

Flexsafe® Pro Mixer Bag

Validation Guide

SARTORIUS

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1. Introduction

Single-use mixing systems are increasingly used in the manufacture of biopharmaceutical products as they allow biopharmaceutical companies to realize the benefits of single-use technology throughout the process. Single-use mixing systems have been widely adopted for buffer and media preparations and are also finding applications in more critical and higher value unit operations in the downstream purification process steps.

Flexsafe® Pro Mixer is an unique, single-use mixer that can accommodate a wide range of mixing steps in both upstream and downstream processes.

Flexsafe® Pro Mixer technology combines speed and efficiency to deliver high performance mixing during powder dissolution and a levitating impeller to preserve the drug during low shear blending applications.

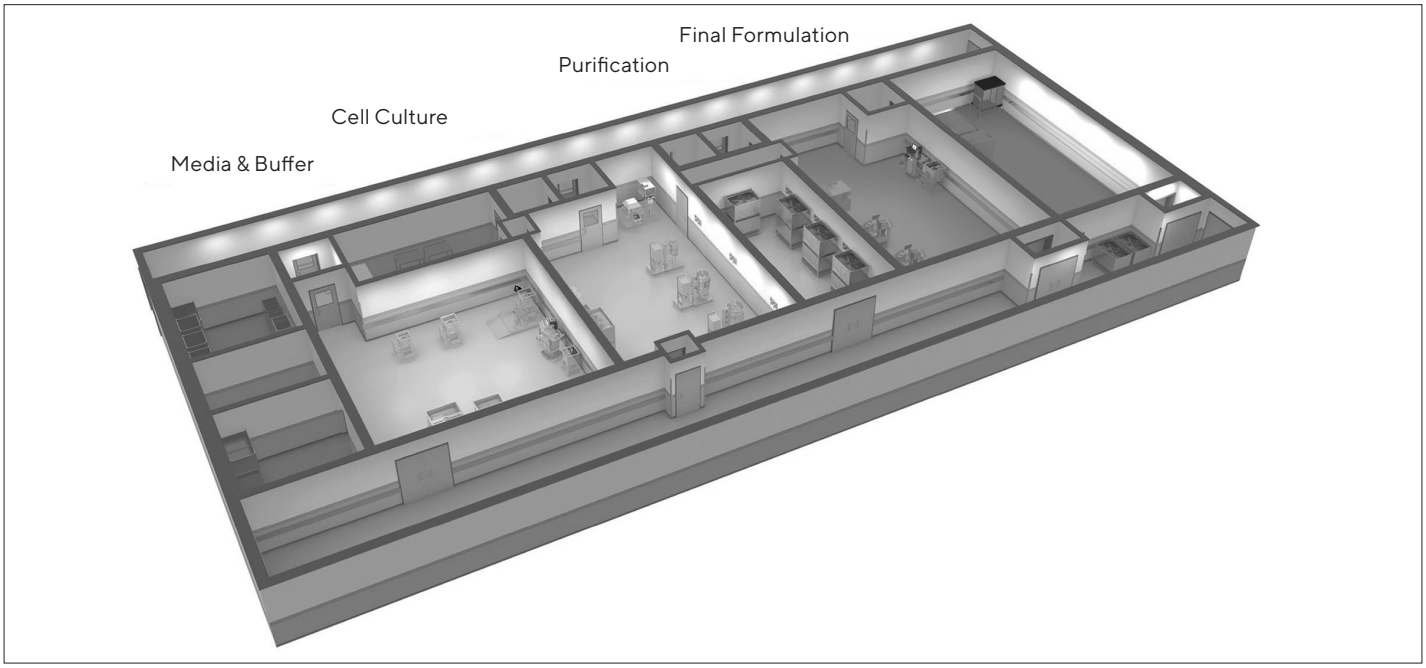
1.1 Component Quality, Change Control and Business Continuity

Fluid-contact components used for standard bags Flexsafe® Pro Mixer are secured by long term contracts and quality agreements to offer the best assurance of supply. Fluid-contact components are also available off-the-shelf to offer the best delivery ability.

Standard Flexsafe® Pro Mixer product's components are evaluated for conformity against the EP and USP standards after reviewing technical documentation and certificates of quality available from our suppliers. Additional internal qualification tests are performed to establish extractable profiles, post gamma sterilization shelf life and consistent functional properties.

Our core expertise in plastics and polymers enables the selection of the cleanest and most inert materials to minimize chemical interactions with biopharmaceutical fluids, and leachable substances.

Component designs are selected to maximize tubing engagement tensile strength and tightness. Test samples are visually inspected during qualification phase and tested for leak, burst pressure, traction and|or compression depending on the test sample.



1.2 Manufacturing Ressources

Sartorius Stedim Biotech's manufacturing resources for Fluid Management Systems are established worldwide in five state-of-the-art facilities that operate under consistent manufacturing process performances.

Sartorius Stedim FMT S.A.S. Aubagne, France:
Date of creation 1979, latest expansion in 2016.
- Total area 37,800 m^2 (406,875 sq.ft) with 5,361 m^2 (57,705 sq.ft) of class ISO 7 cleanrooms (Class 10,000 or Grade C).
- Manufacturing capabilities:
  Bag Chamber manufacturing, sealing, manual assembly, packaging and labelling.

Sartorius Stedim Filters Inc. Yauco, Puerto Rico:
- Total area 9,100 m^2 (98,000 sq.ft) of class ISO 7 cleanrooms (Grade C).
- Manufacturing capabilities:
  Bag Chamber manufacturing, sealing, manual assembly, final packaging and labelling.

Sartorius Stedim SUS SARL M'Hamdia, Tunisia:
Date of creation 2001.
- Total area 3,800 m^2 (40,903 sq.ft) with 1,120 m^2 (12,056 sq.ft) of class ISO 7 cleanrooms (Grade C).
- Manufacturing capabilities:
  Bag Chamber manufacturing, sealing, manual assembly, packaging and labelling.

Sartorius Stedim Plastics GmbH, Gottingen, Germany:
Date of creation 2007.
- Total area 2,750 m^2 (29,600 sq.ft) with 900 m^2 (9,687 sq.ft) of class ISO 7 cleanrooms (Grade C).
- Manufacturing capabilities:
  sealing, manual assembly, final packaging and labelling.

Sartorius Stedim Biotech (Beijing) Co., Limited Beijing, China:
Date of creation 2018.
- Total area 28,937 m^2 (311,475 sq.ft) with 800 m^2 (8,611 sq.ft) of class ISO 7 cleanrooms (Grade C).
- Manufacturing capabilities:
  sealing, manual assembly, final packaging and labelling.

1.3 Quality Management System

Our quality system is in compliance with ISO 9001 standards for all manufacturing facilities. Sartorius Stedim Biotech is a registered device manufacturer with the FDA for the production of single-use bags and Fluid Management Systems (FMS).

Sartorius Stedim FMT SAS, Aubagne, France
FDA registration N° 8044085
FDA owner|operator N° 9005426

ISO 9001 is recognized as the root Quality Management System throughout the Sartorius Stedim Biotech corporation. As such, the Quality System of the manufacturing site located in Aubagne, France is certified by an accredited notified body. Additionally, other elements are built into the system to address biopharmaceutical customer's requirements such as relevant Good Manufacturing Practices. Gamma sterilization is validated and conducted according to ISO 11137.

Fluid Management Systems made of Flexsafe® Pro Mixer are qualified according to most stringent performance and safety industry standards as described in this Validation Guide. All critical manufacturing operations for Flexsafe® Pro Mixer bags are conducted in ISO 7 cleanrooms environment. Continuous personnel training and qualification ensure employee awareness to the required standards. Employee aptitude is measured through strict initial selection and continuous competence testing.

The quality and safety of our mixing systems are ensured by our supplier management policy, quality controls of in-coming raw materials, in process monitoring and finished product batch release testing. Our change control management and centralized documentation system ensure product and process consistency while enabling continuous improvement.

