assessment.
/	0.84	0.79	15.86	Oral LD50 > 10,000 mg/kg (rats) IV LD50 = 43 mg/kg (mice) Eye, skin, and respiratory tract irritant. Classified as mutagen by RTECS Inactive in CDER consult assessment.
/	0.64	0.60	12.08	Oral LD50 = 10,080 mg/kg (rat) IV LD50 = 600 mg/kg (mouse) Irritating to eyes, skin, and respiratory tract. Classified as mutagen by RTECS; sex chromosome loss and nondisjunction in S. cerevisiae (5 ppm). Negative in Ames assay.
/	0.49	0.46	9.25	Oral LD50 > 10 g/kg (rats) IV LD50 = 129 mg/kg (mice) Eyes, skin, and respiratory tract irritant. Classified as mutagen by RTECS criteria, recent test shows no mutagenicity in bacterial tests (HSDB). No evidence of carcinogenicity in oral studies in rats.

Extractable	Max. amt. present (— extraction) ppm	Expected max. human exposure µg/day	Expected max. human exposure ng/kg/day	Comments
—	1.58	1.49	29.83	Oral LD50 > 10 g/kg (rats) IV LD50 = 57 mg/kg (mice) Irritant to eyes, mucous membranes, upper respiratory tract. Neoplastic in a mouse implant study.

* Detected by — extraction.

Assessment of USP Biological Reactivity Studies on Actuator Extractables:

The following modified USP Biological Reactivity Tests on actuator extractables were submitted:

Study No. 1297EB0118; Acute Intracutaneous Irritation Test (Propellant Extraction Procedure) Using Bronze Beige Actuator, Lot 113850-67 in Albino rabbits

Study No. 1297AM0119; Acute Systemic Injection Test (Propellant Extraction Procedure) Using Bronze Beige Actuator, Lot 113850-67 in Albino mice

Study No. 1297AM0120; Acute Intracutaneous Irritation Test (Propellant Extraction Procedure) Using Bronze Beige Actuator, Lot 113850-70 in Albino rabbits

Study No. 1297AM0121; Acute Systemic Injection Test (Propellant Extraction Procedure) Using Bronze Mauve Actuator, Lot 113850-70 in Albino mice

Study No. 0396EB0302; Intracutaneous Irritation Test (Propellant Extraction Procedure) Using Bronze RS42660, Beige in Albino rabbits

Study No. 0396AM0303; Acute Systemic Injection Test (Propellant Extraction Procedure) Using Bronze RS42659, Beige in mice

Study No. 0396EB0304; Intracutaneous Irritation Test (Propellant Extraction Procedure) Using Bronze RS42659, Mauve in Albino rabbits

Study No. 0396AM0304; Acute Systemic Injection Test (Propellant Extraction Procedure) Using Bronze RS42659, Mauve in mice

Studies were performed in female rabbits or male CD-1 mice. The test article was held in pressurized vessels with HFA-134a/ethyl alcohol for 72 hours. The vessels were then vented and the propellant evaporated. The remaining residue was reconstituted in saline or cottonseed oil. In the intracutaneous irritation tests in rabbits, the extract was injected 10 times into the left side

of each animal, while an equal volume of the control article was injected into 10 sites on the right side. The sites were then grossly examined and scored for erythema and edema over the next three days. In mice, the extract was injected (50 ml/kg) either IV (saline) or IP (cottonseed oil). A control article was prepared in the same manner. Negative results in terms of irritation properties or systemic effects were observed in all of the above mentioned studies.

Summary and Evaluation: A safety review was performed on studies submitted by the sponsor: Bioassessment of Extractable Compounds in Drug Product (AIR-158-97, Vol 1.4) and Modified USP Biological Reactivity Tests on Actuator Extractables (Vol 1.4). Extractables listed in Tables 1, 2 and 3 were qualified for safety at the levels indicated by the sponsor. However, three of the drug product extractables listed in Table 4 [redacted] have not been fully qualified due to limited toxicity data and reported potential for mutagenicity. These extractables should be fully qualified by the sponsor. Negative results in terms of irritation properties or systemic effects were observed in all of the modified USP biological reactivity tests on actuator extractables.

