WATSON MARLOW Fluid Technology Solutions

Flexicon Liquid Filling

Validation guide summary

asepticsu

Contents

1. Introduction

Flexicon asepticsu™ is a sterile, single-use, filling assembly. A complete assembly for use in Flexicon's filling and dispensing equipment comprises a single-use product bag, high-accuracy AccusilTM pump tubing and filling nozzles. All the fluid-contacting components have been validated to fulfil the exacting requirements for aseptic filling of pharmaceutical products. This validation guide covers the components, materials, and the manufacturing processes, including sterilisation of the whole assembly.

asepticsu™ is the ideal product for a wide range of filling and dispensing operations in the biopharmaceutical industry or any filling application requiring superior accuracy and sterile conditions.

asepticsu™ presents the plant operator with a method of assuring sterile manufacturing conditions and rapid, reliable changeover. It also minimises the validation work required through eliminating the need for a cleaning validation in the final filling operation.

1a Company

Flexicon, founded in 1986 in Denmark, specialise in the development and manufacture of aseptic filling systems for the biopharmaceutical market, with emphases on precision, efficiency and flexibility.

Flexicon became part of Watson-Marlow Fluid Technology Solutions in 2008, forming Watson-Marlow Flexicon, fusing Watson-Marlow's expertise in peristaltic pump and tubing manufacture with Flexicon's in aseptic filling systems.

asepticsu™ is manufactured to Flexicon specifications at Watson-Marlow in Falmouth, UK, in a facility comprising over 7,500 sq m (80,000 sq ft) of production and office space.

The Watson-Marlow Fluid Technology Solutions is a wholly owned subsidiary of Spirax-Sarco Engineering plc. Spirax-Sarco has its headquarters in Cheltenham, England, and is listed on the London Stock Exchange.

1b Quality systems at Flexicon and Watson-Marlow

Flexicon and Watson-Marlow as the supplier and the manufacturer of asepticsu™, employ ISO 9001 quality systems in every part of their business. Watson-Marlow also has ISO 14001 certification for environmental management.

2. Product specification

asepticsu™ is a single-use, sterile filling assembly, available in a variety of configurations for use in Flexicon's filling and dispensing equipment.

The basic asepticsu™ assembly comprises tubing and a filling nozzle. In other configurations a bag is added to contain the product. Subsidiary components include connectors, cable ties, clamps, and protective bagging.

The assembly is double-bagged in vacuum-sealed pouches and sterilised by gamma irradiation with a minimum dose of 25kGy.

The product bags are offered in 1 litre, 5 litre, and 10 litre capacities. Tubing IDs of 0.8mm, 1.2mm, 1.6mm, 3.2mm, 4.8mm or 6.0mm are available.

2a Configuration A

This simple assembly comprises high-accuracy pump tubing and a filling nozzle

Configuration A

- Two parallel silicone tubing lengths which fit into the pumphead
- Y-connector
- Silicone tubing from Y-connector to filling nozzle
- Filling nozzle

2b Configuration B

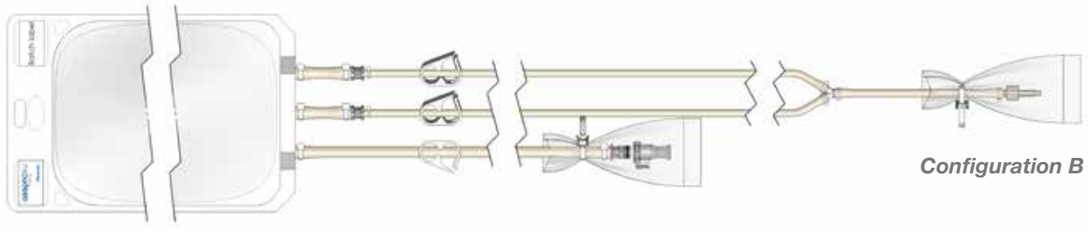
The asepticsu™ product bag is filled through an inlet tube and, depending on batch size, can be used as a break tank. For smaller volumes, it may hold the complete batch. Outlet tubing passes through the peristaltic pumphead and the product is then dispensed through the integrated filling nozzle.

