WATSON MARLOW Fluid Technology Solutions

bio PURE

Validation guide summary

BioBarb, FlatBioEndCap and BioEndCap

Contents

1. Introduction

BioPure based in Hampshire, UK manufactures a range of components for use in biotechnology and pharmaceutical manufacturing. In particular, it is well known for its single-use fluid path components.

These include:

- **BioBarb™ – Hose tail to Tri-Clamp adaptors**
- **FlatBioEndCap™ – End caps for connectors**
- **BioEndCap™ – End caps with pull tab**

BioBarb, FlatBioEndCap and BioEndCap are manufactured from a USP <88> Class VI material in ISO 14644-1 class 7 cleanrooms operating within an ISO 9001 quality management system. BioBarb, FlatBioEndCap and BioEndCap is compliant with a list of compendial testing as summarised in section 5A.

Developed for the biotechnology and pharmaceutical industry, BioBarb, FlatBioEndCap and BioEndCap are suitable for sterilisation by autoclave and gamma irradiation. The component material of construction is gamma stable.

BioBarb, FlatBioEndCap and BioEndCap have the following features:

- **Full traceability as the LOT number and size identification are permanently molded**
- **Very low extractable, non-toxic and animal derived content free**
- **Comprehensive stock of a wide range of sizes**
- **Excellent general chemical resistance and life**

This guide relates to the BioBarb, FlatBioEndCap and BioEndCap and from this point on will be referred to as BioPure fluid path components.

2. Conditions of use

BioPure fluid path components are suitable for sterilisation using either gamma irradiation or autoclave.

BioPure fluid path components are suitable for gamma irradiaton to 50 kGy, and autoclaved to 135C (275F) for up to 30 minutes.

2a Working temperature range and pressure rating

The working temperature range of BioPure fluid path components is between -4C to 40C (24.8 F to 104F).

BioPure fluid path components can be used up to 4 bar (58 psi).

3. Chemical compatibility

Based on the material of construction, BioPure fluid path components should be compatible with a variety of fluids including weak and strong acids and bases. However for specific applications, it is advisable for the BioPure fluid path components to be tested under the actual process conditions.

4. Materials, manufacturing and regulatory compliance statements

4a Materials of construction

BioPure fluid path components are made out of polypropylene.

4b Manufacturing environment

BioPure fluid path components are manufactured according to the principles of Good Manufacturing Practice in ISO 14644–1 class 7 cleanrooms within a facility operating an ISO 9001 quality management system.

4c Country of origin

BioPure fluid path components are manufactured in Hampshire, UK.

4d Compliance declaration summary

Table 1 details the different substances that are not present in the raw material, manufacturing process or final composition of BioPure fluid path components.

Table 1: List of compliance statements and substances not found in the processing of or raw materials for BioPure fluid path components

Named substance/compliance statement	Raw material	Manufacturing process	Final product
Animal Derived Content	–	–	–
Melamine	–	–	–
Phthalates	–	–	–
Bisphenol A (BPA)	–	–	–
Latex	–	–	–

'–' denotes not present or not added

For the full list of compliance statements and substances absent from these components, please refer to compliance guide.

4e REACH legislation

All raw materials, compounds used in the manufacturing process and the final BioPure fluid path components comply with the REACH regulations.

None of the chemicals used in the manufacture of BioPure fluid path components are on the candidate list or the list of substances of very high concern (SVHC).

4f RoHS

In compliance with the restriction of hazardous substances (RoHS) directives, no listed substances are used in the manufacture of BioPure fluid path components.

4g Storage conditions

To maintain the performance of the components throughout their lifecycle, they should be stored in a cool, dry environment away from direct sunlight without exposure to chemicals and not subjected to stress. Normal warehouse conditions of 5C–40C (41F–104F) are acceptable. Wherever possible, original packaging should be maintained. Stock should be rotated on a first in, first out (FIFO) basis.

The performance of any component beyond its use by date, or which has not been stored according to the recommendations outlined above, cannot be assured.

