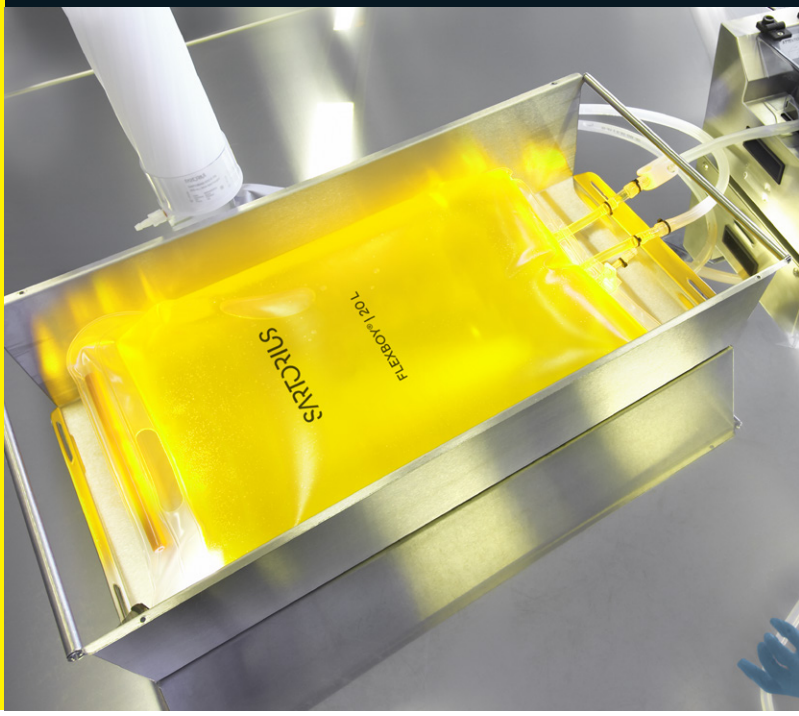
SARTORIUS

Product Datasheet

Flexboy® 2D Pre-Designed Solutions for Storage Throughout All Process Steps



The growing adoption of Single Use Systems (SUS) in all process steps of cGMP clinical and commercial production requires enhanced assurance of supply and robust product performance.

Flexboy® PDS: Our Solution

- Industry leading assurance of supply
- Proven robustness
- Container closure integrity
- Excellent and reproducible cell growth
- Consistent extractable profile

Single-use technology is increasingly being applied in more critical process steps such as drug substance and drug product storage. This has raised new challenges and a critical review of the risks associated with their use in these applications is needed. Facilitating the implementation of SUS is the industry's main concern, as highlighted in Aspen Brook and Bioplan Associate surveys. Quality assurance, supply chain reliability, change control, raw material transparency and integrity testing all rank highly in end-user feedback when asked about the necessary improvements needed in SUS.

- How should I assess my supply chain for robust assurance of supply? When selecting a SUS, more than 70% of industry players see the vendor's supply chain as the dominant criteria that determines their choice[3]

- How should I assess toxicity concerns with plastics, their additives, by-products and other formulated plastic leachables for product and patient safety? "The discovery of the cytotoxic leachate bDtBPP raised industry concerns on potential impact of plastics used in SUS[4]

- How should I assess product and process integrity when implementing SUS in cGMP commercial manufacturing? "Lack of robustness can lead to contamination of products and loss of time and material" (W. Wing, Amgen). "Bag failures cost ~$100K to $1M per bag" (R. Wong, Bayer)

These key concerns from the users are made more worrisome by the perceived loss of control when converting to SUS.

The outstanding assurance of supply, robustness, closure integrity and biocompatibility of Flexboy® 2D bags provide safe and convenient storage for all process steps.

Building on more than 20 years of experience in designing Flexboy® 2D bags, we have established Pre Designed Solutions (PDS) for every media, buffer, harvest and downstream intermediates, drug substance and drug product process step.

[1] 6th Annual Survey of the single use Bioprocessing Market; Aspen Brook Consulting, LLC
[2] Report and Survey of Biopharmaceutical Manufacturing Capacity and Production; Bioplan Associates, Inc.
[3] Pharma IQ's research | DS, Disposable Solutions, March 2016
[4] PDA J. Pharm. Sci. and Tech. 67 (2) 2013: 1

Assurance of Supply: Consistent Quality, Change Control and Business Continuity

Partnerships, supply contracts and quality agreements with our suppliers

Our supply contracts and quality agreements with our resin suppliers and our film partner guarantee the traceability and control of the raw materials and the film formulation.

Our long term contracts include a six months change notification clause for the resins and a two years change notification for the film, in case of changes in the raw materials and | or manufacturing processes. Following such a notification, we own a last buy option of unchanged material for two years of resin and film demand. In addition we hold stocks of resins and films sufficient for 1.5 year of demand. This guarantees four years of unchanged film materials at any time before notification to the market.

