ZEPHEX®

THE REGULATORS QUESTIONS & REQUESTS FOR ZEPHEX®134a: VERSION 1

The Regulators' Questions and Requests for ZEPHEX®134a: Koura's Answers and Responses

As the leading supplier of medical propellants to the pharmaceutical industry Koura's ZEPHEX®134a has been under the scrutiny of Regulatory Authorities across the world. Koura's technical information package '1,1,1,2-Tetrafluoroethane as an Excipient in a Medicinal Product' has been incorporated into marketing authorisation applications in many different countries and has been the subject of many regulatory reviews. As the pharmaceutical industry and its suppliers, know all too well, regulatory reviewers frequently seek that supplementary piece of information, or a further explanation or clarification. Sometimes it can appear that the submitted documentation has not been read! Notwithstanding, responses must be provided. Koura has always been able to provide prompt answers to the questions raised. Koura is proud to be able to claim that regulatory scrutiny of ZEPHEX® propellants have never been the cause of a delay in the granting of a marketing authorisation. Below are the issues raised, and the answers and responses given.

LIST OF SECTIONS:

QUESTIONS ON SPECIFICATIONS

Request 1

Please amend the 'Appearance' description from 'Clear and Colourless' to 'Clear, colourless, non-flammable gas, that exists as a liquid when under pressure. No malodour is detectable'.

Response 1

The proposed description of 'Clear and Colourless' is more appropriate. Firstly, because odour, or lack of malodour is not an attribute of appearance; odours cannot be seen. A separate test is undertaken to ensure that ZEPHEX®134a contains no malodour, but this is separate from the appearance assessment.

Secondly, the purpose of a specification is to list parameters, which can be assessed, or could vary to the extent that they cause the product to fail specification. ZEPHEX®134a is non-flammable, and this is a property, which does not change. It is inappropriate to list non-flammability in the specification, since that would imply that the product is tested for flammability on a fairly regular basis, which clearly it is not. Similarly, the fact that it exists as a liquid when under pressure is a property, which cannot be changed, and it is inappropriate to include it in the specification.

Request 2

The specification for ZEPHEX®134a does not appear to control all the impurities listed in the specification attached to the CPMP Coordinated Review of 1,1,1,2-tetrafluoro-ethane (i.e. the IPACT-I specification). For example, there do not appear to be clauses to control impurities like HFC 245cb or HFC 152a. Please clarify how the levels of such impurities are controlled.

Response 2

The named analytes in the Koura specification for ZEPHEX®134a were selected at the time that the initial specification for a pharmaceutical grade of HFA 134a was developed. These analytes were selected because they were either known or suspected to be impurities from the chosen route of synthesis. Clauses are also included in the specification to provide control over the permitted levels of any other impurities such as those named in the IPACT-I specification. Thus, the impurities which are named in the IPACT-I specification which are not named in the ZEPHEX®134a specification will be controlled by the clause:

Total other saturated impurity:	10 ppm w/w maximum
-provided that any individual saturated impurity is:	3 ppm w/w maximum

Impurities such as HFC 245cb or HFC 152a, both of which are occasionally detected in ZEPHEX®134a, would be controlled by this clause. The specification would therefore allow HFC 152a, for example, to be present at levels up to 3 ppm w/w, although in reality the levels are much less than this.

In addition to HFC 152a and HFC 245cb the following impurities, which are named in the IPACT-I specification would be controlled by this clause: CFC11, HCFC 123, HCFC 123a, HCFC 124a, HCC 40, HFC 152, HCFC 132b, HCFC 31. The limits applied to these impurities by the ZEPHEX®134a specification are therefore equal to or tighter than limits applied by the IPACT- I specification.

In the event that any other named saturated organic impurities were detected in ZEPHEX®134a, they would be controlled by this limit of not more than 3 ppm w/w for each individual impurity. There is also the additional control that the total of these impurities, which are not individually named in the ZEPHEX®134a specification, must be not more than 10 ppm w/w.

Request 3

Please amend the clause 'Total unsaturated impurities' to 'Total identified unsaturated impurities' and clarify whether the limiting value of 5 ppm w/w would apply to the permitted level of a single compound.

Response 3

This is an unnecessary modification since an impurity could not be included in the total for 'unsaturated impurities' unless it had been identified and was known to be unsaturated.

The limiting value of 5 ppm w/w for unsaturated impurities refers to the total value of unsaturated impurities. However, if there was only one unsaturated impurity present, then that individual impurity could be present at a level up to 5 ppm w/w. The Certificates of Analysis, which are supplied with ZEPHEX®134a, will identify the individual impurities, which are present in addition to listing the total value of the unsaturated impurities.

Request 4

Please clarify how any unidentified impurities would be controlled by the specification.

Response 4

The specification for ZEPHEX®134a allows for the fact that occasionally there may be small quantities of unknown impurities detected in the product.
Experience with gas chromatographic techniques for the detection of related impurities has also shown that baseline noise can occasionally appear as a peak due to an impurity. The specification for unidentified impurities is designed to provide a real level of control over the possibility that an unidentified impurity may be present, whilst allowing a practical solution to the possibility that baseline noise can be interpreted as being a real chromatographic peak. There are no means of distinguishing between an unidentified 'saturated' impurity, and an unidentified 'unsaturated' impurity, since to make this distinction an impurity would need to be identified. Once identified, an impurity would cease to be controlled by the 'unidentified impurities' clause of the specification and would be controlled by one of the clauses for identified impurities.

