Vendor Partnering in a Bioprocess Manufacturing and Supply Chain Ecosystem

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INTRODUCTION

Supply constancy, cost, sterility – even a subset of the factors that impact materials selection can be daunting for biopharmaceutical companies embarking on a new drug development project. These considerations, when coupled with the intersecting pressures that influence them, such as regulatory constraints, institutional inexperience, and long-term market outlooks, can drive many companies to default to traditional, industry-standard material choices to meet their needs.

The inclination to defer to "the old way" has the potential to create new problems in a paradigm beset by change. Many pharmaceutical companies can find themselves well into the drug development process before materials issues become apparent. Perhaps they have already filed an IND and begun producing drug substance, relying on materials chosen for their widespread use and longstanding market acceptance, only to encounter process challenges that force them to reevaluate parts of their supply chain.

As novel therapies produced and stored under extreme conditions become more common, containers that were adopted decades ago are increasingly unable to meet project needs and regulatory standards, Figure 1. This shift is becoming increasingly apparent with multilayer bag assemblies, which began to see increased use decades ago as a cost-effective alternative to constructing stainless steel facilities. These technologies, originally transferred from the food industry, are applicable for many projects, but that applicability is being tested every day by new production techniques involving new chemistries, wider operating temperature ranges, and increasingly complex and sensitive drug substances.

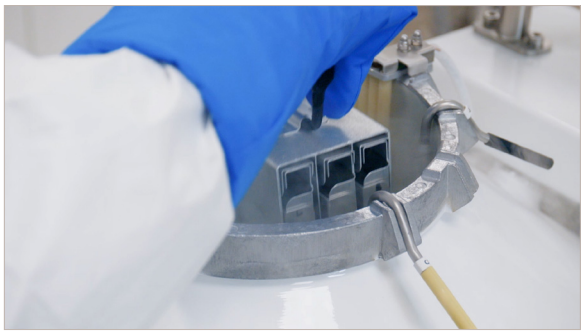

Figure 1. As therapies are stored under more extreme conditions such as liquid nitrogen-level temperatures, new robust bag assembly materials are needed.

Of course, alternatives to these bag assemblies are available to meet the needs of more complex projects. New single-layer assemblies, made with more robust materials and without the curing agents, antioxidants, plasticizers, or adhesives that represent potential contamination sources, may offer companies a safer and more efficient solution. Identifying the need for these technologies and implementing them requires thorough validation and testing efforts. By partnering with the right vendor, companies can gain access to the expertise, partnerships, and innovations that will help them safeguard their treatments from development to commercialization and beyond.

A FIVE-PRONGED APPROACH TO MATERIALS VALIDATION

Sterility assurance, integrity assurance, component ecosystem/user enablement, supply assurance, change control: each of these, when undertaken as part of a concerted effort to vet materials, can provide key insights into a material's long-term viability for drug development and production. This five-pronged approach is important because materi als selection has long-ranging implications; once a process has been codified and approved by a regulatory authority, changing a given aspect of it requires retreading many validation, testing, and regulatory steps, incurring additional costs and extending timelines.

Sterility is one of the single most critical considerations for manufacturers, particularly those producing cell and gene therapies that utilize patient cells and necessitate a coordinated, bespoke approach. Evaluating the sterility of a material hinges on more than just its sterility upon arrival. Ensuring that materials can maintain their sterility throughout the entirety of a process requires a holistic understanding of how those materials interact with every phase of manufacture. This is inextricably linked to integrity assurance, which serves, in part, to guarantee a process remains closed from end to end and sterile at all potential points of contamination. Materials must be vetted thoroughly to confirm that they are not reactive, additive, or absorptive in a way that compromises the final drug product. This can prove challenging with a standard multilayer bag assembly, which is frequently constructed from polyethylene or a similar material. Depending on the temperature or duration that a drug product is stored, additives from the bag assembly may leach into it, irreversibly contaminating the product.

But ascertaining the sterility and integrity of a bag assembly only solves part of the puzzle when it comes to determining its viability for a project. Entegris' tested approach is to partner with customers enabling their technology solutions, within a verified component ecosystem, balanced with the user enablement review process to evaluate both a material's availability and the relative convenience of its use. These factors, when viewed together, can force companies to perform an intricate balancing act – how can they limit the number of components incorporated in the process, improving its workability, and thereby decreasing its complexity, while still maintaining enough complexity to solve unique challenges?

The answers come from partnering with vendors that have supply chain access to vet components on a number of fronts. This includes a supply chain transparency assessment that encompasses N-1 suppliers, as well as securing the materials certifications for given components from the outset of a project. This up-front information gathering is critical; without it, projects can lock in given components and, when forced to double back for a handover package from suppliers, realize their chosen components cannot conform to a project's unique needs.

