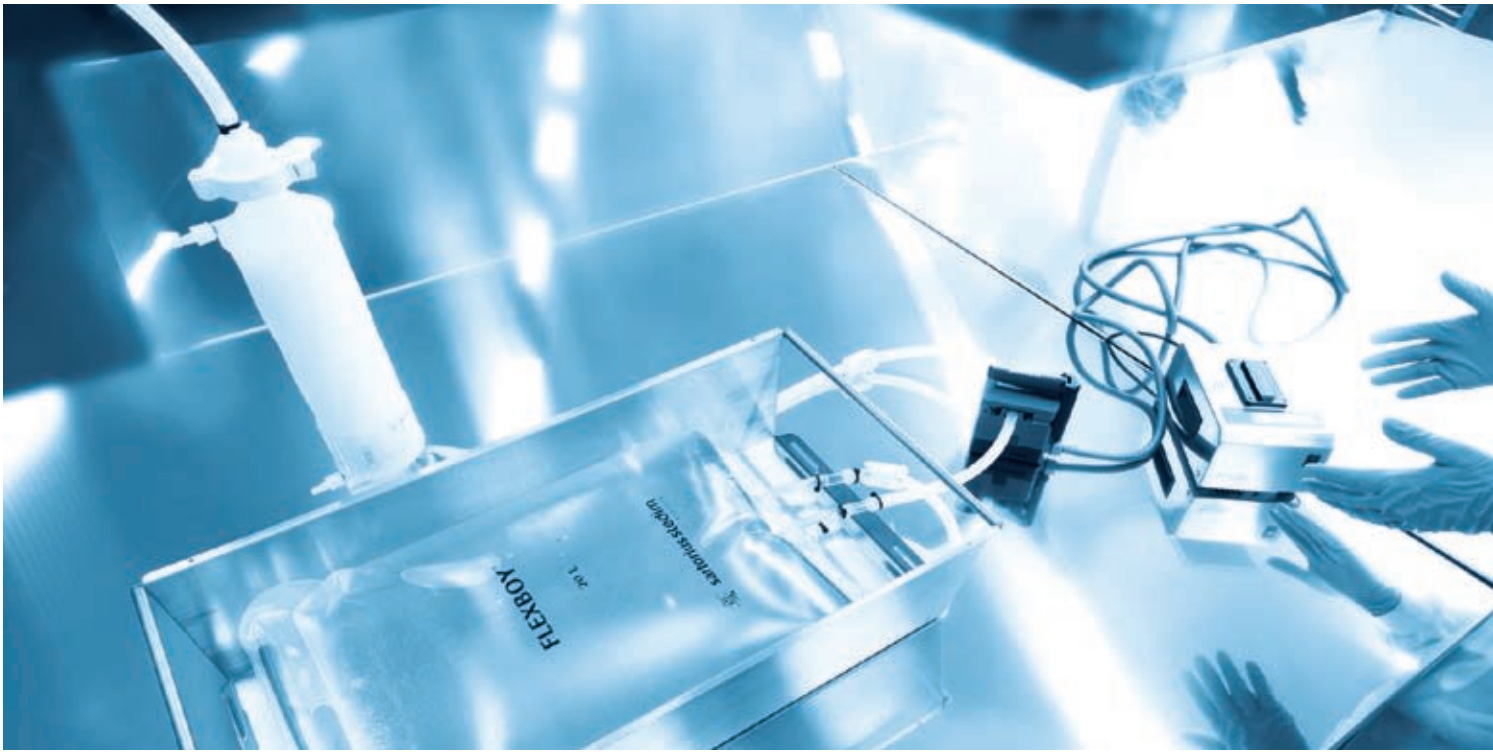
sartorius stedim biotech

Validation Guide
Flexboy®



The results shown in this Validation Guide are indicative and do not constitute product specifications.

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1. Introduction

Sartorius Stedim Biotech Flexboy® bags and systems are widely used in bio-pharmaceutical processes for a variety of unit operations of the commercial production of drug products such as vaccines, recombinant proteins and monoclonal antibodies and for the development of future biomolecules in clinical phases.

Buffers and media are increasingly formulated, sterile filtered and stored in Single Use Fluid Management Systems (FMS) that involve Flexboy® bags integrated with filters, tubing, connectors and monitoring tools. Product intermediates are also filtered and stored between UF|DF and chromatography purification steps in Gamma sterile Fluid Management Systems. Flexboy® bags and FMS are also adopted for the formulation, filtration and aseptic processing of final drug products.

Flexboy® systems are qualified, manufactured and released according to most stringent product validation protocols, cGMP requirements and Quality Control testing to offer safe and robust single use processes to the end users of the biopharmaceutical industry.

This Validation Guide describes the qualification, manufacturing conditions, quality standards, QC inspection and physicochemical properties of Sartorius Stedim Biotech Flexboy® bags made of Ethylene Vinyl Acetate (EVA) contact layer S71 film. It also gives a general view of the security of supply offered by Sartorius Stedim Biotech multiple location manufacturing facilities.

1.1 Security of Supply

As a result of the broad adoption of Flexboy® bags and FMS in critical process steps of commercial drug manufacturing, security of supply has become the major issue for our customers. The robustness of our supply chain relies on continuous, dynamic improvement of our supplier management, multiple manufacturing sites with consistent industrial processes, expertise for designing Fluid Management Systems, close collaborative relationships with customers and senior management's strong commitment.

Sartorius Stedim Biotech offers the most secured manufacturing resources and capabilities on the market to ensure the strongest security of supply. We hold the most modern facilities in Europe, North America and North Africa for production of pharmaceutical and medical plastic Fluid Management Systems with a total of 4800 m^2 (48.000 sqft) of ISO 7 clean room (Class 10.000 or Grade C).

Our manufacturing plants operate under a common information system in order to offer flexibility and reliable product transfer from one location to the other. Consistent process performance is ensured by the on-going qualification of all components and assemblies, manufacturing processes and personnel.

As part of our continuous efforts to meet the demand and quality requirements of our growing base of customers we are currently qualifying and securing a second supply source of the S71 film EVA resin to ensure greater security of supply of our Flexboy® bags and FMS.

1.2 Manufacturing Resources

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

Sartorius Stedim Biotech S.A. Aubagne, France:
Date of creation 1979, latest expansion in 2003.

- Total area 15.000 m^2 (150.000 sq.ft) with 3000 m^2 (30.000 sq.ft) of class ISO 7 cleanrooms (Class 10 000 or Grade C).
- Manufacturing capabilities: film extrusion, injection moulding, sealing and manual assembly performed in two cleanrooms of 1500 m^2 (15.000 sq.ft) each.

Sartorius Stedim Biotech Inc. Concord, USA:
Date of creation 1990, latest expansion in 2005.

- Total area 2.800 m^2 (28.000 sq.ft) with 900 m^2 (9.000 sq.ft) of class ISO 7 cleanrooms (Class 10 000 or Grade C).
- Manufacturing capabilities: sealing, manual assembly, final packaging and labelling.

Sartorius Stedim SUS SARL M'Hamdia, Tunisia:
Date of creation 2001.

- Total area 4.000 m^2 (40.000 sq.ft) with 900 m^2 (9.000 sq.ft) of class ISO 7 cleanrooms (Class 10 000 or Grade C).
- Manufacturing capabilities: sealing, manual assembly, packaging and labelling.

1.3 cGMP Quality Assurance System

Our Quality System is in compliance with ISO 9001:2000 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:

Sartorius Stedim Biotech S.A.
Aubagne, France

- FDA registration N° 8044085
- FDA owner|operator N° 9005426
- D.M.F. #: 13014 (Type III Drug Master File, for Flexboy® bags)

Sartorius Stedim Biotech Inc.
Concord, USA

- FDA registration N° 3003914055
- FDA owner|operator N° 9005426

The sites located in France and in Tunisia are also certified according to ISO 13485:2003 and Directive 93|42|EEC for Medical Devices sold to the European market. All manufacturing sites are audited by the notified body SGS International Certification Services Limited.

Our Quality Systems therefore follows all the applicable ISO and FDA regulations for Medical Devices. Design, manufacture and sterilization processes are conducted under conditions that mirror biopharmaceutical operations and in compliance with cGMP.

Fluid Management Systems made of Flexboy® bags are qualified according to most stringent performance and safety industry standards as described in this Validation Guide. All critical manufacturing operations for Flexboy® bags and FMS are conducted in ISO 7 (Class 10.000) cleanrooms. 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 Flexboy® 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

Flexboy® FMS manufactured in Aubagne, France are packaged in cardboard boxes and shipped on pallets to Isotron for Gamma irradiation. Flexboy® FMS manufactured in Concord-CA are shipped to Steris-Isomedix for Gamma irradiation. All Flexboy® FMS are irradiated at a minimum dose of 25 kGy.

