Electronic Mail Message

Date: 4/25/00 2:20:15 PM
From: Neugebauer, Kenneth (Kenneth.Neugebauer@solvay.com)
To: 'Chamberlinn@cder.fda.gov' (Chamberlinn@A1)
Cc: Pischtiak, Anja (Anja.Pischtiak@solvay.com)
Cc: Neugebauer, Kenneth (Kenneth.Neugebauer@solvay.com)
Subject: 4 minute Presentation to Advisory Committee for Orally inhaled an d nasa

Nancy:

Sorry for the delay, but due to travel and inoperative e-mail system I am only now able to forward the following Statement which I intend to Present during my 4 minute time allocation:

I have not timed it yet. I will shorten it if needed in order to run no more than 3 minutes give or take a few ums, uhh's, and coughs.

I will present an streamlined version of the following:

My name is Ken Neugebauer and I am Director of Marketing and Sales for Solvay Fluorides responsible for the NAFTA Regional Business Unit. I am speaking on behalf of and presenting the comments of:

Ms. Anja Pischtiak
Product Manager Pharmaceutical Aerosols
Solvay Fluor, SFD-KP, Hans-Böckler-Allee 20, 30173 Hannover, Germany
Tel.: +49 (511) 857-3448; Fax: +49 (511) 857-2146; e-mail:
anja.pischtiak@solvay.com

I ask that questions related to these comments be submitted in writing for response by Ms. Pischtiak.

"Solvay Fluor as a manufacturer of the propellants HFA 227 and HFA 134a used in inhalation drug products, marketed by Solvay under the tradenames Solkane®
227 pharma and Solkane® 134a pharma, would like to make two comments on the major excipients in MDIs, the noncompendial propellants HFA 227 and HFA 134a. The comments relate to the Draft Guidance for Industry - Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products - Chemistry, Manufacturing, and Controls Documentation:

1. Lines 288 to 295 identify a requirement for a toxicological qualification of the novel excipients HFA 134a and HFA 227 but do not give directives of what comprises a toxicological qualification.
The consortia IPACT-I and IPACT-II (IPACT = International Pharmaceutical Aerosol Consortium for Toxicology Testing) already have submitted to the FDA extensive safety data on HFA 134a (generated and submitted by IPACT-I) and HFA 227 (generated and submitted by IPACT-II) intended for inhalation which may sufficiently demonstrate the toxicological suitability of the novel excipients HFA 134a and HFA 227 for use in medical products, incl. MDIs.
Solvay believes that the uncertainty on the requirements for a toxicological qualification of the pure excipients stops the pharmaceutical industry from reformulating its CFC containing products using HFAs and therefore proposes to add a definition for the toxicological qualification of the noncompendial propellants HFA 134a and HFA 227.

2. Lines 381 to 405 show impurity acceptance criteria limits for HFA 134a impurity by impurity, which are, given in such a detail, process related. Solvay, for example uses for the manufacture of Solkane 134a pharma a process starting from trichloroethylene, which is not mentioned in the FDA specification, but is present in trace but detectable amounts (at concentrations of < 1 ppm) in
Solkane 134a pharma and therefore are specified by Solvay. While Solvay has four additional impurites not shown in the specification quoted by the FDA, other impurities which are listed in the Draft Specification are not contained in Solkane 134a pharma.
Therefore Solvay proposes to replace detailed impurity-by-impurity limits by acceptance criteria based on toxicological tests performed, both for HFA 134a and for HFA 227."

In addition I am submitting with these comments Solvay's Specifications of Solkane® 134 pharma with detailed description of the differences in comparison with the Draft Guidance 134a specification.

Additionally I submit the Specification for Solkane® 227 pharma as filed with the FDA in our DMF - to be added to the Draft Guidance in case the 134a Specification remains.

Finally, Solvay agrees in principle with comments previously submitted by IPAC as published in the August 1999 " Gold Sheet " and are submitted again here with key points highlighted.

Thank you.

Mit freundlichen Grüßen / meilleures salutations / Best regards,
> Ken Neugebauer
> Director of Sales/Marketing - Inorganic Fluorides, Manager TQM
> Solvay Fluorides, Inc. 41 W. Putnam Ave, Greenwich CT 06830
> phone: (203) 629-7900 Fax: (203) 629-9074
> e-mail:mailto:kenneth.neugebauer@solvay.com web:
> http://www.solvay-fluor.com http://www.solvay.com
>

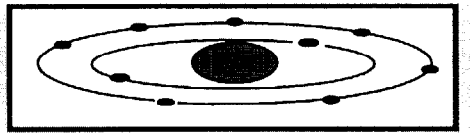
SOLVAY

Solvay Fluorides, Inc.

Solvay Fluor und Derivate

Manufacturer of Propellants HFA 134a & HFA 227ea Pharma

Ken Neugebauer - **Director of Sales / Marketing - NAFTA**
41 W. Putnam Ave., Greenwich CT. 06820
203-629-7900



Comments to Draft Guidance for Industry (MDI's)

- Add a definition for the toxicological qualification of the noncompendial propellants HFA 134a and HFA 227 - promotes accelerated CFC phaseout.
- Establish acceptance criteria based on toxicological test results for 134a and 227 propellants instead of using detailed impurity by impurity limits which are process / producer dependent.

