

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20983

PHARMACOLOGY REVIEW



MEMORANDUM

FROM: Mark Vogel, HFD-570 (Pulmonary), PKLN, 10B-45
TO: NDA 20-983 Ventolin HFA Inhalation Aerosol
DATE: June 28, 1999
RE: Pharmacology/Toxicology Team Leader Memo

151
6/28-99

This product is a reformulation of a previous albuterol metered dose inhaler that replaces the ozone-depleting CFC propellant with the newer HFA propellant. The Agency and the applicant agreed that 13-week inhalation studies in rats and dogs plus an embryo-fetal developmental study in one species by the inhalation route would be sufficient to characterize the toxicity profile of the new HFA formulation in relation to the previously well documented toxicity profile of other albuterol formulations. The inhalation toxicity studies of this formulation were supported by toxicokinetic studies, that allowed comparison of systemic exposures resulting from inhalation of CFC and HFA formulated albuterol.

No biologically significant differences in systemic albuterol exposure were observed between the CFC and HFA formulations. In dogs exposure was slightly greater for the CFC formulation, in rats exposure was greater for the HFA formulation. Both rats and dogs exhibited manifestations of mild airway irritation in response to inhalation of the albuterol HFA formulation. In rats this was observed as minimal laryngeal epithelial hyperplasia and necrosis in a small number of high-dose animals; no changes were present after a 4-week recovery period. Dogs exhibited mild laryngeal epithelial hyperplasia in vehicle and drug treated groups. There was no direct head-to-head comparison with the CFC formulation in either species. The consensus from published literature is that such findings are typical of non-specific, mild, reversible irritation. Mild airway irritation has previously been observed in animal inhalation toxicity studies with albuterol and other beta-agonists. These findings indicate that this formulation has the potential to be irritating to the respiratory tract. It is difficult to extrapolate the degree to which potential airway irritation would be expressed in the human clinical setting. Since airway irritation can be monitored symptomatically, the best assessment of clinical potential for airway irritation would be analysis of adverse events in clinical safety studies.

The inhalation embryo-fetal developmental study in rabbits revealed dose-related increases in the incidence of enlargement of the anterior fontanelle. This is consistent with delayed cranial ossification, a finding typically induced in rabbits by beta-adrenergic agonists. This and other

developmental abnormalities (such as cleft palate) are consistently observed in animal studies of beta-agonists. The relevance of such findings for human use have never been convincingly demonstrated. This, like other albuterol products, is appropriately labeled as pregnancy category C.

In summary, the animal toxicity studies of this albuterol HFA formulation revealed a toxicity profile qualitatively similar to other albuterol products. The application is approvable from a preclinical standpoint with minor changes to the preclinical sections of the labeling. With respect to animal findings, the only substantive difference between the applicant's proposed labeling and that recommended by the primary reviewer is in the description of the effects on the fontanelle in the new rabbit inhalation developmental toxicity study. The applicant's proposed labeling limits the finding to doses of 28 and 149 mcg/kg. The primary reviewer recommends that the finding was evident at doses of 19 mcg/kg and above. Since the finding was dose-related without a clear-cut no effect level, I concur with the reviewer's recommendation. An acceptable alternative would be to list the incidence of the finding in vehicle controls and at each of the dose levels.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Formulation:*

Components	Theoretical Quantity/Actuation
Active agent- Albuterol sulfate	120.5 mcg
Solvent-propellant- GR106642X (HFA 134a)	to 75 mg

*120 .5 mcg of albuterol sulfate is equivalent to 100 mcg of albuterol. Each actuation delivers 120 mcg of albuterol sulfate, USP from the valve and 108 mcg of albuterol sulfate, USP from the actuator which is equivalent to 90 mcg of albuterol base from the actuator. The proposed product contains 200 actuations.

Route of Administration: Inhalation

Clinical Dose for Adults and Children 4 years and older: 2 actuations (120 mcg/ actuation) every 4- 6 hours or 240 mcg x 6 or a total dose of 1440 or 28.8 mcg/kg for a 50 kg person or 90 mcg/kg for a 4 year old weighting 16 kg.

Disclaimer: Some of the materials in this review has been taken directly from the sponsor's submission.