1.4 Gamma Sterilization

Flexsafe® Pro Mixer bags manufactured in Aubagne, France are packaged in cardboard boxes and shipped on pallets to the sterilization center for gamma irradiation. In order to assure a security of supply, three sterilizers are qualified for the manufacturing site in France. All Flexsafe® Pro Mixer bags are irradiated at a minimum dose of 25 kGys.

The efficiency of the minimum dose of 25 kGys has been validated according to the ISO 11137 standards in order to obtain a 10^{-6} Sterility Assurance Level (SAL).

The products are shipped to the customers after irradiation with an irradiation certificate which mentions the minimum doses and the certificate of release.

1.5 Testing Conducted for the Validation and Lot Release of Flexsafe® Pro Mixer Bags

Qualification Tests

- Biocompatibility Testing
  - USP <87>: Biological reactivity tests, In Vitro
  - USP <88>: Biological reactivity tests, In Vivo

- Mechanical Properties (on film samples)
  - ISO 527-3|ASTM D882:
    - Ultimate tensile strength
    - Elongation at break,
  - ASTM F392 C: Flex durability
  - ASTM D3787: Resistance to puncture

- Gas Transmission Property (on film samples)
  - ASTM F3985: Barrier to oxygen
  - ISO 15106-3: Barrier to water Vapor
  - ASTM F2476: Barrier to Carbon Dioxide

- E.P. 3.1.5.: PE with additives for containers (film samples)

- Chemical resistance of Flexsafe® 3D bags based on a model solvent approach
  - ASTM D543-06 "Method for resistance of Plastic to chemical reagents"

- Seal strength integrity:
  - Film|Film bag seal
  - Film|Port bag seal
  - Bag

- Component|Assemblies integrity
  - Connexion tightness
  - Fitting strength
  - Dust cap pulling strength
  - Clamping force
  - Cracking for PC components only

- USP <661> Containers, physico-chemical Tests

Monitoring Tests

- USP <85> Bacterial Endotoxins test and E.P. 2.6.14 Bacterial endotoxins
- USP <788> Particulate Matter in Injections and E.P. 2.9.19 Particulate contamination – Subvisible particles
- ISO 11737 Sterilization of medical devices – Microbiological methods: Bioburden
- ISO 11137 Sterilization by irradiation of Medical Devices: Sterilization of Medical Devices
- ISO 14644 Cleanrooms and associated controlled environment: Cleanroom environmental controls
- Particles prevention program: Visible Particles monitoring

Lot Release Tests

- 100 % visual testing of bag and seal
- Technical drawing compliance
- Packaging and labelling inspection
- Gamma sterilization

2. Production and Quality

2.1 Human Resources

Sartorius Stedim Biotech recognize 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 Infrastructure

The buildings, equipment and work environment at Sartorius Stedim Biotech have been designed to maximize employee comfort and safety while responding to current GMP requirements for the manufacture of single-use Fluid Management Systems destined to the pharmaceutical industry and medical applications. All infrastructure (equipment, utilities, etc.) that has an impact on the product quality is inventoried and undergoes an appropriate qualification.

2.3 Purchasing

2.3.1 Supplier and Raw Material Qualification

All our suppliers are carefully selected according to internal standards and applicable regulations. Each raw material and|or component used in Flexsafe® Pro Mixer put through prior qualification. 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
- TSE|BSE statement
- EP conformity (if applicable)
- Change notification statement
- REACH

Beyond these requirements, Sartorius Stedim Biotech perform a qualification of the proposed component and|or raw material internally. For raw materials, the internal qualification will include machinability and physical performance of the Flexsafe® Pro Mixer 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 and|or bags that will be attached.

2.3.2 Supplier Evaluation

Suppliers are periodically evaluated on the basis of the following performance metrics:

- Criticality of the supplier
- Delivery conformity
- Conformity of products on reception
- Compliance with delivery deadlines

2.3.3 Verification of Purchased Product (Incoming QC)

Raw materials, components and sub-contracted products are inspected upon arrival at Sartorius Stedim Biotech against approved control specifications. Typical testing requirements applied and if applicable at incoming quality inspection are listed below:

- Supplier documentation controls (Certificates)
- Packaging identification and integrity
- Material identification by Infra Red spectroscopy (FTIR) for fluid contact components
- Visual inspection
- Dimensional check
- Functional test

Only approved materials will be allowed to be used in production of Flexsafe® Pro Mixer manufactured by Sartorius Stedim Biotech.

2.4 Production

2.4.1 Production Planning

Customer orders are registered in the Computer Aided Production (CAP) system for planning and scheduling. Planning draws up a production plan which will be used to establish the workload per workshop. Scheduling then verifies and implements the planning per workshop and prepares the batch file. This batch file is then transferred to the corresponding workshop manager. The workshop managers are in charge of following the production schedule and recording the production carried out before making it available to packaging.

2.4.2 Production Documents

When a work order is put into production, the operators have all the necessary data available in the batch file or associated documentation. Gradually as operations progress, the operators fill in the blank forms provided for in the batch file. This is the basis for the complete traceability of the production process.

2.4.3 Qualification of Equipment

All equipment used in production goes through a detailed qualification plan 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 and Master Validation Plan.

2.4.4 Production Environment

Production of single-use Fluid Management Systems is carried out in controlled environment ISO 7 cleanrooms, that are regularly cleaned and monitored. Controlled environment contributes to the control of microbiological and particulate contamination of Flexsafe® Fluid Management Systems.

2.4.5 Identification

Identification of Raw Materials:
The raw materials are identified by the designation and the batch number attributed to the delivery date or the supplier.

Identification of Semi-finished and Finished Products:
Single-use products are identified by their part number and by their batch number that is visible on all Flexsafe® Pro Mixer. The batch numbers are issued when the manufacturing order is launched.

2.4.6 Traceability

Sartorius Stedim Biotech has an upstream traceability system for incoming raw materials and a downstream traceability system for customer production batch.

Upstream Traceability:
This is based on the establishing of a batch file for each product manufactured according to the applicable procedure.

The batch file includes more particularly the following information:

- Results of in-process controls on the batch (or unit, for equipment)
- The quantities of raw materials and|or components used
- The batch numbers of the raw materials and components used
- The operator identification
- The machine parameters (where applicable)
- The tooling used (where applicable)
- The dates of manufacture.

Complete traceability of the alternative sources is always documented. Homogeneity within a batch of finished product is guaranteed.

With this system, it is possible to work back through the history of a product and to seek the causes of any failure.

Downstream Traceability:
Shipping documents systematically indicate the shipped batch number.

This system is a way of locating all the customers who have received a given manufacturing batch in the eventuality of a product recall.

2.5 In Process Controls

Quality controls are performed at various stages during the manufacturing process. Some of these controls are listed below. Other specific controls can be performed that are not listed and depend on the specific application of the products.

- Product conformity against technical drawing
- Visual inspection (seals, particles or contamination, film, etc.)
- Seal strength testing with a dynamometer
- Dimensional check
- Product packaging controls
- Product labeling controls

2.6 Control of Finished Products

Representative samples of finished products are tested for the following:

Endotoxins:
Samples are tested according to current USP <85> Bacterial Endotoxins test by LAL and EP 2.6.14. The acceptance criteria used for release is set at < 0.125 EU/mL.

Particulate:
Samples are tested according to current USP <788> (Light Obscuration Method) and EP 2.9.19. The acceptance criteria used for release follows the requirements for solutions for parenteral infusion or solutions for injection supplied in container with a nominal content of more than 100 mL.

	Particle Size ≥ 10 µm [particles/mL]	≥ 25 [particles/mL]
For solutions for parenteral infusion or solutions for injection supplied in container with a nominal content of more than 100 mL, the numbers of particles must not exceed these limits	≤ 25	≤ 3

Bioburden:
Samples are tested according to the filtration method described in the ISO 11737. The acceptance limits have been determined during the sterilization validation and validation of the testing method.

Alert limits are set for the above monitoring tests in order to track the on-going performance of the whole manufacturing process.

