Validation Guide
MYCAP® Bottle Closures
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1. Introduction

Sartorius-Stedim Biotech’s MYCAP® bottle closures and fluid management systems with MYCAP® bottle closures are used in a variety of process areas for and in support of the discovery, development and clinical or commercial production of drug products such as vaccines, recombinant proteins and monoclonal antibodies.

Fluid management systems with MYCAP® bottle closures are qualified, manufactured and released under a Quality Control system which is compliant to the key principles of cGMP.

This Validation Guide describes; qualification of materials, performance specifications, manufacturing conditions and quality control systems of fluid management systems with MYCAP® bottle closures.

1.1 Scope Statement

MYCAP® is a one-piece closure system for containers with threaded closures. MYCAP® bottle closures feature integral tubing and a robust platinum-cured silicone seal. MYCAP® bottle closures are available as free-standing units or as part of a fluid management system which may include containers, connectors, tubing, filters and other accessories.

Components and assemblies considered for this validation guide are as follows:
## Containers

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Brand</th>
<th>Size(s)</th>
<th>Materials of Construction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ThermoFisher Scientific</td>
<td>Nalgene®</td>
<td>Square Media</td>
<td>30 mL – 2 L</td>
</tr>
<tr>
<td>ThermoFisher Scientific</td>
<td>InVitro™</td>
<td>Biotainer®</td>
<td>1 L to 20 L</td>
</tr>
<tr>
<td>Corning Falcon®</td>
<td></td>
<td></td>
<td>15 mL</td>
</tr>
<tr>
<td>Corning Falcon®</td>
<td></td>
<td></td>
<td>50 mL</td>
</tr>
<tr>
<td>Corning Erlenmeyer</td>
<td></td>
<td></td>
<td>125 mL – 3 L</td>
</tr>
<tr>
<td>Cellon®</td>
<td>Pharmatainer®</td>
<td></td>
<td>125 mL – 20 L</td>
</tr>
</tbody>
</table>

## Tubing

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Brand</th>
<th>Brand</th>
<th>Name</th>
<th>Materials of Construction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saint-Gobain Performance Plastics</td>
<td></td>
<td>C-Flex®</td>
<td></td>
<td>Thermoplastic Elastomer (TPE)</td>
</tr>
<tr>
<td>Saint-Gobain Performance Plastics</td>
<td></td>
<td>STHT-C®</td>
<td></td>
<td>Platinum-Cured Silicone Sil (Pt)</td>
</tr>
<tr>
<td>Dow-Corning®</td>
<td></td>
<td>Pharma Series Tubing</td>
<td></td>
<td>Sil (Pt)</td>
</tr>
<tr>
<td>Watson-Marlow</td>
<td></td>
<td>Pumpsi®</td>
<td></td>
<td>Sil (Pt)</td>
</tr>
<tr>
<td>Advantapure</td>
<td></td>
<td>Advantaflex®</td>
<td></td>
<td>Thermoplastic Elastomer (TPE)</td>
</tr>
<tr>
<td>Sartorius</td>
<td></td>
<td>Tutix®</td>
<td></td>
<td>TPE</td>
</tr>
</tbody>
</table>

## Connectors & Fittings

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Brand</th>
<th>Type</th>
<th>Brand</th>
<th>Materials of Construction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td></td>
<td>Opta®</td>
<td></td>
<td>Aseptic connecting device Polycarbonate, Santoprene, Polysulfone</td>
</tr>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td></td>
<td>Sanitary Fittings</td>
<td></td>
<td>High-Density Polyethylene (HDPE)</td>
</tr>
<tr>
<td>Nordson Medical</td>
<td></td>
<td>Tube to Tube Fittings</td>
<td></td>
<td>Polypropylene, PVDF (Kynar®)</td>
</tr>
<tr>
<td>Nordson Medical</td>
<td></td>
<td>Luer Fittings</td>
<td></td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Nordson Medical</td>
<td></td>
<td>Sanitary Fittings</td>
<td></td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Colder Products</td>
<td></td>
<td>AseptiQuik® S &amp; G</td>
<td></td>
<td>Aseptic connecting device (regular service temperature) Polycarbonate, Sil (Pt), Polyethylene</td>
</tr>
<tr>
<td>Colder Products</td>
<td></td>
<td>AseptiQuik® S &amp; G</td>
<td></td>
<td>Aseptic connecting device (autoclave) Polycarbonate, Sil (Pt), Polysulfone</td>
</tr>
<tr>
<td>Colder Products</td>
<td></td>
<td>MPC, MX and MPU Quick Connectors</td>
<td></td>
<td>Polycarbonate, Sil (Pt) or Polysulfone, Sil (Pt)</td>
</tr>
<tr>
<td>Pall Corporation</td>
<td></td>
<td>Kleenpak®</td>
<td></td>
<td>Aseptic connecting device Polycarbonate, Polysulfone, TPE</td>
</tr>
<tr>
<td>EMD Millipore Corporation</td>
<td></td>
<td>Lynx®</td>
<td></td>
<td>Steam to Connector Polyetherimide, Sil (Pt)</td>
</tr>
</tbody>
</table>