Introduction and History:

Albuterol/GR106642X Inhalation Aerosol is to be used in the treatment of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm. Albuterol/GR106642X uses non- ozone-damaging hydrocarbon propellant HFA 134a instead of CFCs. The product is intended as a replacement for Ventolin (albuterol, USP) Inhalation Aerosol (NDA 18-473).

This is a 505(b) type of NDA. Since the toxicity profile for albuterol is well known, the FDA and the sponsor agreed that the sponsor should carry out 13 weeks inhalation subchronic toxicity studies in 2 animal species plus an inhalation reproduction embryo-fetal development study in an animal.

species. The objective of these studies was to compare the toxicity and pharmacokinetic profile of albuterol when different propellants are used. The 2 subchronic inhalation studies were submitted as part of IND [(Albuterol/GR106642X Inhalation Aerosol) and reviewed (see attached pharmacology review dated October 5, 1996).

Studies Reviewed in this Submission: salbutamol and albuterol are interchanagable.

1. Bioanalytical Support Data for Salbutamol: 13 Week Repeat Dose Inhalation Toxicity Study in Rats on Salbutamol Formulated with GR106642X (Study # D13338).
2. Bioanalytical Support Data for Salbutamol: 13 Week Repeat Dose Inhalation Toxicity Study in Dogs on Salbutamol Formulated with GR106642X (Study # D13335).
3. A Study to Assess the Effects of Administration by Inhalation on Pregnant New Zealand White Rabbits and Their Progeny (Study # L13931).
4. Labeling for Albuterol/GR106642X Inhalation Aerosol

Pharmacokinetic/Toxicokinetics:

PK data for the 13 week inhalation subchronic toxicity studies in the rat and the dog are reviewed below. As mentioned previously, the toxicity studies have been reviewed, however, the methodology and summaries of the studies are summarized in this review so that the reader may review the PK data more easily.

1. **Bioanalytical Support Data for Salbutamol: 13 Week Repeat Dose Inhalation Toxicity Study in Rats on Salbutamol Formulated with GR106642X (Study # D13338).**

Methodology :

Wistar rats (6 weeks of age), WI BR, 12/sex were included in each dose group. An additional 8 M and F rats were included in each dose group and used for an interim study of 2 weeks. And finally, 6 M and F rats were included as part of each dose group (satellite) and used to determine plasma concentrations. The

snout only inhalation doses of albuterol (batch #s, U92/019A and U92/021A) were given 1 hour daily, 7 days a week for 13 weeks. There was a 4 week withdrawal period as part of this study in an attempt to determine whether tissue changes were reversible or irreversible. Doses were placebo (GR 106642x), 200, 800, 1,900 µg/kg. The positive control was albuterol, CFC 11 and 12 (batch # WA 40500), used at a dose of 2100 µg/kg. Ninety three percent of the particles in this study were 7 µm (aerodynamic diameter) or less. Albuterol in this study was supplied using metered-dose, pressurized aerosol cans.

As mentioned, rats were dosed 1 hour daily as follows : placebo- 8-12 metered doses (md) every 9-10. 2 seconds, low dose- 1 md every 10.3-12.8 seconds, mid dose- 3-4 md every 9.4-11.5 seconds and high dose- 8-12 md every 9.6-11.5 seconds.

Summary of the 13 week Toxicity Study in the Rat :

Inhalational albuterol (with HFA 134a) was administered to Sprague-Dawley rats 1 hour daily for thirteen weeks. The doses were 0, (placebo), 200, 800 and 1,900 µg/kg. The positive control was albuterol with CFCs administered at a dose of 2100 µg/kg. This study included interim sacrifices (2 weeks) as well as a 4 weeks withdrawal period. Results of this study reveal that albuterol (HFA 134a) inhibited body weight gain in rats after the drug was discontinued. However, rats treated with albuterol gained weight during the study. Albuterol induced increased heart weight in all treated rats. However, after a 4 week withdrawal the heart weights of the control and albuterol-treated rats were comparable. Additionally, albuterol at the high dose induced epithelial hyperplasia in the ventral aspects of the larynx as well as necrosis in the ventral cartilage. The NOAEL in this study is unclear.

The study data did not include results of the rats treated with the positive control (albuterol with CFCs) used in the study.