The efficiency of the minimum dose of 25 kGy 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 a certificate of release and an irradiation certificate which mentions the minimum doses.

1.5 Testing Conducted for the Validation and Lot Release of Flexboy® Fluid Management Systems

Qualification Tests

- **Biocompatibility Testing (on film samples|or bags)**
  - USP <87>: Biological reactivity tests, In Vitro
  - USP <88>: Biological reactivity tests, In Vivo
- **Mechanical Properties (on film samples)**
  - Ultimate Tensile Strength
  - Elongation at break
  - Toughness
  - Secant modulus at 2 %
  - Resistance to tearing
  - Flex Durability
  - Impact Resistance
- **Gas Transmission Property (on film samples)**
  - ASTM D3985: Barrier to Oxygen
  - ASTM F1249: Barrier to Water Vapor
  - ASTM F2476: Barrier to Carbon Dioxide
- E.P. 3.1.7.: "Ethylene-Vinyl Acetate copolymer for containers and tubing for parenteral nutrition preparations
- E.P. 5.2.8. on TSE-BSE
- Stability of Water for Injection stored in Flexboy® bag
  - USP
  - E.P.
- Chemical Resistance of Flexboy® 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|Tubing|Film
  - Bag
- Component|Assemblies Integrity
  - Connexion Tightness
  - Fitting Strength
  - Dust Cap Pulling Strength
  - Clamping Force
  - Cracking for PC components only <USP 643> Total Organic Carbon; <USP 661> Containers, Physico-chemical Tests

Monitoring Tests

- Bacterial Endotoxins test USP <85> and E.P. 2.6.14
- USP <788> and E.P. 2.9.19: Particulate
- ISO 11737: Bioburden
- ISO 11137: Sterilization of Medical Devices
- ISO 14644: Cleanroom environmental controls

Lot Release Test

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

1.6 References

- ISO 9001:
  Quality systems
- ISO 13485:
  Medical Devices – Quality systems
- ISO 10993:
  Biological evaluation of Medical Devices
- ISO 14644:
  Cleanrooms and associated controlled environment
- ISO 11137:
  Sterilization by irradiation of Medical Devices
- ISO 527:
  Determination of tensile properties
- ISO 7765-2:
  Determination of impact resistance by the free falling dart method
- ISO 15747:
  Plastic containers for intravenous injection
- ASTM D882:
  Standard test method for tensile properties of thin plastic sheeting
- ASTM D1004:
  Standard test method for initial tear resistance of plastic film and sheeting
- ASTM F 392:
  Standard test method for flex durability of flexible barrier materials
- ASTM F-2097:
  Standard guide for design and evaluation of primary packaging for medical products
- ASTM D3985:
  Oxygen Transmission rate
- ASTM F1249:
  Water Vapor Transmission rate
- ASTM F2476:
  Carbone Dioxide Transmission Rate
- USP <85>:
  Bacterial Endotoxins test
- USP <87>:
  Biological reactivity tests, In Vitro
- USP <88>:
  Biological reactivity tests, In Vivo
- USP <661>:
  Containers, Physicochemical tests - Plastics
- USP <788>:
  Particulate Matter in Injections
- European Pharmacopoeia:
  E.P. 3.1.7.:
  "Ethylene-Vinyl Acetate copolymer for containers and tubing for parenteral nutrition preparations"
- European Pharmacopoeia:
  E.P. 2.9.19:
  Particulate contamination – Subvisible particles
- European Pharmacopoeia:
  E.P. 2.6.14:
  Bacterial endotoxins
- European Pharmacopoeia:
  E.P. 5.2.8.:
  Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products
- EMEA|410|01:
  Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products
- Directive 93|42|EEC:
  applicable for Medical Devices

2. Production and Quality

2.1 Human Resources

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 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 FMS 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 FMS is 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 and|or ISO10993 conformity
- TSE|BSE statement
- EP conformity (if applicable)
- Change notification statement

Beyond these requirements, Sartorius Stedim Biotech performs 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 FMS made with this raw material. For components, the qualification will be centered around 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:

- Delivery conformity
- Conformity of products on reception
- Compliance with delivery deadlines.

2.3.3 Verification of Purchased Product (Incoming QC)

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 listed below:

- Supplier documentation controls (Certificates)
- Packaging identification and integrity
- Material identification by Infra Red spectroscopy (FTIR)
- E.P. (e.g. EVA)
- Visual inspection
- Dimensional check
- Functional test

Only approved materials will be allowed to be used in production of single use FMS 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 FMS is carried out in class ISO 7 (Class 10000 or Grade C) cleanrooms, that are regularly cleaned and inspected. Controlled environment contributes to the control of microbiological and particulate contamination of Flexboy® FMS.

2.4.5 Identification

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

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 Flexboy® FMS. The batch numbers are issued when the manufacturing order is launched.

2.4.6 Traceability

Sartorius Stedim Biotech has an upstream traceability system for in coming raw materials and a downstream traceability system for customers 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,
- the quantities of raw materials and|or components used,
- the batch numbers of the raw materials and components used,
- the operators identification,
- the machine parameters (where applicable),
- the tooling used (where applicable),
- the dates of manufacture.

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, assembly, etc.)
- Seal strength testing with a dynamometer
- Air leak test for Flexboy® bags up to 50 liters
- Dimensional check
- Product packaging controls
- Product labeling controls

2.6 Control of Finished Products and Batch Release

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 method D. The acceptance criteria used for batch 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 batch release follows the requirements for Large Volume Injections.

	Particle Size ≥ 10 µm [particles/mL]	**≥ 25 µm [particles/mL]**
For Large Volume Injections, 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.

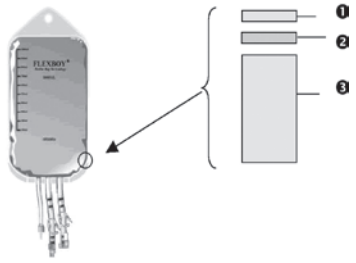
After production, every batch of finished products will be released by Quality Assurance before it can be shipped to the customer. The release will be documented in the batch record and in the computer system. The system for product release is constructed in such a way that only batches that have been 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. Film and Properties

3.1 Film Structure

The S71 film used for the manufacture of all the Flexboy® bags utilizes multiple layers of different materials to provide a robust high barrier structure.

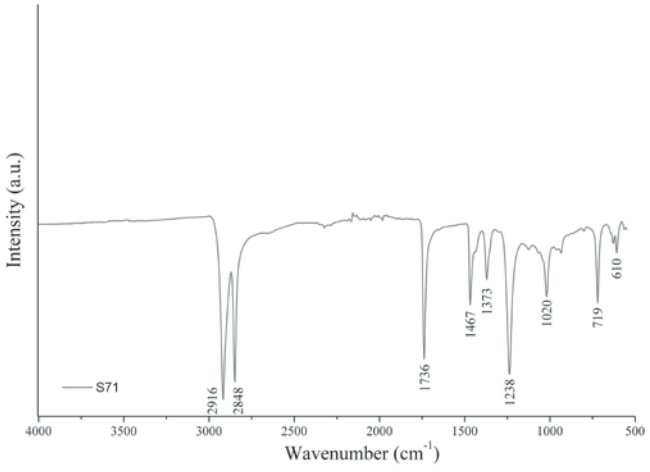


Materials of Construction:

1. Ethylene Vinyl Acetate Copolymer (EVA) – acts as a strong and protective outer layer.
2. Ethyl Vinyl Alcohol (EVOH) – acts as the main gas barrier minimizing transmission of gases such as O_2 and CO_2 across the film.
3. EVAM® layer – Ethylene Vinyl Acetate Copolymer (EVA) – acts as the fluid contact layer. E.V.A. is in compliance with the European Pharmacopoeia, § 3.1.7. "Ethylene-Vinyl Acetate copolymer for containers and tubing for parenteral nutrition preparations".

The total film thickness is 300 ± 25 µm for all bags under 20 L and 360 ± 45 µm (360 µm Film thickness is only present on 50 L Flexboy® bags).

Flexboy® bags are certified BSE|TSE free. They are in compliance with the EMEA's guidance (EMEA|410|01) and the European Pharmacopoeia # 5.2.8. on minimizing the risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Product.



Graph: FTIR identification spectrum of the contact layer.