## Air Vent Filters

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Brand</th>
<th>Size(s)</th>
<th>Materials of Construction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td></td>
<td>25 mm Minsart®</td>
<td></td>
</tr>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td></td>
<td>15 mm Minsart®</td>
<td></td>
</tr>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td></td>
<td>50 mm MidiSart®</td>
<td></td>
</tr>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td></td>
<td>50 mm Sartopore® Air</td>
<td></td>
</tr>
</tbody>
</table>
### Accessories

<table>
<thead>
<tr>
<th>Manufacturer/Brand</th>
<th>Brand/Description</th>
<th>Materials of Construction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td>Anti-Suction Dip Tube Tip</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td>MYCAP® 20 mm to 24 – 415 Adaptor</td>
<td>HDPE</td>
</tr>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td>Z-Flex™ Articulator</td>
<td>Polycarbonate</td>
</tr>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td>Drain Port</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td>Flexboy® Single-use Bag</td>
<td>EVA</td>
</tr>
<tr>
<td>Sartorius-Stedim Biotech</td>
<td>Flexsafe® Single-use Bag</td>
<td>Polyethylene</td>
</tr>
<tr>
<td>Nordson Medical</td>
<td>Check Valves</td>
<td>Styrene acrylonitrile (SAN), Sil (Pt)</td>
</tr>
<tr>
<td>Halkey-Roberts</td>
<td>Robertsite® Luer activated access site</td>
<td>Polycarbonate, Sil (Pt)</td>
</tr>
<tr>
<td>Qosina</td>
<td>Stopcock Valve</td>
<td>Polycarbonate, HDPE</td>
</tr>
</tbody>
</table>

Unless otherwise stated, tests described in this validation guide were performed on the MYCAP® bottle closure and may not include all or any of the components, assemblies or accessories described above.

Wherever possible, Sartorius refers to our supplier’s product validation documentation. Supplier documentation is available upon request or by contacting the supplier directly.
1.2 Security of Supply

Assurance and security of supply is a significant market requirement for MYCAP® bottle closures. The robustness of our supply chain relies on effective supplier management, multiple manufacturing sites with consistent industrial and quality processes, process automation, application of lean manufacturing practices, expertise for designing fluid management systems, close collaborative relationships with customers and senior management’s strong commitment to continuous and dynamic improvement.

1.3 Manufacturing Resources

Sartorius Stedim Biotech’s manufacturing resources for MYCAP® bottle closures operate under strictly controlled manufacturing procedures and quality system.

New Oxford, Pennsylvania – United States of America
80 Progress Avenue
New Oxford, PA 17350

Total Facility Size: 17,000 square feet
ISO 7 Manufacturing & Raw Materials: 3,100 square feet

- Manufacturing Competencies
  - MYCAP® CCX Gas Exchange Cartridge
  - MYCAP® bottle closures Subcomponent assembly
  - Final assembly
  - Packaging & Labelling

Stonehouse – United Kingdom
Sperry Way
Stonehouse Park Stonehouse
GL10 3UT

Total Facility Size: 52,800 Square Feet
ISO 7 Manufacturing & Raw Materials Space: 2,600 square feet

- Manufacturing Competencies
  - MYCAP CCX Gas Exchange Cartridge
  - Final assembly
  - Packaging & Labelling

1.4 Quality Management System

Sartorius Stedim Biotech implemented Quality Management Systems to assure consistent high quality.

- Exemplary Quality Systems Certificates
  - Quality Management System ISO 9001

Our documented quality system is consistent with industry-recognized quality standards including the following: The FDA current Good Manufacturing Practices (cGMPs)

Note:
Sartorius is not a manufacturer of finished pharmaceuticals or finished medical devices, yet we have chosen to align our quality system clauses of 21 CFR Parts 210, 211 and 820 that apply to our processes and products.

These quality system processes direct and inform our entire quality system and all the procedures, work instructions, forms, etc. contained therein:

- Management Responsibility & Review
- Document Control
- Records Control & Retention
- Corrective & Preventive Action
- Internal Auditing
- Personnel Training & Competency
- Customer Notification & Recall

1.5 Gamma Irradiation

Fluid management systems with MYCAP® bottle closures are packaged and shipped in cardboard boxes on pallets to Steris Isomedix for gamma irradiation.

