

The Regulators' Questions and Requests for ZEPHEX[®]227ea: Koura's Answers and Responses

Koura's technical information package '1,1,1,2,3,3,3- heptafluoropropane as an Excipient in a Medicinal Product' has been incorporated into successful marketing authorisation applications and has therefore been the subject of regulatory review. 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 have to 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
QUESTIONS ON TEST METHODS
QUESTIONS ON PACKAGING
QUESTIONS ON STABILITY

QUESTIONS ON SPECIFICATIONS

Request 1

Please clarify the conditions under which the characterisation 'highly volatile liquid' described under 'Appearance' is applicable. A more suitable specification would be 'liquid under pressure'. Please comment.

Response 1

During the development of the GC related impurities method, extensive studies using gas chromatography-mass spectrometry (GC-MS) were performed to identify the impurities in 1,1,1,2,3,3,3-heptafluoropropane (ZEPHEX[®]227ea).

These compounds were then classified as either saturated or unsaturated. The retention times of these compounds are used in the routine application of the method to detect their presence in the sample under test.

In the event that a new impurity were consistently to appear in the ZEPHEX[®]227ea then the cause of its appearance would be investigated, and the impurity identified, and classified as 'saturated' or 'unsaturated' accordingly.

The specification for ZEPHEX[®]227ea does however allow for the fact that occasionally there may be small quantities of unknown impurities detected in the product. Experience with the gas chromatographic techniques used 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 at the same time providing 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 the impurity would have to be identified. In the event that an impurity was present which could not be identified and could not therefore be classified as either 'saturated' or 'unsaturated' it would be controlled by the clause in the specification, which tightly controls unidentified impurities.

QUESTIONS ON TEST METHODS

Request 1

All impurities listed within the scope of the 'Related Impurities by Gas Chromatography' test method should be routinely assessed.

Response 1

In the routine operation of the 'Related Impurities by Gas Chromatography' test method all the impurities listed within its scope are assessed, although only impurities actually present in the ZEPHEX[®]227ea will be reported.

As part of the installation procedure for the related impurities method on the gas chromatographic equipment it is necessary to determine the retention times of the individual impurities, and to demonstrate that the individual impurities are resolved from the main peak due to ZEPHEX[®]227ea and from each other.

Adequate sensitivity of the system to the individual impurities also must be demonstrated. In the subsequent routine operation of the method the presence of any of the impurities within the method's scope would be detected, and could therefore be assessed, because the retention time of any of the impurities would be known and the sensitivity of the chromatographic system to the impurities would be known to be adequate.

Request 2

Please explain how the impurities, which have been identified as potential impurities of synthesis were selected, and why this selection is considered to be comprehensive.

Please confirm that during the operation of the 'Related Impurities by Gas Chromatography' method the major peak due to the HFA 227ea (ZEPHEX[®]227ea) does not mask any other impurities.

Response 2

The impurities identified as potential impurities in ZEPHEX[®]227ea were identified on the basis of extensive gas chromatographic and GC-MS examination of the technical (i.e. crude) grade of HFA 227ea used to manufacture the inhalation grade (ZEPHEX[®]227ea).

Further samples were examined to confirm the list of impurities. These samples were from within the manufacturing process for the technical grade of material, and from a batch of development inhalation grade material. (The development inhalation grade material was produced by selective operation of the technical grade facilities prior to the construction of the dedicated inhalation grade manufacturing plant).

In this way all impurities which were related to the structure of HFA 227ea and which could potentially be formed as by-products during its synthesis and manufacture, were considered.

The methodology used for identifying the potential impurities of synthesis is based upon gas chromatographic methods, which utilise columns with different separation mechanisms (polarity and boiling point). The use of cryogenic temperature programmes in conjunction with a boiling point column also ensured the maximum scope for separation of potential impurities by this column. The use of differing but complementary separation techniques for this examination and analysis provided the initial basis for concluding that all possible impurities, which were present were resolved and detected.