code	formule	Solvay (draft FDA) spec ppm (v/v)
CFC-11	CCl3F	- (5); not present
CFC-1112a	CF2=CCl2	- (5); not present
CFC-113	CCl2F-CClF2	- (5); not present
CFC-114	CClF2-CClF2	- (5); not present
CFC-114a	CCl2F-CF3	10 (25); present only in raw material
CFC-115	CClF2-CF3	5 (5); present only in raw material < 1ppm
CFC-12	CCl2F2	5 (100); present only in raw material < 1ppm
CFC-12B1	CClBrF2	- (5); not present
CFC-13	CClF3	5 (5); present only in raw material < 0,5 ppm
CFC-217ba	CF3-CClF-CF3	5 (-); present
FC-1318my-C	CF3-CF=CF-CF3 c	5 (5); present
FC-1318my-T	CF3-CF=CF-CF3 t	5 (5); present
HCC-1120	TRI	5 (-); present in traces < 0,3 ppm; starting material
HCC-30	CH2Cl2	5 (-); present in traces < 0,3 ppm
HCC-40	CH3Cl	5 (5); present only in raw material
HCFC-1121	CHCl=CClF	- (5); not present
HCFC-1122	CHCl=CF2	5 (5); present
HCFC-1122a	CHF=CClF	5 (5); present
HCFC-1131	CHF=CHCl	5 (-); present
HCFC-123	CHCl2-CF3	- (5); not present
HCFC-123a	CHClF-CClF2	- (5); not present
HCFC-124	CHClF-CF3	10 (100); present only in raw material
HCFC-124a	CHF2-CClF2	- (5); not present
HCFC-132b	CClF2-CH2Cl	- (5); not present
HCFC-133a	CH2Cl-CF3	5 (5); present
HCFC-22	CHClF2	5 (50); present only in raw material < 1ppm
HCFC-31	CH2ClF	5 (5); present only in raw material < 1 ppm
HFC-1123	CHF=CF2	- (5); not present !
HFC-1132	CHF=CHF	5 (5); present
HFC-1225ye	CHF=CF-CF3	5 (5); present only in raw material
HFC-1234yf	CH2=CF-CF3	5 (5); present only in raw material
HFC-1243zf	CH2=CH-CF3	5 (5); present
HFC-125	CHF2-CF3	5 (5); present
HFC-1336mzz	CF3-CH=CH-CF3	- (5); not present
HFC-134	CHF2-CHF2	100 (1000); present
HFC-134a	CH2F-CF3	CP: 99,9% (v/v)
HFC-143a	CH3-CF3	10 (10); present
HFC-152	CH2F-CH2F	- (5); not present
HFC-152a	CH3-CHF2	5 (300); present
HFC-161	CH2F-CH3	- (30); not present
HFC-23	CHF3	- (5); not present
HFC-245cb	CF3-CF2-CH3	5 (5); present only in raw material
HFC-32	CH2F2	- (5); not present

Specification Solkane 134a pharma based on the first 5 batches manufactured on pilot scale
April 11, 2000

- **4 impurities added** (217ba, HCFC-1131, HCC-30 and HCC-1120)
- ***16 impurities not present; not even in the raw material*** (CFC-11, CFC-1112a, CFC-113, CFC-114, CFC-12B1, HCFC-1121, HCFC-123, HCFC-123a, HCFC-124a, HCFC-132b, HFC-1123, HFC-1336mzz, HFC-152, HFC-161, HFC-23, HFC-32)
- **11 impurites present only in the raw material** (CFC-114a, CFC-115, CFC-12, CFC-13, HCC-40, HCFC-124, HCFC-22, HCFC-31, HFC-1225ye, HFC-1234yf, HFC-245cb)
- **16 impurities present** (CFC-217ba, FC-1318my-c, FC-1318my-t, HCC-1120, HCC-30, HCFC-1122, HCFC-1122a, HCFC-1131, HCFC-133a, HFC-1132, HFC-1243zf, HFC-125, HFC-134, HFC-134a, HFC-143a, HFC-152a)

SOLVAY FLUORIDES

SOLVAY FLUORIDES, INC.
41 West Putnam Avenue, Greenwich, Connecticut 06830-6091 Tel: (203) 629-7900 Fax: (203) 629-9074

TELEFAX

CONFIDENTIALITY NOTICE

Date:

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Subject:

SOLVAY
FLUOR UND DERIVATE GMBH
WERK WIMPFEN

Abt. Qualitätswesen
Postfach 180, D-74206 Bad Wimpfen

Spezifikation/Specification

Spez.Nr.: 158610 Rev.: 3

Material: **Solkane(R) 227 pharma**

Kunde/Customer:
Solvay Frankfurt

Formel/
Formula: CF3-CHF-CF3 MW: 170,03 CAS-Nr.: 431-89-0

Physikalische Eigenschaften / physical properties

Beschreibung/
description: colourless liquified gas

Siedepunkt/
boiling point: - 16.5 °C

Schmelzpunkt/
melting point:

Dichte/
density: 1.42 kg/l (20°C)

Löslichkeit
(Wasser)/

Specifications

Determination:	Solvay Method:	Specification:	Units:
Content (GC)	403	≥ 99.99	% vol.
Appearance	404	colourless gas	
Identification (FTIR)	401	complies with standard	
Volatile Rel.Substances (GC)	402	:	
- Hexafluoropropene	402	≤ 5	ppm vol.
-1,1,3,3,3-Pentafluoropropene	402	≤ 5	ppm vol.
-Hexafluorocyclopropane	402	≤ 5	ppm vol.
- 1-Chloro-1,2,2,2-tetrafluoroethane	402	≤ 10	ppm vol.
- Sum of others *)	402	≤ 5	ppm vol.
Water	415	≤ 10	µg/g
Non-volatile matter	407	≤ 20	ppm(m/m)
Acidity (Hydrogen fluoride)	408	≤ 0.1	µg/g
Non-condensable gases	405	≤ 1.5	% vol.

*) includes unsaturates

09.03.00

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