

### Stability studies for ZEPHEX<sup>®</sup>227ea A significant requirement

Demonstration of the stability of ZEPHEX<sup>®</sup>227ea is critical information concerning the product, which is required by both the pharmaceutical industry and regulatory bodies. Koura are currently undertaking detailed studies into the stability of ZEPHEX<sup>®</sup> 227ea at temperatures up to 40°C. These studies were commenced in July 2001.

### Stability protocol

Two separate batches of product were placed on trial in accordance with the protocol presented in Table 1.

**Table 1: Stability Protocol**

Storage Condition	Storage time (months)									
	0	3	6	9	12	18	24	36	48	60
2°C/ ambient humidity	X	X	X	X	X	(X)	X	X	X	X
30°C/ ambient humidity	X	(X)	(X)	(X)	X	(X)	X	X	(X)	X
40°C/ ambient humidity	X	X	X	X	X	(X)	X	X	X	X
() Testing optional at these points										
ZEPHEX 227ea is manufactured with a moisture content of less than 10 ppm w/w, and is stored in pressure tight containers. The humidity to which the stability samples of ZEPHEX 227ea were exposed could not therefore change without irretrievable loss of material. For this reason the condition of ambient humidity was considered appropriate for the trial.										

Initially and at intervals indicated by the letter X samples were examined for:

- i) Content of related impurities by gas chromatography
- ii) Water content of ZEPHEX<sup>®</sup>227ea
- iii) Purity of ZEPHEX<sup>®</sup>227ea

All samples were examined for identity by infrared spectroscopy, at the initiation of the trials; all spectra showed concordance with the spectrum of the reference sample.

The test methods used to indicate the stability of ZEPHEX<sup>®</sup>227ea are the same as the methods used routinely for the analysis of the product.

## Storage containers

One batch of ZEPHEX<sup>®</sup>227ea was placed on storage under the various stability test conditions in stainless steel cylinders of nominal fill capacity 1 litre. The second batch of material was placed on storage under the various stability conditions in carbon steel cylinders of nominal fill weight 9.5 kg. The containers used for the stability studies are therefore made of the same materials of construction as those used for commercial storage and supply. Commercial containers are typically 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 of 18 tonnes. 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 ZEPHEX<sup>®</sup> 227ea.

## Results and discussion

Summaries of the results obtained are presented in Table 2, for the trial conducted in stainless steel cylinders, and in Table 3 for the trial conducted in carbon steel cylinders.

The data show that no significant change has occurred in the related impurity levels or the purity of the samples stored under the test conditions, and that the material still complies with the specification applied to ZEPHEX<sup>®</sup>227ea.

## Life to retest

The data presented demonstrate the good stability of ZEPHEX<sup>®</sup>227ea at temperatures up to 40°C for 60 months and adequately support a life to retest of 60 months when stored below 40°C.

The full results for the stability studies for ZEPHEX<sup>®</sup>227ea are included in the information, provided by Koura under obligation of confidentiality, for inclusion in a manufacturer's marketing authorisation application within the EU member states. The full results are also included in the US Drug Master File.

## Ongoing testing

The stability testing programme for ZEPHEX<sup>®</sup>227ea is consistent with the ICH Guideline Good Manufacturing Practice Guide For Active Pharmaceutical Ingredients. Although the pharmaceutical propellants are not active pharmaceutical ingredients, this guideline is considered by Koura to be relevant to ZEPHEX<sup>®</sup> propellants.

The stability monitoring section of this guideline requires inter alia that:

Normally the first three commercial production batches should be placed on the stability testing programme to confirm the retest or expiry date. However, where data from previous studies shows that the API is expected to remain stable for at least two years then fewer than three batches may be used.

and:

Thereafter at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring programme and tested at least annually to confirm the stability.

As described above two batches of ZEPHEX®227ea have been the subjects of full five year stability studies.

Ongoing stability testing of ZEPHEX® 227ea will comprise of one sample per year being taken and stored in a carbon steel container at a temperature of 40°C. The testing interval will be every twelve months from the commencement of the individual testing programmes.

**Table 2: Summary of stability**

Storage Condition	Test	Storage									
		0	3	6	8	12	18	24	36	48	60
2°C	Total related impurities ppm w/w	4	5	4	3	4	NT	4	4	3	3
30°C		4	NT	NT	NT	5	NT	4	3	3	3
40°C		4	3	4	3	4	NT	4	3	3	NA
2°C	Purity % w/w	99.9996	99.9995	99.9996	99.9997	99.9996	NT	99.9996	99.9996	99.9997	99.9997
30°C		99.9996	NT	NT	NT	99.9995	NT	99.9996	99.9997	99.9997	99.9997
40°C		99.9996	99.9997	99.9996	99.9997	99.9996	NT	99.9996	99.9997	99.9997	NA
2°C	Moisture content ppm w/w	3	6	3	5	6	NT	5	7	6	NA
30°C		4	NT	NT	NT	5	NT	7	7	10	7
40°C		8	4	2	3	5	NT	7	5	6	NA
NT = Not tested at this point NA = Not available											

**Table 3: Summary of stability results carbon steel containers**

Storage Condition	Test	Storage									
		0	3	6	8	12	18	24	36	48	60
2°C	Total related impurities ppm w/w	3	3	4	4	4	NT	4	3	3	3
30°C		4	NT	NT	NT	4	NT	4	3	3	3
40°C		3	3	4	4	4	NT	4	3	3	3
2°C	Purity % w/w	99.9997	99.9997	99.9996	99.9996	99.9996	NT	99.9996	99.9997	99.9997	99.9997
30°C		99.9996	NT	NT	NT	99.9996	NT	99.9996	99.9997	99.9997	99.9997
40°C		99.9997	99.9997	99.9996	99.9996	99.9996	NT	99.9996	99.9997	99.9997	99.9997
2°C	Moisture content ppm w/w	3	3	2	2	3	NT	3	7	10	6
30°C		6	NT	NT	NT	4	NT	6	8	6	5
40°C		3	2	2	2	3	NT	4	7	7	3
NT = Not tested at this point											

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## Amendments from previous issue:

1. Document format standardised.
2. Mexichem Fluor updated to Koura