ZEPHEX®

TOXICOLOGY DATA FOR HFA 134a AND HFA 227ea: VERSION 1

TOXICOLOGY DATA FOR HFA 134a AND HFA 227ea: THE CONCISE STORY

Koura markets HFA 134a and HFA 227ea under the registered trade name ZEPHEX®.

INTRODUCTION

When the industries, which used CFCs, both pharmaceutical and refrigerant, were faced in the late 1980s with the phase out and disappearance of these widely used products, perhaps the most critical issue to address with respect to the HFA alternatives was that of their safety under the proposed conditions of use. As a result, an enormous amount of testing of the alternatives was undertaken by different consortia, and by some individual companies, to provide complete confidence in the safety of the replacement products. Such was the extent of these evaluation programmes that HFA 134a can now claim the accolade of being the most tested chemical ever used.

The status, availability and applicability of the various sets of toxicology data can sometimes seem a complex, almost mysterious, issue. Here is the unravelling of the mystery.

EVALUATIONS
HFA 134a and PAFT 1

The initial evaluation of HFA 134a was initiated by a consortium of the world's chemical companies, including Koura. The Programme for Alternative Toxicological Testing (PAFT) was a programme of research aimed at evaluating the 'alternative' fluorocarbons to health and safety standards.
HFA 134a was studied as part of the 'PAFT 1' programme, which was principally designed to demonstrate the toxicological acceptability of HFA 134a in general applications, such as refrigeration. The Joint Assessment of Commodity Chemicals No. 31 (1,1,1,2-Tetrafluoroethane), published by the European Centre for Ecotoxicology and Toxicology of Chemicals (ISSN-0773-6339-31) provides a comprehensive summary of this initial level of evaluation.

Pharmaceutical Applications

Valuable as the initial PAFT testing was to the pharmaceutical industry, this programme was not intended to cover all the aspects and the detail needed to support the use of HFA 134a in pharmaceutical applications. Additional studies, designed to evaluate HFA 134a to pharmaceutical standards, were therefore needed and to this end two separate programmes were initiated. In

1989 Glaxo (now GlaxoSmithKline) decided that it would independently evaluate HFA 134a using material supplied by Koura; concurrently a consortium of other pharmaceutical companies (IPACT-I; International Pharmaceutical Aerosol Consortium Toxicology I) initiated studies using material supplied by DuPont, the only other credible supplier of pharmaceutical grade HFA 134a. A separate consortium (IPACT-II) was formed later, to develop and evaluate HFA 227ea, which was proposed initially solely for pharmaceutical use. The end result of these toxicological studies was the definition of specifications, which described minimum propellant purity levels, and detailed maximum impurity levels, which had been demonstrated to be toxicologically safe.

To expedite the development of products containing the HFA propellants both the EU's Committee for Proprietary Medicinal Products (CPMP) and the US FDA agreed to review the pre-clinical data on the propellants well in advance of any applications for marketing authorisations being made for products containing HFA propellants. The CPMP reviews were undertaken for the IPACT-I and Glaxo data files for HFA 134a in July 1994 and October 1994 respectively and for the IPACT-II data file in September 1995. Several non-EU regulatory authorities agreed to review the data packages, and the EU assessment reports were made available.

EUROPE
The CPMP Opinions

In the published opinions on HFA 134a the CPMP concluded that HFA 134a, which complied with the specification contained within the annexes to the opinions, could be a suitable alternative to the CFCs, which were (then) currently used. In the published opinion on HFA 227ea the CPMP concluded that the HFA 227ea, which complied with the submitted application, was a suitable alternative to the CFCs, although in this case no specification was published. With the publications of the CPMP opinions a very favourable environment for the use of HFA propellants in pharmaceutical applications had been created. However there are always, in reality, scenarios for which questions arise. For example, would a company, which was a member of the IPACT-I consortium, be able to rely upon the IPACT-I data to provide the necessary toxicological cover whilst sourcing its HFA 134a from Koura? Would a company, which was a member of the IPACT-II consortium, be able to rely upon the IPACT-II studies whilst sourcing its HFA 227ea from Koura? And what about a company, which was not a member of the IPACT-I consortium? Would it be able to rely upon the IPACT-I data, or even the GlaxoSmithKline data, whilst sourcing its HFA 134a from Koura?

The answer to all these questions is in the affirmative.