Plasma Concentrations* (ng/mL) of Albuterol in Rats following a One Hour Per Day Inhalation Dosing for 13 Weeks.

<u>Group</u>	<u>Dose</u> (μ g/kg)	<u>Plasma Conc (Mean)</u> (ng/mL)
Placebo (HFA 134a)	0	0
Low	200	27
MID	800	72
High	1900	133
Positive Control (CFC)	2100	77

* 2 males and 2 females per dose group.

Evaluations:

Rats in each dose group received systemic exposure of albuterol except the placebo animals. There were no apparent differences in albuterol concentrations measured in the plasma of male and female rats. The data suggests that plasma concentrations increased linearly with increasing dose. There were no apparent differences in the levels of albuterol observed in the top dose when comparing formulations that contained GR106642X or CFC P11/P12. There was no evidence of accumulation of albuterol after repeat dosing.

2. Bioanalytical Support Data for Salbutamol: 13 Week Repeat Dose Inhalation Toxicity Study in Dogs on Salbutamol Formulated with GR106642X (Study # D13335).

Methodology :

Beagle dogs, 6/sex (placebo and the high dose), 4/sex (interim doses) and 2/sex CFC dose) were administered albuterol (batch # U92/021A) by inhalation. Doses were 0 (placebo), 14, 47 and 142 µg/kg. Albuterol (batch # WA40500) with CFCs was used as the positive control at a dose of 153 µg/kg. The drug was administered morning and afternoon with an interval of 4-6 hours. The number of metered doses (md) were as following: placebo (60 md), low dose (6 md), mid dose (20 md) and high dose (60 md).

Summary of the 13 weeks Toxicity Study In the Dog :

Inhalational albuterol with 134a was administered to beagle dogs daily for 13 weeks. The doses were 0, (placebo), 17, 47 and 142 µg/kg. Albuterol with CFCs, the positive control was used at a dose of 153 µg/kg. There was no saline or distilled water control included in this study. Even through, there was positive control in this study, the sponsor did not keep and/or submit data concerning the results of this dose group. The results of this study reveal an unexplainable decrease in the relative heart weight in all albuterol treated dogs. Further, albuterol GR106642X induced hyperplasia at all doses in this study (approximately 4-35 x the human dose, assuming 100 % is inhaled into the pulmonary tissues).

Plasma Albuterol Concentrations (ng/mL) in Dogs following Inhalation Dosing-2 X daily for Thirteen Weeks with a Formulation Containing GR 106642X or CFCs P11/P12 .

<u>Dose</u> (mcg/kg)	<u>AUC_∞</u> (ng.h/mL)	<u>C_{max}</u> (ng/mL)	<u>T_{1/2}</u> (h)
142*	195	31	3
153** (positive control) with CFCs	254	48	3

* Albuterol with GR106642X-PK carried out using 4 males and 4 females.

** Albuterol with CFCs-PK carried out using 2 males and 2 females.

Evaluations:

There were no significant differences in the plasma pharmacokinetics in dogs administered albuterol by inhalation using formulations with different propellants. There were no significant differences in albuterol concentrations in the plasma of male and female dogs.

Summary of the Pharmacokinetic Data in Rats and Dogs.

The objective of these studies was to compare pharmacokinetic parameters of albuterol administered by inhalation using formulations with different propellants (HFA 134a vs CFC P11/P12) in 2 animal species, the rat and the dog.

In the rat study, inhalation doses 200, 800 and 1900 mcg/kg and a positive control, 1900 mcg/kg were administered 1 hour daily for 13 weeks. Results of this study reveal that rats in each dose group received systemic exposure. There were no differences in albuterol concentrations in the plasma in male and female rats. There was no evidence of accumulation of albuterol in the rats after repeat dosing.

In the dog study, inhalation doses of 14, 47, 142 mcg/kg and a positive control dose of 153 mcg/kg were administered twice daily with an interval period of 4-6 hours between doses. The results of this study reveal that there were no significant differences in the plasma pharmacokinetics in dogs administered

albuterol using formulations with different propellants. There was no evidence of albuterol accumulation in the plasma of the dogs.

