WATSON MARLOW Tubing

Summary validation guide

Bioprene®

WATSON MARLOW Fluid Technology Solutions

This is the summary validation guide for Bioprene Tubing. Full test methods and results are available in the full validation guide, by filling in a request form on the website: https://www.wmfts.com/en/validation/request/

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1. Introduction

Bioprene is manufactured at Watson-Marlow Ltd, Bickland Water Rd, Falmouth, UK TR11 4RU.

Bioprene has the following features:

- Meets FDA regulations CFR 177.2600 (aqueous food)
- Made from NSF/ANSI food compliant raw material
- Long peristaltic life
- Opaque to visible and UV light
- Low extractables; no phthalates added, no latex used

2. Conditions of use

Bioprene is suitable for use according to the conditions in Table 1.

Table 1. Conditions for manufacturing, sterilisation, working and storage.

Manufacturing	Sterilisation	Working	Storage
Thermal plastic elastomer (TPE) USP Class VI[1]	Gamma irradiation ≤ 45 kGy[2]	5°C to 80°C (41°F to 176°F) Brittle temperature is <-60°C (140°F).	-10°C to 40°C (14°F to 104°F)
ISO 14644–1 class 7 cleanroom[1] (at rest)	Autoclave to 121°C (249.8°F) for 30 minutes[3]		Dry environment, away from direct sunlight
ISO 9001 quality management system			No exposure to chemicals or stress

[1]Except for product codes: 088.T400.EOP, 088.T400.EOG and stainless steel components.

[2] Functional testing of Bioprene in a pump head shows acceptable performance at 45 kGy. All validation test data within this guide for irradiated samples are subjected to a gamma irradiation dose of 50 kGy prior to testing.

[3] Bioprene LoadSure Elements part numbers 933.P120.PFT & 933.P170.PFT are not suitable for autoclaving, please use gamma irradiation.

Original packaging must be retained and stock rotated on a first in, first out (FIFO) basis.
The performance of components cannot be assured beyond use by date or when not stored according to recommendations above.

3. Chemical compatibility

A general guide on chemical compatibility of Bioprene tubing can be found on the Watson-Marlow Fluid Technology Solutions website: www.wmfts.com/en/support/chemical-compatibility-guide/. It is advisable for Bioprene to be tested under actual process conditions (see section 5 validation testing services).

4. Validation testing

4a. Summary table

Table 2. Testing summary of evaluated standards.

Test	Description	Result
USP <85>	Bacterial endotoxins test	PASS
USP <87>	Biological reactivity tests, *in vitro*	PASS
USP <88>	Biological reactivity tests, *in vivo*	PASS
USP <381>	Elastomeric closures for injections	PASS
USP <788>	Particulate matter in injections	PASS
ISO 10993-4	Biological evaluation of medical device, interactions with blood	PASS
ISO 10993-5	Biological evaluation of medical devices, *in vitro* cytotoxicity	PASS
ISO 10993-6	Biological evaluation of medical devices, local effects after implantation	PASS
ISO 10993-10	Biological evaluation of medical devices, skin sensitisation Klingman maximisation	PASS PASS
ISO 10993-11	Biological evaluation of medical devices, systemic toxicity	PASS
Extractables	Analysis of material extracts for organic extractables and extractable metals	REPORT
Nitrosamines	Detection of Nitrosamines	REPORT
X-ray equivalency	Equivalency for X-ray and Gamma irradiated product	REPORT

4b. USP <85> Bacterial endotoxins test

Limulus Ameobocyte Lysate (LAL) detects and quantifies endotoxin levels in samples. Test samples, negative control and endotoxin standards were extracted in LAL reagent water at room temperature for 60 minutes. LAL was added to samples and incubated at 37°C (98.6°F).

Results: *<0.005 EU/mL*
Result is <0.25 EU/mL (water for injection limit), passing USP <85> requirements.

4c. USP <87> Biological reactivity tests, *in vitro*

USP <87> determines the biological reactivity of cell cultures in response to samples. Test, positive and negative control samples were prepared at 37°C (98.6°F) for 24 hours. Biological reactivity was rated on a scale from Grade 0 (no reactivity) to Grade 4 (severe reactivity).

Results: *Grade 0 - No reactivity or cytotoxicity, passing USP <87> requirements.*

4d. USP <88> Biological reactivity tests, *in vivo*

USP Class VI Plastics Test assesses the toxicity of test articles systemically, intracutaneously and through implantation. Samples were immersed in: USP 0.9% NaCl, cottonseed oil, 1 in 20 ethanol in NaCl and polyethylene glycol 400 at 70°C (158°F) for 24 hours. Injection sites were monitored for 72 hours.

Results: *No toxicity, passing USP <88> requirements.*

4e. USP <381> Elastomeric closures for injections

Extracts were prepared in accordance with USP <381> Elastomeric closures for injections.

Results: *All results pass USP <381> requirements.*

4f. USP <788> Particulate matter in injections

This test determines the number of particulates measuring ≥10 µm and ≥25 µm present in the fluid pathway. The test article was flushed with low particulate water. The extraction fluid was left to stand for 2 minutes and the particles were measured.