3.2 Bag Sizes and Surface Areas

Bag Capacity [mL]	Surface Area [cm²]
50	143
150	275
500	452

Bag Capacity [liter]	Surface Area [cm²]
1	707
3	1346
5	1929
10	3528
20	4826
50	8106

3.3 Physico-Chemical Properties

3.3.1 Mechanical Properties

3.3.1.1 Tensile Properties

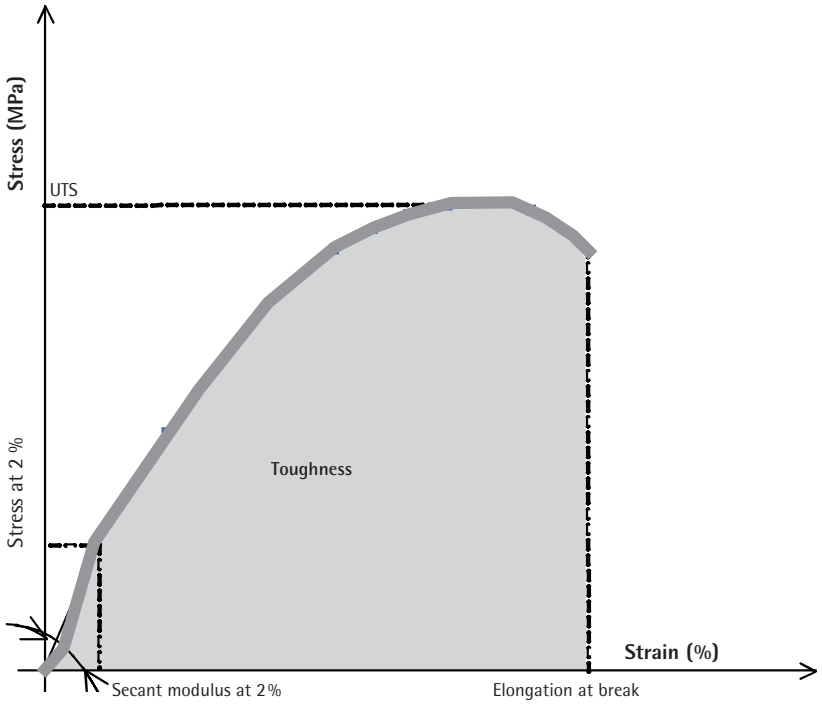
Purpose and Test Method
A tensile test consists in applying an elongation to a film specimen and measuring the resulting strength. Mechanical properties can then be defined from the stress-strain curve.

- Utimate Tensile Strength (UTS):
  The maximum stress a material can withstand is calculated by dividing the maximum load by the original cross sectional area of the specimen.
- Elongation at Break:
  The elongation is recorded at the moment of specimen rupture and often expressed as a percentage of the original length. Materials with high elongation at break withstand a high deformation before rupture. A high elongation at break means high flexibility.
- Toughness:
  Toughness is the resistance to fracture of a material when stressed. It is defined as the amount of energy that a material can absorb before rupturing, and can be found by calculating the area underneath the stress-strain curve.

  A material can be strong but not tough; it is therefore said to be brittle.

- Secant Modulus at 2% is a measure of the material stiffness. It is calculated as the stress at 2% divided by 0.02. The higher the modulus, the higher is the rigidity of the material. The lower the modulus, the higher is the ductility and therefore the flexibility of the material. The secant modulus is an approximation of the elastic modulus, also called Young's Modulus, for some materials such as film, where the elastic portion of the stress-strain curve may not be straight enough to measure the slope of the stress-strain curve.

  The values given are „reference values". They have been obtained by testing different irradiated batches (between 25-45 kGy) of the S71 film. For all the mechanical tests described, the standards recommend to test a number of specimens to have a representative mean for the results.



Test Results
The following properties have been tested on Gamma irradiated samples of the S71 film at Room temperature (23 °C) (25–45 kGy):

Properties Film Thickness	Standards	Units	Limits	Reference Value 300 µm	 360 µm
Ultimate Tensile Strength	ISO 527	MPa	MD > 14.4	24	26
			TD > 13.3	19	19
Elongation	ISO 527	%	MD > 440	590	608
			TD > 540	840	793

Properties Film Thickness	Standards	Units		Reference Value 300 µm	 360 µm
Secant Modulus at 2%	ISO 527	MPa	MD	59	50
			TD	57	57
Toughness	ASTM D882	MJ/m^3	MD	83	89
			TD	85	80

3.3.1.2 Resistance to Tearing

Purpose and Test Method
Tear resistance is a complex result of other basic properties, such as modulus and tensile strength. It is a measure of the ability of the film materials to resist tearing. Different standard methods are available for determining tear resistance of plastic films. Some methods measure the force required to propagate a pre-cut slit across a sheet specimen whereas ASTM D1004 details a method for determining the force to initiate tearing in the film. The specimen geometry produces a stress concentration in a small area of the specimen.

Test Results

Properties Film Thickness	Standards	Units		Reference Value 300 µm	 360 µm
Initial Tear Resistance	ASTM D1004	N	MD	23	27
			TD	24	28

3.3.1.3 Flex Durability

Purpose and Test Method
Flex durability is determined by measuring the pinholes formed in the S71 barrier structure after being subjected to the Gelbo Flex test. This test combines twisting motion with an horizontal pushing motion, thus repeatedly twisting and crushing the film.

Test Results

Properties Film Thickness	Standards	Units	Limits	Reference Value 300 µm	 360 µm
Flex Durability	ASTM F392 C	Nb of pinholes	MD < 5	0	0
			TD < 5	0	0

3.3.1.4 Impact Resistance

Purpose and Test Method
Impact resistance testing predicts the durability of the S71 film while in use, especially the resistance to damage by impact of another object. Films with high impact resistance correspond to materials that can absorb the energy of an impact by both resistance to deformation and increased elongation. Impact resistance evaluates the film strength and extensibility properties.

Test Results

Properties Film Thickness	Standards	Units	Reference Value 300 µm	 360 µm
Impact Strength	ISO 7765-2	N	244	300
Total Energy of Perforation	ISO 7765-2	J	4	5

3.3.2 Barrier Properties

The S71 film is a barrier structure.

ISO or ASTM standards on barrier properties describe the method used to measure the amount of gas (O_2, CO_2 or water vapor) that passes through a film. In particular, they describe the sensors used to detect the gas (Electrolytic detection sensor, Modulated Infrared Sensor, Humidity detection sensor, Coulometric Sensor), which will determine the equipment to use. The test conditions, such as the temperature and the relative humidity, which have a great influence on the permeation values, are not recommended by the standards. Selected testing conditions described in this report are chosen to simulate realistic conditions as close as possible, while making sure of the consistency between these conditions and the techniques of measurement. Barrier properties have been tested on Gamma irradiated samples (25–45 kGy) of the S71 film.

3.3.2.1 Barrier to Water Vapor

Purpose and Test Method

This property is very important when the concentration of the products inside the Flexboy® bag is critical. Barrier to water vapor is directly linked to the water loss.

The values displayed in this table are the maximum values obtained.

Test Results

Properties Film Thickness	Standards	Units	Reference Value 300 µm	 360 µm
Water Vapour Transmission Rate	ASTM F1249	g/m² per day	< 2.5	< 2.4

Conditions of Test

		External Side T° = 23 °C
Film	↑	RH = 0%
	↑	Internal Side
	Water Vapour	T° = 23 °C RH = 100%

3.3.2.2 Barrier to Oxygen

Purpose and Test Method
This property is important when the product inside the Flexboy® bag 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 being driven by the partial pressure equilibrium on both sides of the film[1], no oxygen will enter the container if it is not consumed by the solution.

The values displayed in this table are the maximum values obtained from S71 film.

Conditions of Test

	Oxygen ↓	External Side T° = 23 °C RH = 50 %
Film	↓	Internal Side T° = 23 °C RH = 90 %

Test Results

Properties **Film Thickness**	**Standards**	**Units**	**Reference Value** **300 µm**	 **360 µm**
O_2 Transmission Rate	ASTM D3985	cm^3/m^2 per day	< 12	< 8

The results obtained for the 2 film thicknesses are equivalent. The value of the experimental gas transmission rate must be considered as an order of magnitude. What is important is the decade (0.1, 1, 10, 1000) in which the film falls.

3.3.2.3 Barrier to Carbon Dioxide

The values displayed in this table are the maximum values obtained from S71 film.

