INTERVIEW with Niranjan Kulkarni, Senior Director, **Allan Bream**, Process Specialist, and **Grace Linton**, Process Architect at CRB.



How commercial biopharma experience is shaping cell & gene therapy facility design

Niranjan Kulkarni, PhD, is the senior director of CRB's consulting group. He holds a doctorate and master's degree in industrial and systems engineering from Binghamton University. He is also a certified Lean Six Sigma Master Black Belt. Niranjan has over 15 years of experience in business process and data modeling, operations and process simulations, process improvements, layout optimizations and supply chain management. He has worked with the pharmaceutical, biotech, food, chemical, semiconductor, electronics assembly and packaging, manufacturing and financial industries.

Allan Bream has more than 35 years of engineering and manufacturing experience including 30 years in the biotechnology industry. His expertise includes large-scale bacterial fermentation, mammalian cell culture, vaccines, downstream processing, protein purification and immobilization and CGMP facility design, operations and assessment.

Grace Linton, RA, AIA, LEED AP BD+C, has over 12 years of architectural experience in a variety of project types including over eight years in process architecture with CRB. Her experience encompasses domestic and

international CGMP regulatory, process design and development, and facility design for biotech, pharma, and medical device industries. Grace's combined knowledge of architecture, process, and sustainable design provides a strong basis for integrated facility design. Her ability to conceptualize ideas in BIM environment serves as an effective method of communication.

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Q How does the cell and gene space differ to other sectors when it comes to facilities design, and what are the unique design parameters?

GL: Cell and gene therapies cover a wide range of platforms, from vector production to different types of cell therapies and tissues. With all these different platforms and process technologies involved, as well as the scale of the processes, there are challenges that are unique to each of our projects. For instance, viral vector facilities require a robust containment and segregation strategy, typically involving unidirectional flow and airlock design utilizing bubble/hill (high pressure) and sink/valley (lower pressure) strategy for containment. Architecturally, the finishes need to be compatible for decontamination cycles. This means all the joints, surface finishes, and the ducts need to be designed for proper seal and durability against decontamination chemicals.

Autologous facilities have their own set of challenges. Since chain of identity is critical for patient-to-patient products, these facilities are designed in a way we can prevent mix up of batches through clear organizational flows and transition points from one unit operation to the next.

Another issue is that some of these processes involve deep freezing their products, with the need for controlled rate freezers and cryo freezer storage. High volume of liquid nitrogen use could become a complex design and operations issue. In case of a bulk liquid nitrogen tank with distribution system, something as simple as grouping the equipment in a location that's very close to the bulk tank could result in significant cost savings as vacuum insulated piping can be very expensive. Where gas cylinders are used, designing sufficient spaces for storage and transport, along with monitoring and emergency exhaust system are all critical to ensuring safety of building occupants.

> "...something as simple as grouping the equipment in a location that's very close to the bulk tank could result in significant cost savings..." -GL

AB: One of the characteristics you're going to see, particularly in autologous cell therapy facilities, is the higher percentage of facility area dedicated to quality control labs. In the case of autologous cell therapies, you're literally testing each patient batch. Quality testing for vaccines or human therapeutics, is done for each production batch but each batch contains thousands of doses.

You also need to rethink your warehouse strategy and apply it to the scale and batch throughput of these production facilities. In this situation, you're not going to have as many bulk chemicals, but you will transition more into heavy use of single use technologies, tubing sets, as well as other consumables. You need to be prepared for that and have an expandable warehouse solution to manage your variable storage needs.

Another factor that can impact a client's facilities design is whether they wish to make or buy their media and buffer solutions. Almost exclusively on the larger human therapeutic production facility side, clients make them in house, but the volumes are so greatly reduced that companies start to think about whether it is actually more advantageous to purchase from a vendor and eliminate that activity in their facility.

Q What are the key initial considerations and need-to-knows for yourself and client before you embark fully on a new GMP facility design project?

AB: Early in the design process, I need to understand where the client is at with their process. All of this is relatively new technology, and some of the technology or production platforms might be sourced from just one or two vendors. I need to get a feel for the state of their process technology and how familiar they are with it.

An issue I see with a number of clients is that they own the product and they may have carried out the basic research and development but they are subcontracting the production for clinical trials to a contract manufacturing organization (CMO), and sometimes don't always know all the details of what that production method is.

Beyond their immediate manufacturing needs, I also want to understand what the future state of production is. Often early in development, you're doing things that are perhaps not the way you

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want to do things 5 years out. So, I need to know from a client: what's your planned technology changes? How will this process train be different in the future? And look to design their facility with that in mind.

GL: For me it's essential to understand the functional needs of the facility, in order to come up with a design for a space that meets those needs. In addition to that, and perhaps more important are three things: the client's process, their operations strategy, and business drivers. Upfront it's critical to understand the ripple effect these three items have in how I design the overall facility.