Particles Prevention Program
Representative products are analyzed for particles with sizes ≥ 100 µm according to internally developed and validated method. Results are monitored.

2.7 Batch Release

After production, every batch of finished products will be released by Quality Assurance before it can be shipped to the customer. The release will be documented in the batch record and in the computer 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. Flexsafe® Pro Mixer Bag

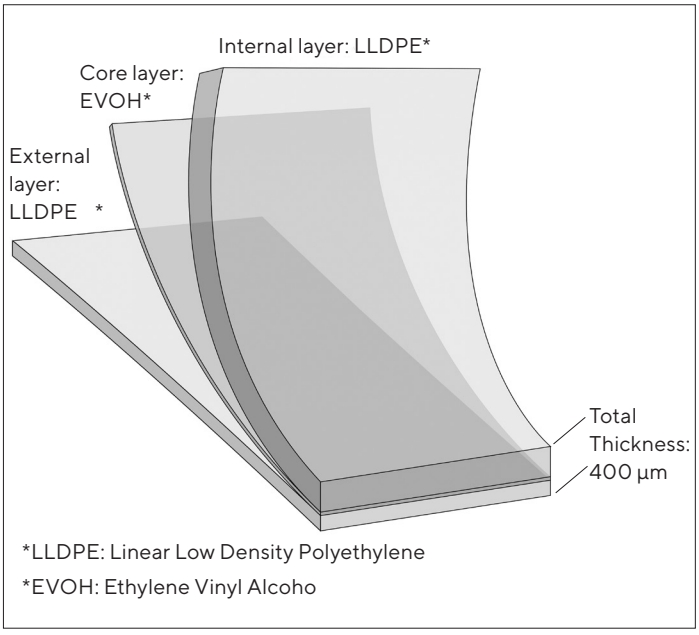
3.1 Flexsafe® Film Description

Flexsafe® film is based on a multiple layers of different materials which provide a strong, robust and flexible 400 µm structure. This structure offers low gas permeability, high chemical resistance, superior cell growth compatibility and low extractable profile.

The film is mainly composed of Linear Low Density Polyethylene which combines excellent sealing properties, chemical resistance and flexibility. The additive package has been optimized to limit the potential source of extractable compounds while maintaining the film properties after having been submitted to gamma irradiation and over the bag shelf life.

The barrier properties are achieved by the combination of an Ethylene Vinyl Alcohol layer for barrier to oxygen and Polyethylene based inner and outside layers for humidity protection.

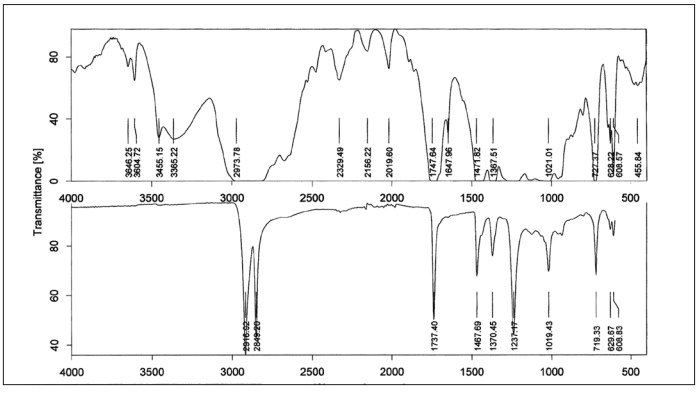
Structure of the Flexsafe® Film – Patent Pending



*LLDPE: Linear Low Density Polyethylene

*EVOH: Ethylene Vinyl Alcoho

Functional layers are linked together with tie layer

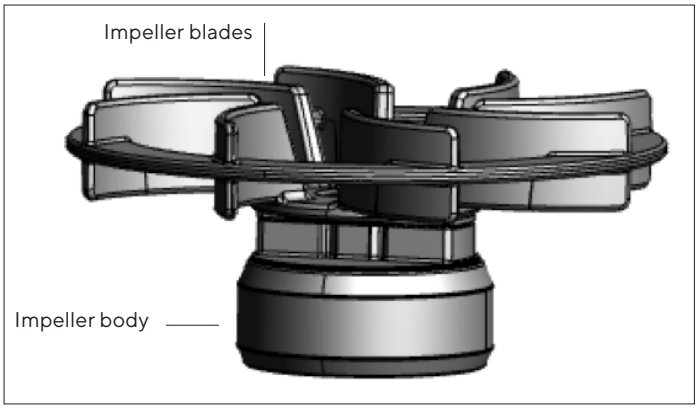


3.2 Pro Mixer Impeller

Pro Mixer Impeller is made of:

- Impeller blades:
  USP Class VI High Density Polyethylene (HDPE)
- Impeller body:
  Low Density Polyethylene (LDPE) embedded circular magnet
- Impeller cup:
  USP Class VI High Density Polyethylene (HDPE)

The impeller outer diameter (Impeller Blade Tip OD) is 160 mm (6.29")





Impeller cup

3.3 Bag Ports

Injection molded bag ports are manufactured from high purity USP Class VI Polyethylene (PE).

Port Description	
Bag port	hose barb for ¼", ⅜", ½", ¾" and 1" ID tubing

3.4 Top Port

8 inch injection molded top port are manufactured from high purity USP Class VI Polyethylene (HDPE).

4 inch injection molded top port is manufactured from USP Class VI High Density Polyethylene (HDPE).

Top Port Description

Diameter	8 inches	4 inches
Open top port	8 inch triclamp	4 inch triclamp
Closed top port	8 inch fully closed cap	NA

3.5 pH Sensor

The single-use pH sensor is based on an electrochemical pH glass electrode with an integrated temperature sensor (Pt1000). The electrochemical pH glass electrode is assembled with an insertion device composed of high purity USP Class VI High Density Polyethylene (HDPE) and silicone components. The electrode tip is made of alkali lead free glass. The glass pH electrode is stored in a pH = 6.5 ± 0.3, sterile, gamma stable, buffered solution.



pH sensor

Composition of the Buffer Storage Solution

Chemical	CAS-No	Concentration [g/L]
Potassium chloride (KCl)	7447-40-7	224
Potassium dihydrogen phosphate (KH_2PO_4)	7778-77-0	8
Sodium hydrogen phosphate Na_2HPO_4	7558-79-4	15

pH Sensor Specifications

Measurement range	pH 2–11, 4 – 50 °C
System accuracy	± 0.08 pH over entire measurement range
Drift	< 0.03 pH per 24 h
Working temperature	4 – 50 °C
Maximum application time	2 days
Calibration	2-point calibration within port possible: once before process, once during process

3.6 Conductivity

The single-use conductivity sensor is based on a thick film system which is sealed into a ceramic module. The single-use conductivity sensor is based on 4 electrodes system with an integrated temperature sensor (Pt1000). The housing of the sensor is composed of high purity USP Class VI High Density Polyethylene (HDPE). The sensor is pre-calibrated.



Conductivity sensor

Conductivity Specifications

Measurement Range	0.1 mS/cm up to 200 mS/cm
Accuracy	2% < 100 mS/cm 5% 100 mS/cm – 200 mS/cm

3.7 Thermowell

The single-use thermowell is manufactured with high purity USP Class VI Low Density Polyethylene (LDPE) and silicone components.



Thermowell

Thermowell Dimensions

Internal Diameter	**3.2 mm**
Length	135 mm

3.8 Drain Valve

The drain valve is manufactured from USP Class VI High Density Polyethylene (HDPE).

3.9 Bag Volumes and Surface Areas

Bag Vol ume [L]	Surface Area [m²]
50	0.897
100	1.312
200	2.079
400	3.364
650	4.621
1,000	5.793
1,500	8.226
2,000	10.339
2,500	12.176
3,000	14.204

3.10 Point-of-Use Leak Test

A Point-of-Use Leak Test using pressure decay* is available for end-users to test Flexsafe® Mixing bags in a fast and reliable way with the Sartocheck® 4 plus Bag tester.