Conditions of Test

	Carbon Dioxide ↓	External Side T° = 23 °C RH = 0 %
Film	↓	Internal Side T° = 23 °C RH = 0 %

Test Results

Properties **Film Thickness**	**Standards**	**Units**	**Reference Value** **300 µm**	 **360 µm**
CO_2 Transmission Rate	ASTM F2476	cm^3/m^2 per day	< 38	< 27

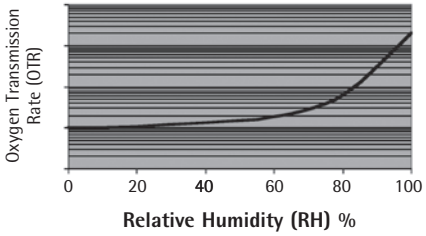
[1] Van Krevelen D.W., "Properties of polymers", Chapter 18, 3rd revised edition, Elsevier, 1997.

3.3.2.4. Remarks Regarding the Influence of the Film Thickness on Barrier Properties

In a multilayer film in general and in the S71 film in particular, the barrier to oxygen and carbon dioxide is given by the EVOH layer. Indeed, the EVA itself is a very poor barrier to O_2 (1080 cc/m² × day[1]). However, the EVA thickness plays a role in the overall structure barrier properties as explained below.

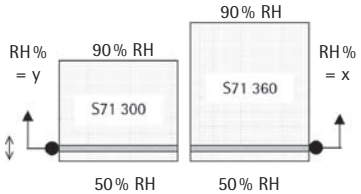
An important factor that influences the gas permeability of EVOH is its moisture sensitivity. The moisture content of an EVOH layer in monolayer or multilayer structures, is determined by the relative humidity of the surrounding atmosphere (on both sides of the EVOH layer). For EVOH monofilm, the relative humidity of the film equals the surrounding humidity. For multilayer structures, the relative humidity depends on the water vapor barrier properties and the thickness of the surrounding materials. As shown on the graph below[2], the permeation rate increases with higher water sorption in a logarithmic scale. Above 60 % RH in the EVOH layer, small % increases of the RH can double or more the OTR of the EVOH layer.

Influence of the relative humidity of an EVOH film on its oxygen transmission rate



Both S71 films (300 and 360 µm) were tested in the same conditions. Consequently, the gradient of relative humidity in each film structure is different: As displayed in the sketch below, the EVOH layer of the 300 µm film is more humid than the EVOH layer of the 360 µm film (y > x), it is therefore less efficient in term of barrier to oxygen.

Film internal layer



Film external layer

3.4. Operating Temperatures

The mechanical properties of the S71 film have been validated between -70 °C and +45 °C.

Please refer to our Celsius application (controlled freeze thaw) for validation testing at low temperature.

[1] see EVAM® Technical Data Sheet on our website

[2] Permeability and other film properties of plastics and elastomers, Plastic Design Library, 1996

4. Fluid Management Systems Integrity

The physical and microbial integrity of Flexboy® bags is guaranteed by the initial qualification tests preformed on seals and connections to other components as well the validation and the capabilities of the manufacturing process.

The qualification program for Flexboy® bags and FMS integrates the recommendations of standards such as ASTM F-2097 (Standard Guide for Design and Evaluation of Primary Packaging for Medical Products) and ISO 15747 (Plastic containers for intravenous injection) or "Pharmaceutical Package Integrity" (PDA Journal of Pharmaceutical Science and Technology) and „Container closure system for packaging Human drugs and biologics Guidance for Industry" issued by FDA-CBER on May 1999.

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

4.1 Seal Strength Integrity

Sample	Testing Method	Acceptance Criteria
Film|Film Bag Seal	Visual inspection	No bubble, no infiltration, no channel, no fold, clear welding and constant width.
	Tensile test of a 15 mm width sample at a pulling speed of 500 mm/min	Film break or F > 20N
	Red ink test: The absence of channels is checked through dye penetration.	0 penetration or channel
Film|Tubing|Film	Visual inspection	No bubble, no infiltration, no channel, no fold, clear welding and constant width.
	Tensile test of a 15 mm width sample at a pulling speed of 500 mm/min	Film break or F > 15N
	Red ink test: The absence of channels is checked through dye penetration.	0 penetration or channel
Bag	Drop test	No leak
	Provaset (bag is inflated and restrained between two rigid plates, a pressure decay is noted)	No pressure decay
	Leak test (bag is submersed and inflated: Bubbles issued from leaks in the package seal or material are noted)	No leak
	Burst test: Bag is inflated until it bursts.	Weakest area is noted.
Secondary Packaging	Visual inspection	No bubble, no infiltration, no channel, no fold, clear welding and constant width.

4.2 Component|Assemblies Integrity

Sample	Testing Method	Acceptance Criteria
Connection Tightness	The connected parts are submersed, a pressure of 1 bar is applied. The bubbles issued from leaks between the connected parts are noted.	0 bubble
Fitting Strength	The connected parts are pulled in a tensile test at a speed of 500 mm/min. The strength F is measured.	If FD[1] < 5 mm then F > 25N If 5 < FD[1] < 7 mm then F > 40N If FD[1] > 7 mm then F > 60N
Dust Cap Pulling Strength	The connected parts are pulled in a tensile test at a speed of 500 mm/min. The pulling strength F is measured.	F > 5N and F < 40N
Clamping Force	A force is applied on the clamp in a compression test at a speed of 200 mm/min. The force required to clamp is measured.	Small clamp/F < 80N Medium clamp/F < 165N. Big clamp/F < 330N
Cracking (PC components only)	Components are submersed into the appropriate crack revealing solution during 3 min. cracks are noted.	No crack

[1] FD Functional Diameter

5. Biocompatibility

Purpose and Test Method
Biocompatibility tests are performed to demonstrate that all components used for the manufacture of S71 film are biocompatible and meet or exceed the current USP and ISO requirements. Tests are carried out on S71 film samples after Gamma irradiation (50 kGy) and after accelarated ageing conditions.

Film samples were supplied to an independent testing facility for evaluation under the current USP <87>, USP <88> Class VI Plastics Tests:

- Cytotoxicity test
- Intracutaneous test
- Systemic injection test
- Implantation test (7 days)

Test Results
All material used in the construction of the S71 film meet or exceed the requirements of the USP Class VI– 70 °C Plastics tests and are considered as non cytotoxic. The complete test reports are available upon request.

The following certificates were released as a result of the testing of S71 film used in the manufacture of Flexboy® bags.

Cytotoxicity Test: USP <87>: Report Summary S71 at t = 0

SGS

Sartorius Stedim Biotech
ZI des Paluds
Avenue de Jouques
BP1051
F-13781 Aubagne cedex

For the attention of Mr Samuel Dorey

Order N°: 191504

Bierges, August 05 2008

ASSAY REPORT ADDEMDUM

Product name	:	Flexboy (S71-2)
Batch	:	RD017_013-50
Assay	:	In vitro cytotoxicity according to USP 87
Method	:	Elution Test
Duration of the assay	:	01.07.08 to 04.07.08

Monolayers of cultured cells are incubated with dilutions of the product under investigation in culture medium.
After incubation (48 h, 37 °C, 5 % v/v CO_2), the cytotoxic effect of the product is observed by microscopic examinations (magnification: 100 x).

Negative and positive controls are checked simultaneously. The sample meets the requirements of the test if the culture treated with the sample extract shows no greater than a mild reactivity (grade 2) and no significantly greater reaction than the culture treated with the negative control.

4. CONCLUSION

In the conditions of the assay, the tested product "Flexboy (S71-2)" (batch RD017_013-50) must be considered as non cytotoxic.

05/08/08

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Biocompatibility S71 (USP <88> Class VI) after 3 years accelerated conditions

TOXIKON

Class VI Test – USP
Project Number: 07-3516-N1 - Amended
Test Article: ST71 – EVA [redacted], sterilized at 50 kGys, storage time: 11 months + 3 days at 40°C

STUDY SUMMARY

The USP 0.9% Sodium Chloride for Injection (NaCl), Cottonseed Oil (CSO), 1 in 20 Ethanol in NaCl (EtOH), and Polyethylene Glycol 400 (PEG) extracts of the test article and the test article, ST71 – EVA Dupont, sterilized at 50 kGys, storage time: 11 months + 3 days at 40°C, did not produce a biological response following intramuscular implantation in rabbits, intracutaneous injection in rabbits, or systemic injection in mice. Therefore, the test article meets the requirements of the USP guidelines, for Class VI Plastics – 70 °C.

6. Physico Chemical Test

6.1 European Pharmacopoeia – Ethylene-Vinyl Acetate Copolymer for Containers and Tubing for Parenteral Nutrition Preparation.