Reproductive Toxicology:

3. A Study to Assess the Effects of Administration by Inhalation on Pregnant New Zealand White Rabbits and Their Progeny *in Utero* (Study # L13931- Embryo-Fetal Development).

Test Facilities: [

Study Dates: Started August 10, 1993
Completed October 4, 1993

GLP Compliance: Yes

QA Report: Satisfactory -Lot and Batch Numbers: Batch numbers for (albuterol-U92/047C and U93/247A), (control GR106642X-U92/052A).

Protocol Reviewed by the Division: No

Methods:

Species/Strain: New Zealand White Rabbits-Pregnant

Doses Employed: Air control, GR 106642 X control, 19.3, 28.2 and 149 mcg/kg.

Route of administration: Inhalation

Study Design: Twenty pregnant rabbits were treated one hour daily with albuterol/GR106642X administered by inhalation, days 8-20. All surviving females were sacrificed on day 30. Fetuses were examined for external, visceral and skeletal abnormalities and the sex and body weight of each live fetus.

Number of Animals: 20 pregnant rabbits

Parameters and endpoints: All surviving females were sacrificed on day 30. Fetuses were examined for external, visceral and skeletal abnormalities and the sex and body weight of each live fetus.

Statistical Evaluations: Yes

Results:

Clinical Signs (daily): Clinical signs in both test and control animals include scab formation, hair loss, discharge from the eyes and reduced feces.

Mortality (daily):

Doses:	<u>Air</u>	<u>Gr106642X</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>
	<u>Control</u>	<u>Control</u>			
Number of females mated	20	20	20	20	20
Abortion	0	2	1	0	2
Killed due to poor condition	0	1	0	0	0
Found Dead	0	0	0	1	0

Most of these animals were sacrificed because of sporadic abortions.

Body weight (daily): There were body weight gain reductions in all dose groups, particularly in the high dose group (body weight gain reductions, approximately 10-14 %, were significant during days 8-12 of the study). However, at the end of the dosing period, the bodyweight gain was comparable in all dose groups.

Food Consumption (Weekly): Food consumption was comparable among all dose groups except in the high dose group. The food consumption was reduced by approximately 7 % in the high dose group.

Pharmacokinetics:

Plasma was taken from 5 rabbits from each dose group on days 8 and 20. The analysis was not sophisticated enough to delineate the plasma levels for day 8.

Mean Plasma of Albuterol (ng.mL) in Rabbits Following One Hour Inhalation Dosing of Albuterol (Study # 13931).

Group (mcg/kg)	Day 20 (ng/mL)	
	5 Min	23 hour
Air	NC*	NC
Placebo	NC	NC
19.3	10	NC
28.2	12	7
149	58	8

* Not calculated because half the results were not positive.

Terminal and Necroscopic Evaluations:

Number of Implantations: There was no statistical evidence that exposure to albuterol affected the number of implantations.

Incidence of Pre-Implantation Loss: There was no statistical evidence that exposure to albuterol affected the incidence of pre-implantation losses.

Fetal Observations:

Number of Live Fetuses:

There was no difference in the number of live fetuses between the albuterol – dosed animals and the air control animals

Proportion of Male Live Fetuses:

There was no statistical evidence of a difference between the albuterol-dosed animals and the air controls.

Fetus Body Weight:

Body weight gain in the fetuses born to dams in the high dose group was reduced by approximately 5 %. Body weight gain of fetuses in the other dose groups were comparable with the controls.

Fetal Examinations:

The enlargement of the frontal portion of the anterior fontanella was increased in all dose groups when compared with the controls. The incidences were approximately 1.0, 3, 5 and 8 % in the control, low, mid and high doses, respectively. Alterations in cranial ossification, of which enlargement of the frontal portion of the anterior fontanella is one manifestation, are consistently seen following the administration of beta agonists to pregnant rabbits. The effect is thought to be the result of delay in

ossification and to be confined to the rabbit (data from GlaxoWellcome's historical controls).

