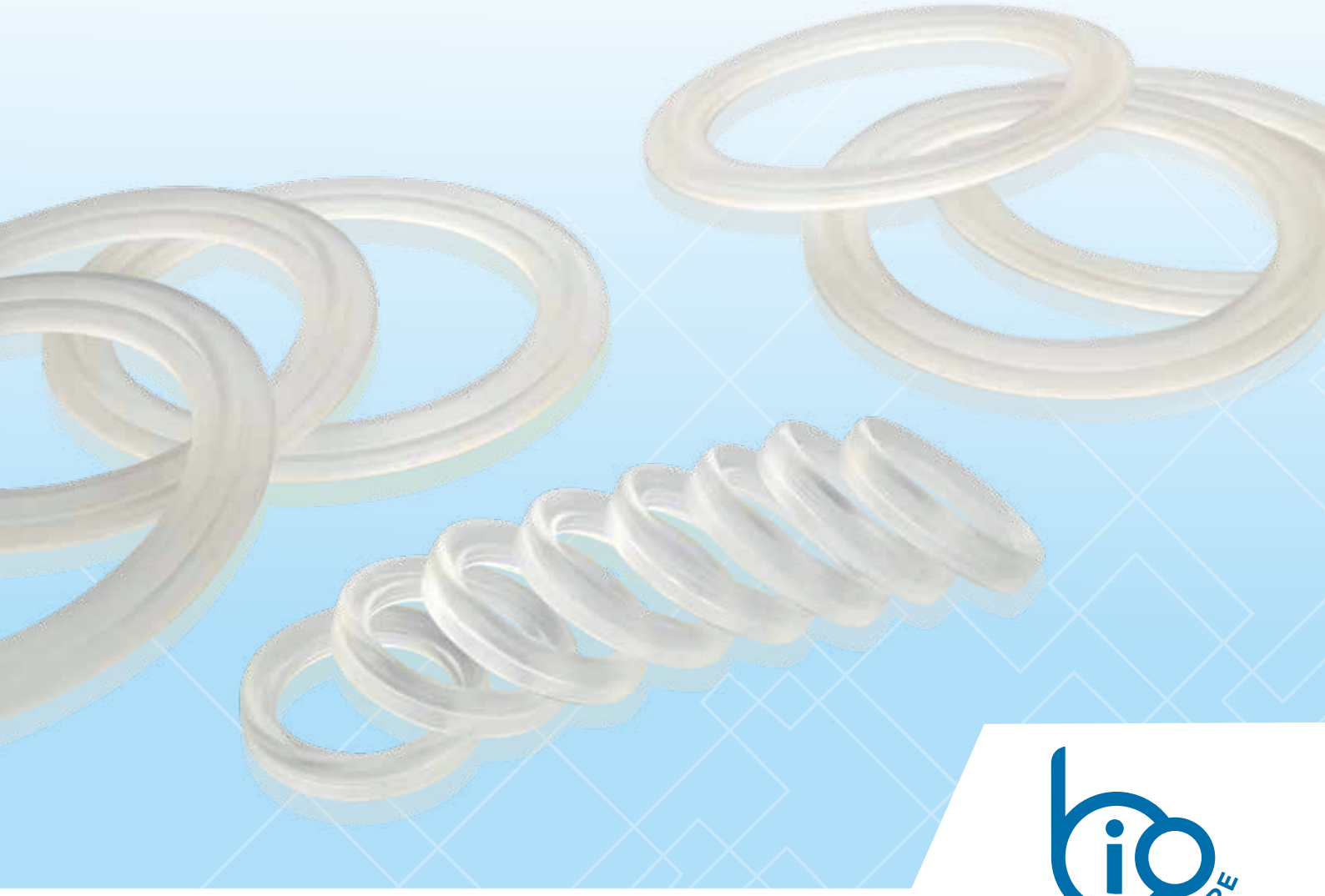
WATSON MARLOW Fluid Technology Solutions



Validation guide summary

Platinum-cured silicone gaskets

Contents

1. Introduction

Watson-Marlow Flow Smart, Inc., based in Seaford, Delaware, USA produces a range of Platinum-cured silicone gaskets for use in biotechnology and pharmaceutical manufacturing. The facility contains 3,000 square feet of cleanroom manufacturing.

