



Validation guide and performance testing summary
ReNu SU Technology cartridge



Contents

- 1 Introduction**
- 2 Irradiation Stability**
- 3 Materials, manufacturing and regulatory compliance statements**
 - a. Materials of construction
 - b. Manufacturing environment
 - c. Country of origin
 - d. Storage conditions
 - e. Compliance declaration summary
 - f. REACH legislation
 - g. RoHS
 - h. Declaration of minimised risk of TSE/BSE
- 4 Compendial and non compendial testing**
 - a. Summary table
 - b. USP <88>
 - c. USP <87>
 - d. ISO 10993-4
 - e. ISO 10993-6
 - f. Kligman maximisation test
 - g. ISO 10993-11
 - h. ISO 10993 10
 - i. USP <85>
 - j. USP <788>
- 5 Extractables testing**
- 6 Performance data**
- 7 Conclusions**



1. Introduction

Watson-Marlow's ReNu SU Technology™ cartridge comprises of polyurethane tubing installed on a high density polyethylene (HDPE) manifold with nylon collets.

All components are manufactured and assembled in ISO 14644 class 7 (class 10,000, Grade C) cleanrooms of production facilities operating ISO 9001 quality management systems. The cleanrooms are air conditioned to ensure that temperature and humidity are controlled within the ISO 14644-1 requirements.

Watson-Marlow ReNu SU Technology cartridge exhibits a number of key features:

- **Excellent flow stability for accurate process control**
- **Repeatability of performance pressure and flow performance between ReNu SU Technology cartridges**
- **Absolute lot traceability with all components controlled under a single ReNu SU Technology lot number, full traceability is guaranteed even when the packaging is removed**
- **Sterilisable through gamma irradiation, with stable performance at levels up to 50kGy**

Watson-Marlow Fluid Technology Solutions (WMFTS) is the world leader in niche peristaltic and sinusoidal pumps and associated fluid path technologies. Founded on nearly 60 years of supplying engineering and process expertise and with over one million pumps installed worldwide, our pumps are tried, tested and proven to deliver.

WMFTS is a wholly owned subsidiary of Spirax-Sarco Engineering plc. Spirax-Sarco's headquarters are in Cheltenham, England and is listed on the London Stock Exchange.

Watson-Marlow Fluid Technology Solutions comprises ten established brands, each with their own area of expertise, but together offering our customers an unrivalled breadth of solutions for their bioprocessing fluid transfer needs.

2. Irradiation Stability

2a Irradiation Stability

The ReNu SU Technology cartridge can be irradiated by gamma irradiation up to 50 kGy.

3. Materials, manufacturing and regulatory compliance statements

3a Material of construction

The ReNu SU Technology cartridge is made of polyurethane tubing installed on a high density polyethylene (HDPE) manifold with nylon collets.

3b Manufacturing environment

The ReNu SU Technology cartridge is assembled and packed in an ISO14644 class 7 cleanroom. The tubing and manifolds used in the assembly are also manufactured in ISO14644 class 7 cleanrooms.

3c Country of origin

The ReNu SU Technology cartridge and the HDPE manifold are manufactured and assembled in Tunbridge, United Kingdom. The tubing used in ReNu SU Technology cartridges is extruded in Falmouth, United Kingdom.

3d Storage conditions

To maintain the performance of the ReNu SU Technology cartridge throughout its life, it should be stored in a cool, dry environment away from direct sunlight. The optimum storage temperature is between -10 to 40°C (14–104F). However, normal warehouse conditions of 5 to 30°C (40 to 86F) are acceptable. Wherever possible, original packaging should be maintained. Stock should be rotated on a first in, first out (FIFO) basis.

3e. Compliance declaration summary

Table 1 details the different substances that are not present in the raw material, manufacturing process or final composition of the ReNu SU Technology cartridge.

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

3f REACH legislation

All raw materials, compounds used in the manufacturing process and the final ReNu SU Technology cartridge comply with the REACH regulations. None of the chemicals used in the manufacture of the ReNu SU Technology cartridge are on the candidate list or the list of Substance of Very High Concern (SVHC).

Table 1: List of compliance statements for the ReNu SU Technology cartridge and substances not found in the processing of or raw materials for the ReNu SU Technology cartridge

Named substance/compliance statement	Raw material	Manufacturing process	Final product
Gluten	–	–	–
Melamine	–	–	–
Phthalates	–	–	–
Bisphenol A (BPA)	–	–	–
Latex	–	–	–
Allergens (as defined by FDA CFR 21.164.110)	–	–	–
Presence of heavy metals	–	–	–

‘–’ denotes not present

3g RoHS

In compliance with the restriction of hazardous substances (RoHS) directives, no listed substances are used in the manufacture of the ReNu SU Technology cartridge.

3h Declaration of minimised risk of TSE/BSE

The processing conditions of the materials used in the ReNu SU Technology cartridge exceeds temperatures stated in EMEA 410/01 rev 3 regulations on the minimisation of risk from TSE/BSE prions. Therefore, it is deemed that these materials comply with EMEA 410/01 rev 3 regulations.