Purpose and Test Method
The EVAM® contact layer of the S71 film used in Flexboy® bags has been tested in compliance with the recommendations of the European Pharmacopoeia E.P. # 3.1.7.

"Ethylene-Vinyl Acetate copolymer for containers and tubing for parenteral nutrition preparation".

Test Results
The EVAM® contact layer made of EVA used for Fleboy® bags meets the requirements of the European Pharmacopoeia 3.1.7.

The test methods, limits and results are those described by the E.P. monograph and listed in the table below.

Test Description	E.P. Limits	EVAM® Contact Layer Results: Pass|Fail
Appearance of solution	clear and colourless	Pass
Acidity or alkalinity	≤ 1.0 mL NaOH 0.01M, blue colour ≤ 1.5 mL HCl 0.01M, orange colour	Pass
Absorbance at wavelengths From 220 nm to 40 nm	≤ 0.2	Pass
Reducing substances	Difference between Test solution and blank ≤ 0.5 mL	Pass
Amide and stearic acid	Pass	Pass
Phenolic antioxidant	Pass	Pass
Substances soluble in hexane	Residue less than 2 %	Pass
Sulphated ash	≤ 1.2 %	Pass
Vinyl acetate	≤ 25 %	Pass
IR-Spectrum	Maxima at 2920 cm^{-1} to 2850 cm^{-1}, 1470 cm^{-1}, 1460 cm^{-1}, 175 cm^{-1}, 70 cm^{-1} and 720 cm^{-1}.	Pass

6.2 USP <661> – Containers, Physicochemical Tests – Plastic

Purpose
Physicochemical tests are designed to determine physical and chemical properties of Flexboy® bag plastics and their extracts. They are performed on S71 film after irradiation (50 kGy) and accelerated ageing conditions. The extraction is done under aqueous conditions.

Test Method and Results on Aqueous Extract
Samples of the S71 film are previously Gamma irradiated, stored in 3 years accelerated ageing conditions and extracted (ratio of 120 cm^2 per 20 mL) in Ultra Pure water at 70 °C for 24 hours.

The following test is conducted in order to determine physical and chemical properties of the test article and its extracts.

The S71 film meets the USP <661> requirements.

Test Description	USP <661> Limits	S71 Results
Non Volatile Residue	< 15 mg	pass
Residue on Ignition	< 5 mg	pass
Heavy Metals	< 1 ppm	pass
Buffering Capacity	< 10 mL	pass

Test Result Certificate USP <661> S71

TOXIKON

Leaders in Life Science and Technology

TEST RESULT CERTIFICATE

Project Number:	**TE 07623**	**Study Number:**	**07-B1887-N1**
Sponsor:	**Stedim Sartorius Biotech**	**Report Date:**	**03/09/2007**
Contact:	*Mrs. Isabelle Uettwiller*		
Address:	ZI des Paluds Av de Jouques BP10 13400 Aubagne France		
		Technical Initiation:	30/08/2007
P.O.Number:	CAA071597	Technical Completion:	31/08/2007

Study	**USP - Physicochemical Test for Plastics**	Temp/Time	70°C / 24Hr
Test Item	St71	Ratio	120cm^2 per 20 ml
Lot	RE109279 lot:06A900052	Vehicle	UPW

REFERENCE: USP 30-NF 25, 2007: <661> Containers, "Physicochemical Tests – Plastics"
Toxikon Reference: SOP 3.2.2, current version

PROCEDURE: The test item was extracted in Ultra Pure Water (UPW), after rinsing in UPW. The following tests were conducted in order to determine physical and chemical properties of the test article and its extracts.

RESULTS:

TEST	TEST RESULT	ACCEPTABLE LEVEL	PASS/FAIL
Non-volatile Residue	1.9 mg	< 15 mg	Pass
Residue on Ignition	Not Applicable	< 5 mg	Pass
Heavy Metals	No Colour	Colour in Test Solution is less than the 1 ppm Reference	Pass
Buffering Capacity	<0.1 ml 0.01N NaOH	10 ml 0.01N NaOH	Pass

CONCLUSION: The test item meets the requirements of the USP 30-NF 25, <661> based upon the methods employed.

RECORD STORAGE: All raw material generated in this study will be archived at Toxikon Europe, according to SOP 4.2.8.

AUTHORIZED PERSONNEL

Edwin De Gelder
Study Director

Gaby Boonen
Quality Assurance

Toxikon Europe nv - Romeinsestraat 12 - B - 3001 Leuven - Belgium - Tel. 32-16-40 04 84 - Fax 32-16-40 13 04 - www.toxikon.com
Fortis 230-0391575-06 - KBC 431-0597001-33 - BTW/TVA BE 0442.395.719 - H.R. Leuven 80.154

7. Stability of Water for Injection

Flexboy® bags are analyzed according to the specifications given in section "Sterile Water for Injection" of both the current USP and EP.

Flexboy® 5 liters storage bag are exposed to a worst case Gamma irradiation at 50 kGy and used for extractables testing.

Tests are conducted at ambient temperature and results are established for intermediate storage times of 1 day, 8 days, 15 days, 1 month, 3 months and 4 months.

7.1 Testing According to USP for "Sterile Water for Injection"

Flexboy® bags are analyzed for particulates, sterility, endotoxins, oxidizable substances, pH, Ammonia, Calcium, Carbon dioxide, Chloride and Sulphate, according to the specifications given in section "Sterile Water for Injection" of the current USP.

7.1.1 Particle Content

Purpose and Test Method

Particle testing is performed to demonstrate that Flexboy® bags meet the limits of the current USP for "Large Volume Parenterals for Single Dose Infusion".

250 mL Flexboy® bag extracts are analyzed with an electronic, liquid borne particle counting system that uses a light-obscuration sensor with a suitable sample-feeding device.

The method is in compliance with the requirements of the USP <788> "Particle matter in injections".

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	$\leq$ 25 particles/mL $\geq$ 10 µm $\leq$ 3 particles/mL $\geq$ 25 µm	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the requirements of the current USP for particle content after 4 months extraction at room temperature.

7.1.2 Sterility Test

Purpose and Test Method
Sterility testing is performed to demonstrate that solutions remain sterile after storage in Flexboy® bags for 4 months at room temperature.

300 mL of Sodium Chloride solution is stored in 5 liters Flexboy® bags at room temperature; Extracts are then tested by applying the Membrane Filtration Test Method according to the USP <71> requirements.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	sterile	passed	passed	passed	passed	passed	passed

Flexboy® bags remain sterile after 4 months storage at room temperature.

7.1.3 Endotoxin Test

Purpose and Test Method
The goal of endotoxin testing is to establish that the amount of endotoxins released from Flexboy® bags in the Water for Injection extracts is less than 0.25 EU/mL after extended storage time.

A volume of 250 mL has been validated to extract all endotoxins contained in a 5 liters Flexboy® bag. Water for Injection extract is tested by applying the quantitative kinetic-chromogenic test method according to the USP <85> requirements.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	< 0.25 EU/mL	passed	passed	passed	passed	passed	passed

Extracts of Flexboy® bags made of S71 film meet the USP limits of less than 0.25 EU/mL bacterial endotoxins after 4 months storage of WFI at room temperature.

7.1.4 Determination of Oxidizable Substances

Test Method
10 mL of 2 N sulfuric acid is added at 100 mL of the WFI extract and heated to boiling. Then 0.2 mL of 0.1 N potassium permanganate is added and the solution is boiled for 5 minutes. If a precipitate forms, it is cooled to room temperature. If the precipitate remains its pink color after cooling to room temperature, the test samples meet the USP specifications for oxidizable substances.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	pink color	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the requirements of the current USP for oxidizable substances.

7.1.5 Determination of pH Values

Test Method
WFI extracts are tested in the specified pH range of 5 to 7 in a solution containing 0.3 mL of saturated potassium chloride solution per 100 mL of extract.

pH value of the WFI extracts is measured using appropriate calibrated pH meter according to the USP regulations.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	5.0–7.0	4.5	4.5	4.5	4.6	4.4	4.3

Due to the EVA contact layer, we can notice an immediate decrease of the pH after storage of WFI in Flexboy® bags. From that point onwards, the pH value stays stable over time. The pH shift is due to the presence of Acetic Acid regardless of the origin of the EVA resin.

This phenomenon has not been noticed when buffered solutions are tested. The results of the stability of one buffered solution stored in S71 are displayed in the paragraph 7.4.