- A single-use product bag of 1 litre, 5 litre or 10 litre capacity
- Inlet port connected to a CPC MPC connector
- Two outlet ports connected to parallel lengths of silicone tubing
- One Y-connector to connect the silicone tubing lengths to the filling nozzle
- Silicone tubing from the Y-connector to filling nozzle
- Filling nozzle
- Clamps for closing the tubing

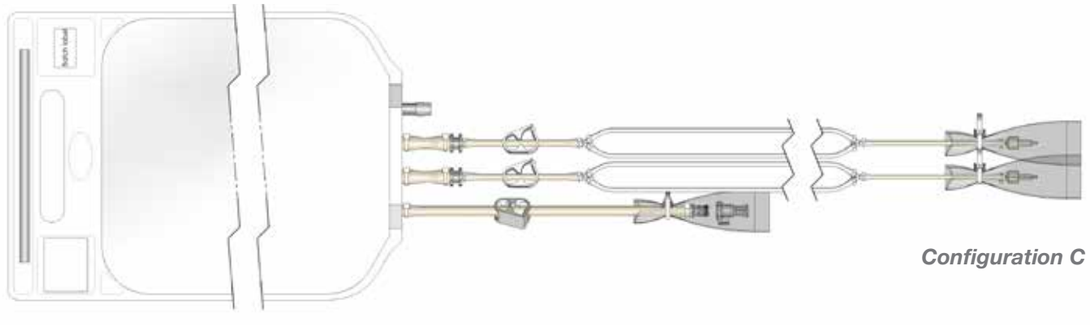
2c Configuration C

Like the B configuration, the asepticsu™ product bag is filled through an inlet tube. Depending on batch size, the product bag can be used as a break tank, or for smaller volumes, hold the complete batch. Two sets of outlet tubing pass through twin peristaltic pumpheads and the product is dispensed through the integrated filling nozzles.

- A single-use product bag of 5 litres or 10 litres
- Inlet port connected to a CPC MPC connector
- Outlet ports connecting to parallel lengths of silicone tubing
- Two Y-connectors linking the two pairs of silicone tubing lengths to the filling nozzles
- Two filling nozzles for filling with parallel pumpheads
- Clamps for closing the tubing at the end of the filling process



Configuration B



Configuration C

2d asepticsu™ filling filter - 0.2µm

Sterile filter with pre-connected tubing and CPC connector for filtering fluid into the product bags. This can be added to configurations B and C.

The above configurations are available as standard products. Contact our sales representatives for further information on custom assemblies: www.flexicon.dk

asepticsu™ filling filter - 0.2µm

3. Validation

Quality is an integral part of this product. The primary purpose of this validation guide is to provide assurance that the whole product and each of its components meet the stringent requirements for aseptic filling applications.

All components in the principal assemblies that have contact with the fluid being handled comply with USP Class VI, FDA 21CFR177 (polymer specific) and ISO 10993-1, and are Animal-Derived Component Free (ADCF). Please note that the latter assurances come from the suppliers of the various components and are not based on in-house testing. In assemblies including a filter, the filter does not have an ADCF statement, but the manufacturer provides details of compliance to EMEA 410/01 revision 2 regarding transmissible spongiform encephalopathies and bovine spongiform encephalopathy (TSE/BSE).

Full details of component qualification are given in later sections of this guide. In addition, the efficacy of the sterilisation treatment and its shelf life have been validated in accordance with ISO 11137-2, using the VDmax25 method, and ISO 11607 (packaging for terminally sterilised medical devices).

Each assembly has a unique lot number that enables each component to be fully traced to its constituent materials.

Reference is also made to the quality processes employed at every stage in the manufacture of the assemblies.