RECOMMENDATION

The sponsor should provide further qualification for the following drug product extractables: [redacted]

/S/ 5/12/99

Timothy J. McGovern, Ph.D., Pharmacologist

/S/ May 12, 1999

CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/A. Schroeder
HFD-570/S. Barnes
HFD-570/T.J. McGovern

Cancer Risk Assessment of Pulmonary Exposure to Polycyclic Aromatic Hydrocarbons

David W. Gaylor

National Center for Toxicological Research
Food and Drug Administration
July, 1993

INTRODUCTION

From aerosol application of drugs, patients are potentially exposed to low levels of a number of polycyclic aromatic hydrocarbons used in the dispensers. Tumor incidence data from studies of intrapulmonary exposure to polycyclic aromatic hydrocarbons (PAH's) in rats (Deutsch-Wenzel *et al.*, 1983; Iwagawa *et al.*, 1989; and Wenzel-Hartung *et al.*, 1990) are used to estimate lung cancer risk. Benzo[a]pyrene (BaP) was examined in all three studies and produced similar results. Hence, the BaP data were pooled (Table 1) to obtain a lung cancer risk estimate. Risk is the probability (proportion) of animals that develop lung cancer during a lifetime.

Rats were administered various doses of several PAH's by pulmonary implants or injections at about 3 months of age. At that age, the rats averaged 245-255 grams of body weight. A weight of 300 grams was used as the average body weight during the experimental exposures for the calculation of daily dose on a body weight basis. For example, a one mg pulmonary injection or implant is equivalent to an average dose of 1 mg / 0.3 kg x (95 x 7 days) = 0.005 mg/kg of body weight per day, assuming 100% absorption of the PAH in animals surviving 95 weeks.

The cancer potency estimate for naphthalene is based on exposure by subcutaneous injection. Cancer potency estimates for fluoranthene, pyrene, and benzo[a]anthracene are based on skin painting studies. The cancer potency for fluorene is based on a feeding study.

RESULTS

The multistage model of carcinogenesis was fit to the lung tumor incidence data to estimate dose-response curves. The multistage model is commonly employed for risk assessment (EPA, 1986). The computer program GLOBAL82 (Howe and Crump, 1982) was used to obtain the lower 95% confidence limit for the dose estimated to produce a 1% lung tumor incidence. The lower confidence limit is used to account for the uncertainty resulting from the limited number of animals used in bioassays. Following a procedure suggested by Gaylor and Kodell (1980), linear extrapolation to zero from the lower confidence limit (LED01) on the dose estimated to produce a 1% tumor risk provides an upper bound estimate of risk at lower doses, if the true dose-response curves upward in the low dose region. That is, the upper bound for cancer potency (risk) is estimated by 0.01/LED01, which is an upper bound on the dose-response slope for low dose extrapolation. The upper bound estimates of cancer potency for various PAH's are given in Table 2. The upper bound for the lifetime lung tumor risk is estimated by multiplying the upper bound on the potency times the maximum human exposure.

For benzo[a]pyrene, the lower 95% confidence limit on the dose estimated to give a 1% lifetime lung tumor incidence was 17.1 ng/kg/d. The upper bound on potency for BaP is $0.01/17.1 = 5.8 \times 10^{-4}$ per ng/kg/d. That is, an exposure to one ng/kg/d of BaP is estimated to have a lifetime lung tumor risk of less than 5.8×10^{-4} (5.8 cases per 10,000 individuals). For a maximum daily exposure of 2.4 ng/kg/d, the lifetime risk is estimated to be less than $2.4 \times 5.8 \times 10^{-4} = 1.4 \times 10^{-3}$ (1.4 cases per 1000 individuals).

The highest potency was estimated for dibenzo[a,h]anthracene. For this chemical there was only one dose level of 0.1 mg, with a high incidence of lung tumors (20/35). By comparison, the same dose of benzo[a]pyrene had a lower incidence of (28/100).

No tumors were observed by skin exposure to acenaphthylene by Cook (1932). Experimental details were not available. No cancer potency estimate can be made, but it is likely to be low as no skin tumors were observed in the lifetime study.

There is no data available to conduct a cancer risk assessment for acenaphthene.

No tumors were observed by Slaga *et al.* (1978) when benzo[a]anthracene was applied to mouse skin. However, when skin exposure was followed by the promoter, 12-0-tetradecanoylphorbol-13-acetate, the cancer potency estimate is less than 46×10^{-6} per ng/kg/d. In the same study, promotion of benzo[a]pyrene gave a skin cancer potency of 670×10^{-6} per ng/kg/d. Since skin promotion of benzo[a]pyrene gave a cancer potency estimate similar to pulmonary exposure, the upper limit on the cancer potency estimate for benzo[a]anthracene, 46×10^{-6} per ng/kg/d, based on skin tumor promotion is used (Table 2).