Critical fluid contact components of Flexboy® PDS such as tubes, fittings and connectors are also secured by strategic partnerships and quality agreements. They are available off-the-shelf to provide best delivery reliability and guaranteed at any time with at least 24 months of change notification.

The establishment of long term supply contracts and quality agreements for the resins, the film and the fluid-contact components ensure unprecedented assurance of supply for Flexboy® PDS.

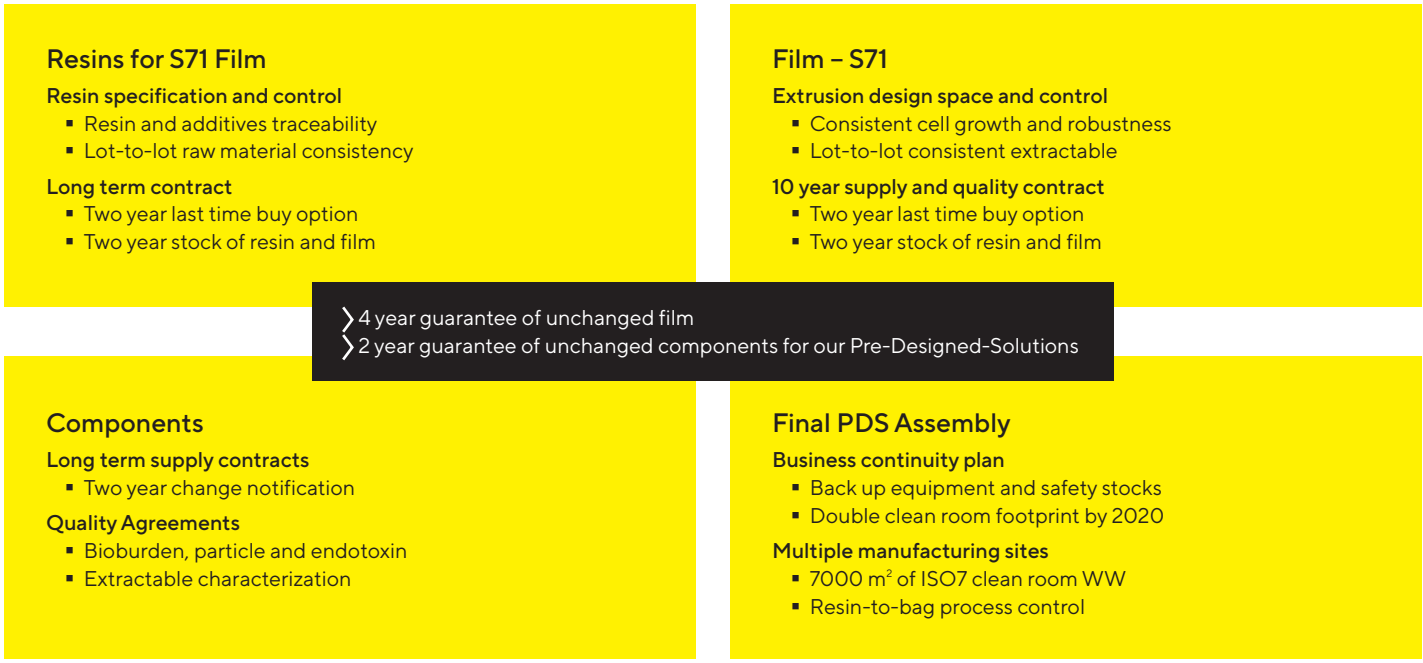


Figure 1: assurance of supply for Flexboy® pre designed solutions (PDS)

Quality by design, material science and film extrusion expertise

The S71 EVA film of Flexboy® 2D bags is the result of applying material science and film extrusion expertise in partnership with our suppliers. Such partnerships ensure a full understanding of the resin formulation and the control of the film manufacturing process.

Following the principles of quality by design (QbD), we have selected the best raw materials and extrusion process parameters that deliver consistent robustness over the entire film extrusion design space.

The resin formulation is optimized to avoid the presence of antioxidant breakdown products such as DtBPP. We have established the resin specification, the extrusion design space and the process controls that provide consistent quality and reproducible performance of the S71 film.