3a Testing summary

The large table in this section serves as a quick reference to the biological safety and physicochemical testing on the fluid-contacting components.

In subsequent sections tables list tests, procedures or standards relevant to the assembly components. The terms used to indicate the outcomes of these tests, procedures and standards mean:

Term	Meaning
Pass	Result meets or exceeds level defined in standard
Report	Descriptive, meeting standard
Compliant	Meets regulation
Certified	Proof of procedure

Part Identification		Gamma sterilisation stable	Biocompatibility													Physicochemical/ Materials safety				Clean
Number	Description		Class VI USP 32NF27 <87> Cytotoxicity	Class VI USP 32NF27 <88> Biological Reactivity in vivo	Class VI USP 32NF27 <85> Bacterial Endotoxin	USP 32NF28 <788> Microscopic Particle Count Test	FDA 21 CFR Part 177 - Polymer specific	ISO 10993 Biological evaluation of medical devices - Part 1 4: Haemolysis	ISO 10993 - 5: Cytotoxicity	ISO 10993 - 6: Implantation	ISO 10993 - 10: Irritation/ sensitisation	ISO 10993 - 11: Acute Systemic Toxicity	EMEA/410/01-rev02	ADCF	European Pharmacopoeia 6.8 <3.1.9>	Conformance to RoHS directive 2002/95/EC	No use of SVHC according to REACH	USP 32NF27 <661> Physicochemical Tests	Clean room certificate/cleaning process
Product bag																				
BC0005	1 litre	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
BC0006	5 litre 3/8in (port size)	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
BC0007	10 litre 3/8in (port size)	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
BC0009	10 litre 1/4in (port size)	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
BC0010	5 litre 1/4in (port size)	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
Tubing, bore x wall																				
84-103-008	Accusil 0.8mm x 1.6mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓
84-103-012	Accusil 1.2mm x 1.6mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓
84-103-016	Accusil 1.6mm x 1.6mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓
84-103-032	Accusil 3.2mm x 1.8mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓
84-103-048	Accusil 4.8mm x 2.0mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓
84-103-060	Accusil 6.0mm x 2.1mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓
84-103-080	Accusil 8.0mm x 2.2mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓
Nozzle - Type 1 - PEI 1000																				
30-033-008	0.8mm ID	✓		✓										✓			✓			✓
30-033-012	1.2mm ID	✓		✓										✓			✓			✓
30-033-016	1.6mm ID	✓		✓										✓			✓			✓
30-033-032	3.2mm ID	✓		✓										✓			✓			✓
30-033-048	4.8mm ID	✓		✓										✓			✓			✓
30-033-060	6.0mm ID	✓		✓										✓			✓			✓
Nozzle - Type 2 - Stainless steel/PEEK																				
30-040-006	0.6 mm ID	✓		✓			✓							✓			✓			✓
30-040-010	1.0 mm ID	✓		✓			✓							✓			✓			✓
30-040-016	1.6 mm ID	✓		✓			✓							✓			✓			✓
30-040-032	3.2 mm ID	✓		✓			✓							✓			✓			✓
30-040-045	4.5 mm ID	✓		✓			✓							✓			✓			✓
30-040-060	6.0mm ID	✓		✓			✓							✓			✓			✓
Y-connectors																				
CN0177	2.4mm 3/32in	✓	✓	✓			✓							✓		✓	✓			
CN0179	4.8mm 3/16in	✓	✓	✓			✓							✓		✓	✓			
CN0180	6.4mm 1/4in	✓	✓	✓			✓							✓		✓	✓			
CN0239	1.6mm 1/16in	✓	✓	✓			✓							✓		✓	✓			
CN0240	4.0mm 5/32in	✓	✓	✓			✓							✓		✓	✓			
Straight connectors																				
CN0252	6.4mm	✓	✓	✓			✓							✓		✓	✓			
CN0262	Luer male 6.0mm	✓	✓	✓			✓							✓		✓	✓			
CN0261	Luer female 0.8mm	✓	✓	✓			✓							✓		✓	✓			
CN0260	Luer male 0.8mm	✓	✓	✓			✓							✓		✓	✓			
CN0263	Luer female 6.0mm	✓	✓	✓			✓							✓		✓	✓			
Straight reducer connectors																				
CN0238	3.2mm - 1.6mm	✓	✓	✓			✓							✓		✓	✓			
CN0245	9.6mm - 3.2mm	✓	✓	✓			✓							✓		✓	✓			
CN0251	9.6mm - 6.4mm	✓	✓	✓			✓							✓		✓	✓			
CN0253	6.4mm - 3.2mm	✓	✓	✓			✓							✓		✓	✓			
Quick release inlet connectors																				
CN0232	Female 6.4mm	✓	✓									✓		✓		✓	✓			✓
CN0233	Male 6.4mm	✓	✓									✓		✓		✓	✓			✓
CN0234	Plug	✓	✓									✓		✓		✓	✓			✓
CN0235	Cap 6.4mm X 9.6mm	✓	✓									✓		✓		✓	✓			✓
Filter																				
XX0303	Sartopore2, 0.2µm, 0.30sq ft	✓	✓	✓	✓	✓							✓							✓