For fluoranthene and pyrene the risk estimates are based upon exposure via the skin (Van Duuren and Goldschmidt, 1976). These studies also included benzo[e]pyrene, benzo[a]pyrene, and benzo[g,h,i]perylene. Cancer potency for these three chemicals were 6.8 times higher (geometric mean) for the pulmonary exposure compared to skin exposure. Hence, the skin cancer potency estimates for fluoranthene and pyrene were multiplied by 6.8 to obtain cancer potency estimates for pulmonary exposures (Table 2).

The potency estimate for naphthalene is based upon exposure by subcutaneous injection (Knake, 1956). The potency estimate was extremely low. Even if the potency by pulmonary exposure were 100 times higher, the contribution of naphthalene to the cancer risk of aerosol devices is inconsequential compared to the total risk of the other PAH's (Table 2).

The cancer potency for fluorene based upon pituitary adenomas from a feeding study in rats (Morris *et al.*, 1960) was extremely low. Even if the potency by pulmonary exposure were 100 times higher, the contribution of fluorene to the cancer risk of aerosol dispensers is inconsequential compared to the total risk of the other PAH's.

DISCUSSION

The risk estimates in Table 2 are based on the assumption that dose expressed on a body weight basis (mg/kg/d) will produce equal tumor incidence in humans and rats. If pulmonary doses of PAH's are equally potent on a surface area basis, then the risk estimates for humans are higher. Calculating surface area as proportional to body weight to the 3/4 power (EPA, 1992), scaling the dose from a 0.3 kg rat to a 50 kg human increases the risk by a factor of

$$\frac{50 \text{ mg}}{(50 \text{ kg})^{3/4}} \Big/ \frac{0.3 \text{ mg}}{(0.3 \text{ kg})^{3/4}} = 3.6 .$$

For example, the upper bound on potency for benzo[a]pyrene becomes $3.6 \times 580 \times 10^{-6} = 2.1 \times 10^{-3}$. The lifetime risk for an exposure to 2.4 mg/kg/d becomes 3.6 times higher or $2.4 \times 2.1 \times 10^{-3} = 5.0 \times 10^{-3}$.

On the other hand, the upper bound estimates of risk are based upon estimates of the maximum human exposure based upon the assumption that 100% of the PAH's in aerosol applicators are absorbed by the lungs. Since this may not be the case, actual risks may be lower.

The risk estimates in Table 2 are based on daily lifetime exposures to the PAH's. The cancer risk for a one year exposure out of a 75 year lifetime, or equivalently exposures for 1 month per year for 12 years, are estimated to be 1/75 of the lifetime risks. For

example, the risk of exposure to 2.4 ng/kg/d to benzo[a]pyrene for one year out of a lifetime is estimated to be less than $1400 \times 10^{-6}/75 = 1.9 \times 10^{-5}$. For 24 months of exposure, lung tumor risk estimated to be less than 3.8×10^{-5}, *etc.* For the Moolgavkar initiation-cell proliferation-malignant transformation model of carcinogenesis, Chen *et al.* (1988) show that fractionating the risk by the fraction of the lifetime exposure may overestimate the risk and is not likely to underestimate the risk of short-term exposures at various ages by more than a factor of 10. Hence, less than lifetime exposures generally result in lowered risks.

At low levels of exposure, the total risk from a mixture of carcinogens is calculated as the sum of the risks from the individual components (EPA, 1986). The sum of the upper estimates of risk from Table 2 is 6.7×10^{-3}. Of this total risk dibenzo[a,h]anthracene accounts for 43%, benzo[a]pyrene 21%, benzo[b]fluoranthene 12%, anthracene 6%, and the remainder of the PAH's account for 18% of the total risk. It is unlikely that all of the potencies of the major components are at their respective upper confidence limits. It can be shown that the upper confidence limit of risk for a mixture is between $\sqrt{\Sigma u_i^2}$ and Σu_i where u_i is the upper estimate of the i^{th} component. The upper bound on the total lifetime risk of the sum of the individual risks listed in Table 2 is between 3.4×10^{-3} and 6.7×10^{-3}. Again, this is assuming maximum daily exposure to each component.

