



Validation guide summary

**piresu**<sup>®</sup>



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## 1. Introduction

Founded in 1986, BioPure Technology Ltd. specialise in the development and manufacture of connectors, clamps and custom assemblies for the bioprocess market. BioPure Technology Ltd. became part of the Watson-Marlow Fluid Technology Group (WMFTG) in 2014. puresu® is a single-use assembly, available in a variety of custom configurations for use in biopharmaceutical bioprocessing.

They comprise of single-use components including Watson-Marlow tubing, ReNu SU cartridges, BioPure connectors and gaskets, as well as a number of industry recognised third party products.

This validation summary guide details the WMFTG components included in the puresu custom assemblies, their manufacturing processes, and the Vdmax study performed to provide a sterility assurance level (SAL) of 10<sup>-6</sup> on the assemblies with the product descriptor suffix (STR).

puresu assemblies present the operator with a method of assuring sterile manufacturing conditions and rapid, reliable changeover. It also minimises the amount of validation work required through eliminating the need for a cleaning validation in the bioprocess operations.



BioPure puresu single-use assemblies come in three categories with the suffixes denoted in **Table 1**.

**Table 1: puresu assembly part numbers include suffix**

Assembly product descriptors and their suffix	
Non irradiated	(NON)
Product exposed to gamma irradiation at a minimum of 25 kGy specification, No Sterility Assurance Claim	(IRR)
Product(s) have been dosimetrically released based on ANSI/AAMI/ISO 11137 per TIR33 (VdMax) which provides a 10 <sup>-6</sup> Sterility Assurance Level (SAL)	(STR)

As the supplier and the manufacturer of puresu assemblies, BioPure employ an ISO 9001 quality management system within their Horndean, UK facility. The assemblies are manufactured and packaged in ISO 14644-1 Class 7 cleanrooms. All personnel have been trained in cleanroom operation and specific procedures relating to the manufacture of single-use assemblies including sealing the pouches. The equipment used in the cleanrooms are dedicated to the manufacture of the assemblies.

puresu assemblies can be provided double or triple bagged depending on customer requirements. These assemblies can also be provided in three categories, either non-irradiated, gamma irradiated to a minimum of 25 kGy with a certificate stating an irradiation dose range or one with a claim of 10<sup>-6</sup> sterility assurance level (SAL). Each assembly has a unique lot number which enables each component to be fully traced to its constituent materials.

2. Qualification

The primary purpose of this validation guide is to provide assurance that the assemblies and each of its components meet the requirements for use in biopharmaceutical manufacturing.

All components in the assemblies that are fluid contact comply with USP 88 Class VI, FDA 21 CFR 177 (polymer specific), and are animal derived component free (ADCF). Where a component does contain an animal derived component, then it has a statement to show it conforms with the requirements to EMEA 410/01 revision 3 regarding transmissible spongiform encephalopathies and bovine spongiform encephalopathy (TSE/BSE).

The compliance statements for the WMFTG products included in the puresu assemblies are available in **Table 2**. In addition, the efficacy of the sterilisation treatment have been validated in accordance with ISO 11137-2, using the VDmax method and ISO 11737 bioburden test. This is described in the section headed bioburden evaluation and sterility validation study.

3. WMFTG Assembly components

All WMFTG components included into the puresu assemblies have been tested post gamma irradiation and comply with the following:

USP 88 Class VI, Biological reactivity tests tests, in vivo

USP 87, Biological reactivity tests, In vitro cytotoxicity

ISO 10993, Biological evaluation of medical devices

The full regulatory compliance list is detailed in Table 2.

3a Pumpsil

Pumpsil tubing is a high-purity product manufactured within an extrusion facility, in an ISO 14644-1 Class 7 cleanroom. The cleanroom and process equipment used to produce Pumpsil dedicated to the production of platinum-cured silicone.

Pumpsil tubing is manufactured from virgin raw material: no rework material is used. All materials are certified ADCF by the suppliers. The raw material is manufactured under strict controls of ingredients, operating procedure and packaging. Full traceability is assured through the lot number of the tubing, enabling identification of the raw material throughout manufacture, in the quality control and production records.

3b Pureweld XL

Watson-Marlow PureWeld XL tubing is a high purity product produced in a state-of-the-art ISO14644-1 Class 7 facility. PureWeld XL is a thermoplastic elastomer tube which is produced from synthetic components. PureWeld XL does not include any natural rubber products. There are no known carcinogens used in the tubing or in the

production of the tubing. The raw material has been fully tested to USP Class VI and 21 CFR 177.1810.

Watson-Marlow PureWeld XL tubing is manufactured from virgin pellet only, no regrind is used in the production. The raw material is manufactured under strict controls of ingredients, operating procedure and packaging. Each lot of raw material undergoes mechanical testing to ensure compliance with the material specification. Full traceability is assured through the lot number of the tubing, this enables the raw material, manufacturing equipment, quality control records and production records to be identified.