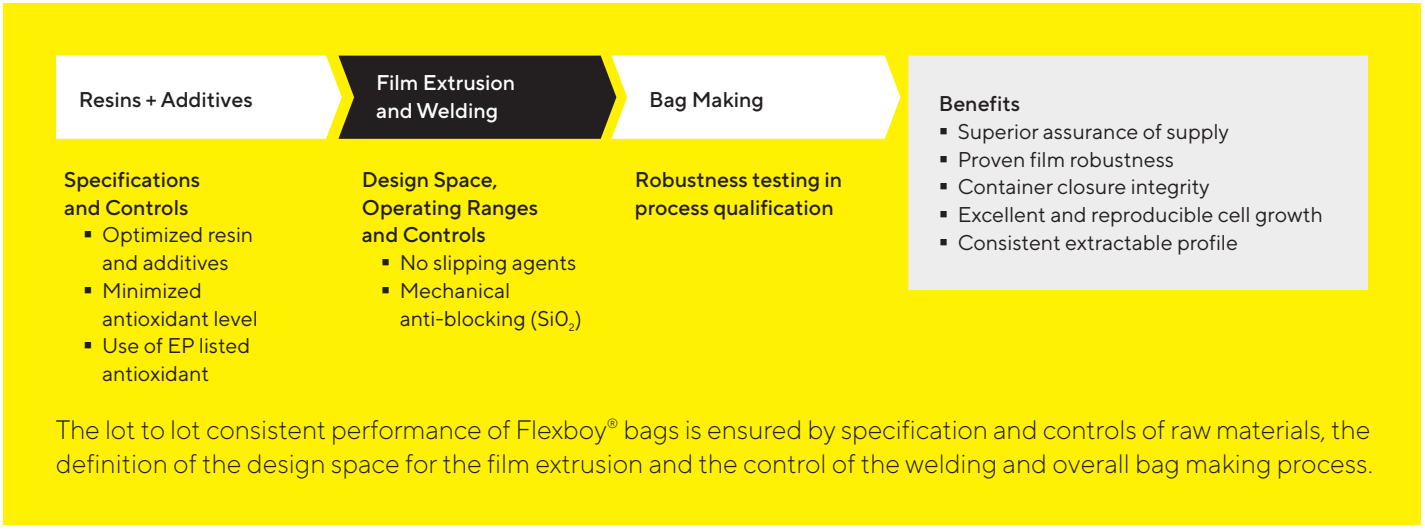


Figure 2: Quality by design principle for the development and validation of Flexboy® 2D bags

The consistent lot-to-lot performance of Flexboy® PDS is ensured by the control of raw materials, the established design space for film extrusion and the control of the overall bag making process.

Control of the entire manufacturing process

The direct access to raw material suppliers provides an unprecedented level of control and quality for the resin and additive formulation. Such control is a key component of the complete control of our entire manufacturing process, from the resins to the finished products

The establishment of resin specifications provides robust quality, change control and facilities change management. With the established specifications and the understanding of the critical quality attributes for the resins and additives, we can rapidly validate an equivalent resin formulation with our supplier.