Watson-Marlow Fluid Technology Solutions (WMFTS) manufactures its BioPure branded Platinum-cured silicone gaskets in its FlowSmart ISO 14644 class 7 cleanroom according to GMP principles within a facility operating an ISO 9001 quality management system.

BioPure Platinum-cured silicone gaskets have a number of key features and benefits. These include:

- **Precision engineered to achieve a smooth bore, contamination free, fluid path under clamping compression**
- **Sterilisation through gamma irradiation or autoclave**
- **Designed in accordance with ASME-BPE standards**
- **Lot numbering enables full product traceability**

BioPure Platinum-cured silicone gaskets are compliant with a range of compendial testing as detailed in Section 5A. Developed for the biopharmaceutical industry, BioPure Platinum-cured silicone gaskets are suitable for sterilisation by autoclave and gamma irradiation.

Watson-Marlow Flow Smart, Inc. (FlowSmart) was formed in 2003 and has been providing a range of single-use components to the biopharmaceutical industry for 14 years. FlowSmart was acquired by WMFTS in 2015. BioPure was acquired by WMFTS in 2014.

2. Conditions of Use

BioPure Platinum-cured silicone gaskets can be sterilised by autoclave and gamma irradiation up to 50 kGY.

2a Working temperature and pressure rating

The working temperature range of BioPure Platinum-cured silicone gaskets is –65C to 254C (–85F to 490F).

3 Chemical compatibility

Currently, there is no data available on the chemical compatibility of the finished BioPure Platinum-cured silicone gaskets with regards to how they perform in the presence of different solvents. As such, it is recommended that the BioPure Platinum-cured silicone gaskets are tested under the actual process conditions.

4 Materials, manufacturing and regulatory compliance statements

4a Materials of construction

BioPure Platinum-cured silicone gaskets are made from polydimethylsiloxane.

4b Manufacturing environment

BioPure Platinum-cured silicone gaskets are manufactured according to the principles of GMP in an ISO 14644 class 7 cleanroom within a facility operating an ISO 9001 quality management system.

4c Country of origin

BioPure Platinum-cured silicone gaskets are manufactured at Watson-Marlow Flow Smart, Inc., Delaware, USA.

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 Platinum-cured silicone gaskets.

For full compliance statements please refer to the compliance summary sheet available from the website on request.

Table 1: List of compliance statements for BioPure Platinum-cured silicone gaskets and substances not found in the processing of or raw materials for BioPure Platinum-cured silicone gaskets

Named substance	Raw material	Manufacturing process	Final product
Animal Derived Content (ADC)	–	–	–
Phthalates	–	–	–
Bisphenol A (BPA)	–	–	–
Latex	–	–	–
Allergens (as defined by FDA CFR 21.164.110)	–	–	–

'–' denotes not present or not added

4e REACH legislation

All raw materials, compounds used in the manufacturing process, and the final BioPure Platinum-cured silicone gaskets comply with the REACH regulation. None of the chemicals used in the manufacture of BioPure Platinum-cured silicone gaskets are on the candidate list of substances from 2008 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 Platinum-cured silicone gaskets.

4g. Storage conditions

Normal warehouse conditions of 5–40C (41–104F) are acceptable. BioPure Platinum-cured silicone gaskets should be stored in the original containers where possible and in a cool dry environment away from direct sunlight. Stock should be rotated on a first in, first out (FIFO) basis.

5. Compendial and Non compendial testing

5a Summary table

Table 2 contains a summary of all the compendial and ISO testing the BioPure Platinum-cured silicone gaskets have been evaluated for. These tests have been completed on autoclaved and gamma irradiated samples. Full test methods and results are available on request of the confidential full validation guide.