To assure security of services, four of Steris’ sites have been qualified for gamma irradiation services:

- 23 Elizabeth Drive
  Chester, NY 10918
  USA
- 9 Apollo Drive
  Whippany, NJ 07981
  USA
- 435 Whitney Street
  Northborough, MA 01532
  USA
- Moray Road
  Elgin Industrial Estate Swindon
  Wiltshire SN2 8XS
  United Kingdom

All fluid management systems with MYCAP® bottle closures are irradiated at a minimum dose of 25.0 kGy. The efficiency of the minimum dose of 25.0 kGy has been validated according to the ISO11137 standards in order to obtain Sterility Assurance Level (SAL) 10⁻⁶.

The Certificate of Release issued with each lot of products indicates the gamma irradiation run identification number. Each shipment includes a Certificate of Processing which reports the irradiation dose and lists the lot number(s) of the Sartorius product(s) included in that irradiation run. The two documents may be cross-referenced.
### 1.6 Validation Test Summary

<table>
<thead>
<tr>
<th>Qualification Tests</th>
<th>Monitoring Tests</th>
<th>Lot Release Test</th>
</tr>
</thead>
</table>
| Biocompatibility Testing  
  - USP <87>: Biological reactivity tests, in-vitro 
  - USP <88>: Biological reactivity tests, in-vivo  
| MYCAP® closure barrier properties 
  - Microbial container Closure | Particulate control 
  - USP <788>: Particulate matter in injections 
  - ISO 14644-1: Cleanrooms and associated controlled environments -- Classification of air cleanliness by particle concentration | 100% Visual inspection 
  - Visible particulate 
  - Component defects |
| Physicochemical  
  - USP <381>: Elastomeric Closure for injections | Bioburden & Sterility 
  - ISO 11137: Sterilization of healthcare products Dose Audit: Quarterly 
  - ISO 14698: Cleanrooms and associated controlled environments - Biocontamination control | Pressure Decay Testing of MYCAP® closure and immediate connections* |
| Extractables  
  - 21 CFR 177.2600: Rubber Articles intended for repeated use | Endotoxins 
  - USP <85>: Bacterial endotoxins test | Packaging and labeling |
| Other material specifications  
  - TSE|BSE risk 
  - REACH 
  - Melamine 
  - Bis-phenol A | | Gamma irradiation |

*Pressure Decay Testing is performed only when the system includes a bottle.*
2. Production and Quality

2.1 Personnel
Sartorius-Stedim Biotech recognizes that human resources and personnel competency are of utmost importance and have therefore established a comprehensive human resources management program. Stringent selection, motivation, initial and continuous training and qualification of personnel at all levels of the company assure that every employee is at his or her best at all times for each step of the manufacturing and control processes. Comprehensive training records are kept for all employees.

2.2 Facilities
The buildings, equipment and work environment at Sartorius-Stedim Biotech have been designed to maximize employee comfort and safety while complying with the key principles of cGMP for the manufacture of fluid management systems with MYCAP® bottle closures destined to the pharmaceutical industry. All infrastructure (equipment, utilities, etc.) that has an impact on the product quality is inventoried and undergoes an appropriate qualification, calibration and maintenance.

2.3 Supply Chain

2.3.1 Supplier Evaluation & Qualification
Suppliers are carefully selected according to internal standards and applicable regulations. Typical requirements for suppliers are the following (not exhaustive list):

- Quality Control System
- Quality Assurance System
- Facility & Cleanroom Controls
- Product Component Lot Traceability System
- Change Notification Procedures

Suppliers are evaluated and approved according to internal standards.

2.3.2 Component & Raw Material Qualification
Each raw material and/or component is qualified. This qualification includes a list of required statements from the supplier that is dependent on the final use of the component and/or raw material. Typical requirements for components that are in contact with the product flow are the following (not exhaustive list):

- USP Class VI and/or ISO 10993 conformity
- TSE/BSE statement
- EP conformity (if applicable)
- Change notification statement
- REACH Compliance
- Bisphenol A free

Beyond these requirements, Sartorius-Stedim Biotech may perform qualification of the proposed component and/or raw material internally.

For raw materials, the internal qualification will include physical performance of the component made with this raw material. For components, the qualification will be centered on the testing of the assembly of the new component with other components that will be attached.

2.3.3 Incoming Quality Controls
All raw materials, components and sub-contracted products are inspected upon arrival at Sartorius-Stedim Biotech against approved control specifications. Typical testing requirements applied at incoming quality inspection are (not exhaustive):

- Supplier documentation controls (Certificates)
- Packaging identification and integrity
- Visual inspection
- Dimensional check

Only approved materials will be allowed to be used in production of fluid management systems with MYCAP® bottle closures.

Approved materials are recorded in Sartorius-Stedim Biotech’s inventory and quality management system and labeled with an internal lot number and designated internal part number and released for use.
3. Production

3.1 Equipment Qualification
All equipment used in production goes through qualification that includes Installation Qualification, Operational Qualification and Performance Qualification. This qualification effort is carried out by a multidisciplinary team and follows the rules described in the corresponding procedure in our Quality System.

Equipment undergoes its applicable calibration schedule the calibration plan described in our Quality System.