7.1.6 Determination of Chloride

Test Method
5 drops of nitric acid and 1 mL of silver nitrate are added to 20 mL samples of the WFI extract and gently mixed. If the turbidity level within 10 minutes is below the control reagent consisting of 20 mL of high purity water containing 0.5 mg/L of Chloride, the test is passed.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	< 0.5 mg/L	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the current USP Limits for Chloride for "Sterile Water for Injection".

7.1.7 Determination of Sulfate

Test Method
1 mL of barium chloride is added to the 100 mL WFI extract. If no turbidity forms the test is passed Flexboy® bags meet the current USP

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	no turbidity	passed	passed	passed	passed	passed	passed

Limits for Sulfate for "Sterile Water for Injection".

7.1.8 Determination of Ammonia

Test Method
2 mL of alkaline mercuric-potassium iodide are added to 100 mL of the WFI abstract. If the yellow color produced immediately is not darker than that of a control containing 30 µg of added NH3 in High Purity Water, the test is passed. This corresponds to a limit of 0.3 mg/L.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	< 0.3 mg/L	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the requirements set by the current USP Limits for Ammonia for "Sterile Water for Injection".

7.1.9 Determination of Calcium

Test Method
2 mL of ammonium oxalate TS is added to 100 mL of the WFI extract. Test is passed if no turbidity is produced.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	no turbidity	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the requirements set by the current USP Limits for Calcium for "Sterile Water for Injection".

7.1.10 Determination of Carbon Dioxide

Test Method
3 g of USP-grade calcium hydroxide are mixed with 1000 mL water at 25 °C for 1 hour. 25 mL of calcium hydroxide TS is added to 25 mL of test sample. Test is passed if the mixture remain colorless.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	colorless	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the requirements set by the current USP Limits for Carbon Dioxide for "Sterile Water for Injection".

7.2 Testing According to European Pharmacopoeia for "Sterile Water for Injection"

Flexboy® bags are analyzed for particulates, sterility, endotoxins, oxidizable substances, acidity & alkalinity, conductivity, residue of evaporation, sulfate, ammonium and calcium & magnesium using the methods and specifications given in section "Sterilised Water for Injection" of the European Pharmacopoeia (E.P.).

7.2.1 Particle Content

Purpose and Test Method

Particle testing is performed to demonstrate that Flexboy® bags meet the limits of the current E.P. for "Large Volume Parenterals for Single Dose Infusion".

The extracts are tested with an electronic, liquid-borne particle counting system that uses a light-obscuration sensor with a suitable sample-feeding device. The method is in compliance with the requirements of the E.P. 2.9.19 "Particle contamination-Sub-visible particles".

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	$\leq$ 25 particles/mL $\geq$ 10 µm	passed	passed	passed	passed	passed	passed
	$\leq$ 3 particles/mL $\geq$ 25 µm	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the requirements of the current E.P. for particle content after 4 months storage of WFI at room temperature.

7.2.2 Sterility Test

Purpose and Test Method
Sterility testing is performed to demonstrate that solutions remain sterile after storage in Flexboy® bags for 4 months at room temperature.

A 300 mL volume of Sodium Chloride solution is stored in 5 liters Flexboy® bags at room temperature. Sodium Chloride extracts are then tested by applying the Membrane Filtration Test Method according to the E.P. 2.6.1 requirements.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	sterile	passed	passed	passed	passed	passed	passed

Flexboy® bags remain sterile after 4 months storage at room temperature.

7.2.3 Endotoxin Test

Purpose and Test Method
The goal of endotoxin testing is to establish that the amount of endotoxins released from Flexboy® bags in the Water for Injection extracts is less than 0.25 EU/mL.

A volume of 250 mL has been validated to extract all the endotoxins contained in a 5 L Flexboy® bag. Water for Injection extracts are tested by applying the quantitative kinetic-chromogenic Test Method according to the E.P. 2.6.14 requirements.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	< 0.25 EU/mL	passed	passed	passed	passed	passed	passed

Flexboy® bag extracts tested, under the conditions of the extraction test described above, show bacterial endotoxin results below 0.25 EU/mL.

7.2.4 Determination of Oxidizable Substances

Test Method
As described in the current E.P, 10 mL of 2 N sulfuric acid is added to 100 mL of the WFI extract and heated to boiling. Then 0.2 mL of 0.1 N potassium permanganate is added and the solution is boiled for 5 minutes. If a precipitate forms, it is cooled to room temperature. If the precipitate remains its pink color after cooling to room temperature, the test samples meet the E.P. specifications for oxidizable substances.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	pink color	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the requirements of the current E.P. for oxidizable substances.

7.2.5 Acidity & Alkalinity

Test Method
0.05 mL of phenol red solution is added to 20 mL of each extract. The test samples meet the E.P. specification if a yellow solution turns to red after the addition of 0.1 mL of 0.01 M Sodium Hydroxide or if a red solution turns to yellow on addition of 0.15 mL of 0.01 M Hydrochloric acid.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	yellow|red	< 0.1 mL	< 0.1 mL	< 0.1 mL	< 0.1 mL	< 0.1 mL	< 0.1 mL

Flexboy® bags meet the requirements of the current E.P. for acidity and alkalinity.

7.2.6 Conductivity

Test Method
Maintaining the sample temperature at 25 ± 1 °C, the conductivity is measured using appropriate calibrated conductivity meter according to the E.P. regulations.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	< 5 µS/cm	12.8	15.0	15.7	17.0	20.1	20.0

The increase of the conductivity is linked with the decrease of the pH. This phenomenon has not been noticed when buffered solutions are tested. The results of the stability of one buffered solution stored in S71 are explained in the paragraph 7.4.

7.2.7 Determination of Residue of Evaporation

Test Method
1100 mL of the extracted WFI is evaporated to dryness on a water bath and dried in an oven at 100–105 °C.

The E.P. specification for Residue of Evaporation is met if a maximum value of 3 mg (0.003 %) is weighed for containers with a nominal volume greater than 10 mL.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	0.003 %	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the requirements of the current E.P. for Residue of Evaporation.

7.2.8 Determination of Sulfates

Test Method
0.1 mL of diluted hydrochloric acid is added to 10 mL of each WFI extract. The test samples meet the E.P. specification if the solutions show no change in appearance for at least 1 hour.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	no modification for at least 1 h	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the requirements of the current E.P. for Sulfates.

7.2.9 Determination of Ammonium

Test Method
1 mL of alkaline potassium tetraiodomercurate solution is added to 20 mL of each WFI extract. At the same time, a standard is prepared by adding 1 mL of alkaline potassium tetraiodomercurate solution to a mixture of 4 mL of ammonium standard and 16 mL of ammonium-free water (corresponds to 0.2 ppm of ammonium content). After 5 minutes, the solutions are examined down the vertical axis of the tube. The test samples meet the E.P. specification if the solutions are not more intensely colored than the standard.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	< 0.2 ppm	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the requirements of the current E.P. for Ammonium.

7.2.10 Determination of Calcium and Magnesium

Test Method
2 mL of ammonium chloride buffer solution pH 10.0, 50 mg of mordant black 11 triturate and 0.5 mL of 0.01 M sodium edetate are added to 100 mL of each WFI extract. The test samples meet the E.P. specification if a pure blue color is produced.

Test Results

Film	Limits	1 Day	8 Days	15 Days	1 Month	3 Months	4 Months
S71	a distinct blue color appears	passed	passed	passed	passed	passed	passed

Flexboy® bags meet the requirements of the current E.P. for Calcium and Magnesium.

7.3 Total Organic Carbon Analysis of "Sterile Water for Injection"

Purpose and Test Method
TOC analysis are performed in static extraction mode. This methodology provides the best representative of actual storage applications determining levels of extractable substances. The quantitative methods is performed according to the USP <643> requirements.

The following bags are used for extractables of Sartorius Stedim Flexboy® bags, representing the individual bag types available: 5 liters storage bag. Prior to the tests the bags are exposed to a Gamma irradiation at 50 kGy.

The following results display the TOC amount quantified in Water for Injection after a storage time at ambient temperature of 1 day, 8 days, 15 days, 1 month 3 months and 4 months. The extractions of the tested bags are carried out with a volume of 5 liters each.
TOC is required by the USP for the Water for Injection produced on site for use in manufacturing.

Test Results

Film	1 Day [ppm]	8 Days [ppm]	15 Days [ppm]	1 Month [ppm]	3 Months [ppm]	4 Months [ppm]
S71	3.5	4.4	4.8	5.4	6.3	6.3

TOC analysis is required by the E.P. for WFI and Purified Water produced in bulks while oxidizable substances is asked for WFI in containers. TOC values are given for information.