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	Haemolysis 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 10093–11	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
USP <788>	USP particulate/microscopic particulate count analysis test	REPORT
E.P. 3.1.9	European Pharmacopeia 3.1.9 silicone elastomer for closures and tubing	PASS

BioPure Platinum-cured silicone gaskets have passed a number of compendial and ISO testing, a summary of the results are disclosed within this document.

5b USP <87> Biological reactivity tests, *In Vitro*, post sterilisation samples

USP <87> determines the biological reactivity of a cell culture in response to a given test article.

Samples of BioPure Platinum-cured silicone gaskets were tested in accordance with USP39, NF 34, <87>, Biological reactivity tests, *In Vitro*.

Extracts, positive control (rubber) and negative control articles were prepared at 37C 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 the BioPure Platinum-cured silicone gaskets. 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 sterilisation samples

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

Samples of BioPure Platinum-cured silicone gaskets were tested in accordance with USP39, NF 38, <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 sodium chloride and polyethylene glycol 400 at 70C for 24 hours

Results: BioPure Platinum-cured silicone gasket extracts and implants show no signs of toxicity, therefore the passed the requirements of USP <88> biological reactivity tests.

5d ISO 10993-4 Haemolysis

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

Samples of BioPure Platinum-cured silicone gaskets were tested in accordance with ISO 10993-4, Biological evaluation of medical devices—Part 4: Selection of tests for interactions with blood.

Results: BioPure Platinum-cured silicone gaskets showed no signs of haemolytic activity. Therefore BioPure Platinum-cured silicone gaskets passed the requirements of ISO 10993-4.

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

The biological reactivity of a cell culture, in response to extracts from BioPure Platinum-cured silicone gaskets was determined. The maintenance medium on the cell cultures was replaced by extracts of BioPure Platinum-cured silicone gaskets, or control article.

The cell cultures were incubated for 48 hours at 37C ±1C. Biological reactivity was evaluated by a photo spectrometer at 450 nm wavelength.

Results: BioPure Platinum-cured silicone gaskets showed no signs of cytotoxic activity. Therefore BioPure Platinum-cured silicone gaskets 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 the BioPure Platinum-cured silicone gaskets, (1 mm x 1mm x 10 mm) and the negative control plastics were tested. The test sites were examined for inflammation, encapsulation, necrosis, haemorrhage and discolouration macroscopically.

Results: BioPure Platinum-cured silicone gaskets 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 purpose of the incutaneous injection study is designed to evaluate local responses to BioPure Platinum-cured silicone gaskets extracts following intracutaneous injection.

Samples of BioPure Platinum-cured silicone gaskets were extracted using 0.9% sodium chloride for injection, cottonseed oil, 1 in 20 parts ethanol in sodium chloride or polyethylene glycol 400 at 70C for 24 hours.

Results: BioPure Platinum-cured silicone gaskets meet the requirements of ISO 10993-10 guidelines for incutaneous injection.

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

The purpose of the systemic injection study is designed to screen test extracts of BioPure Platinum-cured silicone gasket for potential toxic effects as a result of a single dose systemic injection. BioPure Platinum-cured silicone gaskets were extracted using 0.9% sodium chloride for injection, cottonseed oil, 1 in 20 parts ethanol in sodium chloride or polyethylene glycol 400 at 70C for 24 hours.

Results: BioPure Platinum-cured silicone gaskets meet the requirements of ISO 10993-11 guidelines for systemic toxicity.

5i ISO 10993-10 Kligman maximisation test

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

BioPure Platinum-cured silicone gaskets were tested in accordance with ISO 10993-10. Samples of BioPure Platinum-cured silicone gaskets were extracted in USP 0.9% Sodium chloride for injection and cottonseed oil at 70C for 24 hrs. The extracts were injected intradermally. After two weeks, an additional topical application was introduced to the site of intradermal injections.

Results: The skin sites that were exposed to the test articles and negative control showed no signs of erythema or edema. Therefore BioPure Platinum-cured silicone gaskets are deemed not to contain any allergic potential.