Once a component like a single-use bag assembly has been thoroughly vetted for its sterility, integrity, and availability, Entegris launches an evaluation of its supply assurance. While just-in-time delivery of materials has become par for the course across the industry, mitigating circumstances like the COVID-19 pandemic and the Suez Canal blockage have proven that more nuanced approaches to supply chain management are needed. To ensure predictable, just-in-time supply requires a vendor that is highly attuned to their own supply chain and willing to be transparent with their customers about the suppliers that make up that supply chain.

Finally, partnering with a vendor able to adequately manage change control is integral to overseeing timelines and controlling costs. The Biophorum Operations Group (BPOG) and Bio Process Systems Alliance (BPSA) have standards that can help vendors establish and maintain effective change controls, including assessing the potential impact of supply changes on an existing process. Customers should never find themselves in a scenario in which a change only comes to light when it negatively impacts a final drug product.

SINGLE-USE BAG ASSEMBLIES: CONSIDERATIONS AND CONSTRAINTS

In the biopharmaceutical industry, multilayer single-use bag assemblies have largely supplanted more inflexible and expensive stainless-steel equipment, thanks to their simple implementation and cost. These multilayer assemblies, typically made from polyethylene, incorporate multiple layers of plastic constructed for specific purposes – typically, the assemblies include a contact layer and a vapor barrier bound together with an adhesive layer. Adopted decades ago from the food industry, these assemblies were adapted and incorporated in the bioprocessing space, greatly reducing concerns around cleaning and validating multi-use facilities and equipment.

Yet stainless steel retains an important advantage over multilayer bag assemblies, despite their widespread deployment – it does not degrade and when implemented properly does not itself contaminate what it contains. As drug developers have continued to iterate on their processes, and as drug substances have become increasingly complex, the possibility of contamination from these bag assemblies has become a more pervasive concern. That is why single-layer assemblies made from more stable materials have begun to emerge as a valuable alternative to traditional multilayer assemblies, which have proven increasingly incompatible with processes that require extreme temperatures, bulk storage, or long-duration containment. Ultimately bioprocessors are looking to their vendors to find new technology solutions to these challenges.

One of the most flexible single-layer bag assemblies that Entegris recommends is the Aramus™ 2D Single-Use Assembly. This high-grade, gamma-stable assembly offers non-adsorptive universal chemical compatibility and extreme cold resistance, and lacks the adhesives, binders, and other potential leachables and additives that represent potential sources of contamination. Rated for a wide range of applications, Aramus single-layer bag assemblies are made with a fluoropolymer material that acts as a crystalline solid at room temperature, maintaining its flexibility in cold chain applications, and other materials that have demonstrated robustness in ultra-low temperature applications. This flexibility offers a stark contrast to materials with a higher glass transition temperature, which reach a brittle point under the same conditions, Figure 2. The superior stability of fluoropolymer bags is also exemplified by their resilience in shipping; the integrity that keeps impurities from contaminating the drug substance also prevents the loss of any drug substance to the bag itself through adsorption.

