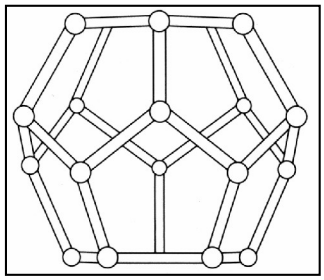
Zotefoams plc



Technical Information Sheet TIS 25
(previously BTI18)
Compliance of Azote Foams with Standards for Medical Appliances

INTRODUCTION

Zotefoams foam products are widely used in medical appliances and packaging applications, where the product purity and stability is greatly valued.

Medical appliances have to comply with strict regulations as described in EU Directive 93/42/EC. This directive describes the requirements for medical devices and thereby also covers the requirements of the component materials used in the manufacture of such devices.

The evaluation of medical devices / materials is comprehensively covered by the International Standard, ISO 10993 which to date is split into 18 separate parts. This set of standards outlines tests methods and requirements for various situations, covering the levels and types of contact of a device (and the materials it is made from) with the body (and bodily fluids).

A further set of recognised tests for polymers and plastics are those described under US Pharmacopoeia Monograph <661> or USP<661>. The USP tests are designed to characterize the physical and chemical properties of plastics by means of four specific tests; non-volatile residue, residue on ignition, buffering capacity and heavy metals content (Pb, Hg, Cr^{6+}, Cd).

The assessments that follow were based on the full testing of a selected foam sample (Plastazote® LD45 Pink) with subsequent demonstration of the toxicological equivalence of the other foams to this representative sample in accordance with the ISO 10993 standard.

SCOPE OF THE EVALUATION

A wide range of Zotefoams products have been assessed for their suitability as parts of surface devices in contact with skin and surface devices in contact with mucosal membranes or breached or compromised surfaces for limited or prolonged exposure (single, multiple or long term use or contact up to 30 days) either directly or through showing toxicological equivalence in accordance with ISO 10993.

The relevant sections in ISO 10993: Biological Evaluation of Medical Devices, are:

ISO 10993: Part 1 [Evaluation and Testing] provides guidance on the types of tests required for a certain level of contact between the device and body. It expresses the fundamental principles of toxicity evaluation which are then subdivided under several headings.

ISO 10993: Part 5 [Tests for In-vitro Cytotoxicity] describes the test methods used to assess in-vitro cytotoxicity of medical devices and component materials. These tests cover exposure of cell cultures either to the device or to extracts from the device. After a controlled incubation period the test cells are visually assessed for changes with quantification of the effect of exposure on cell growth. Dependent on this evaluation the sample is then classed as non-cytotoxic, mildly cytotoxic, moderately cytotoxic or severely cytotoxic.

ISO 10993: Part 10 [Tests for Irritation and Delayed-type Hypersensitivity] outlines the test methods used to assess the potential for irritation and sensitisation during repeated and/or long term exposure to the device / material. A four tier approach is suggested for the assessment of the potential that the devices and / or materials have for causing irritation and sensitisation.

The primary skin irritation test used in these tests involved samples applied to the skin of a test animal (guinea pig). The sensitisation test animals are repeatedly exposed to the sample for several hours. The induction period is followed by 2 weeks without exposure to the samples after which a challenge exposure is applied. The reaction to this challenge is monitored and assessed after specific time intervals.

Results of these tests are based on the mean score of all test animals and responses are classed as negligible, slight, moderate or severe.

ISO 10993: Part 18 [Chemical Characterization of Materials] describes methods for the chemical characterisation of materials. This characterisation includes identification of the chemical nature of the sample and any additives or contaminants that are present. Chemical characterisation is usually performed on extracts of the sample since potential leachables are generally the cause of adverse reactions.

The information obtained from this characterisation can then be used to either identify harmful substances in the product or to establish toxicological equivalence between a known material / product and the test sample.

TEST PROGRAMME

Assessment of the suitability of the foam materials for use in medical devices was carried out by Rapra Technology Ltd, Shropshire, UK.

All foam samples in the table were initially tested according to the requirements of US Pharmacopoeia Monograph testing (USP <661>).

One foam grade, Plastazote® LD45 Pink, was then subjected to full biocompatibility testing as described above and in accordance with ISO 10993: Parts 1, 5, 10 and 18. Additionally other foam grades, selected with the highest density of each product range in Black or Silver Grey, were evaluated against ISO 10993: Part 18.

The information gained on this latter set of samples was used to establish toxicological equivalence between these foams and the fully tested Plastazote® LD45 Pink. Toxicological equivalence was established by comparison of US Pharmacopoeia Monograph testing (USP <661>) results and comparison of substances identified in

aqueous and isopropanol extracts of the samples, in accordance with ISO 10993: Part 18.

RESULTS SUMMARY & CONCLUSIONS

The study, completed in December 2005, concluded that:

'**all of the foam materials represent an acceptable risk for use in parts of surface devices in contact with skin and surface devices in contact with mucosal membranes or breached or compromised surfaces for limited or prolonged exposure (single, multiple or long term use or contact up to 30 days)**.'

This conclusion is a risk assessment based upon the levels of substances with known or suspected health risks, found in the aqueous and isopropanol extracts from the different foam grades.

The following table indicates the equivalence of the other foam samples tested (in terms of useable area x 1cm thick strip), in contact with the body and based upon changes either daily for 30 days or alternatively once after a full 30 day exposure.

PRODUCT	**Maximum acceptable area of 1 cm thick foam [cm^2]**	
	Daily changes of foam[1]	**Change of foam after 30 days[2]**
Plastazote® LD45 Pink[3]	n/a	n/a
Plastazote® LD70 Black	29000	870000
Plastazote® PK80 Silver Grey	10000	300000
Plastazote® HD115 Black	1900	57000
Evazote® EV50 Black	4600	140000
Evazote® VA80 Black	3400	100000
Supazote® EM45 Black	9100	270000

[1] *Assumes all leachable material is released to the patient in one day.*
[2] *Assumes all leachable material is released to the patient during the 30 day period of contact.*
[3] *Plastazote® LD45 Pink was the reference sample (full biocompatibility testing).*

Based on the establishment of toxicological equivalence, all foam grades mentioned in the table above which are of the same formulation but are either of lower density and / or in the colours Black, Grey, White or Pink are also considered to pose an acceptable risk for use in skin contact devices.

All foam samples in the table were tested and shown to comply fully with the requirements of US Pharmacopoeia Monograph <661>.

PAST TESTING AND RESULTS

Prior to the general study above, foam samples from several grades have been tested in isolation to ISO 10993: Part 5 [Tests for In-vitro Cytotoxicity]. These tests were performed in various laboratories using various different types of cell cultures. In some cases the sample was tested using direct exposure while other cases involved tests of extracts of the sample.

In these past tests, the following materials were tested and found to be non-cytotoxic:

- Plastazote®
  - LD24 White, MP45 White
  - LD45 Pink, LD45 White
  - HD115 Black, HD115 White
- Evazote®
  - EV50 White, VA35 White
- Supazote® EM26 White

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