Summary of the Reproductive Toxicology Study:

A embryo-fetal development study was carried out to investigate the effect of albuterol formulated with GR106642X upon pregnant New Zealand rabbits and their offspring *in utero* when the drug is administered by inhalation. In this study, pregnant rabbits were administered albuterol by inhalation daily for one hour, days 8-20 using the following dose groups: air controls, placebo (GR106642X propellant), 19.3, 28.2 and 149 mcg/kg. Results of this study reveal maternal toxicity in the high dose group observed as reduced body weight gain and food consumption. Enlargement of the frontal portion of the anterior fontanella of fetuses was found in all dose groups. This effect is consistently seen following the administration of β_2 agonists to the pregnant rabbit. The effect is a consequence of a delay in frontal bone ossification. Its pharmacological cause has been shown to be confined to the rabbit and is of no clinical significance to man (reproduction study historical control data per GlaxoWellcome).

Reduced bodyweight in the fetuses in the high dose group due mainly to maternal toxicity. No statistical significant maternal or fetal changes up to 19.3 mcg/kg.

In most cases, embryo-fetal development studies would be required in 2 animal species, however, the reproductive toxicity of albuterol is well known. The reproductive toxicity of the propellant, GR106642X has been investigated and reviewed. The FDA concluded that an inhalation study in a single species would be adequate to confirm the reproduction toxicity of albuterol and the propellant, GR106642X.

Labeling:

Labeling for Albuterol GR106642X should be revised as following:

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confidential

commercial

information

Comments:

In the original review (IND [] we had several questions concerning the potential of albuterol GR106642X to induced changes in the larynx of the rat (13 week inhalation toxicity study). Our concerns were mainly the potential of albuterol GR106642X to induce epithelial hyperplasia/metaplasia and necrosis in the larynx. We were also concerned about the potential of these changes to progress to malignant lesions.

In the 13 week study, epithelial hyperplasia and necrosis was detected in the ventral aspect of the larynx of the rats (3/24) in the high dose group, 1900 mcg/kg. After a 2 week recovery period, epithelial necrosis was not found in the larynx of the albuterol treated rats. A re-review of the histological tissues of the rat larynx reveals that the pathologist may have misinterpreted (misread) the slides during the initial evaluations.

Additionally, it has been previously reported that albuterol sulfate has the potential to induce epithelial hyperplasia/metaplasia in the larynx of the rat. It also has been shown that high concentrations of most particulate matters have the potential to induce epithelial hyperplasia/metaplasia in the rat. Epithelial hyperplasia/metaplasia in the rat is thought to be a nonspecific adaptive reaction to the repeated respiratory tract irritation caused by exposure to particulate matter.

Published literature show that epithelial changes are not usually found in dogs or primates (Lewis DJ (1991). Morphological Assessment of Pathological Changes within the Rat Larynx. *Toxicologic Pathology*, 19 (4): 352-357). Published literature also reveals that without accompanying keratinization, inflammation or necrosis, such epithelial changes are common in rats. Therefore, the conclusion that epithelial hyperplasia/metaplasia observed in rats is an adaptive change rather than a toxic reaction is well-founded.

Further, recent animal data developed by GlaxoWellcome show that the hyperplasia induced by albuterol/HFA 134a does not progress to cancerous lesions.

Recommendations:

NDA is approvable from the standpoint of pharmacology. Revised labeling should be conveyed to the sponsor. Please note our revision of lines 254-256 in the Pregnancy: Teratogenic Effects section. The revision is as follows:

Enlargement of the frontal portion of the fontanelles in the fetus was observed at and above inhalation doses of 19 μ g/kg.

/S/
Virgil Whitehurst
Pharmacologist *June 28, 1999*

CC: Division file
HFD-570/VWhitehurst
HFD-570/MVogel
HFD-570/PJani

/S/
6-28-99⁰

Review and Evaluation of Pharmacology/Toxicology Data

Reviewer: VEWhitehurst

Division: Division of Pulmonary Drug Products

HFD: HFD-570

Review Completion Date: June 1, 1999

NDA: NDA 20-983

Type of Submission: Chemistry consult

Information to the Sponsor: No

Sponsor: GlaxoWellcome

Drug: Albuterol/GR106642X Inhalation Aerosol

Relevant NDA: NDA 18-473

Drug Class: Beta Adrenergic Agonist

Indication: Treatment of Asthma

Route of Administration: Inhalation

Introduction and Drug History:

This is a chemistry consult (attached) concerning the safety of levels of drug substance and drug products impurities in Albuterol/GR106642 Inhalation Aerosol . The sponsor is proposing the following for both drug substance and drug product.