3.2 Production Environment
The New Oxford facility houses engineering, product development, warehousing and manufacturing space. Product manufacturing occurs in an ISO 7 (Class 100,000 clean room) per ISO 14644-1 and in accordance with the key principles of cGMPs.

Contact us for further details or precise questions about our quality and operating systems or to schedule an on-site audit.

3.2.1 Viable Organism Control and Monitoring
In addition to line clearance and weekly cleaning of equipment and work surfaces, monthly cleaning of the cleanroom with a schedule of LpH®, Vesphene® and Spor Kienz® occurs per our Cleanroom Management and Cleaning procedures.

Viable organisms are measured quarterly to monitor the effectiveness of the Cleanroom Management and Cleaning procedures and to be compliant to EU GMPs and ISO14698. As of the drafting of this document, viable monitoring is up-to-date:

Air Viables < 100 CFU
Surface Viables < 25 CFU
Wall Viables < 5 CFU

3.2.2 Non-viable Control and Monitoring
Line clearance, weekly cleaning of equipment and work surfaces and monthly cleaning of the cleanroom reduce and control non-viable particles.

Non-viable readings are periodically monitored to ensure 0.5 μm/m² and 5.0 μm/m² particles are within the ISO Class 7 acceptance criteria, per ISO 14644-1. As of the drafting of this document, non-viable monitoring is up-to-date.

3.3 Material Receipt
Components received at New Oxford arrive in two forms; double-bagged and clean or bulk-packed and cleaned. Double-bagged and clean materials (tubing, for example) are received into our Class 7 cleanroom per incoming inspection and testing procedures.

Bulk-packed items are cleaned and transferred into the cleanroom per incoming inspection and testing procedures.

3.4 Traceability & Batch Control
Sartorius-Stedim Biotech has a process and maintains an effective traceability system which can be used in the event of product, component or manufacturing issue to alert impacted customers.

Generally, all finished assemblies are composed of components and subassemblies. Subassemblies are built from components or subassemblies. Components are parts that are purchased or manufactured by Sartorius-Stedim. Each component and subassembly has a unique part number. All components and subassemblies are assigned a unique lot number upon receipt or manufacture/assembly. The lot number is recorded in batch records and maintained in our traceability system.

Batch records provide the operators all the necessary instructions and component and subassembly list to execute the designated procedure. Operators fill in batch records including recording lot number of components and subassemblies. This data is also entered into the traceability system.

The traceability system and batch record system links all manufacturing steps, components and subassemblies to the final assembly, allowing for complete backward and forward traceability of every assembled product.
3.5 In-Process & Product Release Controls

Quality controls are performed at various stages during the manufacturing process. Some of these controls are listed below. Other specific controls dependent on the specific application of the products may be performed but are not listed.

- Product conformity against technical drawing
- Visual inspection (particles or contamination, correctness assembly, etc.)
- Pressure Decay Test (Batch Release)
  Performed when system includes a bottle
- Product packaging controls
- Product labeling controls

After production, every batch of finished products is released by Quality Assurance before it can be shipped. The release will be documented in the batch record and in the traceability system.

The system for product release is constructed in such a way that only batches that have been released by quality can have the corresponding shipping and billing documents.

A Certificate of Release is issued for each batch of finished product that is shipped from Sartorius Stedim Biotech.

3.5.1 Pressure Decay Test

Batches of MYCAP® bottle closure systems that include the container are pressure decay-tested prior to release.

Pressure decay at 2 psi is measured using the TME Worker, Model W-L-015. Pass/Fail criteria is leak rate less than 0.03 psi.

Only devices from batches that pass the pressure decay test are cleared for shipment.

3.5.1.1 Selection of Leak Rate

Deliberate defects were made on devices. Leak rates detected with TME Worker, Model W-L-015 at 2 psi pressure on defective devices were noted and compared with leak rates of devices not made deliberately defective. The threshold of 0.03 psi decay was set.

Related validation testing, including bioburden testing and performance in the field, supports that 0.03 psi decay is a suitable threshold for device integrity.
4. **MYCAP® Bottle Closure Properties**

4.1 **MYCAP® Structure**
MYCAP® is a one-piece closure with integral tubing or other components for rigid containers with threaded closures. Tubing or other components are inserted into preformed holes. Platinum-addition liquid silicone is dispensed into the cap, bonding to and encasing the inserted tubing or component. The assembly is heat-cured to form the MYCAP® closure system.

Only the dispensed liquid silicone should be considered a fluid-contact surface, aside from tubing or components inserted into the cap or components used on the fluid management system with MYCAP® bottle closure. This is true regardless of the tube materials, cap size or closure type.