Qualification and control of single-use manufacturing process

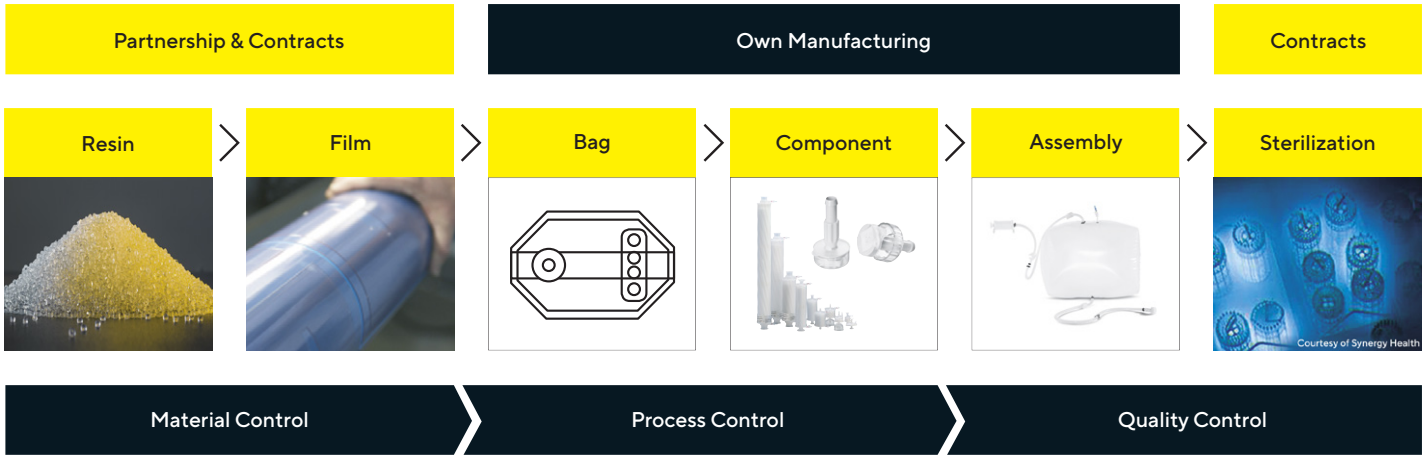


Figure 3: Overall single use solution manufacturing process

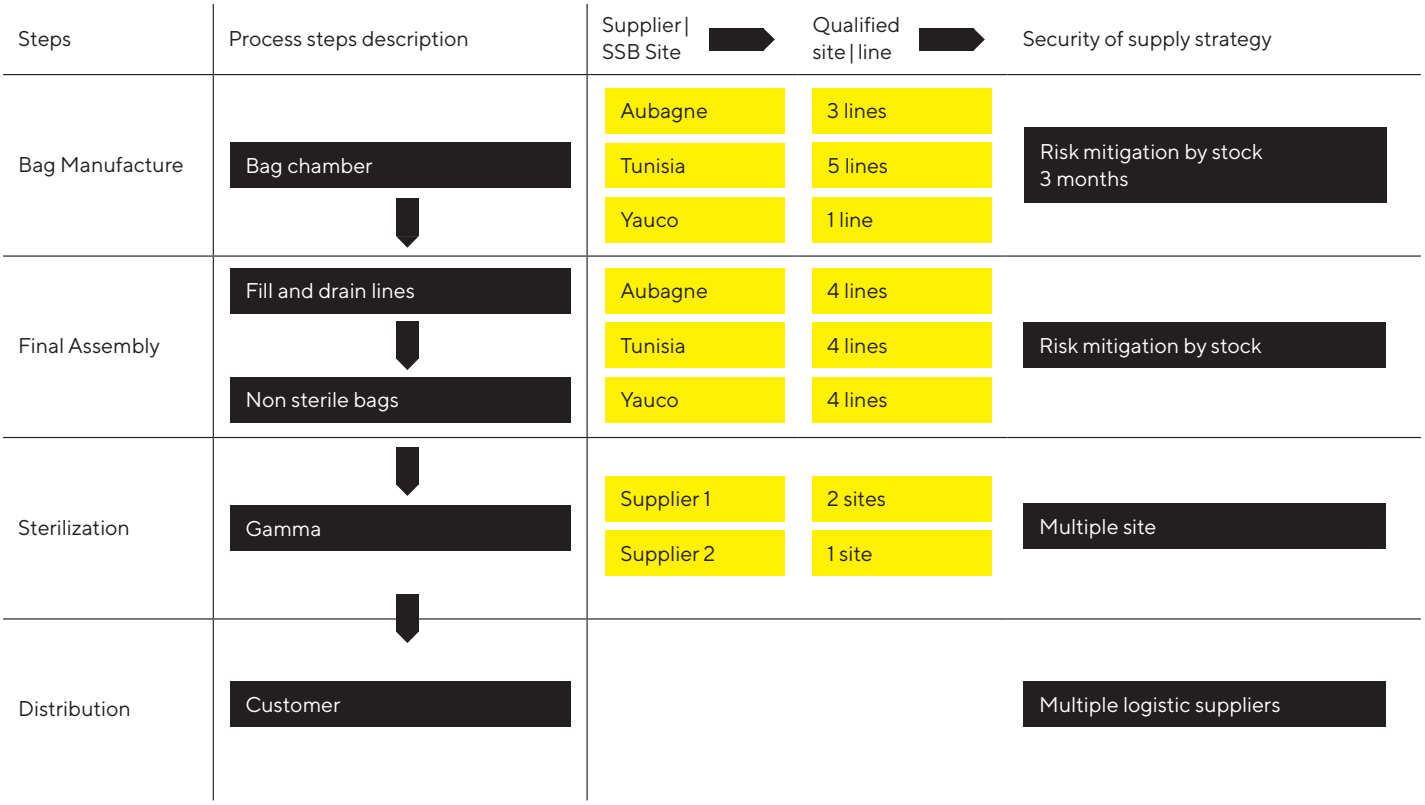


Figure 4: Flexboy® manufacturing process and network for best assurance of supply

Other critical fluid contact components are evaluated for conformity against the EP and USP standards and qualified for their extractable profiles, shelf life and consistent functional properties.

Components are selected to maximize tubing engagement strength and integrity. All components of Flexboy® PDS undergo a three year shelf life qualification for their engagements with all tubing's. Engagement samples are integrity tested for leak, burst pressure, traction and compression.

The complete control of our manufacturing process ensures reliable performance, consistent quality, change control and business continuity for Flexboy® PDS

Multiple Manufacturing Locations And Safety Stocks for Critical Materials

Business continuity is ensured by having multiple bag-making equipment and assembly lines installed in multiple locations in France, Tunisia and Puerto Rico. A manufacturing location will be established in China in future for the final bag assemblies. With this network, we cover unexpected and unlikely events such as raw material discontinuation or operational shut down due to earthquake, fire, flood, storms or other potential disaster. We have combined back-up equipment and safety stocks at both Suedpack, our film extrusion partner, and at Sartorius Stedim Biotech for other critical process steps such as resin or film extrusion. Safety stocks of resins and film for up to 18 months of demand complete our business continuity plan by covering the demand for the time required to install new equipment.

Finally, we also have contracts with multiple gamma sterilization sources and suppliers worldwide.