Impurities

Levels

NMT	.*%
NMT	%

* NMT= Not more than

Calculation for daily exposure in humans:

Drug formulation - recommended maximum daily dose is 2 inhalations (120 mcg per inhalation), 6 times daily, 1440 mcg total daily dose or 28.8 mcg for a 50 kg person.

Evaluation and Conclusion:

Based on ICH guidelines, the impurity levels for [] and the unspecified impurities proposed by the sponsor for the drug substance have not qualified. This conclusion is based on the ICH guideline that states with a daily dose of 2 g or less, the qualification threshold is 1 mg or 0.1 % whichever is lower. The sponsor should be asked to lower the level of the impurities in the drug substance or provide data that show proposed levels are reasonable safe.

The impurities levels for the drug product are reasonable and do not need to be qualified. This conclusion is based on the ICH guideline that states with a daily dose of 1-10 mg, the qualification threshold is 0.5% or 20 mcg, whichever is lower.

Recommendation:

Please convey our conclusions to the chemist.

Virgil Whitehurst
Pharmacologist

CC:

HFD-570/CBertha

HFD-570/MVogel

HFD-570/PJani

HFD-570/VWhitehurst

/S/

7-1-99

/S/

7-1-99

Review and Evaluation of Pharmacology/Toxicology Data

Reviewer: VEWhitehurst

Division: Division of Pulmonary Drug Products

HFD: HFD-570

Review Completion Date: June 30,1999

NDA: NDA 20-983

Type of Submission: Chemistry consult

Information to the Sponsor: No

Sponsor: GlaxoWellcome

Drug: Albuterol/GR106642X Inhalation Aerosol

Relevant NDA: NDA 18-473

Drug Class: Beta Adrenergic Agonist

Indication: Treatment of Asthma

Route of Administration: Inhalation

Introduction and Drug History:

This is a chemistry consult (attached) concerning the safety of extractables from the rubber gasket and the canister coating and the extractable/leachables from the component. The sponsor submitted amended levels for

The sponsor proposed the following extractable specification limits:

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Specs

Evaluation and Conclusion:

For extractables/leachables from the container closure system, provide toxicological data (carcinogenicity, mutagenicity, chronic) to support the safety of estimated human exposure to these extractables/leachables:

If published data or proprietary toxicological data are not available to estimate safe human inhalation exposure to these chemicals, analyze the chemicals for toxicological structural alerts. Computer programs such as DEREK, TOPKAT, and others, would be appropriate for this purpose. Toxicological data on structurally related compounds may also be submitted to estimate safety of anticipated human exposure to these extractables.

The sponsor also should identify the non-assigned peaks, if possible.

Recommendation:

Please convey our conclusions to the chemist.

Virgil Whitehurst

Pharmacologist

CC:

HFD-570/CBertha

HFD-570/MVogel

HFD-570/PJani

HFD-570/VWhitehurst

/S/

7-1-99

/S/

7-1-99

Review and Evaluation of Pharmacology/Toxicology Data

JUN 17 1999

Reviewer Name: V Whitehurst**Division: Division of Pulmonary Drug Products****HFD: HFD 570****Review Completion Date: June 14, 1999.****NDA : NDA 20-983****Type of Submission: Chemistry Consult****Information to be conveyed to the sponsor: Yes****Sponsor: GlaxoWellcome****Drug: Albuterol/GR106642X Inhalation Aerosol****Chemical name: α^1 -[(tert-Butylamino) methyl]-4-hydro-m-xylene- $\alpha \alpha'$ - diol sulfate (2:1) (salt)****Glaxo Wellcome code: AH3365F****CAS Registry Number: 51022-70-9****Molecular Formula: $(C_{13}H_{21}NO_3)_2H_2SO_4$** **Molecular Weight: 576.7****Relevant INDs/NDAs: NDA 18-473-Ventolin Albuterol, NDA 19-489-Ventolin Rofocaps, IND \square Albuterol/GR106642X Inhalation Aerosol.****Drug Class: Beta Adrenergic Agonist****Indication: Treatment of asthma**

Clinical Formulation:*

Components	Theoretical Quantity/Actuation
Active agent- Albuterol sulfate	120.5 mcg
Solvent-propellant- GR106642X	to 75 mg

*120.5 mcg of albuterol sulfate is equivalent to 100 mcg of albuterol. There is approximately 90 mcg of albuterol as albuterol sulfate per each actuation.