It is also informative to consider the way in which the potential impurities are related to each other, and how they can be derived from each other in the synthetic process for the manufacture of the technical (i.e. crude) grade of material from which the inhalation grade is manufactured. This theoretical consideration demonstrates that the compounds, which result from the possible reactions of each of the impurities, are themselves compounds which are considered potential impurities.

i) The first category contains those impurities which are saturated and fully fluorinated, and unable to undergo further fluorination reaction. In this category are:

Octafluoropropane: (HFC 218): $\text{CF}_3\text{CF}_2\text{CF}_3$

Trifluoromethane (HFC 23): CHF_3

1,1,1,3,3,3-Hexafluoropropane (HFC 236fa): $\text{CF}_3\text{CH}_2\text{CF}_3$

1,1,1,2,3,3-Hexafluoropropane (HFC 236ea): $\text{CF}_3\text{CHFCHF}_2$

Pentafluoropropane (HFC 125): CF_3CHF_2

1,1,1,2,2-Pentafluoropropane (HFC 245cb): $\text{CF}_3\text{CF}_2\text{CH}_3$

1,1,1,2,3,3-Heptafluoropropane (HFC 227ca): $\text{CF}_3\text{CF}_2\text{CHF}_2$

ii) The second category contains those impurities, which are unsaturated and could undergo fluorination reactions by addition. In this category are:

Hexafluoropropene, HFC 1216 ($\text{CF}_3\text{CF}:\text{CF}_2$), reacting to give HFA 227ea (CF_3CHCF_3) and HFC 227ca ($\text{CF}_3\text{CF}_2\text{CHF}_2$),

1,1,1,3,3-Pentafluoropropane, HFC 1225zc (CF_3CHCF_2), reacting to give HFC 236ea ($\text{CF}_3\text{CHFCHF}_2$) and HFC 236fa ($\text{CF}_3\text{CH}_2\text{CF}_3$),

Chlorotrifluoroethene, HCFC 1113 ($\text{CF}_2:\text{CFCl}$), reacting to give HCFC 124a ($\text{CHF}_2\text{CF}_2\text{Cl}$),

Tetrafluoroethylene, HFC 1114 ($\text{CF}_2:\text{CF}_2$), reacting to give HFC 125 (CF_3CHF_2),

1,1,1,2,3-Pentafluoropropene, HFC 1225ye ($\text{CF}_3\text{CF}:\text{CHF}$), reacting to give HFC 236ea ($\text{CF}_3\text{CHFCHF}_2$) and HFC 236fa ($\text{CF}_3\text{CH}_2\text{CF}_3$),

In this category can also be included hexafluorocyclopropane, C216 ($\text{CF}_2\text{CF}_2\text{CF}_2$) which would undergo an addition reaction in an analogous manner to its unsaturated isomer ($\text{CF}_2:\text{CFCF}_3$) to give HFC 227ca ($\text{CF}_3\text{CF}_2\text{CHF}_2$).

The isomers of perfluorobutene (HFC 1318my $\text{CF}_3\text{CF}:\text{CFCF}_3$) could theoretically undergo addition reactions; however the highly electron withdrawing nature of the surrounding fluorine atoms and CF_3 -groups would preclude this reaction in the absence of more forcing conditions.

iii) The third category contains those impurities, which are saturated but contain chlorine atoms and could therefore undergo fluorination by substitution. In this category are:

2-Chloro-1,1,1,2-tetrafluoroethane, HCFC 124 (CF₃CHFCl), reacting to give HFC 125 (CF₃CHF₂),

2-Chloro-1,1,2,2-tetrafluoroethane, HCFC 124a (CHF₂CF₂Cl), reacting to give HFC 125 (CF₃CHF₂),

2-Chloroheptafluoropropane, HCFC 217ba (CF₃CFCICF₃), reacting to give HFC 218 (CF₃CF₂CF₃),

Chloropentafluoroethane, CFC 115 (CF₃CF₂Cl), which could theoretically react to give HFC 116 (CF₃CF₃); this is however an extremely difficult reaction because of the strength of the carbon-chlorine bond and the unfavourable impact the surrounding fluorine atoms have on the occurrence of a substitution reaction.