4. Components in the fluid path

4a Single-use product bags

The product bags are made of low density polyethylene (LDPE) films which are separated by an ethylene-vinyl alcohol copolymer (EVOH) gas barrier film. Our suppliers certify that the product bag materials comply fully with materials regulations such as REACH and RoHS and are ADCF. The product bags are manufactured in an ISO 9001 certified plant in an ISO 14644-1 Class 7 cleanroom in accordance with cGMP principles.

The product bags include several design features that significantly improve the robustness of single-use systems while still enabling high product recovery. The product bags have been designed with a robust, flexible connection utilising a boat-shaped, injection-moulded, multiple port system. The boat connector allows various size tubing connections but always maintains the same outer size and shape; thus creating consistency and robustness when sealed to the product bag film.

Testing

The product bags have been subjected to tests in a number of categories:

- Mechanical tests to examine the integrity of the containers before and after gamma irradiation
- Resistance to gamma sterilisation and transport test
- Resistance to freezing test
- Connections test
- Shelf life studies, up to three years following irradiation, include mechanical and leak tests
- Extractables / leachables study
- Biological safety tests
- Physicochemical tests

Results from all of the studies met or exceeded the required standards and qualify the product bags for use in biopharmaceutical filling applications.

The following table summarises the tests that have been carried out on the product bags.

Test	Result
Class VI - L929 Elution Test – ISO 10993-5/ USP 32NF27 <87>	Pass
Class VI – Injections – USP 32NF27 <88>	Pass
Class VI Bacterial Endotoxins Test – USP 32NF27 <85>	Pass
Particulate Matter in Injections – USP 33NF28 <788>	Pass
Hemolysis – Human Blood - ISO 10993 - 4	Pass
Intramuscular Implantation - ISO 10993 - 6	Pass
Intracutaneous Injection Test – ISO 10993 - 10 and 12	Pass
Systemic Injection Test - ISO 10993 - 11 and 12	Pass
Physicochemical Tests USP 32NF27 <661>	Pass
Ph. Eur. 6.8:3.1.5. Total Extractables Tests	Report
JP61 pt1 – Extractables and Biological Safety Tests	Pass
Gamma Irradiation (25-40kGy) Stable – ISO 11137-2: 2006	Pass
Mechanical tests following irradiation: drop tests, leak tests, product bag integrity	Pass

4b Tubing

Flexicon Accusil™ tubing is a high-purity product that is made in a state- of-the-art extrusion facility, in an ISO 14644-1 Class 7 cleanroom. The cleanroom and process equipment used to produce Accusil™ are dedicated to the production of platinum-cured silicone.

Accusil™ tubing is entirely 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, and in the quality control and production records.

