ZOTEFOAMS

# Technical Information Sheet TIS 25

## 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 such as UK MDR 2002 (SI 2002 No 618, as amended) or Regulation (EU) 2017/745 for placing devices on the market in the UK and Europe respectively. These directives describe 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 23 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 or USP. 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).

### SCOPE OF THE EVALUATION

A wide range of Zotefoams products have been assessed for their suitability as parts of surface devices which make contact with intact skin for a limited to long-term duration. Within ISO 10993-1:2018, cytotoxicity, irritation/intracutaneous reactivity and sensitisation are seen as the main biological endpoints, which do not depend on the duration of contact.

Zotefoams materials are typically used in medical devices that are applied to the skin such as orthosis and prosthetics. We have not considered the foam for use in implantable devices or otherwise in contact with blood. Therefore, the relevant sections in ISO 10993: Biological Evaluation of Medical Devices we have conducted evaluations against 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.

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**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 tiered 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 reaction to this exposure 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.

**ISO 10993: Part 23 [Tests for Irritation]** describes a step-wise approach to determine the material, medical device or extract's potential to produce irritation where data is gathered on the materials to select the appropriate test(s) needed. In vitro testing is considered before in vivo testing where reconstructed human epidermis (RhE) models are used to resemble the structure of the human epidermis. Material extracts are exposed to the tissue samples which are then incubated for a period of time. If the mean tissue viability in relation to the negative control is above 50%, then the device material is classified as non-irritant.

In vivo tests are also described in ISO 10993-23, however it is advised to use this method only if in vitro testing is not feasible. In general, if the device is intended for intact skin or a breached or compromised surface, in vitro testing is the right strategy.

**TEST PROGRAMME**

Testing for assessment of the suitability of the foam materials for use in medical devices was carried out at NAMSA. All current and past biocompatibility test reports relevant to current Zotefoams products were sent to Bibra Toxicology Advice and Consulting Ltd along with details of the production process and the raw material (CAS number, raw material/masterbatch supplier trade name and weight percentage in masterbatch and final product). Bibra was asked to review the biological safety of the AZOTE® materials, utilising proprietary biological test data on the materials themselves (and similar materials) as well as toxicological, sensitisation and irritation data identified in the literature on their chemical constituents. Gaps in the data identified by Bibra were addressed by further testing.

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### Cytotoxicity tests

Various ISO 10993-5 compliant assays have been carried out by NAMSA on a range of representative products of the following grades: Plastazote® LD, Plastazote® HD, Evazote® EV and Plastazote® MP. All tests confirmed that samples had no cytotoxic potential. Bibra carried out a gap analysis and identified that testing was needed on Plastazote HD White and Evazote EV Blue to cover all ranges. Consequently, ISO 10993-5 cytotoxicity testing was performed on these two grades in 2022 which confirmed no cytotoxic potential for either material.

Although Evazote VA has not been tested specifically, Evazote EV foams are considered as a worse-case scenario for the Evazote foam range due to the increased monomeric proportion of vinyl acetate in the polymer relative to ethylene. Since Evazote EV foams have been tested to show a lack of cytotoxicity potential, Evazote VA can be assumed to perform similarly.

Across the product range, all colours tested demonstrated a lack of cytotoxicity potential. The pigments involved were blue, black and pink (as well as no pigment – white).

Whilst not all densities within each grade were tested, maximum and minimum densities were tested for Evazote EV grades which confirmed that density does not have a significant impact on cytotoxicity for white variants. Maximum and minimum densities reflect the limits of Zotefoams' processing conditions. Therefore, the complete range of densities for Plastazote HD, Plastazote LD, Plastazote MP, Evazote EV and Evazote VA are all considered to be highly unlikely to have cytotoxic potential.

### Irritation and Sensitisation

Bibra reviewed raw materials used in Zotefoams' products using relevant irritation and sensitisation data identified in literature alongside spot testing on Zotefoam's products. ISO 10993-10 (in vivo) compliant studies have been performed by NAMSA on various Plastazote® LD products. These studies confirmed a lack of significant irritation. Using this previous test data and other studies on similar resins, Bibra identified gaps where further testing was required.

These gaps were addressed with further irritation and sensitisation testing of Plastazote LD in White and Evazote EV in Blue in 2022. ISO 10993-23 (in vitro) tests were performed on Plastazote LD White and Evazote EV Blue to determine skin irritation potential. Again, both materials showed a lack of irritation potential in both studies. ISO 10993-10 studies were also implemented on Plastazote LD White and Evazote EV Blue in 2022 showing no evidence of causing skin sensitisation on the guinea pigs.

Polyethylene (base resin of Plastazote LD, HD and MP) has been reviewed by Bibra from other studies in their library for skin irritation and sensitisation. Bibra concluded that Plastazote LD and HD grades are highly unlikely to cause any skin irritation or sensitisation. Similarly, EVA copolymer was also reviewed using the same technique using literature and relevant test

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data and the same conclusion was drawn, meaning Evazote EV and VA are unlikely to cause skin irritation or sensitisation.

ISO-compliant testing described above, as well as evidence in literature for the specific pigments used, confirms a lack of skin irritation and sensitisation potential for the following pigments in the concentrations used in the foam: black, pink and blue (and no pigment – white).

**RESULTS SUMMARY AND CONCLUSION**

The data available from testing in compliance with ISO 10993 alongside information found in relevant literature provides reassuring evidence regarding the cytotoxicity, irritation, and sensitisation endpoints for various foam products. In general, the assessment, completed by Bibra in March 2023, concluded that the following materials do not raise any significant concerns when used in skin contact applications.

*Table 1: Zotefoams' products considered to be low risk, by Bibra, when used in skin contact applications.*

| Grade | Density (kg/m$^3$) | Colour |
|---|---|---|
| Plastazote® LD | 15 - 70 | Black, White, Blue, Pink |
| Plastazote® HD | 30 -115 | Black, White |
| Plastazote® MP | 15 - 45 | Black, White, Blue |
| Evazote® EV | 30 - 50 | Black, White, Blue |
| Evazote® VA | 35 | Black, White, Blue |

Please note further testing may be required for the end-product where the foam material is used as part of a medical device. Testing carried out by Zotefoams mentioned in this document is to give an indication of how materials are expected to perform in ISO 10993 tests. For evidence of the third-party assessment and gap analysis performed by Bibra Toxicology Advice and Consulting Ltd an executive summary is available on request.

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Zotefoams plc Management systems are covered by the following:

**Quality**
FM 01870
ISO 9001 2015

**Safety**
OHS 52538
OHSAS 18001 2007

**Environment**
EMS 36270
ISO 14001 2015

**ZOTEFOAMS plc**

675 Mitcham Road
Croydon
Surrey
CR9 3AL
United Kingdom

Tel: +44 (0) 20 8664 1600
Fax: +44 (0) 20 8664 1616
Email: info@zotefoams.com

**ZOTEFOAMS inc**

55 Precision Drive
Walton
Kentucky
41094
USA

Tel: +1 859 371
Freephone: (800) 362 8358 US only
Fax: +1 859 371 4734



Issue 3 Revision 1
May 2023

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TechSupport@zotefoams.com
or visit our website **www.zotefoams.com**