Understanding the process down to the level of characterization of product material is essential. For instance, is there something that would qualify as BSL2 type of cells or viruses, or are there viruses that will require special containment and decontamination cycle strategies? Is there a virus reduction or clearance step that requires physical segregation? Unit operations and level of process closure are also important; all these things really point me to specific regulatory requirements, or guidelines, that will shape how I design the facility to meet proper room classifications, flows, and segregation and containment strategy.

On the operation strategy side, I need to understand the redundancy criteria and equipment utilization rates, as this can really drive up the quantity of the equipment or sometimes the number of production suites themselves, if companies want to have the capacity to have one shut down for maintenance while the other one still operates. It is also important to understand their strategies around manual operations versus automated systems, as well as shift structure. How they plan on operating the facility would have an impact on the overall facility and site; lockers rooms should be sized to avoid bottleneck during shift change, and sufficient parking spaces for employees when they arrive at work.

Lastly, the business driver, as in the projected market demand and their tolerance for business risk, really sets the dial for what level of flexibility and future expansion capabilities need to be built into the facility. In the early conceptual phase of a project, there's usually a wide range for the projected market demand. Sometimes I hear 'if this product takes off and we outgrow this building in 3 years, that would be a good problem to have'. But we're also sensitive to the fact that would mean there are sick patients with unmet needs. On the flip side, there's also a concern that maybe the market demand or approval process through clinical trial won't go as planned, and if that's the case, what do we do with this capital investment? Understanding that range of market demand in both extremes helps me design the facility in ways that would meet their primary target, as well as providing them with a space that could be prepared for secondary or even tertiary plans if things don't go quite as planned.

NK: I agree that a major concern is if the trials do not go as planned or demand is not as you expect. There's a lot of uncertainty and variability in the processes. One of the tools we have used successfully, and I recommend very highly, is discrete event simulations. These tools are essentially a specialized or advanced version of a Monte Carlo simulation, so you have a Markovian chain of Monte Carlo simulations.

This allows you to characterize any uncertainty, for example any unplanned downtime of equipment, patient demand explodes tenfold, or you fail in clinical trial 3. Beside this we also use visualization models to visualize the operations and the process. The tools are capable to import a layout, then overlay your operations on top of that to help visualize whether this room is adequately sized or whether you need to expand the room so that you don't have people bumping into each other or working shoulder to shoulder.

These tools can also reveal a lot of different nuances. For example, a sample management room is usually only manned by one or two people inside the room, but at 8 o'clock in the morning everyone comes to collect samples or handover their samples, which creates a traffic or choke point in that particular corridor. This helps understand operations and overlaying those operations on the layout can visualize those areas where they need to give more attention.

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There is also a tool we have used successfully, computational flow and dynamics that, instead of modeling operations, helps model the air flows or gas flows or fluid flows,

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and helps understand how we want to design our HVAC systems, and locate supply and return systems, etc., to minimize the risk of cross contamination and improve air flows within spaces.

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Q How do you deal with the fact there is currently a shortage of first-hand large-scale commercial manufacturing experience in the sector?

GL: There are some relevant large-scale commercial manufacturing experiences we can draw from decades of work in biotech. And we do rely on our experiences in the ATMP world over the last 5 to 10 years. But more importantly, we rely on our expertise and knowledge base of the science behind it, as well as our regulatory expertise. It's not so much repeating your past project experiences, such as 'I've done this for a similar client before; therefore I can do the same for you'. It's more the approach, 'I understand this to be your process which is new and unique, and I understand this to be the requirement for this type of aseptic processing. So let's figure out a way together to make that work in the most efficient way and minimize the risk to the product'.

It's important to be honest up front that sometimes there are projects out there that we've not done anything remotely similar. But we are confident that we can work together with our clients to come up with a solution by combining our regulatory expertise, process and equipment knowledge, and creativity.

AB: Most of the time, these early stage gene therapy and viral vector cell therapy companies are very research based and may not know how to make the leap from a research type platform to a robust commercial GMP manufacturing scheme that can be repeated over and over again, and be faithful to that product, and have a high degree of assurance that product is produced in the same way with the same purity time after time after time.

We have a broad experience and exposure to not just current technologies, but what the emerging technologies are. For instance, one of the big pushes now in cell therapy is looking at how we close up these process systems, and if we can't close up the process system itself, how do we provide an environment for aseptic processing, such as an isolator? We're working to adapt isolators that have traditionally been used for filling operations or potent compounding of chemicals, to the cell processing world in which we need to do aseptic processing.

Q How do you work with clients to help them understand the new process, technology and practical requirements they may encounter?

AB: As you look at autologous therapies, something to keep in mind, whether it's on the facilities side or process side, is because it's a single patient therapy, if you want to expand the capacity or facility you have to scale out because you can't scale up.