To provide a final confirmation that the list of potential impurities was comprehensive, and that there were no impurities beneath the HFA 227ea band some additional tests were undertaken on samples of inhalation grade HFA 227ea manufactured on the dedicated plant for its manufacture. In these tests, the standard HFA 227ea method gas chromatography column was installed in an Agilent 6850 gas chromatograph and interfaced with a 5973N series mass selective detector. Two samples of HFA 227ea were tested. One sample was the primary reference standard (Batch 00-227-284, cylinder 151732); the second sample was from a recent production batch (Batch 01-227-115). Both samples were initially analysed with the mass selective detector configured in scan mode (mass range 15 to 200). The HFA 227ea spectra was then electronically subtracted from the entire length of the total ion chromatogram providing the means to determine if anything lay beneath the main band. The HFA 227ea retention time window (between 9 and 10 minutes) was observed as a noisy faltering region containing a sharp detector signal spike followed by a void of approximately 16 seconds, and finally an erratic signal tailing off to baseline at between 9.6 and 9.7 minutes.

No matches were found in the available libraries (NIST98, Wiley 275, NBS75K) for the erratic residual peak. Furthermore when the peak abundances were compared to >7.5 million abundance units due to the HFA 227ea, and even the abundance of the peak due to air it is possible to conclude that this peak can be attributed to a combination of inherent instrument noise, and low level bleed from the analytical column.

Similar results were obtained for both samples.

It has therefore been demonstrated that there are no additional impurities masked by the HFA 227ea band.

The two samples were then analysed with the mass selective detector configured in the selective ion monitoring mode (SIM). The spectra for chlorine and bromine ions were loaded into the method. The instrument was set so that the detector would only 'search' for organic impurities, which contained either chlorine or bromine atoms or both. Chlorine and bromine atoms 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 of their respective total ion chromatograms, which was consistent with the absence of impurities containing either chlorine or bromine.

Request 3

Please confirm how the quality of reference standards, used in the 'Related Impurities by Gas Chromatography Method', is assessed.

Response 3

Prior to being used for the calibration of the gas chromatographic systems for the assay of the impurities, the individual reference standards are subject to an identity check and a purity assessment. The identities of the individual reference standards are confirmed using GC-MS techniques. The bulk purities of the standards are assessed by gas chromatography.

At the time of each assessment the reference standard is assigned a validity period of three years, after which a further assessment is undertaken before further use of the standard.

Request 4

Please explain why resolution data are not given for the peaks attributed to HFC 227ca and HFC 236ea.

Response 4

The retention time and resolution data does not contain 'resolution' (RS) values for HFC 227ca and HFC 236ea because of the way in which these RS values are calculated.

The degree of separation between pairs of adjacent peaks, RS, is given by:

$$R_s = \frac{1.18 (t_{r1} - t_{r2})}{[W_1 + W_2]}$$

where:

t_{r1}	= retention time of component 1 (sec)
t_{r2}	= retention time of component 2 (sec)
W_1	= peak width at half height of peak 1 (sec)
W_2	= peak width at half height of peak 2 (sec)

Impurity HFC 227ca ('peak 1') elutes immediately prior to the main band for HFA 227ea ('peak 2'). Due to the nature of the HFA 227ea main band it is not possible to assign a precise retention time (t_{r2}) or a peak width at half height of peak (W_2). Accordingly it is not possible to calculate the value of RS, or 'resolution'. For the same reason it is not possible to calculate the RS value for the resolution of the main HFA 227ea band from the peak which elutes after this main peak, and which is due to HFC 236ea.

236ea is the last component to elute in the chromatographic run, and there cannot therefore be a resolution (RS) value to demonstrate its resolution from the following peak because there is no following peak. There are no values for t_{r2} or W_2 to be used in the above equations.

Accordingly, RS values are not presented for 227ca, 227ea or 236ea.

