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INTERVIEW

Challenges in cryogenic storage containers for cell & gene therapy

Current options for cryogenic storage containers in cell and gene therapy are limited in their functionality as the industry continues to move towards increased scale and automation. In this episode, Sean Werner and Alex Sargent address specific challenges with current optionality, while also considering what future innovations in this area might look like.

Róisin McGuigan, Editor, BioInsights, speaks to (pictured from left to right)

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Q How have we landed on the current landscape of options for cryogenic storage containers used in the cell and gene therapy space?

SW: I think that there are a few paths as opposed to just one. On one hand, some of the packaging we use originated from the blood industry and what the stem cell

transplanters were using. This involved blood bags and storage bags that worked well for colder cryogenic processes. On the other hand, academic groups that developed some early cell processes were used to screw cap vials used in a biosafety cabinet to control things from an aseptic technology perspective, with not as much sterile fill as you would see in large molecule pharma. As time went by, several unique packages have been developed, moving from glass vials to cyclic olefin copolymer (COC) vials and ready-to-use sterile closed vials. There have also been improvements in bag plastic so they have a lower fracture rate and perform better in liquid nitrogen.

AS: It is often a challenge in cell and gene therapy that many of the options we have available come from research groups and academia. At that point, there is not necessarily a lot of forethought given to how you would fit that into an industrial approach to manufacturing, or in this case, cryogenic containers for cell and gene therapy.

Q Where do the current offerings fall short as the cell and gene therapy industry continues to grow?

AS: There are a number of options, all of them with their own advantages and disadvantages. One of the areas where current containers fall short is scalability. Do you have containers and systems where you can scale up or scale out? We are considering thousands or even tens of thousands of containers in order to meet growing patient demands. We typically see large-scale operations in vials, and we are hopefully moving away from screw top vials towards hermetically sealed and closed vialing systems. The limitation with these is usually around volume constraints, as they typically hold 1–10 mL, although some can go up to 50 mL. Another popular option is cryobags – these provide more flexibility in terms of volume but are more fragile in terms of stability and robustness, especially during the shipping process.

SW: On the small volume side, there are quite a few options that serve the industry fairly well. If you think about scaling up at a small volume, if needed we can move to isolator fill systems. Some of those already exist for the options that are out there. There are filling options that work well in a biosafety cabinet for smaller scale. The small volume options are good and do not require as much improvement.

With larger volumes, there is still a gap. Bags work, but they take a lot of individual manual manipulation to get them in the right form that you need to freeze. There are additional components, like cassettes and racking systems, that you must put into the large dry shippers that are expensive to move around the world. An industry-wide scale for these therapies is a significant ask for the logistics providers for the industry to support. The main gaps exist around how to establish better, larger volume storage containers.

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AS: A few weeks ago, we had a client with a batch size of roughly one hundred bags. They had an elegant process from start to finish, including fill/finish, but at the end of that process, they had an assembly line of laboratory technicians manually fitting the overwrap on the bags for hours. This shows that the large volume systems do have those limitations Sean was talking about.

SW: That is not ideal for taking labor and costs out of a process!

"Automated inspection processes, like looking for particulates and checking for closure integrity, are additional challenges that add to the cost and time of the manufacturing process."

– Sean Werner

Q What will be the negative impacts of continuing with these solutions, as opposed to developing containers that are more specific to industry needs?

SW: From my perspective, the labor and handling that goes into those systems is a huge addition to the cost and the time of developing, manufacturing, and shipping these products. If we are truly going to transition into an industrialized process for these therapies, we cannot be thinking about somebody individually wrapping and pushing air out of these bags to make that a reality. Another challenge is the recovery from bags, which collapse as you drain them. If you have an extremely expensive product and you need to get as much as possible out of that container, it can be challenging. Automated inspection processes, like looking for particulates and checking for closure integrity, are additional challenges that add to the cost and time of the manufacturing process.

AS: Cell and gene therapies are the most expensive in the world, and a real challenge to industrializing these types of medicines is bringing down that cost for our patients. Another part of that is quality control (QC) options. Not just how patient samples or drugs are being stored and shipped to different sites around the world, but also your QC release aisles or products, can be a significant driver in cost. The logistics of shipping and handling these precious therapies are difficult, especially when the cost and the stakes are so high. One could imagine somebody they love having the potential to receive a life-saving cell therapy only to find that during the shipping process, the bag had been damaged to render it unusable. Containers that can overcome this are critical when we think about how important these therapies are for our patients.