7.4 Stability of TrisHCl 50 mM

Purpose and Test Method
30 mL storage bag made with S71 film are exposed to a worst case Gamma irradiation at 50 kGy and used for stability of TrisHCl 50 mM.

The bags have been filled up with 30 mL of the TrisHCl 50 mM buffer solution.

Tests are conducted at ambient temperature and results are established for intermediate storage times of 7 and 30 days.

Test Results for pH
pH value of the buffer extracts is measured using appropriate calibrated pH meter.

Film	T0	7 Days	30 Days
S71	8.00	7.88	7.99

Test Results for Conductivity
Conductivity of the buffer extracts is measured using appropriate calibrated conductivity meter.

Film	T0	7 Days	30 Days
S71	2.88	2.90	2.98

For buffered solution, there is no significant change of pH and conductivity for one month storage duration in Flexboy® bags.

8. Chemical Resistance Studies

Purpose and Test Method
A chemical resistance study is conducted to assess the resistance of Flexboy® bags to a variety of chemical solutions. The test protocol was developed following the principles of the standard test "Method for Resistance of Plastic to chemical reagents" D543-06.

Three 500 mL Flexboy® bags with EVA tubing, Polycarbonate connectors and ABS additive port previously Gamma irradiated at 50 kGy are filled with 400 mL of solution.

One additional bag system filled with purified water is used as a reference. Bags are stored at room temperature during a specific contact time and tested for compatibility:

- 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 and miscellaneous solutions are summarized in the table hereunder.

The Flexboy® bags show excellent compatibility with buffers, alkaline and acidic solutions and amino-acid solution.

In general, high concentrations of organic solvents are not recommended and should be tested on a case by case basis.

Chemical resistance studies can be proposed upon customer's request according to specific process conditions (i.e. time, temperature and type of solution).

Organic Solvents % w/v	Compatibility Status	Contact Time	Storage Temperature
Acetone	Not recommended use	7 days	22 ± 3 °C
70 % Ethanol denatured	Excellent compatibility	6 weeks	22 ± 3 °C
95 % Ethanol	Excellent compatibility	7 days	22 ± 3 °C
50 % Ethanol	Excellent compatibility	7 days	22 ± 3 °C
100 % Benzene	Poor compatibility	7 days	22 ± 3 °C
100 % Carbon tetrachloride	Not recommended use	7 days	22 ± 3 °C
100 % Chloroform	Not recommended use	7 days	22 ± 3 °C
0.5 % Chloroform	Excellent compatibility	3 months	5 ± 3 °C
0.5 % Chloroform	Excellent compatibility	6 months	5 ± 3 °C
100 % Dichloromethane	Not recommended use	7 days	22 ± 3 °C
100 % Diethyl ether	Acceptable compatibility	7 days	22 ± 3 °C
100 % Dimethylformamide	Poor compatibility	7 days	22 ± 3 °C
1.2 Ethanediol	Acceptable compatibility	7 days	22 ± 3 °C
100 % Ethyl acetate	Acceptable compatibility	7 days	22 ± 3 °C
100 % Ethylene dichloride	Not recommended use	7 days	22 ± 3 °C
1.2.3 Propanetriol (100 % Glycerol)	Fair compatibility	7 days	22 ± 3 °C
100 % Heptane	Poor compatibility	7 days	22 ± 3 °C
100 % Iso octane	Not recommended use	7 days	22 ± 3 °C
30 % Isopropanol	Excellent compatibility	7 days	22 ± 3 °C
100 % Methanol	Not recommended use	7 days	22 ± 3 °C
100 % Phenol	Not recommended use	7 days	22 ± 3 °C
100 % 1.2 Propanediol	Not recommended use	7 days	22 ± 3 °C
100 % Toluene	Not recommended use	7 days	22 ± 3 °C

Acid Solvents % w/v	Compatibility Status	Contact Time	Storage Temperature
100 % Acetic acid	Not recommended use	7 days	22 ± 3 °C
5 % Acetic acid	Excellent compatibility	7 days	22 ± 3 °C
50 % Acetic acid	Excellent compatibility	1 month	22 ± 3 °C
50 % Acetic acid	Excellent compatibility	10 days	22 ± 3 °C
40 % Chromic acid	Acceptable compatibility	7 days	22 ± 3 °C
1 % Citric acid	Excellent compatibility	7 days	22 ± 3 °C
10 % Hydrochloric acid	Excellent compatibility	7 days	22 ± 3 °C
10 % Nitric acid	Excellent compatibility	7 days	22 ± 3 °C
40 % Nitric acid	Excellent compatibility	7 days	22 ± 3 °C
10 % Oleïc acid|ethanol	Excellent compatibility	7 days	22 ± 3 °C
25 % Phosphoric acid	Excellent compatibility	30 days	5 ± 3 °C
30 % Sulfuric acid	Excellent compatibility	7 days	22 ± 3 °C
0.1 % Trifluoro acetic acid	Excellent compatibility	7 days	22 ± 3 °C

Alkaline Solutions % w/v	Compatibility Status	Contact Time	Storage Temperature
100 % Aluminum hydroxide	Excellent compatibility	7 days	22 ± 3 °C
10 % Ammonium hydroxide	Excellent compatibility	7 days	22 ± 3 °C
25 % Ammonium hydroxide	Not recommended use	30 days	5 ± 3 °C
2 % Sodium carbonate	Excellent compatibility	7 days	22 ± 3 °C
20 % Sodium carbonate	Excellent compatibility	7 days	22 ± 3 °C
1 % Sodium hydroxide	Excellent compatibility	7 days	22 ± 3 °C
10 % Sodium hydroxide	Acceptable compatibility	7 days	22 ± 3 °C
40 % Sodium hydroxide	Excellent compatibility	30 days	5 ± 3 °C
60 % Sodium hydroxide	Excellent compatibility	7 days	22 ± 3 °C

Buffers & Salts % w/v	Compatibility Status	Contact Time	Storage Temperature
Buffer pH = 4	Acceptable compatibility	7 days	22 ± 3 °C
Buffer pH = 5	Acceptable compatibility	7 days	22 ± 3 °C
Buffer pH = 7	Excellent compatibility	7 days	22 ± 3 °C
Buffer pH = 10	Excellent compatibility	7 days	22 ± 3 °C
1 M Ammonium chloride	Excellent compatibility	7 days	22 ± 3 °C
10 % Calcium carbonate	Excellent compatibility	7 days	22 ± 3 °C
3M Calcium chloride	Excellent compatibility	7 days	22 ± 3 °C
750 mM Citrate	Excellent compatibility	7 days	22 ± 3 °C
Saline solution citrate buffer (SSC)	Excellent compatibility	7 days	22 ± 3 °C
2 M Sodium acetate	Excellent compatibility	1 month	22 ± 3 °C
0.3 M Sodium acetate	Excellent compatibility	1 month	5 ° ± 3 °C
10 % Sodium chloride	Excellent compatibility	7 days	22 ± 3 °C
4 M Sodium chloride	Excellent compatibility	7 days	22 ± 3 °C
0.25 M Phosphate, 3.75 M Sodium chloride	Excellent compatibility	7 days	22 ± 3 °C
0.25 M Triphosphate, 3.75 M Sodium chloride	Excellent compatibility	7 days	22 ± 3 °C

Amino-Acids % w/v	Compatibility Status	Contact Time	Storage Temperature
Mixture amino acid (BME)	Excellent compatibility	7 days	22 ± 3 °C
100 % Aniline	Acceptable compatibility	7 days	22 ± 3 °C

Disinfectants % w/v	Compatibility Status	Contact Time	Storage Temperature
30 % Hydrogen peroxide	Excellent compatibility	7 days	22 ± 3 °C
28 % Hydrogen peroxide	Excellent compatibility	7 days	22 ± 3 °C
4-6 % Sodium hypochlorite	Good compatibility	7 days	22 ± 3 °C

Detergents % w/v	Compatibility Status	Contact Time	Storage Temperature
30 % Magnesium carbonate	Acceptable compatibility	7 days	22 ± 3 °C
100 % Triton X-100	Good compatibility	7 days	22 ± 3 °C
1 % Soap solution	Excellent compatibility	7 days	22 ± 3 °C