4.2 **Cap & Closure Sizes**
Nearly any container with a threaded closure can be fitted with a MYCAP® bottle closure. Cap and closure sizes available are listed below (not exhaustive list):

- 20-415 (with adaptor)
- 24-415
- 38-430
- 48 mm (Nalgene Biotainer®)
- 53B
- 83B
- GL25
- GL32
- GL45
- 33 mm (50 mL Falcon® Tube)
- 33 mm (Corning® Erlenmeyer Flasks, Cell-STACK®)
- 38 mm (Corning® Erlenmeyer Flasks)
- 43 mm (Corning® Erlenmeyer Flasks)
- 48 mm (Corning® Erlenmeyer Flasks)
- 70 mm (Corning® Erlenmeyer Flasks)
- 48 mm (Cellon® Pharmatainer)
- 70 mm (Cellon® Pharmatainer)

4.3 **Properties**
The following table describes general properties of MYCAP® bottle closure only and does not consider properties of tubing, fittings, container or other components that may be included in the fluid management system with MYCAP® bottle closure.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap Material (non-fluid contact)</td>
<td>Polycarbonate</td>
</tr>
<tr>
<td>Seal Material</td>
<td>Platinum-cured silicone</td>
</tr>
<tr>
<td>Appearance</td>
<td>Translucent</td>
</tr>
<tr>
<td>Maximum Use Temperature</td>
<td>138 °C</td>
</tr>
<tr>
<td>Minimum Use Temperature</td>
<td>-65 °C</td>
</tr>
<tr>
<td>Brittleness Temperature (of cap material)</td>
<td>-135 °C</td>
</tr>
<tr>
<td>Heat Deflection Temperature (of cap material)</td>
<td>138 °C</td>
</tr>
<tr>
<td>TSE/BSE</td>
<td>Animal Derivative Component Free</td>
</tr>
<tr>
<td>Container Closure by Immersion</td>
<td>Pass</td>
</tr>
<tr>
<td>USP &lt;87&gt;</td>
<td>Pass</td>
</tr>
<tr>
<td>USP &lt;88&gt;</td>
<td>Pass</td>
</tr>
<tr>
<td>USP &lt;788&gt;</td>
<td>Pass</td>
</tr>
<tr>
<td>USP &lt;85&gt;</td>
<td>Pass</td>
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<td>USP &lt;381&gt;</td>
<td>Pass</td>
</tr>
<tr>
<td>21CFR 177.2600</td>
<td>Pass</td>
</tr>
<tr>
<td>Melamine Content</td>
<td>Melamine Free</td>
</tr>
<tr>
<td>BisPhenol-A Content</td>
<td>BisPhenol-A Free</td>
</tr>
<tr>
<td>Pthalate Content</td>
<td>Pthalate Free</td>
</tr>
</tbody>
</table>
4.3.1 Torque Specification

Sartorius considers torque specification provided by a container manufacturer important but not applicable. The dimensions and materials of the Sartorius MYCAP® cap may be different from the cap supplied by the container manufacturer and MYCAP® bottle closure includes the robust platinum-cured silicone seal. Silicone has low stress-to-seal properties and provides a leak-free seal across a wide range of torque.

A study was executed to affirm MYCAP® bottle closures are easily and appropriately installed.

A torque wrench was used to install MYCAP® bottle closures precise torque application for MYCAP closure testing. Once a closure was torqued to a known value, the vessel was pressure decay tested using TME Worker, Model W-L-015. Passing criteria is less than 0.03 psi, in accordance with the MYCAP® bottle closure pressure decay test. Torque values and corresponding pressure decay results are shown below:
4.3.2 Microbial Container Closure

A study to evaluate the barrier properties of MYCAP® bottle closures was performed. Barrier properties are measured by immersing the containers into a solution containing a microbial challenge for a specified time, pressure, and vacuum.

Tested containers with MYCAP® bottle closure were assembled according to Sartorius' operating procedures. All containers passed the pressure decay test release criteria. Containers were gamma irradiated and shipped to Nelson Laboratories for test.

Test articles were aseptically filled with Soybean Casein Digest Broth (SCDB). The test articles were immersed in a microbial challenge of Brevundimonas diminuta, American Type Culture Collection (ATCC) #19146. Vacuum pressure of 5 ± 1 inHg was applied for 10 ± 1 minutes. Pressure is applied to the vessel at 5 ± 0.5 psig for 5 ± 1 minutes.

Containers are removed from the challenge solution inverted so the medium is in contact with the cap and incubated at 30 ± 2 °C for 7 days. Containers are inverted at least once during the incubation.

After incubation, each container was observed for growth. All test articles were negative for Brevundimonas diminuta indicating MYCAP® bottle closures are a microbial barrier.

The test included positive and negative controls.

Positive controls were aseptically filled with SCDB, punctured with a 22 gauge needle and treated in the same manner as test articles. Positive Controls were positive for growth of Brevundimonas diminuta.