* Pressure decay test according to ASTM F2095-07:
"Standard Leak test for Pressure Decay Leak Test for Nonporous Flexible Packages with and without Restraining Plates"

4. Film Properties

4.1 Flexsafe® Film Properties

The film is only one component of the complete single use solution, contributing to the overall performances of the system for a specific application. The testing of the system performances according to the application cannot be substituted by film characterization data generated at a laboratory scale. The application chapter of this validation guide provides relevant data for the end user to assess the suitability of the complete single use system to the intended application.

The biocompatibility and regulatory compliances which are linked to the film, but not only, are also addressed in dedicated chapter. Extractable data are reported in a separate guide.

However, the Flexsafe® film is characterized by some intrinsic mechanical and barrier properties, measured according to standard commonly used in the packaging industry. These properties and tests have been selected to characterize as much as possible the behavior of final bag assemblies used in biotechnology manufacturing. They can be summarized by the following features:

- Resistance to flexion and fatigue
- Resistance to uniaxial traction
- Resistance to puncture
- Barrier to oxygen and water vapor.

In addition, we applied an in-house developed water burst test to confirm the robustness of the bag seals.

Sampling
For each property, three different batches of Flexsafe® film samples have been gamma irradiated at 50 kGy. A first set of data was collected within 6 months after irradiation. Additional tested samples were taken from Flexsafe® film aged under accelerated conditions up to an equivalent of 3 years natural ageing after gamma, according to ASTM F1980 and 3 years natural ageing.

4.1.1 Resistance to Flexion and Fatigue

Purpose and Test Method
Resistance to flexion and fatigue is determined by measuring the number of pinholes formed in the Flexsafe® film after being subjected to the Gelbo Flex Test (flex durability). This test combines repeated twisting and horizontal pushing motion. This test was selected to characterize the mode of stress representative of fluid movements inside the container in filled bag during shipping application, rocking or orbital shaking. These applications are considered as the most critical solicitation for products.

Equipment

Gelbo Flex Tester

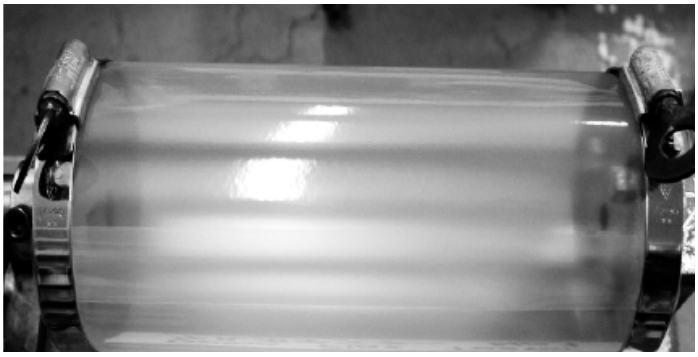


Fig. 5: Flex durability test|1



Fig. 6: Flex durability test|2

Results

Feature	Test	Standard	No. of Samples	Temperature	Result
Resistance to flexion and fatigue	Flex durability	ASTM F392 C	90	22 °C ± 3	< 5 pinholes

4.1.2 Resistance to Uniaxial Traction

Purpose and Test Method
The resistance to uniaxial traction is determined by measuring the Tensile Strength and the Elongation at break. Since this test is mono directional by nature, it cannot be directly correlated to bag robustness during use. However, it is widely and commonly used because it is easy to perform in routine testing.

The tensile strength at break is the maximum stress the specimen can withstand. It is calculated by dividing the maximum load by the original cross sectional area of the specimen.

The elongation at break is recorded when specimen breaks. It is commonly expressed as a percentage of the original length. Materials with high elongation at break withstand a high deformation before rupture, which means high flexibility.

Equipment
Dynamometer set up with an initial gauge length of 100 mm and a separation grip speed of 500 mm/min until film rupture.

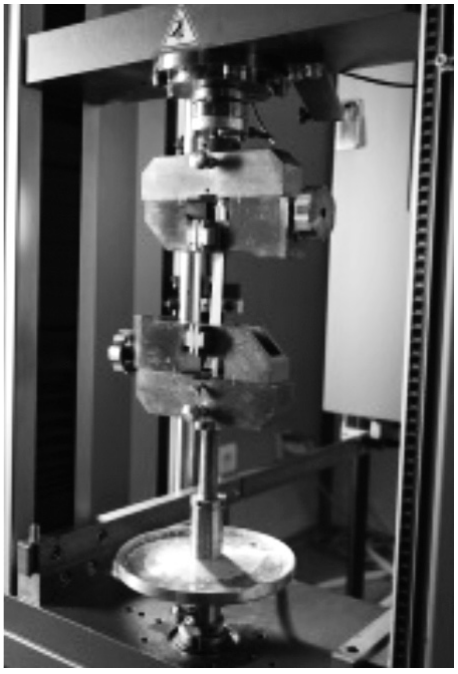


Fig. 7: Specimen mounted in jaws

Test Results

Feature	Test	Standard	No. of Samples	Temperature	Value
Ultimate Tensile Strength (UTS)	Tensile test	ASTM D882 ISO 527	180	22 °C ± 3	> 10 MPa
Elongation at break			180	22 °C ± 3	> 200%

4.1.3 Resistance to Puncture

Purpose and Test Method
Puncture testing predicts the resistance of the Flexsafe® film, especially the resistance to damage by penetration of another object. While the tensile test only provides a uniaxial solicitation, the puncture test creates a multi-axial stress which is more representative of the stress imposed on bags in use.

Puncture resistance evaluates the film strength and extensibility properties. High puncture resistance is representative of films that can absorb the energy of penetration by both resistance to deformation and increased elongation.

Film samples are tested according to ASTM D3787, adapted to the Flexsafe® film: samples and tools dimensions met standard requirements, the speed is kept constant as requested by the standard. The speed was increased from 305 to 500 mm/min to reach the rupture of the Flexsafe® film sample, since the film did not break at the specified speed. The film robustness is characterized by maximum strength in N and elongation in mm at break.

Equipment
Dynamometer set up with a ball diameter of 25.4 mm on a film sample diameter of 45 mm at constant speed of 500 mm/min until film rupture.

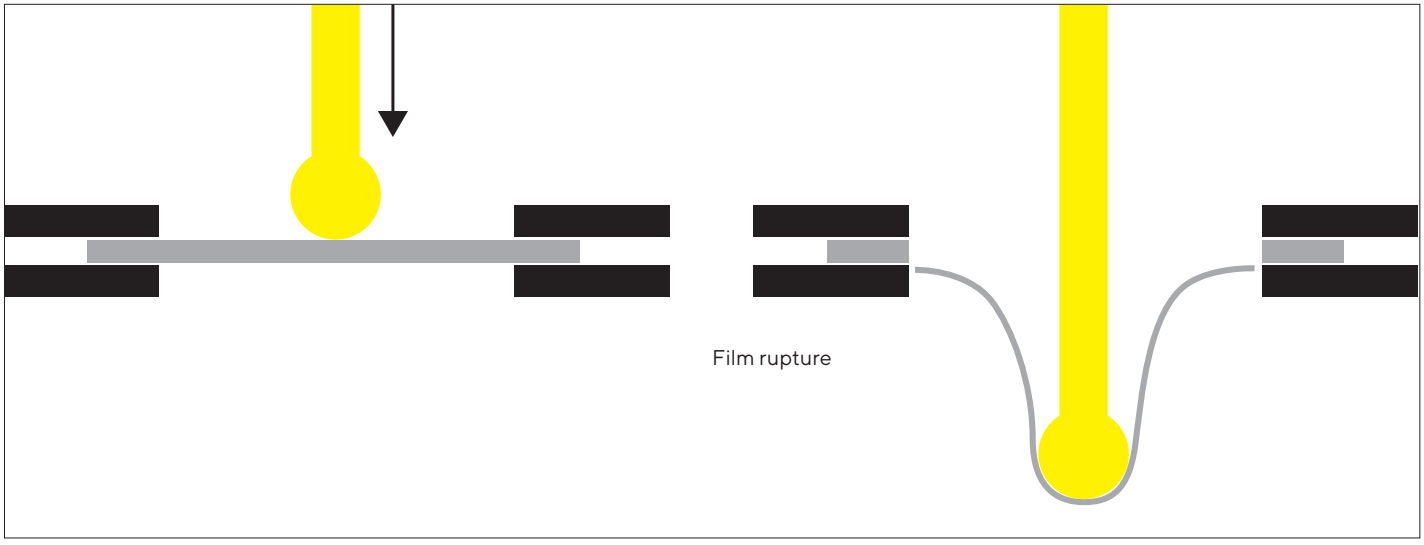


Fig. 8: Puncture Test Principle

Test Result

Feature	Test	Standard	No. of Samples	Temperature	Value
Maximum strength at break	Ball Burst test	ASTM D3787 500 mm/min	270	22 °C ± 3	> 350 N
Elongation at break		ASTM D3787 500 mm/min	270	22 °C ± 3	> 15 mm