Results: *14 particles/mL ≥10 µm and 0 particles/mL ≥25 µm, passing USP <788> requirements.*

4g. ISO 10993-4 Biological evaluation of medical device, interactions with blood

The haemolysis test assesses the potential to cause rupture of erythrocytes (red blood cells) from indirect contact of samples. Samples were extracted with 0.9% NaCl at 70°C (158°F) and incubated at 37°C (98.6°F) for 1 hour. The absorbance of each sample was measured.

Results: *No haemolytic activity, passing ISO 10993–4 requirements.*

4h. ISO 10993–5 Biological evaluation of medical devices, *in vitro* cytotoxicity

The biological reactivity of a cell culture, in response to samples was determined. The cell culture medium was replaced by samples and control articles. The cultures were incubated for 48 hours at 37°C (98.6°F).

Results: *No cytotoxicity, passing ISO 10993–5 requirements.*

4i. ISO 10993–6 Biological evaluation of medical devices, local effects after implantation

This test evaluates samples for inflammation, encapsulation, necrosis, haemorrhage and discolouration in direct contact with living tissue. Strips of test samples and negative controls were tested.

Results: *No reactivity, passing ISO 10993–6 requirements.*

4j. ISO 10993–10 Biological evaluation of medical devices, skin sensitisation

The intracutaneous test evaluates local responses to samples following intracutaneous injection. Samples were extracted using 0.9% NaCl, cottonseed oil,1 in 20 ethanol in NaCl or polyethylene glycol 400 at 70°C for 24 hours. Injection sites were monitored for 72 hours.

Results: *No reactivity, passing ISO 10993–10 requirements.*

Kligman Maximisation

This test detects the allergenic potential of a test article. Samples were extracted using 0.9% NaCl, cottonseed oil,1 in 20 ethanol in NaCl or polyethylene glycol 400 at 70°C for 24 hours and injected intracutaneously.

Results: *No allergic potential, passing ISO 10993–10 Klingman maximisation requirements.*

4k. ISO 10993–11 Biological evaluation of medical devices, systemic toxicity

The systemic injection study evaluates samples for toxic effects from a single dose systemic injection. Samples were extracted using 0.9% NaCl, cottonseed oil, 1 in 20 ethanol in NaCl or polyethylene glycol 400 at 70°C for 24 hours.

Results: *No toxicity, passing ISO 10993–11 requirements.*

4l. Extractables

Samples were subjected to extraction in multiple solvents at controlled temperatures. The solvent extracts were analysed using:

- Liquid Chromatography- Mass Spectrometry (LC/MS) to detect non-volatile and UV active compounds

- Direct injection Gas Chromatography-Mass Spectrometry (DI-GC/MS) to detect semi-volatile compounds
- Headspace Gas Chromatography-Mass Spectrometry (HS-GC/MS) to detect volatile compounds
- Inductively Coupled Plasma-Mass Spectrometry (ICP/MS) to detect elemental impurities

Results: *Extractables were indicative of materials of construction. Validation testing services can provide further information in the evaluation of extractable data for risk assessment purposes. Please see section 5.*

4m. Nitrosamines

Test samples were analysed for the following using DI-GC-MS:

- N-Nitrosodimethylamine (NDMA)
- N-Nitrosomethylethylamine (NMEA)
- N-Nitrosodiethylamine (NDEA)
- N-Nitrosodipropylamine (NDPA)
- N-Nitrosodibutylamine (NDBA)
- N-Nitrosopiperidine (NPIP)
- N-Nitrosopyrrolidine (NPYR)
- N-Nitrosomorpholine (NMOR)

Results: *Nitrosamines were undetectable.*

4n. X-ray equivalency

There is a foreseeable shortage of gamma irradiation capacity. BioPhorum and Bio Process Systems Alliance (BPSA) committees have steered supply chain representatives to adopt X-ray irradiation to mitigate this risk. The mechanism of X-ray irradiation is very similar to gamma.

Testing for X-ray irradiation equivalency was conducted as follows:

- Extractables (Reduced BPOG)
- Cytotoxicity (USP <87> / ISO 10993-5)
- Hydrostatic pressure testing
- Dimensional measurement

Results: *Validated to be irradiated with gamma or X-ray irradiation.*

5. Validation testing services

Our Validation testing team will design your validation studies using the most up to date industry recognised standards alongside fully qualified testing partners. We will provide a bespoke results assessment to ensure you meet your specific quality assurance requirements.

Testing protocols cover a wide range of industry recognised validation tests for one-off or lot-release testing. These include but are not limited to:

- Bioburden
- Particulates
- Endotoxin
- Leak
- Pressure
- Extractables
- Leachables
- Sterility
- Nitrosamines

- Chemical compatibility

Contact Validation.WMArchitect@wmfts.com or your WMFTS representative for more information.

6. Conclusions

Bioprene has passed testing standards as summarised in this guide.

For more information on quality and compliance information not stated in this guide, please contact your WMFTS representative or qualityrequests.wml@wmfts.com.

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