5j USP <85> Limulus amebocyte lysate (LAL) bacterial entoxin 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.

The BioPure Platinum-cured silicone gasket extract was assayed in duplicate at the undiluted concentration. A positive control was prepared using serial dilution of the endotoxin standard. A product sample was prepared from the BioPure Platinum-cured silicone gasket extract and the endotoxin standard. LAL was added to the samples, which were incubated at 37C for 10 minutes.

Results: BioPure Platinum-cured silicone gaskets had an EU/mL value of 0.005 which is less than the value of 0.25 EU/mL stated for water for injection.

5k USP <788> USP particulate/microscopic particulate count analysis test

This test is used to determine a level of particulates measuring 10 micron (µm) or smaller and 25 µm or smaller that may be present in any given drug product.

A sample of BioPure Platinum-cured silicone gasket was added to ultrapure, particle free water and shaken 20 times. The extraction fluid was then recovered and the particles were measured using light obscuration microscopy.

Results: Extracts from BioPure Platinum-cured silicone gaskets contained one particulate less than 10 microns or smaller and one particulate less than 25 microns or smaller.

5l European Pharmacopeia 3.1.9

Extracts of BioPure Platinum-cured silicone gaskets were prepared in accordance with the requirements of European pharmacopoeia, 6.8, Chapter 3.1.9 Silicone elastomer for closures and tubing. The results of the tests are summarised in *Table 3*.

Results: Based on the results of the tests, BioPure Platinum-cured silicone gaskets meets the requirements of EP 3.1.9 section for Physiochemical tests for silicone elastomer.

Table 3: List of test parameters and results for E.P. 3.1.9

Test	Test Results	Evaluation Criteria	Result
Appearance of solution	Clear, 0.55 NTU	< 3 NTU	PASS
Acidity	2.5 ml NaOH to produce blue colour	< 2.5 ml 0.01M NaOH to produce a blue colour	PASS
Alkalinity	1 ml 0.01 M HCl to change yellow to orange	< 1 ml 0.01 M HCl to begin the colour change from yellow to orange	PASS
Reducing substances	0.2 ml	< 1 ml	PASS
Relative density	1.16	Between 1.05 and 1.25	PASS
Volatile matter	1.42%	< 2.0% (Pt cured)	PASS
Mineral oils	No fluorescence	Fluorescence less intense than 1 ppm	PASS
Substances soluble in hexanes	1.7%	< 3%	PASS
Phenylated compounds	Max absorbance , < 0.001 A.U	Max .absorbance < 0.4 A.U (between 250 and 340 nm)	PASS
Platinum	Colour less intense than 30 ppm Pt reference	Colour less intense than 30 ppm Pt reference	PASS
Identification A	IR spectrum similar to reference material	IR spectrum similar to reference material	PASS
Identification B	The solution is violet	The solution is violet	PASS
Identification C	Residue of combustion gives the reaction of silicates	Residue of combustion gives the reaction of silicates	PASS

6. Extractables testing

BioPure Platinum-cured silicone gaskets were subjected to extraction in multiple solvents at controlled temperatures. The solvent extracts were then analysed using high performance liquid chromatography -diode array detector-mass spectrometry (HPLC-DAD/MS), headspace gas chromatography mass spectrometry (HS-GC/MS), direct injection gas chromatography mass spectrometry (DI-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 the extractables are indicative of the materials of construction. WMFTS can provide assistance in the evaluation of extractables data for risk assessment purposes.

7. Conclusions

BioPure Platinum-cured silicone gaskets have been evaluated using a range of compendia and ISO testing summarised within this guide. For further information with full compliance statements and test reports, please contact your WMFTS representative.

The compliance summary and the full validation guide for BioPure Platinum-cured silicone gaskets are available by filling in a request form on the wmfts.com website:

www.wmfts.com/biopure-validate-us

WATSON MARLOW Fluid Technology Solutions

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