4.1.4 Resistance of the Seals

Purpose
The objective is to assess the ability of sealing properties of the materials. After optimization of the welding parameters for film and components, 2D bags were produced and tested for water burst test. Three film batches are tested. Three bags per batch are filled until burst. The test demonstrates the sealing resistance and the bag deformation.

Feature	Test	Standard	No. of Samples	Results
Seal resistance	Water Burst test	Overfilling until burst	9	Pass

4.1.5 Barrier Properties

Purpose
Barrier to oxygen is an essential property when product stored inside the Flexsafe® Pro Mixer bags is sensible to oxidation. If the solution is not oxidizable, the oxygen contained in the headspace above the solution will not be consumed. The permeation phenomenon is driven by partial pressure equilibrium on both sides of the film (3- Van Krevelen). Therefore no oxygen will enter the container if it's not consumed by the solution.

Barrier to water vapor is directly linked to water loss. It is a relevant property when the concentration of the aqueous solution stored inside the bag must stay stable overtime.

The structure of the Flexsafe® film offers a very high barrier to gas. This leads to the limit of standard testing equipment capability and makes difficult to control test conditions such as temperature, relative humidity and stabilization of samples prior testing. These testing conditions have a high impact on permeation measurements. They therefore have to be carefully selected and controlled to reach a reproducible and relevant figure, above the limit of detection of standard testing equipment.

The tests described in this chapter allow the characterization of the film intrinsic barrier properties in laboratory conditions, to show the consistency of the Flexsafe® film barrier properties after gamma irradiation and over the bag shelf life.

In addition, the assessment of the barrier properties of a single-use system must take into account not only the film but the complete bag design, including fittings.

4.1.5.1 Barrier to Oxygen

Method
Barrier to oxygen is measured by Oxygen transmission rate (OTR). This test was performed according to ASTM D3985: "Standard Test Method for Oxygen Gas Transmission Rate through Plastic Film and Sheeting using a Coulometric Sensor on Flexsafe® film samples irradiated at 50 kGy for T = 0 and T = 3 years (in accelerated conditions and natural ageing).

Equipment
Permeation test system: (MOCON Oxtran 2/61)

Conditions of Test

	Oxygen	
Film external side	↓	External Side 23 °C ~ 0% RH
	↓	Internal Side 23 °C ~ 0% RH

Result

Feature	Test	Standard	No. of Samples	Value
Barrier to oxygen	O_2 transmission rate (OTR)	ASTM D3985	T = 0: 6 T = 3 years: 6 (accelerated ageing) + 3 (natural ageing)	0.4 $cm^3/m^2/24$ h

4.1.5.2 Barrier to Water Vapor

Method
Barrier to water vapor is measured by Water Vapor Transmission Rate (WVTR). This test was performed according to ISO 15106-3: "Plastics, Film and Sheeting, Determination of water vapor transmission rate, Part 3: Electrolytic detection sensor method" on Flexsafe® film samples irradiated at 50 kGy for T = 0 and T = 3 years (in accelerated conditions and natural ageing).

Equipment
Permeation test system (Systech 7001)

Conditions of Test

Film external side	↑	External Side 23 °C ~ 0% RH
Water vapor	↑ **H_2O**	Internal Side 23 °C ~ 90% RH

Result

Feature	Test	Standard	No. of Samples	Value
Barrier to Water Vapor	H_2O transmission rate	ISO 15106-3	T = 0: 6 T = 3 years: 6 (accelerated ageing) + 3 (natural ageing)	0.3 $cm^3/m^2/24$ h

4.1.5.3 Barrier to Carbon Dioxide

Method
Barrier to carbon dioxide (CO_2) is measured by CO_2 transmission rate (CO_2TR). This test was performed according to ASTM F2476 on Flexsafe® film samples irradiated at 50 kGy for T = 0 and T = 3 years (in accelerated conditions and natural ageing).

Equipment
Permeation test system: (MOCON Permatran)

Conditions of Test

	CO_2 ↓	External Side 23 °C ~ 0 % RH
Film external side	↓	Internal Side 23 °C ~ 0 % RH

Result

Feature	Test	Standard	No. of Samples	Value
Barrier to Carbon Dioxide	CO_2 transmission rate	ASTM F2476	T = 0: 6 T = 3 years: 6 (accelerated ageing) + 3 (natural ageing)	0.6 cm^3/m^2/24 h

5. Integrity of Flexsafe® Pro Mixer

The physical and microbial integrity of Flexsafe® Pro Mixer is guaranteed by the initial qualification tests performed on seals and connections to other components as well the validation and the capabilities of the manufacturing process.

In addition, in order to ensure that the integrity of the Flexsafe® Pro Mixer is maintained when shipped in boxes to our customers, packaging has been validated under the ASTM D4169 & ASTM D7386 worst case tests.

The list of tests performed on Flexsafe® Pro Mixer as part of our product and process validations are as described hereafter.

5.1 Seal Strength Integrity

Sample	Testing Method	Acceptance Criteria
Film|film bag seal	Visual inspection	No bubble, no infiltration, no channels, no folds Clear welding and constant width
	Tensile test of a 15 mm width sample at a pulling speed of 500 mm/min	F > 50 N and film break Elongation > 100%
	Ink test the absence of channel is checked through dye penetration	No penetration nor channel
Film|port seal	Visual inspection	No bubble, no infiltration, no channels, no folds Clear welding and constant width
	Tensile test of a 15 mm width sample at a pulling speed of 500 mm/min	F > 50 N and film break Elongation > 100%
	Ink test the absence of channel is checked through dye penetration	No penetration nor channel
Packaging seal (overpouches)	Visual inspection	No bubble, no infiltration, no channel, no fold Clear welding and constant width
	Tensile test of a 15 mm sample width at a pulling speed of 200 mm/min	F > 10 N
	Ink test the absence of channel is checked through dye penetration	No penetration nor channel

5.2 Component|Assemblies Integrity

Sample	Testing Method	Acceptance Criteria
Connexion tightness	A pressure test is applied onto the connection until 1 bar	No bubble
Fitting strength	Tensile test of a 15 mm sample width at a pulling speed of 500 mm/min FD: functional diameter	Fitting strength for FD < 3.5 mm: > 15 N Fitting Strength for FD (3.5 – 5 mm): > 25 N Fitting Strength for FD (5 – 7 mm): > 40 N Fitting strength for FD (7 – 9 mm): > 60 N Fitting strength for FD > 9 mm: > 80 N
Clamping force	A force is applied in a compression test at a speed of 200 mm/min. The force to clamp is measured	< 80 N for small clamps < 165 N for medium clamps < 330 N for large clamps

6. Biocompatibility

All materials used in the construction of the film, the bag ports, the top port, drain valve, pH sensor, conductivity sensor, thermowell and the impeller meet the requirements of the USP <87> (in vitro) and USP 88 Class VI–Plastics and are considered as non cytotoxic.