Pre designed solutions offer the best assurance of supply and delivery performances for all your process steps and optimize your inventory

- Access to resin suppliers
- Resin specification and control
- Film extrusion design space and control
- 10-year supply contract for films
- Last-time buy option for two years of resin and two years of film demand
- 2-year customer change notification
- Safety stocks of resin and film for up to 18 months
- Multiple bag manufacturing sites
- Backup EVA resin reactor

Proven Robustness: Film Strength and Flexibility

Material science and film extrusion expertize

Applying material science and film extrusion expertize helps select the best raw materials and extrusion process parameters to achieve the outstanding robustness and other critical quality attributes of Flexboy®.

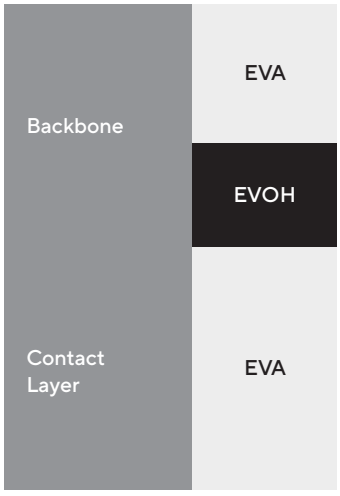
The robustness of Flexboy® PDS is obtained by a combination of the strength and flexibility of the film and the weld. It makes this product easy to handle for all media, harvest, buffer, drug substance and drug product process steps providing safe and convenient storage for all process steps.

Heat-laminated EVA | EVOH | EVA structure

- 300 µm thickness from 5 mL to 20 L bags and 360 µm thickness for 50 L bags
- Balance between strength, flexibility and gas barrier
- Large sealing window for bag robustness
- Best puncture resistance and elongation at break

S71 film features and benefits

- Superior robustness: strength and flexibility. The film strength offers safety during handling while flexibility ensures integrity during storage and shipping
- High gas and water barrier properties: suitable for long term storage of media, buffers and drug substances
- Low and consistent extractable profile: ideal for drug substance and drug product process steps
- Excellent biocompatibility: ideal for media storage and cell culture process steps



Backbone:
- Superior strength and flexibility
- High gas barrier propertiesExcellent biocompatibility

Contact layer:
- Superior strength and flexibility
- Weld strength
- Low extractable level
- Excellent biocompatibility

Figure 5: S71 EVA film structure of Flexboy® 2D bags

Design of experiment and design space for extrusion process optimization

The lot to lot robustness consistency of Flexboy® 2D bags is guaranteed by applying QbD principles, optimizing the extrusion and welding processes and validating robustness in the entire design space.

The robustness is established over the entire design space using 220 test samples from 11 extrusion runs (three center points | eight parameters variation), three critical process parameters and two acceptance criteria.

Critical film extrusion process parameters for design of experiment (DoE)

- Embossing | lamination temperature
- Embossing | lamination pressure
- Quantity of material extruded per hour (output)

Acceptance criteria

- Tensile strength (110 samples)
- Delamination (110 samples)

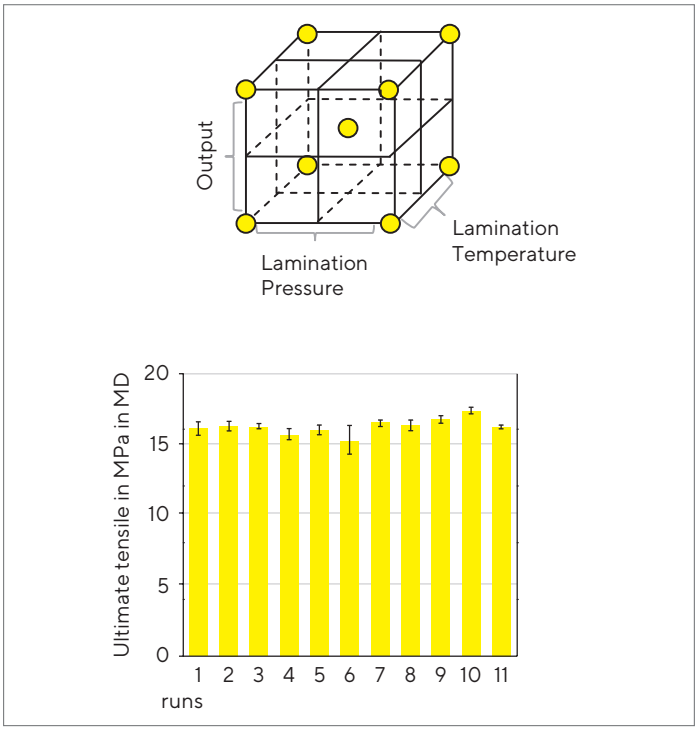


Figure 6: S71 EVA film structure of Flexboy® 2D bags

Process controls

The formulation of the resins and additives for both the contact layer and the backbone are known.
The extrusion process parameters are controlled within the established design space and specifications to ensure consistent robustness.

Robustness is also routinely controlled in production by means of multiple mechanical tests such as thermal seal strength, delamination and puncture test, elongation at break or flex durability.