4. Compendial and non compendial testing

4a Summary table

Table 2 contains a summary of all the compendial and ISO testing qualifications against which the ReNu SU Technology cartridge has been evaluated. All samples were gamma irradiated to 45–55 kGy prior to testing. Full test methods and results are available on request of the full validation guide.

Table 2: A summary of the compendial and ISO tests performed on the ReNu SU Technology cartridge

Test reference	Test description	Result
USP <88>	Biological reactivity test, <i>In Vivo</i>	PASS
USP <87>	Biological reactivity tests, <i>In Vitro</i>	PASS
ISO 10993-4	Hemolysis test—Autian method	PASS
ISO 10993-6	Biological evaluation of medical devices, implantation	PASS
ISO 10993-10	Kligman maximisation—test for irritation and delayed type hypersensitivity	PASS
ISO 10993-11	Biological evaluation of medical devices, systemic toxicity	PASS
ISO 10993-10	Biological evaluation of medical devices, irritation	PASS
USP <85>	Limulus amoebocyte lysate (LAL) bacterial endotoxin assay	REPORT
USP <788>	USP particulate/microscopic particulate count analysis test	REPORT

The ReNu SU Technology cartridge has passed a number of compendia and ISO testing, a summary of the results are disclosed within.

4b USP <88> Biological reactivity tests, *In Vivo*, post gamma irradiation

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

Samples of the ReNu SU Technology cartridge were 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 sodium chloride and polyethylene glycol 400 at 70C for 24 hours.

Results: ReNu SU Technology cartridge extracts and implants showed no toxicity, therefore the ReNu SU Technology cartridge passed USP Class VI testing.

4c 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 the ReNu SU Technology cartridge 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 ReNu SU Technology cartridge, therefore it is considered non cytotoxic.

4d 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 the ReNu SU Technology cartridge were tested in accordance with ISO 10993-4, Biological Evaluation of Medical Devices—Part 4: Selection of Tests for Interactions with blood.

Results: ReNu SU Technology cartridge showed no signs of hemolytic activity. Therefore the ReNu SU Technology cartridge passed the requirements of ISO-10993-4.



4e 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 ReNu SU Technology cartridge (1mm 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: The ReNu SU Technology cartridge did not demonstrate any remarkable difference as compared to the control implant sites. Therefore the ReNu SU Technology cartridge passed the requirements for ISO 10993-6.

4f ISO 10993-10 Kligman maximisation test

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

Samples of the ReNu SU Technology cartridge were extracted in USP 0.9% sodium chloride for injection and cottonseed oil at 70C for 24 hrs and then injected intradermally. After two weeks, an additional topical application was introduced to the site of intradermal injections.

Results: The sites that were exposed to the test articles and negative control showed no signs of erythema or edema. Therefore, the ReNu SU Technology cartridge is deemed not to contain any allergenic potential.

4g ISO 10993-11 Biological evaluation of medical devices, systemic toxicity

The systemic injection study is designed to screen test extracts of ReNu SU Technology tubing and manifolds for potential toxic effects as a result of a single dose systemic injection. ReNu SU Technology tubing and manifolds were extracted using 0.9% sodium chloride for injection, cottonseed oil, 1 in 20 Ethanol in sodium chloride or Polyethylene glycol 400 at 70C for 24 hours.

Results: The ReNu SU Technology cartridge meets the requirements of ISO 10993-11 guidelines for the systemic toxicity.

4h ISO 10993-10 Biological evaluation of medical devices, irritation

The intracutaneous test is designed to evaluate local responses to the extracts of the ReNu SU Technology cartridge following intracutaneous injection. ReNu SU Technology tubing and manifolds were extracted using 0.9 % sodium chloride for injection, cottonseed oil, 1 in 20 Ethanol in sodium chloride or Polyethylene glycol 400 at 70C for 24 hours.

Results: The ReNu SU Technology cartridge meets the requirements of ISO 10993-10 guidelines for the intracutaneous injection.

4i USP <85> Limulus ameobocyte 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.

The ReNu SU Technology cartridge 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 ReNu SU Technology cartridge extract and the endotoxin standard. LAL was added to the samples, which were incubated at 37C for 10 minutes.

Results: The ReNu SU technology cartridge extracts had a value of 0.005 EU/mL which is less than the limit for water for injection 0.25 EU/mL

4j 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 length of ReNu SU Technology tubing was filled with 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 a ReNu Technology cartridge contained 2 particles measuring 10 μm or smaller and 1 particle measuring 25 μm or smaller.

5. Extractables testing

The complete ReNu SU Technology assembly was 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 the extractables are indicative of the materials of construction. Watson-Marlow can provide further information and assistance in the evaluation of extractables data for risk assessment purposes.

6. Performance data

The ReNu SU Technology cartridge 600 20/3P was tested in combination with the Quantum 600 Universal Pump and testing data includes:

- **Flow rate performance**
- **Flow linearity**
- **Pulsation testing**
- **Shear testing**

Detailed information and results are included in the ReNu SU Technology cartridge full validation guide.

7. Conclusions

ReNu SU Technology cartridges 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 ReNu SU Technology cartridges are available by filling in a request form on the wmfts.com website:

wmfts.com/quantum-ReNuSU-validate



BIOTECHNOLOGY AND PHARMACEUTICAL SOLUTIONS



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