The following table gives a summary of the biological safety tests and physicochemical investigations on the tubing. A separate validation guide for Accusil™ is available giving full details of the test procedures, results and reports. https://www.watson-marlow.com/us-en/validation/request/

Test	Result
Class VI - L929 Elution Test – ISO 10993-5/ USP 32NF27 <87>	Pass
Class VI – Injections – USP 32NF27 <88>	Pass
Class VI Bacterial Endotoxins Test – USP 32NF27 <85>	Pass
Particulate Matter in Injections – USP 33NF28 <788>	Pass
Total Extractables – FDA 21CFR 177.2600	Pass
European Pharmacopoeia 6.8 Chapter 3.1.9	Pass
Haemolysis – Human blood - ISO 10993 - 4	Pass
Intramuscular Implantation - ISO 10993 - 6	Pass
Intracutaneous Injection Test – ISO 10993 - 10 and 12	Pass
Kligman Maximisation Test – ISO 10993-10	Pass
Systemic Injection Test - ISO 10993 - 11 and 12	Pass
Physicochemical Tests USP 32NF27 <661>	Pass
Physicochemical Tests USP 33NF28 <381> including Total Organic Carbon	Report

4c Filling nozzles

Two types of filling nozzle are available for asepticsu™. The first is made from SUSTA PEI and the second is a combination of PEEK and stainless steel. In the second type, only the stainless steel has contact with the product being dispensed. A material certificate, type 3.1, is available for the medical grade of AISI 316L stainless steel. Both types of nozzle meet the requirements for materials contacting fluids used for injection.

Both types of nozzle are made under controlled conditions and undergo stringent, documented cleaning procedures. All materials used in both nozzles are certified ADCF by the suppliers.

PEI filling nozzles

Test	Result
Class VI – Injections – USP 32NF27 <88>	Pass
Class VI – Injections – USP 32NF27 <88>	Certified

Stainless steel/ PEEK filling nozzles

Test	Result
Class VI	Compliant
Gamma irradiation (25-40kGy) stable	Certified
Cleaning	Certified

4d Fittings

This category includes Y-connectors, straight connectors and reducing connectors. All of these are made from KYNAR 1000HD (PVDF). These components meet the strict requirements for biopharmaceutical use. The suppliers certify that the raw materials used in manufacture are ADCF.

Test	Result
Class VI – Injections – USP 32NF27 <88>	Pass
Total Extractables – FDA 21CFR 177: 2510	Pass
Gamma irradiation (25-40kGy) stable	Certified
RoHS directive 2002/95/EC	Compliant
REACH	Compliant

4e Inlet connectors

These connectors (male and female) are constructed from moulded polycarbonate. These parts meet the crucial USP Class VI criteria shown in the table below. The manufacturer declares that the raw materials are ADCF.

Test	Result
Class VI – Cytotoxicity – \ USP 32NF27 <87>	Pass
Class VI – Injections – USP 32NF27 <88>	Pass
RoHS directive 2002/95/EC	Compliant
REACH	Compliant

4f Filters

The filters are constructed from polypropylene, housing polyethersulfone membranes (supported by polyester), rated to 0.2µm. The manufacturers guarantee compliance to EMEA 410/01 rev.2. The filters can be sterilised by gamma irradiation up to 50kGy. Manufacture is in accordance with ISO 9001.

Test	Result
Class VI – L929 Elution Test – ISO 10993-5/ USP 32NF27 <87>	Pass
Class VI – Injections – USP 32NF27 <88>	Pass
Class VI Bacterial Endotoxins Test – USP 32NF27 <85>	Pass
Particulate Matter in Injections – USP 33NF28 <788>	Pass
Correlation of diffusion and bubble point values with HIMA/ASTM bacteria challenge	Pass
pH change of the filtrate	Pass
Conductivity changes of the filtrate	Pass
Water flow rates under various conditions	Pass

5. Components with no fluid contact

5a Medical clamps

Although medical clamps have no direct contact with the product, they have passed the USP Class VI <87> and <88> tests. The polypropylene material is stable to gamma irradiation up to 50kGy.