- The tensile strength, in Newtons (N), measures the force required to break a film and represent the strength of the film
- The elongation at break, expressed in percentage, is the maximum elongation that a film can withstand before breaking. It characterizes the behavior of a film with regard to deformation and resistance to breakage and represents its flexibility.
- The combined strength and flexibility provide the outstanding robustness of Flexboy® 2D bags

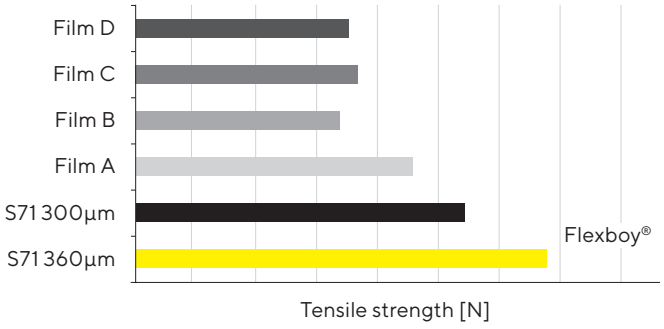


Figure 7: Flexboy® shows best tensile strength in comparison to other available films

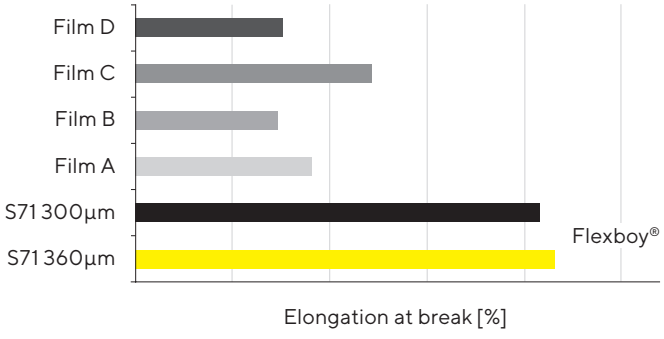


Figure 8: Flexboy® shows best elongation at break in comparison to other films

Robustness is demonstrated during process validation by testing in the entire extrusion design space and by routine production controls and quality controls on the film and the seals.

The superior strength and flexibility of Flexboy® 2D bags provide safe liquid storage of your biopharmaceutical products

- 20-year experience in EVA film extrusion and 2D bag making
- 20 million 2D Bags produced worldwide
- Manufacturing process optimization with extrusion design space

Container Closure Integrity Is the Result of QbD, Process Validation, Process Control, Supplier Integrity Testing and Point-of-Use Leak Testing

With the increasing advances of single-use bags into commercial cGMP production, the industry requires a higher assurance of single use container closure integrity and more reliable integrity test methods at both the supplier and the end user.

Standards organization initiatives are ongoing to support industry and authorities in reaching consensus and mutual agreement on best practices

- PDA TR66 2014 application of single-use systems in pharmaceutical manufacturing
- PDA TR27 1998 pharmaceutical package integrity
- USP <1207> 2016 package integrity evaluation – sterile products Proposed Revisions to General Chapter
- ASTM F2095-01 Standard Leak Test for Pressure Decay Leak Test for nonporous flexible packages with and without restraining plates
- ASTM E55 WK43741 2014 standard practice for testing integrity of single-use systems at vendors manufacturing facilities (balloting)
- ASTM E55 WK47355 2014 standard practice for controlling integrity of single-use systems during biopharmaceutical manufacturing process at end-user factory (balloting)
- BPSA (release Nov. 2016) approach to assessing integrity of single-use systems

Process validation and process controls

The assurance of integrity of Flexboy® PDS starts during process validation with multiple mechanical and microbial tests

- Seal strength and bag chamber integrity test
- Component | tube assembly integrity test
- Microbial challenge test by immersion according to ISO 15747

Assurance of integrity is further tested at multiple critical process steps during the manufacture of Flexboy® 2D bags

- Seal quality tests on each lot of bag chamber
- 100% visual inspection
- Quarterly microbial challenge test by immersion according to ISO 15747 on representative samples

Flexboy® closure integrity is demonstrated during process validation and by routine process controls and quality controls such as seal strength, 100% bag chamber leak testing and microbial challenge testing.

Process qualification at supplier

- Robustness validated in the extrusion design space
- Mechanical tests on film and weld
- Microbial immersion test
- Packaging validation
- Shipping validation

Process control and quality control at supplier

- Control of resin, extrusion and welding process parameters
- Seal quality tests
- Visual inspections
- Microbial immersion test
- 100% bag chamber leak test
- Supplier integrity testing

Process validation and process controls at end user

- Package integrity
- Visual inspection
- Media hold, media fill and stability test
- Microbial immersion test
- Operator training
- Point-of-use leak testing

Figure 9: Assurance of Flexboy® container closure integrity along the entire life cycle

Integrity testing throughout the product life cycle

In addition to process validation and controls, pressure decay and helium test methods are available for testing the bag chambers or entire PDS, at the supplier and at the end-user.