SW: In stem cell transplant labs, clinicians have lots of experience of treating patients with extremely valuable products, without a second chance. Transplant clinicians have told me that when they have had breakages in the labs, they cover the patient with additional antibiotics and dose anyway. That is how important this stuff is, so this is something that we need to figure out how to get past.

Q What should the cryogenic container of the future look like? And what would you pick out as the most important considerations or features?

AS: I want out of a cryogenic container what I want out of my pickup truck – something that is rugged, tough, dependable, and adaptable. Cell and gene therapies are so complex and diverse. You need a container solution with a wide degree of adaptability in terms of volumes and the ease with which you retrieve and administer the sample. It also needs to be reliable, and like my pickup truck it needs to get you where you need to go.

SW: That is exactly it – we need cryogenic containers to be reliable, robust, and reproducible. We need something that is not going to fail, and that we can rely on. We want to enable a simple, repeatable process in which we do not have to worry about it being very easy to get out of spec from the fill process. We need a consistent form factor that allows you to get the same kind of freezing profiles from small volume to large volume, does not require continuous optimization, and is going to take variability out of the process. We have to move to something more like what we have for smaller volumes – a rigid container that works well, can fit into an automated process, and give you the same results every time.

AS: In my experience, containers are often something can be neglected or an afterthought, as this industry is thinking about the process and the therapies. But it is critical to have the right container, formulation, and fill/finish option in place for your final product. We cannot neglect that when thinking about cell and gene therapies.

Q What additional considerations need to be addressed if truly allogeneic therapies, with tens of thousands of doses, are found to be more universally successful?

AS: Allogeneic therapies are on the rise. I am a big proponent of allogeneic therapies to help drive down costs and overcome other limitations seen with autologous cell or gene therapies. The challenge is that tens of thousands – and one day in the future possibly even millions – of doses are needed. For that, you need a container that is scalable, and can be

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– **Alex Sargent**

implemented into an automated platform and solution. There needs to be adaptability in terms of volume because these therapies might not be given at extremely small volumes. Large doses at a higher volume range beyond what vials can cover now may be necessitated. Finally, there is a need for containers that are reliable and rugged, because when you have tens or hundreds of thousands of doses being shipped all over the world, you need that stability and protection for these therapies.

SW: One of the additional pieces that I have heard folks starting to talk about more is the logistics side. In addition to making sure you have sufficient protection for a container as you ship, you need to know how to ship at large scale. It seems impossible to do this in the current dry shipper type of configuration. We must find ways where high-density packaging is possible. If you are going to have these stored at a central location, then maybe you have smaller versions of shippers that go out to the clinic as needed, but that will no longer be possible with millions of doses going around the world. Figuring out how to do high density storage of these products on location at different places or in regional hubs is key. A container that can support a variety of different logistics opportunities still needs to be developed. During the pandemic, we were not ready to ship the volume of vaccines that were shipped. It is time for us to start looking at how to deliver these therapies, keeping in mind that the container is a part of this.

AS: An allogeneic therapy may be in transit for multiple days. Having a container that can hold that temperature in the right shipping conditions over multiple days is going to be critical to making that therapy more accessible to patients, to get it to where it needs to go.

SW: Everybody in the industry is so excited about how far we have come already and is looking forward to where we are going. The fact that we are talking about storage and logistics shows that we are undergoing a transition from concept to the industrialization phase. This is exciting for me, and for our company.

BIOGRAPHIES

SEAN WERNER is the Chief Technology Officer – Cell Processing at BioLife Solutions, a leading provider of bioproduction tools and services to the cell and gene therapy and broader

biopharma markets. BioLife acquired Sexton Biotechnologies in 2021 where Sean was President of the company known for providing processing and handling solutions for the CGT industry. Sean received his PhD from Purdue University in Biology followed by post-doctoral positions at the Indiana University School of Medicine and Eli Lilly. Sean has previous experience filling various roles in the global regulatory and general management functions supporting medical devices, autologous cell therapy, and single use disposable development programs. In his 15 years working in the life science industry, he has guided pre-clinical and clinical testing and submission strategies leading to global commercialization of multiple medical devices and bioprocessing tools.