Route of Administration: Inhalation

Clinical Dose for Adults and Children 4 years and older: 2 actuations (120 mcg/ actuation) every 4- 6 hours or 240 mcg x 6 or a total dose of 1440 or 28.8 mcg/kg for a 50 kg person or 90 mcg/kg for a 4 year old weighting 16 kg.

Introduction and History:

The chemistry consult is to evaluate the safety of _____ in the drug substance proposed by the sponsor. _____ is used in converting the albuterol base to albuterol sulfate.

The limit of _____ in the albuterol sulfate drug substance for 3M's Proventil HFA MDI (N 20-503) as approved is 0.5 ppm. However, Dr Mark Vogel found a report of a 6 months chronic study in the rat in which the lowest reported toxic dose for _____ was _____ mg/kg (from _____)

The human daily exposure of _____ from Albuterol/GR106642X is approximately _____ mcg/kg.

Conclusion:

5 ppm of palladium in the drug substance is acceptable.

Virgil Whitehurst
Pharmacologist

6-17-99

6-17-99

Jani
JUN - 7 1999

Review and Evaluation of Pharmacology/Toxicology Data

Reviewer: VWhitehurst

Division: Division of Pulmonary Drug Products

HFD: HFD-570

Review Completion Date: June 2, 1999

NDA: NDA 20-983

Type of Submission: Chemistry consult-

Information to the Sponsor: No

Sponsor: GlaxoWellcome

Drug: Albuterol/GR106642X Inhalation Aerosol

Relevant NDA: NDA 18-473

Drug Class: Beta Adrenergic Agonist

Indication: Treatment of Asthma

Route of Administration: Inhalation

Introduction and Drug History:

This is a chemistry consult (attached) concerning the safety of residual
mg per canister of drug product. The acceptance
limits of the residual is 1.0 mg with a maximum dose of 12 actuations a day
and a 75 mg shot weight, the maximum inhalation per day of
is approximately mcg mcg/kg for a 50 kg
person).

Evaluation and Conclusion:

There are limited data concerning the toxicity of _____
_____ are practically inert _____ which are present in

cosmetics, toiletries, processed foods and household products. They are widely used in the practice of medicine.

G Oberdorster in Toxic and Carcinogenic Effects of Solid particles in the Respiratory Tract reveals that the limit to prevent particle overload of extrapolated from rat data is approximately mcg/kg. This calculation was based on occupational exposure to inert particles ~ 3microns (see attachment). The levels of proposed by the sponsor are reasonable.

Recommendation:

Please convey our conclusion to the chemist.

Virgil Whitehurst

CC:

HFD-570/CBertha

HFD-570/MVogel

HFD-570/PJani

HFD-570/VWhitehurst

ISL
6-7-99

Review and Evaluation of Pharmacology/Toxicology Data

APR 22 1999

Reviewer: VWhitehurst**Division: Division of Pulmonary Drug Products****HFD: HFD-570****Review Completion Date: April 15, 1999.****NDA: NDA 20-983****Information to the Sponsor: No****Sponsor: GlaxoWellcome****Drug: Albuterol/GR106642X Inhalation Aerosol****Relevant NDA: NDA 18-473****Drug Class: Beta Adrenergic Agonist****Indication: Treatment of Asthma****Route of Administration: Inhalation****Introduction and Drug History:****This is a chemistry consult (attached) concerning the safety of**

Conclusion:

reasonably safe.

Virgil Whitehurst
Pharmacologist

4/22/99

proposed by sponsor is

FEB - 4 1999

Review and Evaluation of Pharmacology/Toxicology Data

Reviewer: VE Whitehurst

Division Name: Division of Pulmonary Drug Products

HFD: HFD 570

Review Completion Date: January 27, 1999.

Review Number: # 1

NDA: NDA 20-983

Type of Submission: Chemistry consult dated September 10, 1998.