Unidentified impurities are controlled by the limit of 10 ppm w/w maximum, provided that any individual unidentified impurity is limited to not more than 3 ppm w/w maximum.

Request 5

To provide in the specification a set of results to define the microbiological aspects of ZEPHEX® propellants.

Response 5

There is no specification in the EP or the USP that requires HFA-134a to be tested for microbiological contamination. Koura's own specification does not and has never included microbiological contamination. Koura have a confidential report that details that HFA-134a is an inhospitable environment for microorganisms.

Mitigation for the manufacturing process that Annex 10 of the Orange guide/Eudralex states

"5. All fluids (e.g. liquid or gaseous propellants) should be filtered to remove particles greater than 0.2 micron. An additional filtration where possible immediately before filling is desirable."

A 0.2 μm filter is considered a sterilising filter.

For reference: USP method: USP: <1111>
USP<1111> is for finished drug forms and involves a risk assessment and states:
"Manufacturers have therefore to ensure a low bioburden of finished dosage forms by implementing current guidelines on Good Manufacturing Practice during the manufacture, storage, and distribution of pharmaceutical preparations.".
There is no reference for excipients to be tested, risks should be mitigated.

QUESTIONS ON TEST METHODS

Request 1

Please demonstrate that the main peak of 1,1,1,2-tetrafluoroethane in the gas chromatography method for the detection and determination of related impurities does not mask any further impurities.

Response 1

Recognising the need for a gas chromatography (GC) method that resolves, potential related impurities from the main 1,1,1,2-tetrafluoroethane peak, and from each other, Koura embarked upon a major research programme to develop such a method. This development programme took place over three years from 1994 at a cost of several hundred thousand pounds. As a result, a GC method was developed which resolves from HFA 134a, and quantifies, all impurities in

all currently published specifications for the pharmaceutical grades of the product. The GC method relies upon two different columns with different separation mechanisms. It is the use of these differing but complementary separation techniques within the one overall method, which ensures that there are no impurities under the ZEPHEX® 134a peak. Additionally, during the course of the method development programme a wide variety of columns was screened for potential use, and a considerable understanding of the potential impurities in ZEPHEX® 134a wasgenerated.

A confirmatory test demonstrating the absence of impurities 'beneath' the ZEPHEX®134a band has also been undertaken by Koura. In this test, the standard ZEPHEX®134a analytical method gas chromatography column was installed in an Agilent 5890 gas chromatograph and connected to a 5791A mass selective detector. Both an authentic ZEPHEX®134a sample and a sample from the (then) current batch of ZEPHEX®134a were tested. Both samples were initially analysed with the mass selective detector configured in scan mode (mass range 15 to 200). The ZEPHEX®134a spectra was then electronically subtracted from the entire length of the total ion chromatograms. On each occasion no additional spectra, and hence potential impurities, were observed within the boundary of the HFA 134a retention zone.

The two samples were then analysed with the mass selective detector configured in the SIM (selective ion monitoring) mode. The spectra for chlorine and bromine ions were loaded into the method. The instrument was set so that the detector would only 'search' for the organic impurities, which contain either chlorine or bromine ions or both. Chlorine and bromine ions produce very distinctive spectra. The mass selective detector is also at its most sensitive when configured in the SIM mode. Both samples produced typical spectra on their respective total ion chromatograms, which was consistent with the absence of impurities containing either chlorine or bromine.

This work demonstrates that there are no unknown additional impurities eluting with ZEPHEX®134a in the Koura gas chromatography method.

Request 2

Please explain the basis upon which the columns for the 'Related Impurities by Gas Chromatography' method were selected.

Response 2

The gas chromatography columns used for the determination of related impurities were selected on the basis of their ability to resolve the impurities from ZEPHEX®134a and from each other. Having identified columns, which were good at achieving the required separations, and also the conditions under which the resolution was achieved, further columns of the same type were examined to ensure that the results were reproducible, and that any column of the selected type would achieve the desired chromatography. The selected columns and associated conditions were then subject to a formal validation study in which all aspects of the operation of the method were assessed (sensitivity, repeatability, reproducibility etc. etc).

Request 3

Please clarify which non-condensable gases are determined using the Koura method for the determination of non-condensable gas levels in the vapour phase above ZEPHEX®134a.

Response 3

The non-condensable gases that are determined using the Koura method for the determination of non-condensable gas levels in the vapour phase above ZEPHEX®134a are nitrogen and oxygen. The purpose of the non-condensable gases test is to check the level of residual air, which remains in the vapour phase above the liquid propellant, and as such the scope of the test is to detect and quantify the principal components of air (i.e. nitrogen and oxygen). The method is also capable of detecting carbon monoxide.

Request 4

Please provide details of how the calibration standard is created for the determination of non-condensable gases in the vapour phase.