SUMMARY

The highest risk for an individual component of aerosol dispensers (dibenzo[a,h]-anthracene) is estimated to be less than 2.9×10^{-3} and the risk of the total mixture of components listed in Table 2 is estimated to be less than 6.7×10^{-3} for lifetime exposures. For an exposure of one year, these risks are 3.9×10^{-5} and 8.9×10^{-5}, respectively. For an across species dose scaling factor based on surface area from rats to humans the estimates

are 3.6 times higher. If less than the maximum daily exposure to human occurs, then risk estimates would be proportionally less. The issue now becomes whether the benefits of dispensing drugs by aerosols outweigh the potential lung cancer risks. This may warrant an investigation of lung cancer rates in patients using aerosol devices containing PAH's or a case-control study of lung cancer patients and exposure to PAH's via aerosol applicators.

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Table 1. Proportion of animals with lung tumors in rats exposed to benzo[a]pyrene.

Dose (mg)	Deutsch-Wenzel *et al.* (1983)	Iwagawa *et al.* (1989)	Wenzel-Hartung *et al.* (1990)	Pooled
0	0/70	0/40	0/70	0/180
.03	-	1/29	3/35	4/64
0.1	10/35	7/30	11/35	28/100
0.3	23/35	22/29	27/35	72/99
1.0	33/35	9/13	-	42/48

Table 2. Upper bound estimates of cancer potency (lifetime tumor risk per ng/kg/d), maximum human exposure levels, and upper bounds on estimated lifetime tumor risk.

PAH	Upper bound on potency (risk per ng/kg/d)	Maximum exposure (ng/kg/d)	Upper bound for lifetime tumor risk
Naphthalene[a]	4×10^{-6}	4.0	16×10^{-6}
Acenaphthylene	low	2.4	low
Acenaphthene	unknown	2.4	unknown
Phenanthrene	1×10^{-6}	12.8	13×10^{-6}
Anthracene	130×10^{-6}	3.2	420×10^{-6}
Fluoranthene[b]	27×10^{-6}	10.4	280×10^{-6}
Pyrene[b]	17×10^{-6}	10.4	180×10^{-6}
Benzo[e]pyrene	6×10^{-6}	2.4	14×10^{-6}
Benzo[a]pyrene	580×10^{-6}	2.4	1400×10^{-6}
Benzo[g,h,i]perylene	13×10^{-6}	6.4	83×10^{-6}
Fluorene[c]	4×10^{-6}	2.4	10×10^{-6}
Benzo[a]anthracene[d]	46×10^{-6}	2.4	110×10^{-6}
Chrysene	37×10^{-6}	2.4	89×10^{-6}
Benzo[b]fluoranthene	130×10^{-6}	6.4	830×10^{-6}
Benzo[k]fluoranthene	39×10^{-6}	2.4	94×10^{-6}
Indeno(1,2,3-cd)pyrene	70×10^{-6}	3.2	220×10^{-6}
Dibenzo[a,h]anthracene	1800×10^{-6}	1.6	2900×10^{-6}
Total		maximum	6700×10^{-6}

[a]Based on fibrosarcoma potency for sc exposure x 100.

[b]Based on skin cancer potency x 6.8.

[c]Based on pituitary adenoma for dietary exposure x 100.

[d]Based on skin cancer promotion.

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Chemistry Consult #2

NDA No. 20-911 **Date of Consult:** 23 DEC 1998

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 11 MAY 1999

Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: 3M Pharmaceutical Division

Drug Name: *Generic:* Beclomethasone dipropionate *Commercial:* QVAR™

Chemical name: 9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Formula: $C_{28}H_{37}ClO_7$

Molecular Weight: 521.05

Drug Class: Steroid

Proposed Clinical Dose: Dosing range of 80-640 µg/day: total daily dose of 80-320 µg/day (40-160 µg twice daily) in mild to moderate asthmatics, 480-640 µg/day (240-320 µg twice daily) in more severe cases. Actuators may produce 40 or 80 µg/actuation with a maximum of 16 actuations/day recommended. The recommended total daily dose is less than that for current CFC products due to increased lung deposition.

Clinical formulation: Beclomethasone dipropionate (QVAR™) in propellant HFA-134a and ethanol

Review:
Dr. Alan Schroeder requested a safety assessment of proposed impurity specifications for drug substance and degradation product specifications for the drug product, and the proposed drug product impurity specification for — content.