Information to Sponsor: Yes

Sponsor: Glaxo Wellcome Inc

Drug: Ventolin HFA (albuterol sulfate inhalation solution)

Drug Class: Beta Adrenergic Agonist

Treatment: Treatment of Asthma

Route of Administration: Inhalation

Introduction:

The chemistry consult is a request to evaluate the safety of 3 impurities. The sponsor is requesting an increase in the following 3 impurities as follows:

Impurities	FDA Recommendation	Sponsor Request
	ppm	ppm
	ppm	ppm
	ppm	ppm

Sample Calculation:

cc: NDA 20-983
HFD-570 Division File
HFD-570 Jani
HFD-570 Bertha
HFD-570 Poochikian
HFD-570 Huff

Memorandum

To: NDA 20-983
From: Robin A. Huff, Ph.D., Acting Pharmacology Team Leader /S/ ¹² 2-25-99
Date: February 26, 1999
Re: Addendum to CMC consult stamp dated February 4, 1999

This memo does not alter the conclusion reached in the above-referenced consult that the specifications requested by the sponsor for HFA-134a impurities^s are supported by preclinical toxicology studies. However, in the consult, comparisons between clinical and preclinical exposure were made simply by comparing ppm concentrations of clinical and preclinical batches. The comparisons should have taken into account the total dose of each impurity achieved in humans and animals; doing so greatly increases the safety margin (see below for tabulated calculations). Furthermore, it should be noted that the levels of impurities reported in the preclinical batches were in fact levels detected prior to dosing of animals, as opposed to levels measured only at the completion of the studies. The DMF indicates that the sponsor prepared "toxicology grade" batches by deliberately adding impurities for the specific purpose of assessing the toxicology of propellant-related impurities.

The February 4, 1999 consult refers to chronic toxicology studies in dog, and chronic/carcinogenicity studies in mice and rats. Studies in all species provided significant margins of safety for the proposed impurity specifications. Calculations of safety margins based on rat and dog data are tabulated below for each impurity.

Rat: high dose of 9.6 g/kg HFA was the NOAEL

Impurity	Proposed Specification		Preclinical Batch		Safety Margin
	ppm	max mg/m ² dose	ppm	mg/m ² dose	

Dog: high dose of 10 g/kg HFA was the NOAEL

Impurity	Proposed Specification		Preclinical Batch		Safety Margin
	ppm	max mg/m ² dose	ppm	mg/m ² dose	

The sponsor states that the increase in the limit of these impurities has been qualified via preclinical studies. Ventolin HFA with these impurities was used in 6 subchronic/ chronic/ carcinogenic studies in the mouse, rat and dog. The mean range of _____ in these studies was _____ the mean range for _____ was _____ and for _____ the mean range was _____

The impurities administered at these concentrations did not induce a significant increase in tumors in these animal models or have an effect on life expectancy when used in subchronic/ chronic/carcinogenic studies.

The studies, study numbers, animal models, duration and mean range for each impurity are listed below:

Study	Number	Model	Duration	Impurity (mean ppm)	Route
Carcinogenic	M12416	mouse	104 wk		Inhal
Subchronic	M11982	mouse	90 day		Inhal
Chronic	R12098	rat	50 wk		Inhal
Carcinogenic	R12099	rat	108 wk		Inhal
Chronic	D12102	dog	52 wk		Inhal
Chronic	D12758	dog	12 months		Inhal

- These studies were reviewed in the original review for DMF dated 8/7/96. The drug name is GR106642X and the sponsor is Glaxo. These studies, batch analyses of the drugs used in the studies and the mean range for impurities are listed in a table on page 47, volume #3 of DMF

Conclusion:

The results of the subchronic/chronic/carcinogenic studies reveal that impurities administered at mean range levels of for and for were not carcinogenic/ did not have a significant effect on the life expectancy in the mouse, rat or dog. It is our conclusion that the sponsor's proposal for a level of ppm for and ppm for is reasonable.

Recommendation:

Please convey our conclusions to the chemist.

Virgil Whitehurst
Pharmacologist

SI
2-4-99

CC: Division File
HFD-570/VWhitehurst
HFD-570/CBertha
HFD-570/RHuff
HFD-570/PJani
HFD-570/ATrontell

RAH 2-4-99