3c Bioprene

Watson-Marlow Bioprene® is a thermoplastic elastomer tube produced from synthetic components. No natural rubber is used in the production of Bioprene tubing. The raw material has been fully tested to USP 88 Class VI and ISO 10993-1, and a MAF (Device Master File) has been established with the US FDA.

The raw material is manufactured under strict controls of ingredients, operating procedures and packaging. Watson-Marlow Bioprene tubing is manufactured from virgin pellet only: no regrind is used in the production of Bioprene. Full traceability is assured through the lot number of the tubing, which enables the raw material, primary manufacturing equipment, quality control records and production records to be identified.

3d Third party tubing

WMFTG work with industry recognised and qualified third party suppliers. There are other tubing products that could be part of puresu® custom assemblies. Information on these parts are provided on project quotation and initiation

3e Fluid path components

BioPure fluidpath components consisting of Biobarbs, Bio-Ys, BioEndcap and FlatBioEnd caps, are produced out of a fully qualified polypropylene material and are manufactured in an ISO14644-1 Class 7 facility. BioPure fluid path components are manufactured from virgin material only, no regrind is used in the production. The raw material is manufactured under strict controls of ingredients, operating procedure and packaging. Full traceability is assured through the lot number of the components, this enables the raw material, manufacturing equipment, quality control records and production records to be identified.

3f Third party components (including tube connectors, cross connectors, plug, tube coupling, flowmeters, gaskets, luer connectors and pressure sensors)

WMFTG work with industry recognised and qualified third party suppliers. There are third party components

such as tube connectors, cross connectors, plug, tube couplers, flowmeters, gaskets, luer connectors and pressure sensors which could be part of puresu custom assemblies. Information on these third party components are provided on project quotation and initiation.

3g ReNu Cartridge

ReNu cartridges are manufactured in an ISO14644-1 Class 7 facility from a combination of polyurethane tubing integrated into polyethylene framework. ReNu cartridges are manufactured from virgin material only, no regrind is used in the production. The raw material is manufactured under strict controls of ingredients, operating procedure and packaging. Each lot of raw material undergoes mechanical testing to ensure compliance with the material specification. Full traceability is assured through the lot number of the cartridge, this enables the raw material, manufacturing equipment, quality control records and production records to be identified.

3h BioPure platinum cured silicone ‘500 series’ gaskets

The platinum cured silicone ‘500 series’ gaskets are manufactured in an ISO 14644-1 Class 7 cleanroom. BioPure gaskets are manufactured from virgin material only. Full traceability is assured throughout the

manufacturing process, which enables the raw material, primary manufacturing equipment, quality control records and production records to be identified.

3i BioPure platinum cured silicone braided hose

The platinum cured silicone braided hose is manufactured in an ISO 14644-1 class 7 cleanroom. BioPure braided hose is manufactured from virgin material only. Full traceability is assured through the lot number of the hoses, which enables the raw material, primary manufacturing equipment, quality control records and production records to be identified.

3j Flexicon nozzles

Two types of filling nozzles are available for puresu. The first is made from SUSTA polyetherimide (PEI) and the second is made of a combination of polyether ether ketone (PEEK) and stainless steel. A material certificate type 3.1 is available on request for the medical grade of 316L stainless steel. Both of the nozzle types meet the requirements for materials contacting injectable drug products.

All materials used in the nozzles are ADCF and are compliant with USP 88 Class VI testing.

Table 2: The following table gives a summary of the biological safety tests and physicochemical investigations on the components which make up the customisable open architecture assemblies. Product validation guides for ReNU cartridges, Pumpsil, BioPure silicone hoses, BioPure fluidpath components, Pureweld XL and Bioprene tubing are available from WMFTG validation landing page giving full details of the test procedures, results and reports.

Components list	USP 88	USP 87	ACDF	ISO10 993-5	ISO10 993-6	ISO10 993-10	ISO10 993-11	USP 788	EMEA/410/01 rev3
Pumpsil	✓	✓	✓	✓	✓	✓	✓	✓	–
Bioprene	✓	✓	✓	✓	✓	✓	✓		✓
Pureweld XL	✓	✓	✓	✓	✓	✓	✓	✓	–
ReNU cartridge	✓	✓	✓	✓	✓	✓	✓	✓	✓
BioPure fluid components	✓	✓	✓	✓	✓	✓	✓		–
BioPure silicone gaskets	✓	✓	✓	✓	✓	✓	✓	✓	–
Flexicon nozzles	✓	–	✓	–	–	–	–	–	–

Compliance statements can be found in respective product compliance guides.