Negative controls were aseptically filled with SCDB, but not exposed to the challenge solution and instead treated incubated at 30 ± 2 °C for 7 days. Negative Controls were negative for growth of Brevundimonas diminuta.

An acceptable pressure decay rate was observed with minimal torque applied, 2 in.-lbs., to material failure at 64 and 100 in.-lbs.

Allowing for a torque factor of safety, Sartorius recommends a minimum/maximum closure torque of 6-40 in.-lbs.

Torque is not measured during MYCAP® bottle closure system assembly. Tools are not used in manufacturing to install MYCAP® bottle closure. Instead, Sartorius relies on passing pressure decay test results to confirm correct assembly and installation.

A second study was performed to measure torque applied during installation of MYCAP® bottle closure to containers by Sartorius manufacturing personnel.

The torque applied by a sampling of operators was measured using torque wrench. The data table is shown on the preceding graph.

Torque values confirm operators are able to consistently apply closures within the recommended range of 6-40 in.-lbs.
4.4 Biocompatibility

4.4.1 USP <87>
The purpose of this test is to determine if any chemicals that leach or may be extracted from the MYCAP® bottle closure are cytotoxic. The study is conducted in accordance with United States Pharmacopoeia (USP) Section 87.

A 5.9 gram sample of article was extracted in 29.5 mL of 1X minimum essential media (MEM) with 5% bovine serum for 24-25 hours at 37 ± 1 °C, with agitation.

Multiple well cell culture plates were seeded with L-929 mouse cells and incubated until 80% confluent. Extract solution was added to the wells. Observations for reactivity on were made after incubation for 72 hours at 37 ± 1 °C with 5 ± 1% CO₂.

The requirements of USP Cytotoxicity Test have been met.

4.4.2 USP <88>

Intracutaneous Reactivity
The purpose of this test is to determine if any chemicals that leach or may be extracted from the MYCAP® bottle closure cause local irritation in the dermal tissue of rabbits. The study is conducted in accordance with United States Pharmacopoeia (USP) Section 88.

A 4 gram test article was placed into 20 mL of extraction solution. Extraction of test articles was performed for 72 ± 2 hours at 50 ± 2 °C. Extract solutions are: Normal Saline, Cottonseed Oil, 5% Ethanol in Saline, Polyethylene Glycol.

Observations of reactivity in the rabbits were made at 24, 48 and 72 hours after intracutaneous injection of test extracts.

The requirements of USP Intracutaneous Reactivity Test have been met.

Acute Systemic Injection Test
The purpose of this test is to screen extracts from MYCAP® bottle closure for potential toxic effects. The study is conducted in accordance with United States Pharmacopoeia (USP) Section 88.

A 4 gram test article was placed into 20mL of extraction solution. Extraction of test articles was performed for 72 ± 2 hours at 50 ± 2 °C. Extract solutions are: Normal Saline, Cottonseed Oil, 5% Ethanol in Saline, Polyethylene Glycol.

Observations biological reaction in rabbits were made at 0, 24, 48 and 72 hours after intravenous and intraperitoneal administration of test extracts.

The requirements of USP Acute Systemic Injection Test have been met.

Intramuscular Implant Test
The purpose of this test is to study local effects of MYCAP® bottle closure when in direct contact with living skeletal muscle tissue of rabbits. The study is conducted in accordance with United States Pharmacopoeia (USP) Section 88.

Test articles were cut into 3 mm × 10 mm pieces. Test articles were surgically implanted into the paravertebral. After 7 days, tissue containing the implant was observed for hemorrhage, film, encapsulation, necrosis, discoloration or infections and recorded.

The requirements of USP Intramuscular Implant Test have been met.
4.5 Particulates

4.5.1 USP <788>
The purpose of this test is to detect and quantify particulate matter in MYCAP® bottle closure systems. Particulate matter is defined as extraneous, mobile, undissolved substances, other than gas bubbles unintentionally present in the device.

The USP <788> test is a destructive test and is done as part of product validation. The study is conducted in accordance with United States Pharmacopoeia (USP) Section 788.

Validation testing referred to in this guide was performed on assemblies constructed in the New Oxford site clean room. The tested assembly was selected because it represents and worse-case of facility handling, transport and operator manipulation. The assembly included components from a variety of suppliers and types including; different bottle containers, hose barbed connectors, aseptic connecting devices, vent filters and different tubing sizes with and without QUICKSEAL® aseptic disconnect.

The fluid pathway, including each container of the test article, is filled with low particulate water. Fluid held in each container was pooled for analysis. Particulate from three aliquots from the pooled samples were measured and enumerated using the HIAC Royco Liquid Particle Counting System. The values obtained were averaged.

Acceptance criteria is ≤ 25 particles per mL which are ≥ 10 μm and ≤ 3 particles per mL which are ≥ 25 μm.

The requirement for USP <788> has been met. Particulate testing is done routinely on products manufactured at Sartorius’ New Oxford facility, including MYCAP® bottle closure systems to maintain data on particulate manifested on products.