5. Compendial and non compendial testing

5a Summary table

Table 2 contains a summary of all the compendial testing and ISO qualifications that BioPure fluid path components have been evaluated for. Full test methods and results are available on request. All test work was performed on BioBarb samples and this was used to represent BioPure fluid path components product family as the components are manufactured using the same material at the same manufacturing site. The BioBarbs were gamma irradiated from 45–55 kGy prior to testing.

Table 2: List of compendial and non compendial testing performed

Test reference	Test Description	Result
USP <87>	Biological reactivity test, *In Vitro*	PASS
USP <88>	Biological reactivity test, *In Vivo*	PASS
ISO 10993–4	Hemolysis Test—Autian method	PASS
ISO 10993–5	Biological evaluation of medical devices, tests for *In Vitro* cytotoxicity	PASS
ISO 10993–6	Biological evaluation of medical devices, implantation	PASS
ISO 10993–10	Biological evaluation of medical devices, irritation	PASS
ISO 10993–11	Biological evaluation of medical devices, systemic toxicity	PASS
ISO 10993–10	Kligman maximisation—test for irritation and delayed type hypersensitivity	PASS
USP <85>	Limulus Amebocyte Lysate (LAL) bacterial endotoxin assay	REPORT

BioPure fluid path components have passed a number of compendial and ISO testing, a summary of the results are disclosed within.

5b USP <87> Biological Reactivity tests, *In Vitro*, Post Gamma Irradiation samples

USP 87 determines the biological reactivity of a cell culture in response to a given test article. Samples of BioBarb were gamma irradiated at 45–55 kGy and tested in accordance with USP 39, NF 34, <87>, Biological reactivity tests, *In Vitro*. Extracts, positive control (rubber) and negative control articles were prepared at 37C (98.6F) for 24 hours. Biological reactivity was rated on a scale ranging from Grade 0 (no reactivity) to Grade 4 (severe reactivity).

Results: No reactivity was exhibited by the cell cultures when exposed to BioPure fluid path components. Therefore they passed the requirements of USP 87 biological reactivity tests and have no cytotoxic potential.

5c USP <88> Biological Reactivity tests, In Vivo, Post Gamma Irradiation samples

USP Class VI Plastics Test assesses the potential toxicity of a given test article systemically, intracutaneously and through implantation.

Samples of BioBarb were gamma irradiated at 45–55 kGy and tested in accordance with USP 39, NF 34 <88>, Biological reactivity tests, *In Vivo*. This included the immersion of the test articles in the following solutions: USP 0.9% sodium chloride, cottonseed oil, 1 in 20 ethanol in NaCl and polyethylene glycol 400 at 70C (158F) for 24 hours.

Results: BioPure fluid path components extracts and implants showed no toxicity. Therefore they passed the requirements of USP <88> biological reactivity tests.

5d ISO 10993-4 (Hemolysis)

The hemolysis test assesses the potential for indirect contact of a given sample with blood to cause the rupture of erythrocytes (red blood cells).

Samples of BioBarb were tested in accordance with ISO 10993–4, 2002, Biological Evaluation of Medical Devices – Part 4: Selection of Tests for Interactions with Blood.

Results: BioPure fluid path components showed no signs of haemolytic activity. Therefore they passed the requirements of ISO 10993–4.

5e ISO 10993–5 Biological evaluation of medical devices - part 5: tests for *In Vitro* cytotoxicity

The biological reactivity of a cell culture, in response to extracts from BioBarb was determined. The maintenance medium on the cell cultures was replaced by extracts of BioBarb or control article. The cell cultures were incubated for 48 hours at 37±1C (98.6F±33.8F). Biological reactivity was evaluated by a photo spectrometer at 450 nm wavelength.

Results: BioPure fluid path components showed no signs of cytotoxic potential. Therefore they passed the requirements of ISO 10993–5.

5f ISO 10993–6 Biological evaluation of medical devices, implantation

The purpose of this test is to evaluate the solid material in direct contact with living tissue. Strips of BioBarb (1mm x 1mm x 10mm) and the negative control plastics were tested. The test sites were examined for inflammation, encapsulation, necrosis, haemorrhage and discolouration macroscopically.

Results: BioPure fluid path components did not demonstrate any remarkable difference as compared to the control implant sites when in contact with tissue for 2 weeks.