7. Physico-chemical Tests

7.1 European Pharmacopoeia – Polyethylene with Additives

Purpose and Test Method
The PE contact layer of the Flexsafe® film has been tested in compliance with the recommendations of the European Pharmacopoeia E.P.3.1.5. "Polyethylene with additives for containers for parenteral and ophthalmic preparations".

Description	Norm|Guideline	Results
		Flexsafe® Film
PE Monography	E.P. 3.1.5.	Pass

7.2 USP <661> – Containers Physico-chemical Tests – Plastic

Purpose
Physico-chemical tests are designed to determine physical and chemical properties of Flexsafe® Pro Mixer plastics and their extracts.

7.2.1 Flexsafe® Film

Test Method
Tests are performed on the Flexsafe® film after gamma irradiation at 50 kGy and accelerated ageing conditions up to 3 years (according to ASTM F1980-99) for 3 batches. The extraction is done under aqueous conditions in ultra-pure water at 70 °C for 24 hours. (Ratio of 120 cm^2 per 20 mL).

Test Results

Description	Norm|Guideline	Results at T = 0 and T = 3 Years
		Flexsafe® Film (PE)
Tests for Plastic: physical & chemical properties	USP <661> Non-volatile residue < 15 mg	Pass
	Heavy metals < 1 ppm	Pass
	Buffering capacity < 10 mL	Pass

7.2.2 Flexsafe® Pro Mixer Bag Components

Impeller, bag ports, top ports, pH sensor, conductivity sensor, thermowell and drain valve were extracted in ultra pure water at room temperature for 7 days. The following tests were conducted in order to determine physical and chemical properties of the test article and its extracts.

Test Results

	USP <661> Limits	Results at T = 0
Non-volatile residue	< 15 mg	Pass
Heavy metals	< 1 ppm	Pass
Buffering capacity	< 10 mL 0.01 M NaOH or HCl	Pass

8. Stability of Water for Injection (WFI) for Flexsafe® Pro Mixer Bags

Flexsafe® bags have been tested according the specifications given in the section "Sterile Water for Injection" of both current USP and E.P.

Flexsafe® Pro Mixer 9 L and 50 L bags have been tested and are representative of the manufacturing process of Flexsafe® Pro Mixer bags from 50 L to 3,000 L.

Tests have been conducted at ambient temperature and results are established for 7 days and 1 month of storage when filled.

8.1 Sterility Test

Purpose and Test Method
Sterility testing is performed to demonstrate that the solution remains sterile after storage in Flexsafe® Pro Mixer bags up to 1 month at room temperature.

The storage test was performed at room temperature, on 50 L Flexsafe® Pro Mixer non-aged bags that have been gamma irradiated at 50 kGy (worst case condition) and filled with 6L of Sterile Sodium Chloride solution. The test was performed on 3 different batches of 3 bags each.

Extracts are then tested by applying the membrane filtration test method according to USP <71> and E.P.2.6.1 requirements.

The acceptance criterion is no growth.

Results

Feature	Specimen	Test Method	Ageing	Limit	Number of Samples	Total	Result	
							7 Days	1 Month
Sterility	Flexsafe® Pro Mixer 50 L	USP <71> E.P. 2.6.1	T = 0	No growth	3 bags × 3 batches	9	Pass	in progress

Filled Flexsafe® Pro Mixer bags remain sterile at room temperature at different due dates.

8.2 Bacterial Endotoxin Test

Purpose and Test Method
The goal of endotoxin testing is to establish the amount of endotoxins released from Flexsafe® Pro Mixer bags in the water for injection extracts after extended storage time.

The storage test is performed at room temperature, on 50 L Flexsafe® Pro Mixer non-aged bags that have been gamma irradiated at 50 kGy (worst case condition) and filled with 6 L of WFI. The bags represent a surface|volume ratio of 1.11 cm^2/mL (worst case condition). The test was performed on 3 different batches of 3 bags each.

Water for injection extract is tested by applying:
- the quantitative chromogenic test method according to the USP <85>
- and the quantitative kinetic colorimetric test method (method D) according to the E.P. 2.6.14.

The acceptance criteria are:
- < 0.5 EU/mL for USP Sterile Water for Injection monography
- < 0.25 EU/mL for E.P. Sterilized water for injection monography

Results

Feature	Specimen	Test Method	Ageing	Limit [EU/mL]	Number of Samples	Total	Result	
							7 Days	1 Month
Sterility	Flexsafe® Pro Mixer 50 L	USP <85>	T = 0	< 0.5	3 bags × 3 batches	9	Pass	in progress
		E.P. 2.6.14		< 0.52			Pass	in progress

Flexsafe® Pro Mixer bags extracts meet both USP and E.P. limits after storage of WFI at room temperature at different due dates.

8.3 Sub-visible Particle Content

Purpose and Test Method
The goal of sub-visible particle testing is to establish the amount of sub-visible particles released from Flexsafe® Pro Mixer bags in the water for injection extracts after extended storage time.

The storage test is performed at room temperature, on 50 L Flexsafe® Pro Mixer non-aged bags that have been gamma irradiated at 50 kGy (worst case condition) and filled with 6 L of WFI. The bags represent a surface|volume ratio of 1.11 cm^2/mL (worst case condition). The test was performed on 3 different batches of 3 bags each.

Water for injection extract is tested by applying the light obscuration particle count test method (method 1) according to both USP <788> and E.P. 2.9.19.

The acceptance criteria are:
- ≤ 25 particles/mL for particles ≥ 10 µm and ≤ 3 particles/mL for particles ≥ 25 µm for USP <788>
- ≤ 12 particles/mL for particles ≥ 10 µm and ≤ 2 particles/mL for particles ≥ 25 µm for E.P. 2.9.19

Results

Feature	Specimen	Test Method	Ageing	Limit [Particle/mL]	Number of Samples	Total	Result	
							7 Days	1 Month
Sub-visible particle content	Flexsafe® Pro Mixer 50 L	USP <788>	T = 0	≥ 10 µm: ≤ 25 ≥ 25 µm: ≤ 3	3 bags × 3 batches	9	Pass	in progress
		E.P. 2.6.19		≥ 10 µm: ≤ 12 ≥ 25 µm: ≤ 2			Pass	in progress

Flexsafe® Pro Mixer bags extracts meet both USP and E.P. limits after storage of WFI at room temperature at different due dates.

8.4 pH, Conductivity, Total Organic Carbon (TOC)

Purpose and Test Method
The goal of pH, conductivity and TOC testing is to establish the conductivity and TOC shifts of water for injection when stored in Flexsafe® Pro Mixer bags.

The storage test is performed at room temperature, on 9 L Flexsafe® Pro Mixer non-aged and aged bags that have been gamma irradiated at 25–45 kGy and filled with 9 L of WFI. The bags represent a surface|volume ratio of 1.11 cm^2/mL (worst case condition).

Water for injection extract is tested by applying:
- USP <791> for pH
- Sterile water test method in USP <645> and E.P. Sterilized water for injection monography test method for conductivity
- Sterile water test method in USP <643> for TOC

Results

Feature	Specimen	Test Method	Ageing	Number of Samples	Result	
					7 Days	21 Days
pH	Flexsafe® Pro Mixer 9 L	USP <791>	T = 0	3 bags	Pass	Pass
Conductivity	Flexsafe® Pro Mixer 9 L	USP <645>	T = 0	3 bags	Pass	Pass
		E.P.				
TOC	Flexsafe® Pro Mixer 9 L	USP <643>	T = 0	3 bags	Pass	Pass
pH	Flexsafe® Pro Mixer 9 L	USP <791>	T = 3 years	3 bags	Pass	Pass
Conductivity	Flexsafe® Pro Mixer 9 L	USP <645>	T = 3 years	3 bags	Pass	Pass
TOC	Flexsafe® Pro Mixer 9 L	USP <643>	T = 3 years	3 bags	Pass	Pass

8.5 Additional E.P. and USP Tests for Stability of Water for Injection

Purpose and Test Method
The goal of additional E.P. and USP tests is to establish if the storage in Flexsafe® Pro Mixer bags modifies the characteristics of WFI.