4.6 Endotoxins

4.6.1 USP <85>
The purpose of this test is to detect and quantify bacterial endotoxins in MYCAP® bottle closure systems. The Limulus Amebocyte Lysate (LAL) test is an in-vitro, destructive test and is done as part of product validation. The study is conducted in accordance with United States Pharmacopoeia (USP) Section 85 and ANSI/AAMI ST72.

Endotoxins are lipopolysaccharides from the cell wall of microorganisms. In some cases, endotoxins from gram-negative bacteria may be pyrogenic (fever inducing). Clean room management procedures described in the New Oxford site quality system include strategies to reduce, control and monitor viable organisms.

Validation testing referred to in this guide was performed on assemblies constructed in the New Oxford site clean room. The tested assembly was selected because it represents and worse-case of facility handling, transport and operator manipulation. The assembly included components from a variety of suppliers and types including; different bottle containers, hose barbed connectors, aseptic connecting devices, vent filters and different tubing sizes with and without QUICKSEAL® aseptic disconnect.

LAL testing is done routinely on products manufactured at Sartorius’ New Oxford facility, including MYCAP® bottle closure systems to maintain data on endotoxin manifested on products.

The fluid pathway of the test article is flushed with LAL Reagent Water heated to 37 ± 1 °C. Fluid was kept in contact with the fluid pathway for >1 hour at 18–25 °C. The extract solution was then analyzed for endotoxin units (EU). Detected endotoxin was below detection limits of 0.0050 EU/mL.

Sartorius’ acceptance criteria is less than 0.25 EU/mL. The requirement for USP <85> has been met.

4.7 Physicochemical and Extractables

4.7.1 USP <381>
This test measures the physicochemical properties of impurities extracted from elastomeric closures. The extract solution is analyzed for acidity/alkalinity, reducing substances, heavy metals and optical absorbance.

A sample of MYCAP® silicone closure of was extracted in purified water in autoclave at 121°C. The extracted solution is tested per USP <381>.

The acceptance criteria for USP <381> has been met.

4.7.2 21 CFR 177.2600
This test measures the extractable content from a sample of the silicone closure of MYCAP® extracted in distilled water for the first 7 hours and next 2 hours of extraction time. Extractable limits are < 20 mg/sq-in for the first 7 hours and < 1 mg/sqin for the next 2 hours.

The acceptance criteria for 21CFR 177.2600 has been met.
5. Leachables & Extractables

Extractables are compounds that have the potential to leach from the materials of the fluid handling system into the solution. The conditions and solvents used in a study of extractables are more extreme than normal process conditions. Aside from the intrinsic properties of the solvent, exposure time and temperature are manipulated in order to extract the most compounds.

Leachables are the compounds that will actually leach from the materials of the fluid handling system into the process fluid. It is important to understand leachables effect on the safety, identity, strength, purity or quality of the drug product. Sartorius is not able to provide applicable leachable studies because the conditions and solutions of our customers’ processes are unknown.

A risk assessment is advised to determine the extent of leachable and extractable studies are required. Considerations should include; the production stage, exposure time and temperature, exposure surface area and the process fluid pH and polarity.

Testing for low risk profiles may be adequately met by USP <87> and USP <88>, which are leachable and extractable studies. These studies do not identify or quantify compounds leaching the materials. Instead, these studies measure biologic and cytotoxic effects of leachables from the materials under the defined extraction parameters. Per guidelines, extractions are performed using:

<table>
<thead>
<tr>
<th>Extract Solvent</th>
<th>Extraction Time [h]</th>
<th>Extraction Temperature [°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Saline</td>
<td>72</td>
<td>50</td>
</tr>
<tr>
<td>Cottonseed Oil</td>
<td>72</td>
<td>50</td>
</tr>
<tr>
<td>5% Ethanol in Saline</td>
<td>72</td>
<td>50</td>
</tr>
<tr>
<td>Polyethylene Glycol</td>
<td>72</td>
<td>50</td>
</tr>
<tr>
<td>1 x minimum essential media (MEM) with 5% bovine serum</td>
<td>24</td>
<td>37</td>
</tr>
</tbody>
</table>

Extracts for all fluid-contact materials of fluid management systems with MYCAP® bottle closures are found to have no cytotoxic or adverse biological effect.

Further leachables and extractables data may be necessary for components with high risk profiles. Confidential information about additional leachable and extractable studies may be available from our component manufacturers.

Sartorius’ Confidence® Services is available to perform customized and confidential extractable and leachable studies on polymer-based process components.
6. Gamma Sterilization Validation

6.1 Purpose
A sterilization validation study has been performed to validate sterility assurance level (SAL) \(10^{-6}\) for the fluid pathway fluid management systems with MYCAP® bottle closures after gamma irradiation to 25 kGy. The method follows the current ISO 11137 guideline.