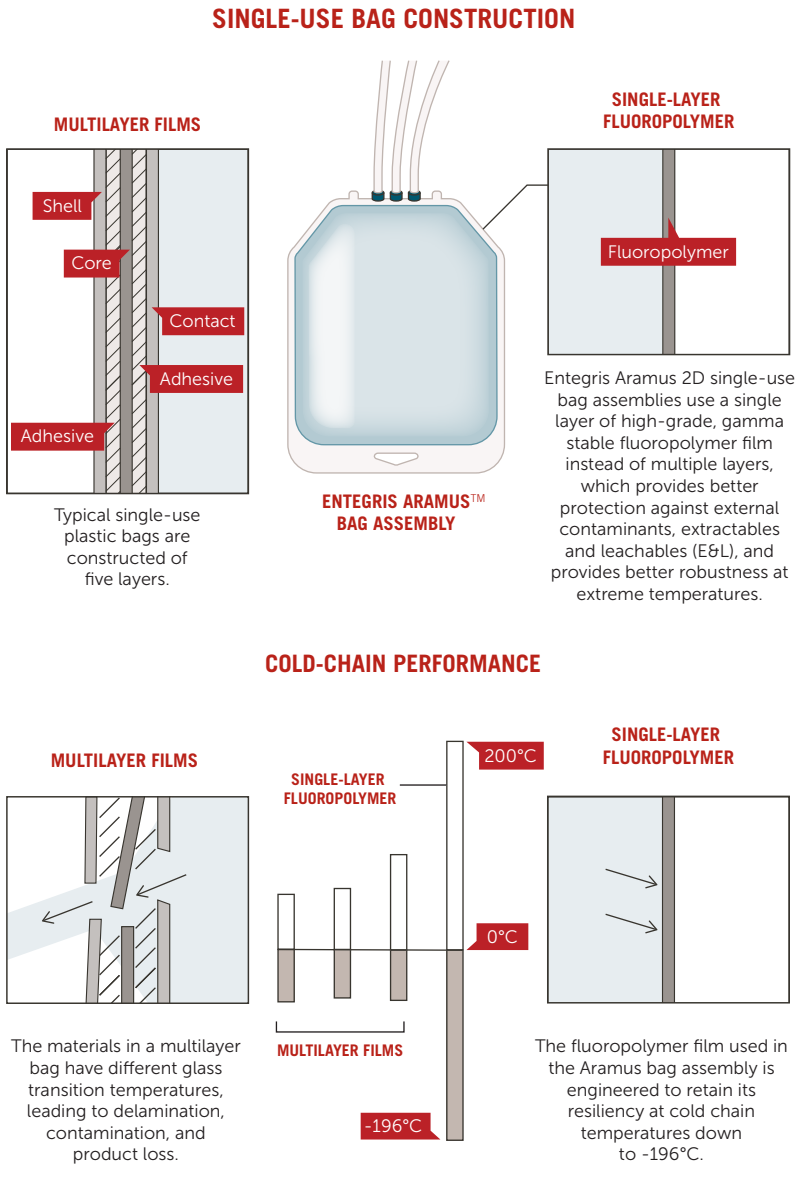

Figure 2. Single-layer fluoropolymer film is better suited than multilayer films for cold-chain applications.

IMPLEMENTING NEW MATERIALS IN A NEW PARADIGM

Despite the mounting challenges in using traditional multilayer bag assemblies in increasingly unique bioprocessing applications, the transition to implementing more flexible containers has been a slow one. This is largely because many companies are reluctant to wade into uncharted territory; for low-risk projects where the drug substance has minimal surface area contact or relatively short durations of storage, the inclination to rely on long-standing materials selection is benign. It is those high-risk projects that stand to gain – or lose – the most in making a transition to newer single-use bag assemblies.

Materials selection is ordinarily conducted pre-phase 1, and those selected materials are locked in for roughly the next decade of development, commercialization, and manufacturing. Understanding their impact on the final drug substance, their interaction with other points in the process, and their supply chain stability is therefore critical. Companies can greatly improve their approach to selecting these materials through partnerships with vendors like Entegris that offer a holistic approach to vetting materials for their process compatibility from start to finish.

Beyond its five-pronged approach to vetting materials, Entegris offers its customers a partnership in support of developing performance metrics for materials, such as freeze/thaw testing and shipping performance information. Entegris can engage with customers conducting their own materials testing, offer complementary testing, or perform comprehensive testing services and offer proof points that demonstrate a material's efficacy in either an analogous paradigm or one fully customized to a given scenario. It is this up-front support, coupled with a focus on agility, efficacy, and safety, that make Entegris a valuable partner for materials and supplies. Entegris is also in the process of increasing its capacity by expanding production in three of its locations and constructing a technology center in Billerica, MA, focused on helping customers navigate process development.

Ultimately, the regulations that govern newer single-layer bag assemblies are not as daunting as companies accustomed to approaching material selection "the old way" might assume. By partnering with a vendor with the expertise and experience to navigate the regulatory paradigm and validate the materials proposed for a process, companies can easily incorporate these newer assemblies in their projects. Entegris can offer its customers a comprehensive approach that addresses the regulatory, clinical, and patient-level challenges inherent to materials selection, leading to the material and performance selections that ensure a treatment's success, as well as provide the supply chain aspects and security of supply, proper material selection, transparency into certifications for the other fluid contact materials beyond single-use bags.

About the Author

Donnie Beers has over 10 years of experience providing single-use and automation solutions into cGMP regulated bioprocessing applications specializing in downstream processing technologies and sensor development. Donnie joined Entegris in 2019 as senior product manager responsible for single-use products in fluid handling, including the Aramus product line. He is lead architect for Entegris' future product development and innovation in life sciences fluid handling focusing on storage, processing, and protection of high value drug substances and therapeutics. He has previously held roles at Parker Hannifin including technical support, engineering management, product management, and technical sales. Donnie earned his B.S. in biochemistry from University of Wisconsin – Madison.

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