The storage test is performed at room temperature, on 9 L Flexsafe® Pro Mixer non-aged bags that have been gamma irradiated at 25–45 kGy and filled with 9 L of WFI. The bags represent a surface|volume ratio of 1.11 cm^2/mL (worst case condition).

Water for injection is tested by applying E.P. Sterilized water for injection monography test method for:

- Acidity or alkalinity
- Chlorides
- Nitrates
- Sulfates
- Ammonium
- Calcium and magnesium
- Residue of evaporation

and is tested by applying both E.P. Sterilized water for injection monography and USP Sterile Water for Injection test methods for oxidizable substances

Results

Feature	Specimen	Test Method	Ageing	Limit	Number of Samples	Result	
						7 Days	21 Days
Oxidizable substance	Flexsafe® Pro Mixer 9 L	USP	T = 0	Pink color does not disappear	3 bags	Pass	Pass
		E.P.		The solution is still pink			
Acidity or alkalinity	Flexsafe® Pro Mixer 9 L	E.P.	T = 0	Yellow –> Red Red –> Yellow	3 bags	Pass	Pass
Chlorides	Flexsafe® Pro Mixer 9 L	E.P. 2.4.4	T = 0	No change of solution aspect after 15 min	3 bags	Pass	Pass
Nitrates	Flexsafe® Pro Mixer 9 L	E.P.	T = 0	Maximum 0.2 ppm	3 bags	Pass	Pass
Sulfates	Flexsafe® Pro Mixer 9 L	E.P.	T = 0	No change of solution aspect after 1 hour	3 bags	Pass	Pass
Ammonium	Flexsafe® Pro Mixer 9 L	E.P.	T = 0	Maximum 0.2 ppm	3 bags	Pass	Pass
Calcium & Magnesium	Flexsafe® Pro Mixer 9 L	E.P.	T = 0	Blue coloration appears	3 bags	Pass	Pass
Residue of evaporation	Flexsafe® Pro Mixer 9 L	E.P.	T = 0	Maximum 3 mg	3 bags	Pass	Pass

9. Flexsafe® Pro Mixer Bags Operating Range for End-user Process Parameters

Qualified Operating Range
The following conditions have been qualified.

- Minimum temperature:
  5 °C ± 3 °C (41 °F)

- Maximum temperature:
  40 °C ± 3 °C (104 °F)

- Maximum pressure in transfer lines:
  1 bar

- Shelf life:
  1 year at room temperature (3 years validation tests are in progress).

The validation and the use of Flexsafe® Pro Mixer bags outside of our unit operation, application, process parameter specifications ranges are under the sole responsibility of end user.

Upon request, Sartorius Stedim Biotech Application Specialists can perform training for optimal use of our mixing products.

10. Chemical Resistance Studies

Purpose and Test Method
A chemical resistance study is conducted to assess the resistance of the bag to a variety of chemical solutions. The test protocol was performed on Flexsafe® bag for storage and developed following the principles of the standard test "Method for resistance of Plastic to chemical reagents" ASTM D543-06 i.e. the determination of the impact of chemical reagents on physical and chemical properties.

Three Flexsafe® 2D Bags 500 mL with Silicone TuFlux® tubing, polycarbonate connectors and ABS additive port are used. The bags have been previously gamma irradiated at 25–45 kGy and are filled with solution. One additional bag system filled with purified water is used as a reference. Bags are stored at room temperature (22 °C ± 3 °C) during 7 days and tested for compatibility according to the following tests:

- Visual inspection
- Drop test
- Physical properties
  - Tensile strength on film
  - Tensile strength on sealing parts
  - Film thickness
- Physico-chemical properties
  - Infra-red Spectroscopy on films
  - Weight tests

Test Results
The compatibility test results are classified as follows:

- Excellent compatibility:
  the product is unaffected in any way for the duration of the test.
- Good compatibility:
  a very slight clouding or discoloration takes place
- Fair compatibility:
  moderate effect and changes in dimensional properties
- Acceptable compatibility:
  changes in non critical but relevant film properties
- Poor compatibility:
  changes in critical quality properties
- Not recommended use:
  severe attack, unusable chemical with this product

Compatibility test results for different families of solutions such as organic solvents, acidic and alkaline solutions, buffers, detergents, amino acids solutions are summarized in the table hereunder.

Solutions	Compatibility Status
95% Ethanol	Excellent compatibility
70% Ethanol	Excellent compatibility
100% Ethyl acetate	Excellent compatibility – Not recommended for PC connectors
100% Glycerol	Excellent compatibility
100% 1-2 Propanediol	Excellent compatibility
3% (1 M) Hydrochloric acid	Excellent compatibility
1% Citric acid	Excellent compatibility
10% (3.3 M) Hydrochloric acid	Excellent compatibility
25% (4.3 M) Phosphoric acid	Excellent compatibility
5 M Ammonium hydroxide (pH 14)	Excellent compatibility – Good compatibility for PC connectors
1% (0.4 M) Sodium hydroxide	Excellent compatibility
50 % (19M) Sodium hydroxide	Excellent compatibility – Good compatibility for Tubing
Buffer pH 4.6: Acetate buffer solution	Excellent compatibility
Buffer pH 10: Borax sodium hydroxide	Excellent compatibility
Buffer pH 7.2: Phosphate buffer solution	Excellent compatibility
27% (50mM) Sodium acetate	Excellent compatibility
100% Triton X-100	Excellent compatibility
100% Tween 80	Excellent compatibility
100% Olive oil	Excellent compatibility

Conclusion

The results show excellent compatibility with buffers, alkaline, acidic and mino-acid solutions.

Sartorius Stedim Biotech offers consultancy and process specific interaction studies i.e. Extractables|Leachables, Chemical compatibility, Integrity test, Bacterial challenge test, ... as part of our CONFIDENCE® Validation services and risk analysis based approach. When customer processing conditions exceed our existing qualification conditions, Sartorius Stedim Biotech scientists will design a customized protocol and perform interaction testing which reproduce the specific product and process conditions.

11. Gamma Sterilization

11.1 Purpose

A sterilization validation study has been performed in order to demonstrate the effectiveness of the sterilization method applied to Flexsafe® Pro Mixer. This sterilization validation addresses the worst-case scenario (WCS) for sterility validation following the current ISO 11137 guideline.

ISO 11137	Process Validation	Process Controls
Establishment of minimum sterilization dose	Sterilization Cycle Development ■ Bioburden Quantification ■ Bioburden Identification ■ Bioburden Resistance Assessment	Maintenance of Sterility ■ Bioburden Quantification ■ Identification & Resistance ■ Environmental Monitoring ■ Dose audit
Establishment of maximum material compatibility dose	At Shelf Life ■ Functional performances ■ Package integrity ■ Biocompatibility ■ Sterility	Product Performances ■ 100% Visual inspection of bags ■ 100% Package inspection ■ Endotoxins, particles
Reproducibility of dose magnitude & distribution	Irradiation Performance Qualification ■ Dose mapping and limit setting ■ Density range and limit setting	Gamma Irradiation Process Consistency ■ Product density and|or product range ■ Min and max irradiation dose

The first step in the validation of our Gamma sterilization cycle is the assessment of the product bioburden. Sterility can only be validated if the bioburden is well characterized and shown not to be resistant to Gamma radiation.

Sterility is defined as the reduction of the initial population (No) to 1 survivor plus 6 additional logs. Therefore, the sterilization dose necessary to sterilize a product will depend on the level of bioburden present on this product. The killing rate of a population of micro-organisms is also dependent on the resistance of the micro-organisms to Gamma radiation. This resistance is quantified by the D-Value, expressed in kGy, which is the Gamma irradiation dose necessary for 1 log reduction of a given microorganism.

It is therefore necessary to quantify, identify and assess the resistance of the total bioburden that may occur in production in order to assure sterility.