6.2 Method
Compliance to ISO 11137 allows Sartorius Stedim Biotech to claim (SAL) \(10^{-6}\) for all fluid management systems with MYCAP® bottle closures included in the product family.

6.2.1 Bioburden Evaluation
As described by the ISO 11137 document, a Simulated Product representing the Product Family is defined to carry out the Gamma Sterilization Validation tests.

Product bioburden is first evaluated for a Simulated Product representing the Product Family. The bioburden evaluation is performed on 10 units selected from 3 different lots.

6.2.2 Verification Dose Experiments
Once the bioburden is established (i.e. quantified, identified and assessed for its resistance) the verification dose to be used for the validation is selected. In accordance with the ISO 11137 document, the verification dose is calculated to produce a SAL \(10^{-1}\). The verification dose experiment is conducted on 10 units. Sterility test must pass the criteria of \(\leq 1\) positive.

After a successful verification dose experiment, SAL \(10^{-6}\) is verified.

6.2.3 Maintenance of Sterility
Environmental monitoring is routinely performed to address potential changes to our manufacturing environment, as described in Section 3.2 Production Environment.

Dosimeters are placed in all sterilization batches to verify that the dose received bags is within specified limits (i.e. greater than 27.5). Dosimeters are placed at minimum and maximum dose locations based upon the specific loading pattern, including density, of each irradiation batch.

The second critical aspect of maintenance of sterility is the routine characterization of product bioburden. Product bioburden is quantified dose audits. Dose audits are performed in accordance with ISO11137. Dose audits verify the initial validation remains applicable and SAL \(10^{-6}\) is valid.

6.3 Product Family Definition
ISO 11137-2:2006 4.3.1.2, prescribes three ways that a product family can be represented for validation; Master Product, Equivalent Product and Simulated Representative Product. The high degree of variability of MYCAP assemblies makes Master and Equivalent Product not feasible as testing representatives. A Simulated Representative which "constitutes an equivalent or greater challenge to the sterilization process than that provided by members of the product family" is the best choice for the MYCAP product family.
6.4 Simulated Representative
Components used in MYCAP assemblies are broken into distinct series; Bottles/Containers, Tubing, Aseptic Connectors, Check Valves and Connectors. Some components do not fit into a series. These components are included by default in the Simulated Representative. The component in each series with the greatest bioburden challenge is selected for use in the Simulated Representative. This approach creates a “worst-case” scenario from a bioburden standpoint to represent the MYCAP product family.

6.4.1 Series Bioburden Testing
Aerobic bacteria and fungal bioburden was done at Nelson Labs. These are the same tests as ISO11137-2 bioburden testing and are commonly tested parameters. Recovery efficiency was performed on each component to validate results and confirm that the extraction method used in the study is effective and accurate. The top three isolates were gram stained for further identification and quantification of bioburden.

Bioburden Testing is performed annually and on all new components added to the MYCAP Product Family. New components are covered under this product family definition if their bioburden evaluation is below the worst-case member of the respective series or the Simulated Product Design is changed and revalidated.

6.4.2 Simulated Product Design
The simulated representative is a one-bottle assembly. A single bottle adequately represents more complex assemblies because, under the kit-concept (5.1.1 of ISO 11137-2), more bottles are repetitions of the same components and “variables such as density and product configuration within its packaging system are not considered in the establishment of these product families because they are not factors that influence bioburden” (4.1 of ISO 11137-2).

6.5 Results
The sterility validation for the fluid management systems with MYCAP® bottle closures Product Family has met the requirements set forth in the applicable regulations.
7. Shelf-Life

Fluid management systems with MYCAP® bottle closures are validated for a 2 year shelf life post Gamma sterilization, using accelerated ageing conditions. If a new component with a shorter shelf life is used in a fluid management systems with MYCAP® bottle closure, the whole fluid management system will receive the shortest shelf life. Design rules control fluid management systems with MYCAP® bottle closures designs.

The critical performance properties and bioburden of the fluid management systems with MYCAP® bottle closures is assessed and compared with original properties after a 2 year storage in accelerated conditions.

7.1 Bioburden Maintenance

Samples of representative product were gamma irradiated and aged for 2 years. At the conclusion of the aging a bioburden evaluation was performed for the fluid pathway.

The fluid pathway was found to be free from bioburden, affirming sterility was maintained after aging.

7.2 Verification of Critical Performance Properties

7.2.1 Container Closure

Samples of representative product were gamma irradiated and aged for 2 years. At the conclusion of the aging a container closure study by immersion was performed.

The samples passed the container closure test affirming closure integrity is maintained after aging.

7.2.2 Pressure Decay Test

Samples of representative product were gamma irradiated and aged for 2 years. At the conclusion of the aging a pressure decay test was performed.

The samples passed the release criteria established for newly constructed systems, thus affirming the closure integrity after aging.