5g ISO 10993–10 Biological evaluation of medical devices, irritation

The intracutaneous test is designed to evaluate local responses to the extracts of BioBarb following intracutaneous injection. BioBarb is extracted using 0.9% sodium chloride for injection, cottonseed oil, 1 in 20 ethanol in NaCl or polyethylene glycol 400 at 70C for 24 hours.

Results: BioPure fluid path components meet the requirements of ISO10993–10 guidelines for the intracutaneous injection test.

5h ISO 10993–11 Biological evaluation of medical devices, systemic toxicity

The purpose of the systemic injection study is designed to screen test articles (BioBarb) extracts for potential toxic effects as a result of a single dose systemic injection. BioBarb is extracted using 0.9% sodium chloride for injection, cottonseed oil, 1 in 20 ethanol in NaCl or polyethylene glycol 400 at 70C for 24 hours.

Results: BioPure fluid path components meet the requirements of ISO 10993–11 guidelines for the systemic injection test toxicity.

5i ISO 10993–10 Kligman Maximisation test

The purpose of this test is to detect the allergenic potential of a test article.

Samples of BioBarb were extracted in USP 0.9% sodium chloride for injection and cottonseed oil at 70C (158F) for 24 hrs and then injected interdermally. After two weeks, an additional topical application was introduced to the site of interdermal injections.

Results: The sites that were exposed to the test articles and negative control showed no signs of erythema or edema. Therefore, BioPure fluid path components are deemed not to contain any allergic potential.

5j USP <85> Limulus amebocyte lysate (LAL) bacterial endotoxin assay

Endotoxins are lipopolysaccharide complexes in gram negative bacterial cell walls. The Limulus Ameobocyte Lysate (LAL) gel clot test is used to detect and quantify endotoxin levels in test samples.

BioBarb (100cm^2) was extracted in 50 mL of LAL reagent water at room temperature for 60 minutes. The BioBarb extract was assayed in duplicate at the neat concentration. A positive control was prepared using serial dilution of the endotoxin standard. A product sample was prepared from the BioBarb extract and the endotoxin standard. LAL was added to the samples, which were incubated at 37C (98.6F) for 10 minutes.

Results: BioPure fluid path components extracts had an EU/mL value of <0.05, which is less than the value of 0.25 EU/mL for water for injection.

6. Extractables testing

BioBarb connectors were subjected to extraction in multiple solvents at controlled temperatures. The solvent extracts were then analysed using high pressure liquid chromatography—diode array detector-mass spectrometry (HPLC-DAD/MS), Direct injection Gas Chromatography—Mass spectrometry (DI-GC/MS), Headspace Gas Chromatography—Mass spectrometry (HS-GC/MS) and Inductively Coupled plasma—Mass Spectrometry (ICP/MS).

HPLC-DAD/MS is used to detect the presence of non-volatile and UV active extractables. DI-GC/MS identifies if there are any semi volatile compounds present in the extracts whilst volatile extractables can be detected using HS-GC/MS. Potential elemental impurities can be identified by ICP-MS.

The extracts were evaluated for the elemental impurities listed in the ICH Q3D and USP <232> guidelines.

Results: These studies have shown that there were extractables indicative of the materials of construction. BioPure can provide further information and assistance in the evaluation of extractable data for risk assessment purposes.

7. Conclusions

BioPure fluid path components have been shown to pass a number of compendial and ISO testing summarised in this guide. For further information with full compliance statements and compendial test reports, please contact your WMFTS representative.

The compliance summary and the full validation guide for BioPure fluid path components are available by filling in a request form on the wmfts.com website:

www.watson-marlow.com/biopure-validation/

WATSON MARLOW Fluid Technology Solutions

BIOTECHNOLOGY AND PHARMACEUTICAL SOLUTIONS

WATSON MARLOW Pumps | WATSON MARLOW Tubing | Flexicon Liquid Filling | BioPure | ASEPCO | AFLEX HOSE

Watson-Marlow Fluid Technology Solutions

Watson-Marlow Fluid Technology Solutions supports its customers locally through an extensive global network of direct sales operations and distributors

wmfts.com/global

A Spirax-Sarco Engineering plc company