5b Cable ties

Nylon cables ties are used in the assembly to secure the tubing to connectors, to product bags, filling nozzles and filters.

5c Packaging

asepticsu™ is vacuum-sealed within a foil-film/ film bag. Further protection is provided by vacuum sealing within a second film / film bag. These bags are manufactured following ISO 9001 procedures in an ISO 14644-1 Class 7 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.

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.

6. Sterilisation

The sterilisation process is carried out on boxes of packaged assemblies using gamma irradiation at Synergy Health plc, (www.synergyhealthplc.com), one of Europe's leading providers of contract sterilisation services.

This process is fully qualified according to ISO 11137-2. In this case the VDmax25 method was used by Synergy Health plc. 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 that dose of gamma irradiation 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.

A dose mapping validation has also been carried out to ensure that every portion of a consignment of assemblies receives the correct dose of irradiation. Each assembly label has a radiation-sensitive strip that turns from light orange to red following irradiation. 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.

Synergy Health plc hold all the relevant quality assurance and compliance registrations: ISO 13485, ISO 9001, ISO 11137-1, FDA 21 CFR Part 820.

As noted in the sections for the individual components, each has been qualified for its integrity following irradiation.

The paragraphs above relate to the important process of sterilisation. Equally important is that the packaging maintains assembly sterility over the stated lifetime, including the potentially adverse effects of transportation. ISO 11607 (packaging for terminally sterilised medical devices) has been taken as the guide for tests evaluating packaging integrity. These tests follow the principle of establishing that the packaging provides an adequate sterile barrier system for the assembly over its intended lifetime. The tests examine both seal strength and integrity using a number of procedures recommended in ISO 11607 (ASTMs F1929, F2054, F1980, and F1886). The packaging meets all the requisite criteria for providing a sterile barrier during transportation in excess of the declared shelf life of two years.

7. Control systems

As well as qualifying the biological safety and irradiation stability of the components, manufacturing is controlled through procedures created in an ISO 9001 environment.

Control of bio-burden level is an extremely important factor in asepticsu™ manufacture. The bio-burden level of components is monitored as part of a statistical control process in manufacturing. These component tests are in addition to those carried out as part of the VDmax25 study.

7a Component control

Suppliers are audited on a three year cycle and qualified for their ability to supply components according to specification, encompassing not only the physical part but also the cleanliness of packaging. Incoming parts are checked by our quality assurance department.

7b asepticsu™ filling manufacturing

asepticsu™ is manufactured in an ISO 14644-1 Class 7 cleanroom in accordance with cGMP principles. All personnel have been trained in cleanroom operation and specific procedures relating to the assembly, such as pressure testing and sealing the vacuum pouches. Equipment used in the assembly and testing has full IQ, OQ and PQ.

8. Usage conditions, storage and shelf life

It is recommended that Flexicon asepticsu™ filling assemblies are used within the temperature range 10°C to 35°C, with a tight control on temperature in order to attain optimal filling accuracy.

The use-by date of the assembly is included on the inner bag and the box labels. To maintain the performance of the assembly throughout its life, it should be stored in a cool, dry environment away from direct sunlight.

Normal warehouse conditions are acceptable (-10C to 40C, 14F to 104F). Temporary excursions outside this range, for example during transport, are also acceptable.

asepticsu™ assemblies are double-bagged, with the inner bag forming the sterile barrier layer. After removal of the inner bag, retain it if possible as its labelling provides a record of the product used.

WATSON MARLOW Fluid Technology Solutions

BIOTECHNOLOGY AND PHARMACEUTICAL SOLUTIONS

WATSON MARLOW Pumps | WATSON MARLOW Tubing | Flexicon Liquid Filling | bioPURE | ASEPCO | AFLEX HOSE

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

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