11.2 Method

Full compliance with ISO 11137 VD_{max} 25 method allows Sartorius Stedim Biotech to validate and claim a Sterility Assurance Level of 10^{-6} for each Fluid Management System over its shelf life. Validation and maintenance of sterility is the result of our long experience in the sterilization of medical devices, bags and Fluid Management Systems and the total respect of ISO norms.

11.3 Establishment of the Minimum Gamma Sterilization Dose

11.3.1 Bioburden Evaluation

Product bioburden is first evaluated for all product families. The worst case product family (i.e. the one that exhibits the highest bioburden) is then selected for the validation study.

As described by the ISO 11137 document, a Sample Item Portion (SIP) is defined to carry out the Gamma sterilization validation tests.

A bag sample item is selected as the most representative Sample Item Portion and the worst case configuration for bioburden. The use of a scale down bag produces accurate and reproducible bioburden recovery results that is the critical cornerstone for the rest of the validation study. Bioburden quantification for larger bags is then compared against the selected SIP bioburden.

The bioburden evaluation is performed on 3 × 10 units of the SIP selected from 3 different lots.

11.3.2 Verification Dose Experiments

Once the bioburden level is established one can define the verification dose to be used for the validation. The verification dose is calculated to produce a SAL 10^{-1} according to the rules defined in the ISO 11137 document. The verification dose experiment is conducted on 10 units of the SIP. Sterility test must pass the criteria ≤ 1 positive.

11.3.3 Routine

Sartorius Stedim Biotech ensures that the minimum Gamma sterilization dose is still valid by routinely monitoring product bioburden (quantification and characterization) on all Fluid Management System families.

In addition, dose audits are performed every quarter according to the ISO 11137 requirements to verify that the initial validation is still applicable. Dose audits are performed using the original verification dose.

11.4 Establishment of the Maximum Irradiation Dose

The maximum sterilization is established to ensure that Flexsafe® Pro Mixer bags fit, form and function is not affected by the Gamma irradiation process.

The compatibility of Flexsafe® Pro Mixer bags with the maximum irradiation dose of 50 kGy is assessed after 1 year accelerated ageing conditions and will be assessed after 3 years accelerated ageing to establish the maximum shelf life (tests are in progress to validate 3 years shelf life).

11.5 Maintenance of Sterility

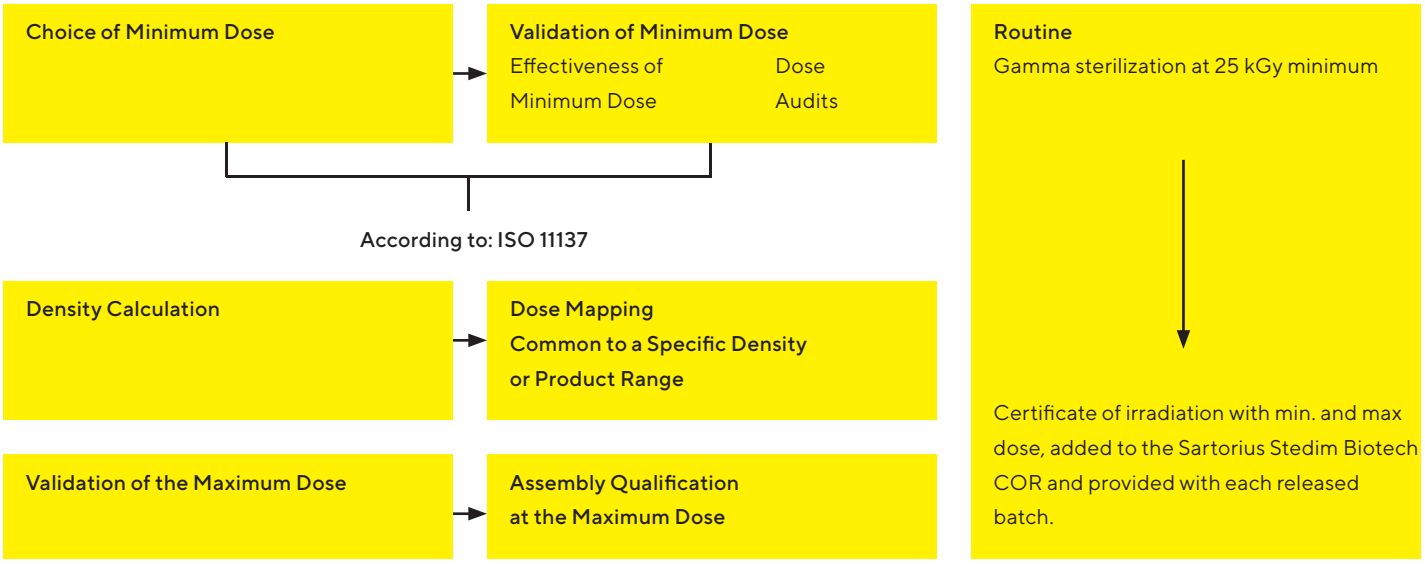
Maintenance of sterility is first verified through routine dose monitoring. Dosimeters are placed in all sterilization batches to verify that the dose received by Flexsafe® Pro Mixer bags is within specified limits (i.e. greater than 25–45 kGy). In routine sterilization, dosimeters are placed at reference position that have been identified during dose mapping. Dose mapping is assessed after each source replanishment to confirm the magnitude, distribution and reproducibility of the irradiation process.

The second critical aspect of maintenance of sterility is the routine characterization of product bioburden. Product bioburden is quantified routinely on each production line. Environmental monitoring is routinely performed to address potential changes to our manufacturing environment.

Finally, dose audits are performed every quarter according to the ISO 11137 requirements to verify that the initial validation is still applicable. Dose audits are performed using the original verification dose.

11.6 Results

The sterility validation for Flexsafe® Pro Mixer bags has met the requirements set forth in the applicable standard.



12. Validation of the Shelf Life

Flexsafe® Pro Mixer bags have a shelf life of 1 year after Gamma irradiation (tests are in progress to validate 3 years shelf life).

If a new component with a shorter shelf life is used in a Flexsafe® Pro Mixer bags the whole product will receive the shortest shelf life. Strict procedures are in place that control the design of the product and define the shelf life specification that will be printed on the product labelling. Customers should always respect the expiry date printed on the product labels.

The physical and chemical charac- teristics, the biocompatibility and the sterility Flexsafe® Pro Mixer bags are assessed and compared with original properties after a 1 year storage in accelerated conditions.

Properties	Tests performed on	Acceptance Criteria	Results at T=0	Results at T = 1 (accelerated ageing)
Functional: filling, mixing (mechanical stress) and draining	Bag and components	Integrity: no leak	Pass	Pass
Subvisible particles USP <788>	Bag and components	25 particles/mL ≥ 10 µm 3 particles/mL ≥ 25 µm	Pass	Pass
Sterility and cleanliness	Bag and components	Bioburden < 1000 CFU VD_{max} 25 No growth Endotoxin < 0.125 EU/mL	Pass	Pass
Biocompatibility	Bag and components	Biocompatible as per USP <88> Class VI and USP <87>	Pass	Pass
Extractables USP <661>	Bag and components	Non-volatile residue < 15 mg Heavy metals < 1 ppm Buffering capacity < 10 mL	Pass	Pass
Chemical resistance	Bag	Resistant to chemicals as per list on chapter 10	Pass	Pass
Overpouch strength	Over-pouch	> 10 N	Pass	Pass
Overpouch integrity	Over-pouch	Ink penetration: no penetration no channel	Pass	Pass
Label	Over-pouch	Readable after IPA cleaning No infiltration	Pass	Pass
BCT*	Over-pouch	Product impermeability to microorganisms following ISO 15747	Pass	Pass

Specific Shelf Life for Components:
Sartorius Stedim Biotech does not redo the ageing studies performed by its qualified suppliers. We require certification for any claim that a supplier makes on the shelf life of their components.

Shelf Life for Assemblies:
Beyond the requirements from the suppliers, Sartorius Stedim Biotech will perform ageing studies on all new assemblies that require this to be done. This process will guarantee that the assemblies will perform in an identical manner after the stated shelf life as they did just after sterilization.

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