- 100% of Flexboy® 2D bag chambers are leak tested in production using a pressure decay test method[5] with a detection limit of 100 µm for the largest volume.
- A point-of-use leak test using pressure decay[5], with a detection limit of 30 µm, is available for end-users to test Flexboy® PDS in a fast and reliable way with the FlexAct BT® system
- A supplier integrity test using Helium, with a detection limit of 2 µm, is under development for Flexboy® PDS used in critical drug substance and drug product process steps.

[5] Pressure decay test according to ASTM F2095-01: "Standard Leak Test for Pressure Decay Leak Test for Nonporous Flexible Packages with and without Restraining Plates"

With best assurance of container closure integrity, Flexboy® 2D bags provide process integrity, patient safety, operator safety and product safety

"Guazzo* and the rest of the experts, including the FDA, hope that anyone dealing with package integrity testing will not wait for a regulation to take action"
"Better technologies for integrity testing exist and have been evolving for many years [...]"
"[...] firms must be prepared to pay an initial cost for equipment and for staff education, but the benefits far outweigh those costs" (D. Guazzo)
(Pharma online – Oct. 2014)

* D. Guazzo, founder and president of RxPax

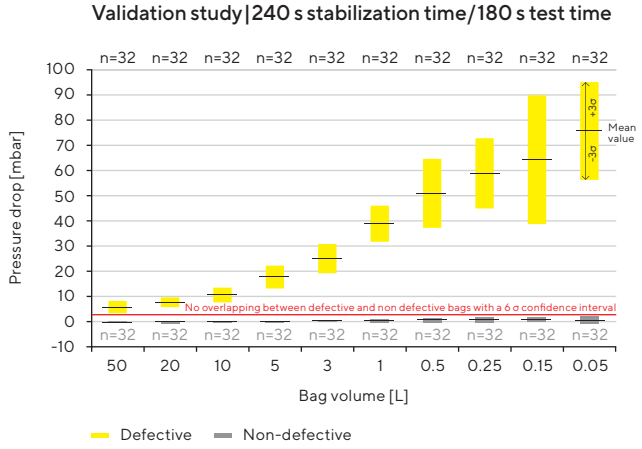


Figure 10: Point of use Flexboy® PDS leak testing using the Flexact BT® Bag Tester System validated for a 30 µm leak detection

Excellent and Reproducible Cell Growth

Optimized resin formulation provides excellent cell growth

The resins and additives formulation used for the S71 EVA film are optimized to avoid the presence in the contact layer of the Tris (2,4-di-tert-butylphenyl) phosphite antioxidant, known to degrade into a reported growth inhibitory substance : bis (2,4-di-tert-butylphenyl) phosphate (bDtBPP)[6].

Extractable studies in WFI confirm the absence of Tris (2,4-di-tert-butylphenyl) phosphite and of Tris (2,4-di-tert-butylphenyl) phosphate components.
The S71 EVA film has proven to support cell growth, using both internal and external labs[7] for standardized media extraction followed by a standardized cell culture assay.

[6] Matthew Hammond, Heather Nunn, Gary Rogers, et al., Identification of a Leachable Compound Detrimental to Cell Growth in Single-Use Bioprocess Containers, PDA J Pharm Sci and Tech 2013, 67 123-134

[7] Interlaboratory test for detection of leachables arising from single-use bags – DECHEMA; Nina Steiger, Lidija Lisica, Regine Eibl | Zurich University of Applied Sciences, School of Life Sciences and Facility Management, Institute of Biotechnology, Biochemical Engineering and Cell Cultivation Technique, nina.steiger@zhaw.ch, Grüental, 8820 Wädenswil, Switzerland

Dechema 2 WFI extraction		Dechema 2 Media extraction	
S80 S71	OK OK	S80 S71	OK OK
4 films 4 films	OK Failed	2 films 6 films	OK Failed

Figure 11: Interlaboratory test for detection of leachables arising from single-use bags – DECHEMA

Process control ensures reproducible cell growth

The reproducible cell growth is guaranteed by the complete control of our manufacturing process from the resins to the final assembly.

Because degradation of antioxidants continues after γ-irradiation and dry storage of bags, we have demonstrated the cell growth performance of Flexboy® right after γ-irradiation until the end of the aging study. This represents 36 months of shelf life under normal conditions.

Cell growth is demonstrated during validation and routine quality control using internal cell growth testing and an external broad panel cell growth test study – Dechema study

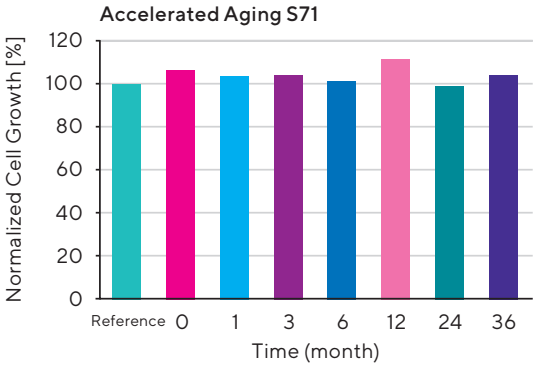


Figure 12: Cell growth testing in freshly γ-irradiated to 36 months shelf life of Flexboy® against glass bottle reference.