Miscellaneous % w/v	Compatibility Status	Contact Time	Storage Temperature
100 % Cetvalon	Excellent compatibility	7 days	22 ± 3 °C
10 % Cetvalon	Excellent compatibility	1 month	40 ± 3 °C
12 % Deoxycholate	Excellent compatibility	10 days	22 ± 3 °C
12 % Deoxycholate	Excellent compatibility	1 month	22 ± 3 °C
Distilled water (WFI)	Excellent compatibility	7 days	22 ± 3 °C
50 % Dextrose, 1 % sulphate magnesium	Excellent compatibility	10 days	22 ± 3 °C
50 % Dextrose, 1 % sulphate magnesium	Excellent compatibility	1 month	22 ± 3 °C
50 mM EDTA, 1 M Sodium chloride	Excellent compatibility	30 days	22 ± 3 °C
50 % Ethylene glycol, 2 M Sodium chloride	Excellent compatibility	7 days	22 ± 3 °C
60 % Isopropanol, 0.1 % trifluoroacetic	Excellent compatibility	7 days	22 ± 3 °C
50 % Maltose	Excellent compatibility	2 months	5 ± 3 °C
Olive oil	Acceptable compatibility	7 days	22 ± 3 °C
60 % Saccharose	Excellent compatibility	30 days	5 ± 3 °C
4 % Saccharose, 0.2 M Sodium chloride	Excellent compatibility	30 days	5 ± 3 °C
2 M Sodium ethylate	Excellent compatibility	7 days	22 ± 3 °C
20 % Sodium iodide	Good compatibility	10 days	22 ± 3 °C
20 % Sodium iodide	Good compatibility	1 month	22 ± 3 °C
Sodium phosphate, sodium chloride, Tween 80	Excellent compatibility	30 days	22 ± 3 °C
Sorbitol, Tween 80, acetic acid, sodium acetate	Excellent compatibility	7 days	22 ± 3 °C
0.2 % Triethylamine	Excellent compatibility	7 days	22 ± 3 °C
100 % Tween 80	Excellent compatibility	7 days	22 ± 3 °C
Tween 80, sodium citrate, citric acid	Excellent compatibility	6 months	22 ± 3 °C
Tween 80, sodium citrate, citric acid	Excellent compatibility	6 months	5 ± 3 °C
10 % Urea	Excellent compatibility	7 days	22 ± 3 °C
White Mineral oil	Excellent compatibility	7 days	22 ± 3 °C

9. Gamma Sterilization

9.1 Purpose

A sterilization validation study has been performed in order to demonstrate the effectiveness of the sterilization method applied to Sartorius Stedim Flexboy® bags and FMS. This sterilization validation adresses the worst-case scenario 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 % Bags air leak tested ■ 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 ■ 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 irradiation.

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 microorganisms 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 micro-organism.

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.

9.2 Method

Full compliance with ISO 11137 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 guidelines.

9.2.1 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 worst case bag range produces accurate and reproducible bioburden recovery results that are the critical cornerstone for the rest of the validation study. Bioburden quantification for Flexboy® 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.

9.2.2 Verification Dose Experiments

Once the bioburden is established (i.e. quantified, identified and assessed for its resistance) one can define the verification dose to be used for the validation. The verification dose is calculated to produce a SAL 10^{-2} according to the rules defined in the ISO 11137 document.

The verification dose experiment is conducted on 100 units of the SIP. Sterility test must pass the criteria of ≤ 2 positives.

9.2.3 Establishment of the Minimum Gamma Sterilization Dose

After a successful verification dose experiment a 25 kGy minimum routine dose is then selected to ensure SAL of 10^{-6} for all ranges of Flexboy® FMS.

A 25 kGy minimum routine sterilization dose will always ensure sterility as long as Bioburden inside bags stays lower than 1000 cfu. Sartorius Stedim Biotech ensures that the minimum Gamma sterilization dose is still valid by routinely monitoring product bioburden (quantification and characterization) on all FMS families.

9.2.4 Establishment of the Maximum Irradiation Dose

The maximum sterilization is established to ensure that Flexboy® FMS fit, form and function is not affected by the Gamma irradiation process. The compatibility of Flexboy® FMS with the maximum irradiation dose of 50 kGy is assessed after 3 years normal ageing conditions to establish the maximum shelf life.

9.2.5 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 Flexboy® FMS is within specified limits (i.e. greater than 25 kGy). In routine sterilization, dosimeters are placed at minimum and maximum dose locations that have been identified during dose mapping. Dose mapping is repeated after source replenishments to confirm the magnitude, distribution and reproducibility of the irradiation process.

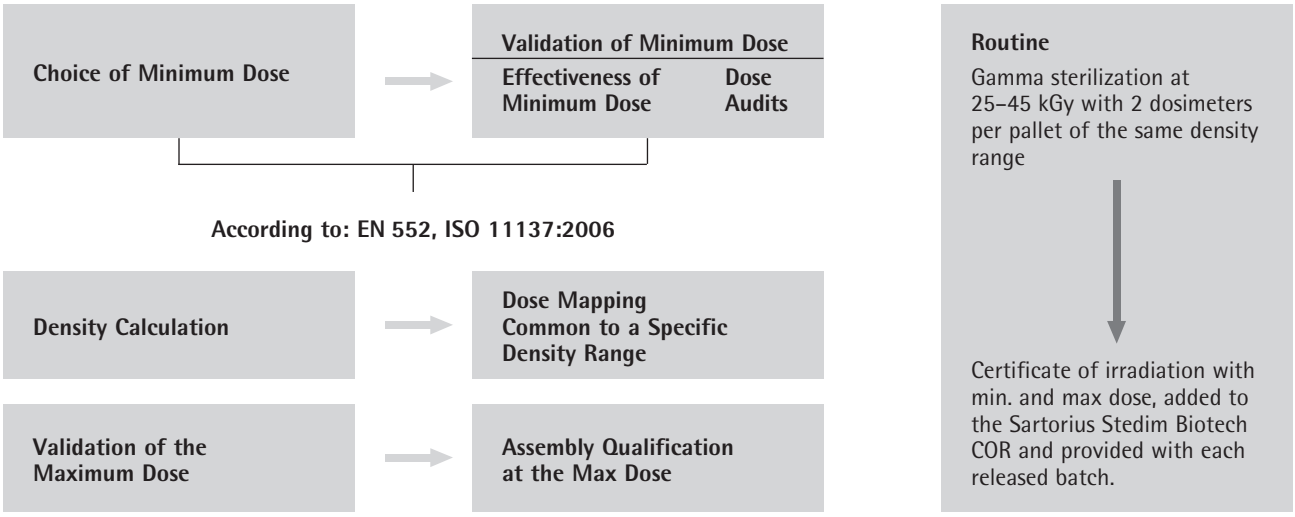
The second critical aspect of maintenance of sterility is the routine characterization of product bioburden. Product bioburden is quantified routinely on each FMS production line and for all size of products to ensure that the limit of 1000 cfu is never exceeded. Environmental monitoring is routinely performed to address potential changes to our manufacturing environment.

FMS product bioburden is also routinely identified to address potential seasonal variations. This identification allows for a resistance assessment of product bioburden against model populations.

Finally, dose audits are performed at the frequency required by ISO 11137 to verify that the initial validation is still applicable. Dose audits are performed using the original verification dose.

9.3 Results

The sterility validation for the Sartorius Stedim Flexboy® bags product line has met the requirements set forth in the applicable regulations



10. Validation of Shelf Life

Flexboy® FMS are normally validated for a 3 year shelf life post Gamma sterilization, using both accelerated and actual time ageing conditions. If a new component with a shorter shelf life is used in a Flexboy® system, the whole Flexboy® FMS will receive the shortest shelf life. Strict procedures are in place that control the design of Flexboy® FMS 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 characteristics, the biocompatibility and the sterility of Flexboy® FMS are assessed and compared with original properties after a 3 year storage in accelerated and|or real conditions.

Test[1]	Reference Values	AT t = 0	AT t = 3 yrs
Gas Transmission			
Oxygen (300 µ film)	< 16 cm^3/m^2 per day	Pass	Pass
Water vapor	< 5 cm^3/m^2 per day	Pass	Pass
Mechanical Properties			
Tensile strength	> 13 MPa	Pass	Pass
Elongation at break	> 400 %	Pass	Pass
Heat seal strength	> 15 N	Pass	Pass
Integrity Properties			
On bag	no leak when filled	Pass	Pass
On connections	1 Bar for 10 sec	Pass	Pass
Physico-Chemical Tests	USP <661>	Pass	Pass
Biocompatibility	USP <88>	Pass	Pass
Material Ageing	reference IR Spectra	Pass	Pass
Primary Packaging			
Seal strength	> 20 N	Pass	Pass
Ink penetration	no channels	Pass	Pass
Sterility Test	no growth	Pass	Pass

[1] See test description in previous chapters.

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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