CPMP Document III/5462/93 European Summary

The key to understanding the applicability and availability of the toxicological data within the European Union is CPMP document III/5462/93 - Final Rev 1, titled Matters Relating to the Replacement of CFCs in Medicinal Products.
This was issued on 17 March 1994, and before any of the CPMP opinions on the alternative propellants were prepared. Of particular relevance is the second paragraph of Section 2 ('Replacement Propellants'), which states:

‘In the event that the CPMP has already formulated an opinion on the acceptability of the propellant then the documentation on the toxicology
and pharmacokinetics of the latter need not be provided, unless in the view of the competent authority the specifications of the propellant are so different from the first propellant that there are serious concerns about the safe use of the propellant in the (reformulated) product.'

The implication of this statement is that provided that the specification for the propellant which is proposed for use in a pharmaceutical product is compliant with that approved in the CPMP opinions, then the European Regulatory Authorities do not wish to receive further toxicology data.

To make sure that Koura's interpretation of this document, and its implications, was correct, confirmation was obtained from Dr Julia Dunn of the UK Medicines Control Agency in February 1996. Dr Dunn advised that the toxicology packages were approved for the particular propellants (ie HFA 134a and HFA 227ea) and that no further data of this nature was required.
The comment was made that there was a certain amount of (commercially understandable) IPACT 'resistance' to this stance being taken by the CPMP.

The CPMP opinions on the HFA 134a and HFA 227ea, in addition to CPMP Document III/5462/93 are available within the Customer Zone of www.zephex.co.uk

Koura is prepared to make copies of the specifications for HFA 134a (ZEPHEX®134a) and HFA 227ea (ZEPHEX®227ea) available under confidentiality agreement (CDA) to enable comparisons to be made with the specifications used for the IPACT Consortia toxicology studies. Visit www.zephex.co.uk

Whilst this detail is only available under CDA, Koura's HFA 134a specification not only complies with, but is tighter than the published IPACT-I specification for HFA 134a. Additionally Koura is also absolutely confident that its HFA 227ea specification complies with the IPACT-II specification for HFA 227ea.

European Summary

The CPMP has twice offered opinions on the suitability of HFA 134a as a propellant in pharmaceutical products. The position taken by the CPMP (as expressed in document III/5462/93) means that both toxicology packages reviewed by the CPMP apply with equal validity to Koura's HFA 134a. Koura's HFA 134a complies with the specifications appended to the CPMP opinions. This means that:

1. Koura's customers for HFA 134a, who are not members of the IPACT-I Consortium are not required by Regulatory Authorities within the European Union to submit toxicology/pharmacokinetic data for HFA 134a.
2. Koura's customers for HFA 134a who are members of the IPACT-I Consortium are able to use Koura's HFA 134a without concern as to the applicability of the IPACT-I toxicology/pharmacokinetic data.

The CPMP has offered an opinion on the suitability of HFA 227ea as a propellant in pharmaceutical products. Although the specification was not published with the opinion Koura is absolutely confident that its HFA 227ea complies with the reviewed specification, and that the toxicology package reviewed by the CPMP is applicable. This means that:

1. Koura's customers for HFA 227ea, who are not members of the IPACT-II Consortium are not required by Regulatory Authorities within the European Union to submit toxicology/pharmacokinetic data for HFA 227ea.
2. Koura's customers for HFA 227ea who are members of the IPACT-II Consortium are able to use Koura's HFA 227ea without concern as to the applicability of the IPACT-II toxicology/pharmacokinetic data.

UNITED STATES
IPACT Applicability

In the United States the position is more straightforward, mainly because the intellectual property of the toxicology studies has been better guarded. This means that for legal reasons a pharmaceutical company has to be a member of the IPACT-I Consortium to rely upon the HFA 134a data, and a member of the IPACT-II Consortium to rely upon the HFA 227ea data. The member companies of the consortia have direct access to this data; it is not linked to, or received via any particular propellant supplier. Although membership of the IPACT-I and IPACT-II consortia is no longer open, the data will continue to be available through a cost sharing licence. (See US Federal Register, August 13, 2002. Volume 67, Number 156, pages 52744-52745).

A key requirement of the US FDA in respect of the propellant part of a NDA submission is inter alia that there should be toxicological cover for the propellant specification. The relevance of the IPACT-I studies to Koura's HFA 134a, and of the IPACT-II studies to Koura's HFA 227ea is not in doubt. Both propellants comply with the specifications, which were the basis of these studies, and the fact that other supplies of HFA 134a and HFA 227ea were used for the original studies is not germane.

Koura is prepared to make copies of the specifications for HFA 134a (ZEPHEX®134a) and HFA 227ea (ZEPHEX®227ea) available under confidentiality agreement (CDA) to enable comparisons to be made with the specifications used for the IPACT Consortia toxicology studies.

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1. Document format standardised. 2. Zephex website address updated 3. Mexichem Fluor updated to Koura

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