# Striking a Balance: Extractables and Functional Design in Bioprocessing Film Development

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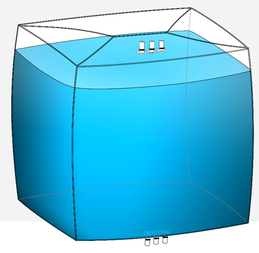


REPLIGEN

## Introduction

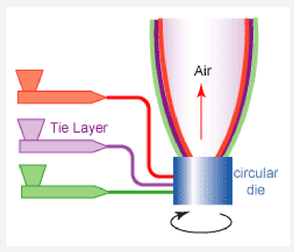
Repligen has developed an innovative single-use film designed to meet the evolving needs of the bioprocessing industry, with a focus on low extractables and robust performance. Engineered for optimal functionality across a wide range of sizes and applications, this film is tailored to enhance process efficiency and product quality. The development and qualification process incorporated a comprehensive evaluation of all manufacturing aspects to ensure consistent, reliable performance in diverse bioprocessing environments.

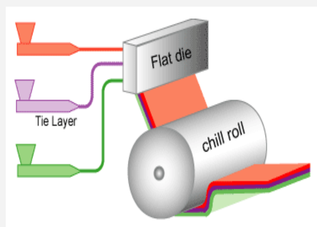
**Single-Use Film Manufacturing**
Single-use films are typically manufactured using advanced multi-layer processes, such as coextrusion, allowing for precise control over material properties and performance characteristics. These films are produced in compliance with ISO-7 cleanroom standards to ensure the highest level of cleanliness and minimize contamination risks. Strict control over particulates and bioburden is maintained throughout the manufacturing process to meet stringent bioprocessing requirements and ensure product safety and integrity.

**Film Design: Process Selection**
The film design process for single-use films begins with the selection of cast film to achieve key goals, including cleanroom compatibility, additive-free processing, and the ability to achieve precise film thicknesses. Process control is a critical aspect of manufacturing, with in-line and off-line monitoring ensuring consistent thickness across each layer. Rigorous control measures, including specifications for gels and black specs, are enforced through vision system monitoring and quality release inspections at the beginning, middle, and end of production. Additionally, the Certificate of Conformance (COC) includes detailed resin lot information and production run data to ensure traceability and quality assurance throughout the process.

**Co-Extrusion Comparison**

| | Blown Film | Cast Film |
|---|---|---|
| MD/TD Property Uniformity | ● | |
| Film Thickness | | ● |
| Thickness Uniformity | | ● |
| Production Output | | ● |
| Cleanroom Compatible | | ● |
| Additive-Free Processing | | ● |
| Flat Tube | ● | |




## Materials and Method

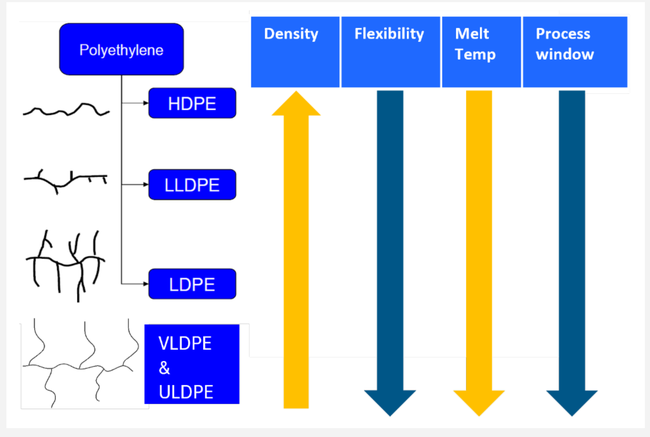
The design and development of the Repligen ProConnex RG-V film aimed to create a single-use bioprocessing film that could meet a wide range of applications. Pilot-scale trials were conducted, evaluating numerous iterations to achieve the optimal balance between performance and flexibility. Benchmark studies comparing existing single-use films on the market were also performed to identify potential gaps and opportunities for improvement, guiding the development of the final product.

**Coextrusion Processing Challenges**
The goal of the film design process is to achieve a homogeneous film free from defects such as flow instability, melt fracture, gels, and carbon specks. To ensure uniformity across all resin layers, key parameters including melt temperature, viscosity, velocity, and pressure drop are carefully controlled. Maintaining consistent extrudate melt strength is also critical to prevent defects and ensure high-quality, reliable film performance throughout the manufacturing process.

**Acceptable Extractable Formats**
To offer single-use suppliers a standardized approach for conducting extractables studies and reporting results, the BioPhorum Operations Group (BPOG), an industry trade association representing leading biopharmaceutical manufacturers and end users, developed a standardized extractables testing protocol, which has been the industry standard since 2011.

| | Solvents | | | | Time | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 24 hours | 7 days | 21 days | 70 days |
| | | | | | Temperature | | | |
| Component Type | 50% ethanol | 0.5N NaOH | 0.1M phosphoric acid | WFI | 40°C | | | |
| Bag film, bottles, and carboys intended for long-term storage | ● | ● | ● | ● | ● | | ● | ● |
| Tubing intended for storage bags | ● | ● | ● | ● | ● | | ● | ● |
| Bag ports intended for storage bags | ● | ● | ● | ● | ● | | ● | ● |
| Molded stoppers | ● | ● | ● | ● | ● | | ● | ● |
| Bag film, bottles, and carboys | ● | ● | ● | ● | ● | | ● | |
| Bag ports | ● | ● | ● | ● | ● | | ● | |

**Film Design – Polyethylene Product Contact Layer**
The polyethylene product contact layer of single-use bioprocessing film is selected for its simple chemical structure, which contributes to its chemical inertness and low extractables profile. These properties make polyethylene an ideal material for minimizing potential contamination risks in bioprocessing applications. Due to its broad compatibility and widespread use across various industries, polyethylene is a trusted choice for ensuring safe, reliable contact with bioprocessing products.