4. Packaging

puresu assemblies are double bagged and heat sealed within polyamide/polyethylene pouches in an ISO 14644-1 Class 7 cleanroom. These pouches are manufactured following ISO 9001 procedures in an ISO 14644-1 Class 8 cleanroom environment.

Small bags, secured by releasable cable ties, are used to protect the ends of the filling nozzles and connectors. Their specification is identical to the larger bags used to protect the whole assembly.

The supplier of the packaging bags provides assurance that all raw materials are ADCF.



A label specifying the part number, lot number (traceable through to individual batch numbers for the separate components) and use-by date is placed on the outside of the inner bag. The label also specifies the irradiation conditions and a smart strip on the label indicates whether or not irradiation has taken place: red for a completed irradiation process; light orange for non-irradiated. Note that the strip is principally a production control measure. Proof of irradiation to the correct dose is provided by the certificate accompanying each irradiated lot.

An identical gamma-irradiation-sensitive label is used on boxes containing multiple assemblies. It also shows the part and lot numbers, the use-by date and the quantity in the box.

The packaging meets the requisite criteria for providing a sterile barrier during transportation in excess of the declared shelf life of two years.

These assemblies are gamma irradiated at a WMFTG’s supply partner site for irradiation. This facility has been audited by WMFTG and has a number of industry recognised accreditations.

5. Bioburden evaluation and sterility validation

Prior to sterility validation studies, an assessment of the bioburden of the assemblies were carried out using the guidance detailed in ANSI/AAMI/ISO 11137. This provided an overview of the total bioburden on the assemblies as a result of the manufacturing environment/ location, raw materials, components, product design and size, manufacturing equipment and manufacturing process.

For the sterility dose validation study, a simulated product or ‘monster bag’ consisting of sub-assemblies incorporates representative elements of WMFTG products and qualified third party components to provide custom open architecture assemblies with a sterility assurance level claim. The simulated product monster bag was manufactured at the same manufacturing site and location using standard equipment and processes. It comprises of components made from the same raw materials and of similar designs, dimensions and densities as typically provided in custom puresu assemblies. The simulated product monster assembly was constructed to incorporate all representative elements and conditions that drive naturally occurring product bioburden levels ‘enumeration’ as well as supplementary characteristics of product and bioburden. These elements combined provide an estimation of the products’ microbial population and the minimum radiation dosage required to achieve the specified 10<sup>-6</sup> sterility assurance level (SAL).

The sterilisation process was carried out on boxes of packaged assemblies using gamma irradiation.

This process is fully qualified according to ANSI/AAMI/ISO 11137, using the VDmax method.

In summary, this consists of submitting a number of completed assemblies for bio-burden evaluation, using the results to select the irradiation dose (according to predetermined statistical criteria) applying to a further batch of assemblies and then measuring the sterility of those assemblies. A further aspect of the qualification is ensuring the continued effectiveness of the dose through regular audits. The assembly components used in this sterility validation study consist of the WMFTG products detailed in **Table 1** and a selection of third party components provided by WMFTG supply partners. The full validated library consists of more than 1500 fluid contact and non-fluid contact components.

Further information about the full list of components covered by this study is available on request upon project initiation. For components not in the validated library, there will be a risk assessment performed to establish if there is already existing bioburden data within WMFTG to provide a sterility claim based on ‘worst case’ assessment. This will be determined and discussed with the customer on a ‘case by case’ basis.



6. Conclusion

puresu assemblies are designed and produced according to customer specification. They are available in three categories to meet the end-users bioprocess requirements. The first non-gamma irradiated puresu assemblies can be customised with WMFTG products and additional third party components. The second type of puresu assemblies with the product descriptor suffix – IRR are gamma irradiated at a minimum of 25 kGY and can comprise of WMFTG products and third party components. The third type of puresu assemblies with the product descriptor suffix – STR have been dosimetrically

released based on ANSI/AAMI/ISO 11137 per TIR33 (VDMax) which provides a 10<sup>-6</sup> sterility assurance level (SAL) if the assembly components are selected from the validated component library consisting of product families assemblies that form the simulated ‘monster bag’. All assemblies with the product descriptor suffix- IRR and STR are provided with a certification of irradiation detailing the dosimetric release criteria. The packaging meets the requisite criteria for providing a sterile barrier during transportation in excess of the declared shelf life of two years.

Customise to your bioprocess with safe, easy-to-install assemblies

Non Irradiated puresu®	Gamma Irradiated puresu®	Sterile puresu®
Ideal for process development fluid path bioprocess	Suitable for customers who manage microbial control through bioburden reduction	Ideal for critical fluid path bioprocesses and customers unable to terminally sterilise.
Suitable for prototype evaluation and customers who may apply alternative sterilisation methods		Supplied gamma irradiated with a sterile assurance level claim (10 <sup>-6</sup> SAL).  Suitable for customers who require contamination risk mitigation



Fluid Technology Group

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