You can rely on excellent and reproducible cell growth with Flexboy® 2D for the entire three-year shelf life and on a broad panel of different cell lines and media

- Excellent cell growth guaranteed by no Tris (2,4-di-tert-butylphenyl) phosphite antioxidant in EVA film contact layer
- Lot-to-lot reproducible cell growth guaranteed by the complete control of our process from resin to bag
- Cell growth performance is demonstrated by both cell growth testing and extractable study

Consistent extractable profile

Extractable analysis remains a key focus for end users and regulators alike. Control and optimization of raw materials including the identification and strict specification of all additives used in the film extrusion process facilitates toxicological assessments.

The detailed control of materials all the way back to the resin starting material is serving to facilitate and ensure repeatability of material characterization processes. Because we know in detail the formulation of our resins and additives, we can accurately quantify and identify the extractable profiles of Flexboy® 2D bags.

The control of the resins and all other critical process steps such as extrusion, welding and gamma irradiation ensure consistent, lot-to-lot extractable profiles.

The extractable data contained in our extractable guide or the specific leachable studies performed by our Confidence® service remain representative and valid along the product life cycle.

- Specification and control of the resins and the film ensure well characterized and consistent extractables.
- Extractable data is readily available for risk assessment, thus saving end-users the time and money required for generating validation data.
- The validation studies and toxicological assessments remain valid and reproducible from lot-to-lot.

Validation and quality assurance

Flexboy® PDS are qualified against extensive biological, chemical, physical, extractable and cell growth testing to provide reliable validation data applicable to a wide range of process conditions.

Robustness
- ASTM D882, D1004, F392 for tensile properties, tear resistance and flex durability

Gas transmission
- ASTM D3985, F1249, F2476: Oxygen, Water Vapor Transmission Rate

Biocompatibility and chemical compatibility
- USP<87> and ISO 10993: biological reactivity tests, in Vitro
- USP<88>: biological reactivity tests, in Vivo
- Internal standardized methods for cell growth compatibility evaluation
- USP<661> and EP 3.1.5: containers, physico-chemical tests – plastics
- ASTM D543-06: resistance of plastic to chemical reagents

Purity, extractable and leachable
- Extractable data based on knowledge and control of resins and film manufacturing process
- TSE | BSE: EP 5.2.8

Cleanliness, particles
- USP<788> and EP 2.9.19: particulate matter in injections endotoxin
- USP<85> and E.P. 2.6.14: bacterial endotoxins sterility
- ISO 11737: sterilization of medical devices – microbiological methods: bioburden
- ISO 11137: sterilization by irradiation of medical devices: sterilization of medical devices
- ISO 14644: cleanroom environmental controls
- Gamma irradiation dose mapping

Sartorius Stedim Biotech quality systems for single-use products follow applicable ISO 9001 and FDA regulations and ISO 13485 for medical devices. Because single-use systems replace traditional stainless steel equipment, suppliers own a more important part of the drug manufacturing process. Design, manufacture, quality control and sterilization of Flexboy® PDS are conducted under conditions that mirror biopharmaceutical operations and meet cGMP like requirements to ensure they are supplied clean, pure, endotoxin free and sterile

Certificate of Release

Statement	Monitoring[8]	100% Batch testing
USP Class VI USP<87> and ISO 10993: Biological reactivity tests, in Vitro USP<88>: Biological reactivity tests, in Vivo **Physico-chemical testing** USP<661> and EP 3.1.5	**Bioburden** ISO 11737 **Endotoxin:** USP<85> and E.P. 2.6.14 **Sub-visible varticulates** USP<788> and EP 2.9.19	**Gamma irradiation** Dose mapping **Visual inspection** Film, bag, seal and packaging **100% bag chamber leak testing** **Technical drawing conformity** Batch record review

[8] Performed weekly on representative samples for buffer, media, harvest, drug substance and drug product process step

Figure 13: Certificate of release for Flexboy® pre designed solutions

Flexboy® PDS for media, buffer and drug substance process steps are released on the base of a weekly quality control for bioburden, sub-visible particulates and endotoxin performed on representative samples. For the most critical drug product process step bioburden, sub-visible particulates and endotoxin testing is performed on actual product samples for every production batch.

Media, Buffer, Harvest and Downstream Intermediates	Drug Substance	Drug Product[1]
Weekly testing of bioburden, particles and endotoxin on representative sample		Lot release testing of bioburden, particles and endotoxin on actual product sample

[1] Flexboy® PDS for Drug Product not yet released on the basis of a lot release testing

Figure 14: Flexboy® PDS are QC test per process steps

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