**Film Design – Polyester Outer Layer**
The polyester outer layer of single-use bioprocessing film is designed to provide enhanced strength and durability compared to other layers, ensuring protection against common failure modes such as abrasions, punctures, and excess folding. This layer is in direct contact with the outer packaging, exterior vessel, and potential sharp objects, requiring a balance between stiffness/strength and toughness/flexibility. Additionally, care is taken to avoid backside transfer onto the contact layer. Common materials used for the outer layer include TPEs, polyester, nylon, and the polyolefin family. The viscosity and velocity of the polyester must be carefully matched with the other layers, as physical properties can vary significantly depending on the material chosen.

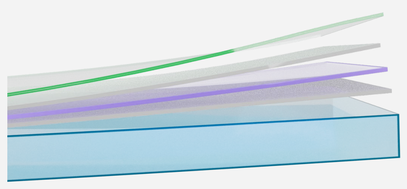
## Results and Discussion

Success was determined by evaluating multiple factors, including standardized tests for films and bags across various industries, practical experience as an end user in deploying and operating single-use bags, and identifying the most stable supply chain for both the film and its individual raw materials. These criteria ensured the development of a reliable and high-performance product suitable for bioprocessing applications.

**Finding the Balance**
The multi-layer cast co-extrusion process provides a repeatable, durable, and flexible film that minimizes contributors to extractables. All layers are I-168 free, ensuring compliance with strict safety standards. This manufacturing approach is well-suited for automated bag production and supports a wide range of applications, making it adaptable to various bioprocessing modalities.

| Customer Requirements | Vendor Requirements |
|---|---|
| Low extractables | Fully compatible film structure |
| Chamber integrity | Process repeatability |
| Modality compatibility | Surface texture / mechanical anti-block |
| Durability | Supply chain security |
| Gas barrier | |

**Film Structure Details**



Outer
Tie
Barrier
Tie
Contact

Outer Layer – Polyester elastomer
- Stable material balancing low coefficient of friction and durability
- Compatible with common tie layers from PE:EVOH and EVOH:Outer
- Thermal barrier to facilitate automated heat bonding

Contact Layer – ULDPE
- >70% of total thickness to minimize influence of other layers
- No anti-block or slip agents needed

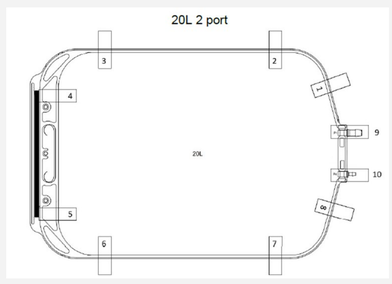
Barrier Layer – EVOH
- EVOH grade selected with highly branched PE portion of EVOH

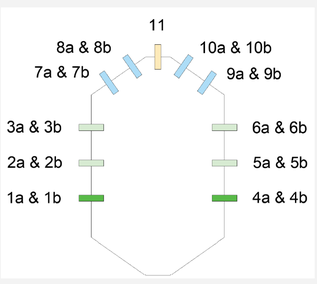
Tie Layers
- ULDPE base polymer for increased flexibility and compatibility with all layers

**Film Properties**

| Test | Standard | ProConnex® RG-V Film |
|---|---|---|
| Abrasion Resistance (Cycles @ 400g) | ASTM F-3300 | 3839 cycles to failure |
| Puncture Resistance | ASTM F-1306 | 22lbf |
| Coefficient of Friction (MD/TD) | ASTM D-1894 | 0.36, 0.41 |
| Flex Crack Resistance (900 Cycles) | ASTM F-392 | 0 pinholes |

**Functional Qualification**
Functional qualification of the single-use bioprocessing film was performed through both 2D and 3D chamber testing to ensure optimal performance and reliability. For 2D chamber qualification, restrained pressure decay and unconstrained burst testing were conducted, alongside tensile testing across all seal and port locations. Seal failure modes and corresponding values were captured to assess the film's integrity. In 3D chamber qualification, a pressure hold test and tensile testing at all seal locations were performed, including tensile testing at bag port seals. Seal failure modes and values were also documented, ensuring the film meets rigorous standards for bioprocessing applications.




## Conclusion

- Repligen successfully developed a robust and repeatable single-use film, capable of supporting a wide range of applications in bioprocessing.
- The film's extractables profile minimizes customer risk.
- A well-balanced combination of film properties and end-use requirements provides optimal performance across various applications.
- The single-use film and associated bags have undergone extensive validation to ensure that all manufacturing processes are optimized for consistency and reliability.

## Future State

The future of film development for bioprocessing will be shaped by the increasing demands of evolving therapeutic approaches, ranging from biologics and vaccine manufacturing to cell, gene, and mRNA therapies. These advancements require single-use suppliers to continuously adapt to new processing needs. Specifically, Antibody-Drug Conjugates (ADCs) present unique challenges due to their use of specialized reagents and polar aprotic solvents, which may impact material compatibility. While current standards such as BPOG and USP <665> (effective May 2026) provide a framework for extractables and leachables (E&L) testing, they do not fully address the complexities of ADC processes.

To navigate these challenges, customers can play a critical role by providing early visibility into the use of new and exotic chemicals, collaborating on the execution of compatibility and E&L studies, and helping to identify model solvents and test conditions (e.g., DMSO, DMAC) to ensure the continued reliability and safety of single-use films.

Learn more at **repligen.com**