QUESTIONS ON PACKAGING

Request 1

Information on the immediate packaging used for the propellant (within Europe) should be provided and confirmation provided concerning the compatibility of materials in contact with the propellant.

Response 1

Two types of packaging are used for the transportation of ZEPHEX[®]227ea; both can also be used for the storage of propellant. Quantities up to 1 metric tonne are supplied in stainless steel upright drums, manufactured by BSI to CODAP 95 design. They are of welded construction, fitted with a liquid outlet valve on the drum bottom and a vapour outlet valve on the top of the drum. They have a nominal capacity for ZEPHEX[®]227ea of 1080 kg. The valves for these upright drums are fabricated from stainless steel with polytetrafluoroethylene (PTFE) valve seats.

For bulk quantities, ISO road tank containers of stainless-steel construction, are used for the transportation, and as appropriate the storage of ZEPHEX[®]227ea. These have a nominal capacity for ZEPHEX[®]227ea of 24 metric tonnes. The valves for these ISO road tankers are fabricated from stainless steel with PTFE valve seats.

Both types of container are supplied with information from the manufacturer confirming completion of rigorous cleaning processes, and the suitability of the containers for the designated use.

Storage of ZEPHEX[®]227ea in fixed installations will be in stainless steel or mild steel tanks of varying capacity (dependent upon site requirements), with connecting pipework also being of stainless steel or mild steel construction.

Valves will be constructed of stainless steel or brass with PTFE valve seats. All valves will have been supplied with prior degreasing to 'oxygen standards', with appropriate certification. Commissioning of fixed installations will include protocols for the cleaning of the installation prior to introduction of propellant.

ZEPHEX[®]227ea is compatible with all metals and metal alloys commonly used in container, machine and equipment manufacture. The stability studies currently being undertaken for ZEPHEX[®]227ea supplied by Koura utilise mild steel containers fitted with brass valves, and stainless steel cylinders fitted with stainless steel valves. In both cases the valve joints to the cylinders incorporate PTFE, thereby ensuring that the propellant under stability trial is in contact with the three materials, which are utilised in the containers for the transport and storage of propellant. The observed stability of ZEPHEX[®]227ea in these containers with no change in the impurity profiles for the samples under test, demonstrates the observed compatibility of ZEPHEX[®]227ea with these materials.

QUESTIONS ON STABILITY

Request 1

Please explain why tests for 'appearance', 'acidity', 'high boiling matter' and 'non-condensable gases in the vapour phase' are not performed during the course of the stability testing.

Response 1

Prior to samples of 1,1,1,2,3,3,3-heptafluoropropane being placed on stability trial the 'production batch' or 'release batch' of material from which the stability samples were packaged will have been tested for compliance with specification.

Routine testing of appearance, acidity, high boiling matter and non-condensable gases in the vapour phase have not been undertaken at each of the stability timepoints because these are not considered to be stability indicating tests.

These tests are not considered stability indicating tests because:

- Acidity and high boiling matter are considered to be attributes of the manufacture of the propellant gas for which appropriate specification limits are applied. There is no mechanism by which these attributes can change upon storage and they are not therefore stability indicating.
- The non-condensable gases in the vapour phase level is considered to be an attribute of the packaging of material into containers, indicating the level of nitrogen and oxygen (i.e. air) in the vapour phase above the propellant. There is no mechanism by which this level can change without irretrievable loss of material, and the level of non-condensable gases is not therefore considered to be stability indicating.
- The appearance of a liquefied propellant gas, unlike a solid or solution, is not considered to be stability indicating. A change in the impurity profile of the propellant, caused by lack of stability, would not have any impact upon its appearance.

Furthermore, given the high purity of the propellant it was considered that conducting the stability indicating tests on the same cylinder of material at each timepoint would allow for a much more accurate assessment of stability, and for any trends which may develop to be very apparent. Such an approach would not have been possible if additional tests had been routinely undertaken due to the quantities of propellant consumed in the course of such testing. Accordingly, the approach was adopted of confining the testing to the stability indicating tests only.

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