Safety Assessment of Degradation Products:

Table 1 lists the degradation products detected in the drug product. The compounds — are also synthetic impurities and are addressed in the following section on Drug Substance Impurities. According to the guidelines published in ICH topic Q3B, Impurities in New Medicinal Products, the threshold for qualification of degradation products in

new drug products is 1.0% or 50 µg Total Daily Intake, whichever is lower, when the maximum daily dose is < 10 mg. All of the listed degradation products are within the limits of the ICH guidance document and, therefore, need no further qualification in regards to daily exposure levels. However, the reviewing Chemist, Dr. Alan Schroeder, has determined that the — degradant displays a structural alert for mutagenicity. This degradant was previously identified in Vanceril Double Strength Oral Inhalation Aerosol — For the current drug product, the sponsor should either lower the proposed limit to 0.1% (from —%) or qualify the degradant (one point mutation and one cytogenetic assay performed with the isolated degradant).

Table 1:

Chemical Name	Abbreviation	Proposed Limit	TDI (µg)

Safety Assessment of Impurities in the Drug Substance:

Table 2 lists the impurities identified in the drug substance which include four compounds also identified as degradation products in the previous section — The ICH guidance document Q3A, Impurities in New Drug Substances, recommends qualification of impurities exceeding the threshold limits of 0.1% or 1 mg TDI, whichever is lower. All of the proposed impurity levels listed below exceed the threshold 0.1%. Impurity analysis from the drug product lot PD3511 used for the 52 week inhalation study in juvenile dogs shows that only — were detected. The drug product analysis for individual impurities was performed 46 months after manufacturing; only a total impurity level was determined at the time the lot was manufactured and cleared for use in the study. Total impurities were increased at 46 months (— at initial testing). At a NOAEL dose of 0.05 mg/kg in the 52 week study, dogs were administered ~ 65 and 75 ng/kg/day of — respectively (see calculations, page 4). These

levels provide a 1.02 and 1.95-fold safety factors, respectively, compared to the maximum human dose. Similarly, — were administered at a dose of ~ 25 and 60 ng/kg/day, providing a safety factor of ~ 0.4 and 0.94-fold of the human dose. These safety factors are below the safety margin of 10 needed for qualification. If based upon the estimated level for each individual impurity at initial testing, the safety factor would likely be substantially lower.

In looking at the structures of the individual impurities, some are not of a significant safety concern due to their structural similarities to the parent compound. For example, — differs from the parent in that the 17α hydroxyl group is missing and this change only removes the glucocorticoid activity (The Pharmacological Basis of Therapeutics, Ninth Edition, Eds. Goodman and Gillman, 1996,). The impurities — differ from the parent molecule only in the chain length on ring — ; — contains an — chain and — contains a — chain rather than the propionate at C 21. These chain structures would be expected to be cleaved in vivo from the larger molecule producing molecules which occur naturally. In addition, a discussion on structure-activity relationships (Goodman and Gillman, 1996) does not indicate that changes of this nature at this position may enhance topical or systemic potency. Thus, the specifications for these impurities should be based upon the initial recommendations by Dr. Alan Schroeder, CMC reviewer (0.1% for — 21BMP, — and — for — 17BMP and — have been identified previously as metabolites of BDP and are, thus, not considered to be a safety concern, while 21-BMP differs from the parent only in terms of a hydroxyl group at the 17α position which is also present on — . The specifications for these impurities should be based upon the initial recommendations by the CMC reviewer (— % for — and — for 21BMP). These compounds need no further qualification for safety at the levels recommended by the reviewing chemist.

— , structures with — added at the — position are of unknown toxicity or potency since the — has greater potential for leaving the molecule. Thus, the sponsor should reduce their proposed levels for — to 0.1% (according to ICH guidelines) or adequately qualify the two impurities. — as mentioned in the previous section should be qualified by the sponsor due to the presence of a structural alert for mutagenicity.

Table 2:

Impurity	Abbrev.	Proposed Limit %	Proposed Limit max ng/kg	Preclinical Dose %*	Preclinical Dose ng/kg	Species	Duration	Route	Safety Margin
		≤ 0.5	64	0.13	65	Dog	52 wk	IH	1.02
		≤ 0.3	38.4	BLQ		Dog	52 wk	IH	
		≤ 0.3	38.4	BLQ		Dog	52 wk	IH	
		≤ 0.3	38.4	BLQ		Dog	52 wk	IH	
		≤ 0.3	38.4	0.15	75	Dog	52 wk	IH	1.95
		≤ 0.2	25.6	BLQ		Dog	52 wk		
		≤ 0.5	64	BLQ		Dog	52 wk		
		≤ 0.5	64		25	Dog	52 wk		0.4
		≤ 0.5	64		60	Dog	52 wk		0.94

* Percentage of individual impurities based upon drug product analysis of lot PD3511 performed 46 months after manufacturing. Only a total impurity level was determined after 12 months. Total impurities increased at 46 months (—— thus, levels at this time are assumed to be greater than when tested during the 52 week study (

BLQ: Below level of quantification.

