Zephex®134a Related Impurities vs FDA Draft Guidance

1. Introduction

Currently only one monograph applies to inhalation grade 134a – the EP monograph. No other Pharmacopoeia have registered monographs. Although there are 134a monographs for topical (dermal) applications, these are not relevant to inhalation grade 134a applications.

Three sets of information do however exist, described briefly below:

1) **The European Pharmacopoeia (Ph. Eur.) Monograph for Norflurane.**
   First implemented 1st April 2013 as supplement 7.7 to the 7th edition of the Ph.Eur.

2) **Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations - Guidance for Industry (Revision 1)**
   Draft FDA guidance April 2018. Not implemented. Part IV B – Description and Composition (P1).

3) **International Pharmaceutical Aerosol Consortium for Toxicity Testing (IPACT-1)**[1]
   Specification for named organic impurities contained within the confidential toxicology report which is owned by a consortium.

For point '1' above, Koura can supply a document entitled 'Assessment of the Impact of the European Pharmacopoeia Monograph for Norflurane (HFA 134a, 1,1,1,2-Tetrafluoroethane)' where required.

The information below will provide information to support point '2' above. The Koura Zephex®134a specification and its known impurities, listed within Koura's 'Related Organic Impurities Method for Zephex®134a', will be compared against the 'Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations - Guidance for Industry (Revision 1)' document. This draft FDA guidance contains non-binding statements and areas which Koura believe improvements can be made. Koura have notified the FDA and are waiting for a response to these queries.

The IPACT-1 specification is a more rigorous specification for the control of impurities in HFA-134a for medical usage. Koura recommends customers to use this criteria, rather than that detailed in the Ph. Eur monograph for Norflurane.

2. Koura's Related Organic Impurities Method for Zephex®134a

Koura holds the following document, which is classified as confidential, however this is available when a CDA is mutually agreed.

Methods for The Analysis of Zephex®134a.
Method Number: 134a/013.
Method Title: Related Organic Impurities in Pharmaceutical Grades of Zephex®134a by Gas Chromatography.

The method is capable of analysing and reporting all impurities detailed in the Ph. Eur., FDA draft guidance and the IPACT-1 specification (1, 2 and 3 in the introduction above).

Zephex®134a CofA

Many of the impurities that are detectable by the related impurities Gas Chromatographic method are never present in the product but are listed as 'N/D – Not Detected' on the Certificate of Analysis (C of A). There are several reasons for this; the most pertinent being that originally there were two manufacturing routes to 134a employed by the industry. The GC analysis method was developed to ensure all possible impurities could be detected and quantified from either manufacturing route. Nowadays, only one manufacturing route is utilized.

Zephex®134a Specification (GCK134PGC15)

The Zephex®134a specification, named hereafter the C15 specification, has clauses that are designed to control groups of impurities. The specification has tighter limits on many of the impurities listed in the FDA's draft guidance. This specification (and subsequent C of A) lists impurities that could be present in the product. All impurities that are not typically present in Zephex 134a are captured within the associated clause. Listed in Table 1.

3. Tabulated Information: FDA Draft Guidance Impurities vs Those of Koura's Related Organic Impurity Method

Impurity	FDA: Draft Guidance (ppm)	Koura: Specification (ppm)	Koura: Related Impurities Method (ppm)	Covered by Clause in Koura's Specification
HCC-40	5	-	3	Any other identified saturated impurity
HFC-23	5	-	3	Any other identified saturated impurity
HFC-32	5	-	3	Any other identified saturated impurity
HFC-125	5	3	-	Listed in Koura C15 Specification
HFC-134	1000	90	-	Listed in Koura C15 Specification
HFC-143a	20	10	-	Listed in Koura C15 Specification
HFC-152	5	-	3	Any other identified saturated impurity
HFC-152a	300	-	3	Any other identified saturated impurity
HFC-245cb	5	-	3	Any other identified saturated impurity
HFC-1123	5	-	5	Total Unsaturated Impurities
HFC-1132	5	-	5	Total Unsaturated Impurities
HFC-1225ye	5	-	5	Total Unsaturated Impurities
HFC-1243yf	5	-	5	Total Unsaturated Impurities
HFC-1243zf	5	-	5	Total Unsaturated Impurities
HFC-1336mzz	5	-	5	Total Unsaturated Impurities
HCFC-22	50	3	-	Listed in Koura C15 Specification
HCFC-31	5	-	3	Any other identified saturated impurity
HCFC-123	5	-	3	Any other identified saturated impurity
HCFC-123a	5	-	3	Any other identified saturated impurity
HCFC-124	100	3	-	Listed in Koura C15 Specification
HCFC-124a	5	-	3	Any other identified saturated impurity
HCFC-132b	5	-	3	Any other identified saturated impurity
HCFC-133a	5	3	-	Listed in Koura C15 Specification
HCFC-161	30	-	3	Any other identified saturated impurity
HCFC-1121	5	-	5	Total Unsaturated Impurities
HCFC-1122	5	-	5	Total Unsaturated Impurities
HCFC-1122a	5	-	5	Total Unsaturated Impurities
CFC-11	5	-	3	Any other identified saturated impurity
CFC-12	100	3	-	Listed in Koura C15 Specification
CFC-12B1	5	3	-	Listed in Koura C15 Specification
CFC-13	5	3	-	Any other identified saturated impurity
CFC-113	5	-	3	Any other identified saturated impurity
CFC-114	5	3	-	Listed in Koura C15 Specification
CFC-114a	25	3	-	Listed in Koura C15 Specification
CFC-115	5	3	-	Listed in Koura C15 Specification
CFC-1112a	5	-	5	Total Unsaturated Impurities
FC-1318my-T	5	-	5	Total Unsaturated Impurities
FC-1318my-C	5	-	5	Total Unsaturated Impurities
Total Unsaturates (incl HCFC-1122)	5	5	-	Total Unsaturated Impurities
Individual Unidentified Impurities	5	3	-	Individual Unidentified Impurities
Total Unidentified Impurities	10	3	-	Total Unidentified Impurities
Other Organic Impurities	50	10	-	Total Other Saturated Impurities
Any Other Identified Saturated Impurity	5	3	-	Any Other Saturated Impurity
Total Impurities	1000	100	-	Total Impurity Level

Table 1

4. References

1. The European Pharmacopoeia (Ph. Eur.) Monograph for Norflurane.

2. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations - Guidance for Industry (Revision 1)

3. International Pharmaceutical Aerosol Consortium for Toxicity Testing (IPACT-1), data on file. Drug Master File 9857, 9859

4. Zephex®134a Product Specification – GC/K134PG/C15

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Amendments from previous issue:
Addition of CFC-13 impurity in Table 1 – omitted in previous version. Some grammatical improvements. Addition of references in section 4.

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