ALEX SARGENT is currently the Director of Process Development at Charles River Laboratories. He obtained his PhD from Case Western Reserve University in Cleveland Ohio, where he studied the challenges and promises of stem cell biology, neuroimmunology, and Cleveland sports teams. After a brief stint in academia at the Cleveland Clinic, he left Cleveland to pursue his industry career in cell therapy. During his many years in this industry, he has had the honor of working at several esteemed enterprises on new technologies and approaches for cell therapy scale up, automation, and gene editing. He is especially passionate about the challenge of curing cancer, working on CAR-T and CAR-NK cell therapy process and analytical development from discovery, through regulatory submission, manufacturing, and pivotal clinical trials. He wakes up each day excited to help advance cell and gene therapy to treat and cure disease, with the steadfast goal of improving human lives.

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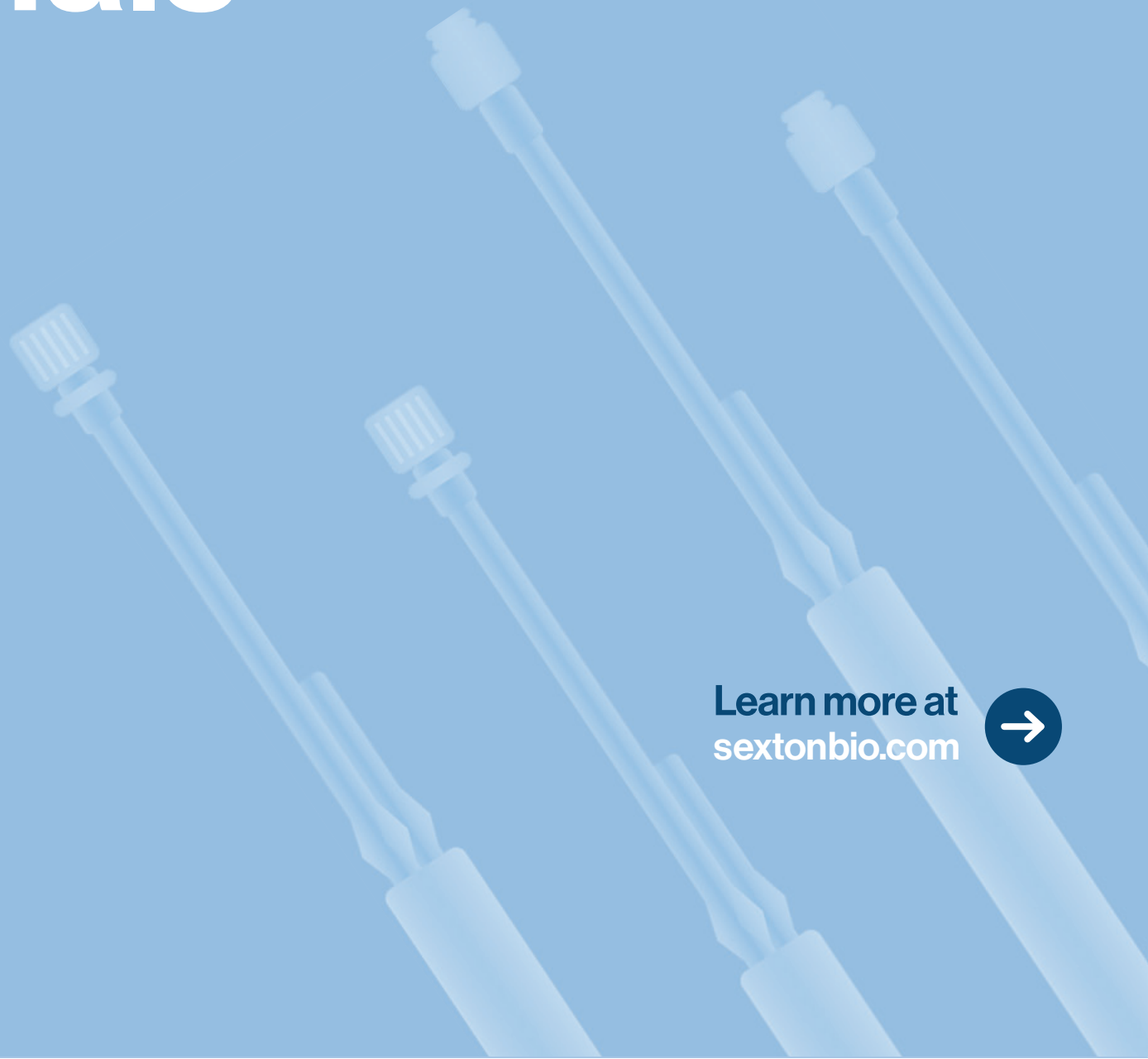

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