Safety Factor Calculations :

Maximum Clinical Dose - [redacted]

(0.5% x 80 µg/actuation x 8 actuations/day) ÷ 50 kg person = 64 ng/kg/day

Preclinical Dose:
0.13% x 0.05 mg/kg (NOAEL dose, 52 wk juvenile dog) = 65 ng/kg/day

Safety margin	=	Preclinical dose ÷ Clinical dose
	=	65 ÷ 64
	=	1.02

Maximum Clinical Dose - [redacted]

(0.3% x 80 µg/actuation x 8 actuations/day) ÷ 50 kg person = 38.4 ng/kg/day

Preclinical Dose:
0.15% x 0.05 mg/kg (NOAEL dose, 52 wk juvenile dog) = 75 ng/kg/day

Safety margin	=	Preclinical dose ÷ Clinical dose
	=	75 ng/kg/day ÷ 38.4 ng/kg/day
	=	1.95

Maximum Clinical Dose – 21BMP:

(0.5% x 80 µg/actuation x 8 actuations/day) ÷ 50 kg person = 64 ng/kg/day

Preclinical Dose:
0.05% x 0.05 mg/kg (NOAEL dose, 52 wk juvenile dog) = 25 ng/kg/day

Safety margin	=	25 ng/kg/day ÷ 64 ng/kg/day
	=	0.39

Maximum Clinical Dose - [redacted]

(0.5% x 80 µg/actuation x 8 actuations/day) ÷ 50 kg person = 64 ng/kg/day

Preclinical Dose:
0.12% x 0.05 mg/kg (NOAEL dose, 52 wk juvenile dog) = 60 ng/kg/day

Safety margin	=	60 ng/kg/day ÷ 64 ng/kg/day
	=	0.94

A TWA value of 10 mg/m^3 was set by ACGIH in 1988/89 for In the current drug product, the sponsor reports that the maximum amount of per individual spray is 4 µg which equates to a possible daily dose of 64 µg (based upon 16 actuations). The sponsor reports that > 95% of the spray is greate. than 9 microns and that ~ 2% was respirable. The proposed specification is NMT ppm (mg drug product per actuation). In one study report, an unusually high value of 60 µg/actuation was reported. This high value could result in a daily dose of 960 µg.

Assuming an average daily intake of 7 m^3 of air during an 8 hour exposure duration, the TWA limit would allow for a daily intake 70 mg of inhaled . Thus, the worst case scenario for exposure to (960 µg/day) is ~ 73-fold lower than the TWA limit allows. The proposed specification limit of ppm is ~ 590-fold lower than that allowed by the TWA. Thus, the proposed specification for in the drug product is acceptable.

Summary and Evaluation: A review of the proposed specifications for degradation products in the drug product, impurities in the drug substance, and the proposed drug product impurity specification for was performed. All of the degradation products identified in the drug product were below the threshold level for qualification as outlined by ICH document Q3B. However, one degradant, will require a limit of % or qualification by the sponsor due to identified structural alerts for mutagenicity. The proposed specifications for substance impurities listed in Table 2 exceed the threshold level for qualification of % and only four of the impurities were identified in the drug lot administered to dogs in a 52-week toxicity study. The administered levels did not provide an adequate safety margin. However, structural similarities to the parent compound, with the exception of and suggest that further qualification is not necessary, although the specifications for these impurities should be based upon the initial recommendations by Dr. Alan Schroeder, CMC reviewer (% for 21BMP, , and % for 21BMP). The sponsor should provide adequate qualification for The proposed specification for in the drug produet (NMT ppm) is acceptable as this level provides a ~ 590-fold safety factor compared to the air exposure limit of 10 mg/m^3 set by ACGIH.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION

1. The degradation products and drug substance impurities listed in Tables 1 and 2, with the exception of those mentioned in Recommendation 2, are adequately qualified for safety at the safety specifications recommended by the reviewing chemist (0.1% —— % for 21BMP, —— and — % for 21BMP).

2. The sponsor should limit the level of —— to less than or equal to 0.1% in the drug substance or adequately qualify the compounds.

3. The sponsor should limit the level of —— to less than or equal to 0.1% in the drug product or should provide adequate qualification for the degradation product.

/S/ May 11, 1999
Timothy J. McGovern, Ph.D., Pharmacologist

/S/ May 11, 1999

CC: HFD-570/Division File
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