Validation summary guide

Platinum-cured silicone gaskets 5000 series

WATSON MARLOW Fluid Technology Solutions

This is the summary validation guide for Platinum-cured silicone gaskets 5000 Series. 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

Watson-Marlow, Devens, Massachusetts, USA, produces 5000 series platinum-cured silicone gaskets used in biotechnology and pharmaceutical manufacturing.

This guide relates to platinum-cured silicone gaskets 5000 series and from this point will be referred to as silicone gaskets.

Silicone gaskets have the following features:

- Full traceability with laser-etched lot numbering
- Platinum-cured
- Designed in accordance with ASME-BPE standards
- Animal derived component free (ADCF)
- Double-bagged and heat-sealed
- Precision engineered for a smooth bore, contamination free, fluid path under clamping compression

2. Conditions of use

Silicone gaskets are suitable for use according to the conditions in Table 1.

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

Manufacturing	Sterilisation	Working	Storage
USP Class VI polydimethylsiloxane	Gamma irradiation ≤ 50 kGy	-55°C–210°C (-67°F–410°F)	5°C–40°C (40°F–86°F)
ISO 14644–1 class 7 cleanrooms	Autoclave to 121°C (249.8°F) for 15 minutes		Dry environment, away from direct sunlight
ISO 9001 quality management system			No exposure to chemicals or stress

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

There is no data available on the chemical compatibility of the finished silicone gaskets with regards to how they perform in the presence of different solvents. As such, it is advisable for silicone gaskets 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

Test	Description	Result
USP <788>	Particulate matter in injections	PASS
ISO 10993-4	Biological evaluation of medical device, Tests for interactions with blood	PASS
ISO 10993-5	Biological evaluation of medical devices, Tests for *in vitro* cytotoxicity	PASS
ISO 10993-6	Biological evaluation of medical devices, Tests for local effects after implantation	PASS
ISO 10993-10 Klingman maximisation	Biological evaluation of medical devices, Tests for skin sensitisation	PASS PASS
ISO 10993-11	Biological evaluation of medical devices, Tests for systemic toxicity	PASS
European Pharmacopeia 3.1.9	Silicone elastomer for closures and tubing	PASS
Extractables	Analysis of material extracts for organic extractables and extractables metals	REPORT

4b. USP <85> Bacterial endotoxins

Limulus Ameobocyte Lysate (LAL) gel clot test 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: *<0.00566 EU/mL*
Result is <0.25 EU/mL for water for injection. 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±1°C (98.6±33.8°F) for 24 hours. Biological reactivity was rated on a scale from Grade 0 (no reactivity) to Grade 4 (severe reactivity).

Results: *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 immerged 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. Samples were immersed in low particulate water, extraction fluid recovered and particles measured.

Results: *51 particles/device ≥10 µm and 47 particles/device ≥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. Phosphate buffered saline was added to samples and incubated in rabbit blood for 3 hours at 37±2°C (98.6±35.6°F). 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±1°C (98.6±33.8°F). Biological reactivity was evaluated by a photo spectrometer at 450 nm.

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 test 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. European Pharmacopoeia 3.1.9 Silicone elastomer for closures and tubing

Extracts were prepared in accordance with the requirements of European pharmacopoeia, Chapter 3.1.9 Silicone elastomer for closures and tubing.

Results: *All results pass E.P. 3.1.9 requirements.*

4m. Extractables

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

- High Pressure Liquid Chromatography- Diode Array Detector-Mass Spectrometry (HPLC-DAD/MS) to detect the presence of 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 identify 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.*

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 testing
- Extractables and Leachables
- Sterility assurance
- Nitrosamines
- Chemical compatibility

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

6. Conclusions

Silicone gaskets 5000 series have 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.devens@wmfts.com.

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