Response 4

The calibration standard for the non-condensable gases test is prepared gravimetrically and is a compressed gas mixture, which will have an approximate composition of 1% v/v nitrogen and 0.5% v/v oxygen in a helium matrix. Preparation of the standard requires specialist skills and it is therefore, provided by a reputable supplier. A certificate of its composition is provided.

Request 5

The identity check by infra-red spectrometry states that the sample under test must be concordant with the spectrum of the authentic 1,1,1,2- tetrafluoroethane. Please clarify what is meant by concordant.

Response 5

The term '...concordant....' means '...agreeing with...' or '....consistent with...' (OED). Thus, in the application of this identity test the infra-red spectrum of the sample under test is generated and demonstrated to be 'concordant with' or 'agreeing with' or 'consistent with' the spectrum of the primary reference standard of ZEPHEX®134a. This comparison is achieved by electronically comparing the sample spectrum with the reference spectrum. The correlation factor will be a number between zero and 1.00, and mustbe
>0.99 for the identity test to be valid.

Request 6

Please clarify why, when performing the two identity checks for ZEPHEX®134a, the identify by infrared test uses the primary standard for the comparison, but the identity by gas chromatography test uses an authentic standard.

Response 6

Two identity checks are performed on ZEPHEX®134a. In the identity check by gas chromatography the standard against which the sample under test is checked is consumed, and for this reason an 'authentic standard' is defined for use in this test. This authentic standard is defined by comparison with the 'primary reference standard'. This enables the primary reference standard to be used only sparingly and therefore preserved. In the identity by infrared test, the spectrum of the sample under test is compared electronically with the spectrum of the primary reference standard. This spectrum only has to be generated once, minimising consumption of the primary referencestandard.

Request 7

Please explain the difference between 'non absorbable gases' and 'non condensable gases'.

Response 7

There is no difference between 'non absorbable' and 'non condensable' gases. The term 'non condensable gases' is strictly more accurate, but the term 'non absorbable gases' is one, which has been used historically, and does still get used.

Request 8

To provide a validation report for "non-condensable gases in the vapour phase" for ZEPHEX®134a

Response 8

The method for testing non-condensable gases is a compendial test, it is listed in the Ph. Eur.
The Zephex®134a C of A indicates that if the product is tested, it would comply with the Ph. Eur.

The Koura method is a very similar method, which has been validated.
The method is calibrated annually against a certified standard.

QUESTIONS ON STABILITY TRIALS

Request 1

Please provide some discussion of the comparability of the containers used for the stability studies to the containers used for the proposed commercial use.

Response 1

Five year full stability studies for ZEPHEX®134a have been undertaken using both stainless steel and carbon steel containers. The containers which are in commercial use are of three types; either carbon steel storage tanks of capacity greater than 10 tonnes, or stainless steel packages of approximate capacity 1 tonne, or stainless steel portable tank containers of approximate capacity 18 tonnes. The containers used for the stability studies are therefore made of the same materials of construction as those used for commercial storage and supply. Thus although the size of the containers proposed for commercial use preclude their use in stability studies, the containers which are used do provide an excellent comparison, particularly with respect to the materials of construction which are in contact with the ZEPHEX®134a.

Additionally, a 12-month high temperature (60°C) study has been undertaken using carbon steel containers. This study was designed to demonstrate the stability of ZEPHEX®134a when stored in external, fixed storage tanks, in locations where mid-summer temperatures could cause brief temperature excursions above the upper temperature limits of the five year full stability studies.

QUESTIONS ON CERTIFICATION

Request 1

Is there a current MHRA certificate for GMP compliance relating to manufacture of Zephex® 134a?

Response 1

A current certificate of GMP Compliance for the site is not available. In 2000, the (then) MCA launched a voluntary inspection scheme for active pharmaceutical ingredients. Although Zephex 134a is an excipient, our Medical Products Business joined this scheme and was audited by the agency for the following 12 years, receiving a GMP certificate each time.
In December 2014, we were notified by the MHRA that the voluntary scheme had been closed due to the introduction of the Falsified Medicines Directive. As our product is not an API, we are not covered by this new legislation, but neither could we continue with the voluntary scheme. We do not therefore, have a current certificate of GMP compliance. We were last audited by the MHRA in May 2012.

Request 2

Is there a statement to explain how Zephex®134a complies with the European Monograph (Ph. Eur.) for Norflurane?

Response 2

Zephex 134a is an excipient which has been tested and complies to a more stringent specification than the Norflurane (EP) monograph. The analytical methods employed by Koura have been validated as equivalent if not superior to the current European Pharmacopoeia (EP) monograph for Norflurane. Zephex 134a, if tested to the European Pharmacopoeia (EP) specifications, would be compliant.

For information, Koura in addition to their standard Zephex 134a CofA can produce an additional CofA which reports the results of the analysis to the specification and limitations of the EP Monograph, however this must be specifically asked for when placing an order with Koura.

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Amendments from previous issue:
Document format standardised. Additional information added: QUESTIONS ON CERTIFICATION (R1) QUESTIONS ON SPECIFICATION (R5)

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