Another of the challenges right now is making the transition from anchorage-dependent cell lines for viral vector production, meaning the cells need to be attached to a solid surface to grow and produce a product. That means you need lots of surface area, which is somewhat difficult to achieve. However, if you're able to transition to a cell suspension like a traditional bioreactor, you really open the doors for much higher production rates and much higher capacity, even within a given facility, as well as helping to drive the cost of goods down.

GL: There is a jump to go from clinical to commercial and sometimes the technology, the platform, or the equipment they may have, may not be conducive to making that large-scale jump in commercialization of their product. One of the things that CRB really prides ourselves in is that we invest a lot of time in educating ourselves, whether that's attending conferences or seminars, or lunch-and-learns multiple times a week. It is a priority of the company to stay current, not just absorbing information on products and equipment but also building partnerships with these vendors and asking questions, trying to influence and challenge and steer the technology in directions where we may see a need.

By having these relationships, we can leverage that network to introduce our clients to some of these equipment vendors. For example, we can send them to the shop, have them get their hands on an isolator, stick their hand in the glove port and really see if that's as burdensome to manipulate as they assumed.

We also understand how the space could be different, how the expansion could impact existing portions of the building and how things could be phased

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in terms of design and construction to minimise impact to existing operation spaces. We bring our tool bag with us to the first meeting we have with our client and as we figure out what their needs really are, current and future state, we introduce them to the appropriate equipment technology that may assist them in the long run, or even setting up the layout of the building in such a way it could be a simple addition and expansion in the future with minimal impact to their existing operations.

NK: Another element that is critical is the supply chain, because when we start scaling up or out, especially looking at increasing demands, the supply chain requirements can get very complex in terms of chain of custody, maintaining a cold chain, and everything from end to end.

Yes, the equipment selection and everything inside the facility is important, but it is critical, especially in the ATMP side – and autologous particularly – that the supply chain is designed for that scale up as well as scale out. This means designing an architecture in terms of how do we ensure the technology for recording the chain of custody, who is the owner of the data, where is that data residing, is it in this level 3 cloud or a true ERP system or RFID that tracks everything from when the blood is transferred to patient all the way to being administered back?

Q What learnings can be taken from CRB's extensive experience in other sectors to really benefit cell and gene therapy facility design?

AB: Even though there are novel challenges to the new wave of biomanufacturing, cell and gene therapy and viral vectors, there are still similarities to a large model, such as mAb production or large scale human therapeutic production, that we can learn from. The drivers for the product are similar, and the mAb facilities we've designed over the past 20 years are really a cousin of the facilities we're designing now. From a high level, product purity, safety and segregation, mitigating any cross contamination, were key in those facilities as well. We use those philosophies and techniques, whether it's on the process side or engineering of systems, or facility design, and apply them to these new technologies. For example, with mAbs, we had to work on segregation both from a process engineering and facilities point of view to make sure the viral containing areas are separate from the non-viral areas. All those principles we learned 20 years ago for mAbs apply to these now.

Biosafety levels are defined by the NIH, and CDC, also apply to these facilities. We're able to take those lessons learned and knowledge and expertise from those mAb facilities and apply it here as well. It helps to explain some of this to our clients, that sometimes they feel like it's a brave new world and they're a little afraid of it but a lot of these problems have been solved before.

GL: At first glance ATMP facilities look very similar to laboratories because most are benchtop scale. And when you look at equipment technologies and flows, they resemble the biotech models we're very familiar with from mAbs and viral vaccines. When you look closer, these are non-terminally sterilised aseptic products that must meet the stringent criteria of aseptic processing. Whether it's CRB's experience in flexible laboratory concept, or single-use technology, or isolator technology, all of these unique characteristics of laboratory, biotech, and aseptic facility types are combined in ATMP facility design.

Q What motivates you to face these challenges we've discussed, and work to support the growth and success of the cell and gene therapy industry?

NK: At the end of the day, what we're doing is altering the outlook for people that we may know personally who can benefit from these kinds of technologies. These are not just band aid solutions, these are truly curative. So I'm energized, because this technology may one day help me and my friends and ultimately revolutionize healthcare.

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GL: Many of the clients I've worked with are developing products targeting different types of cancer,

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whether it's treatment or potential cures. There are also gene therapies for rare diseases that affect infants and young children. It's all about improving the quality of life for patients and their families, as well as potentially extending their lifetime. As a mom, and someone who has witnessed the pain and experienced the loss of loved ones to cancer, I am eager to support the growth and success of this industry.

As these products go from research lab to clinical phases and commercialization, they enter my realm of expertise and professional career, where I can participate in designing a facility that could ensure higher purity of product and decrease the risk to the patient through engineering solutions. As an architect, I consider it a truly unique opportunity and an honour to play a role in this chapter of medical breakthrough.

AB: I truly feel with these types of projects that we are at the cusp of transformational medicine that is going to be changing healthcare for the next century. What we're able to do now is manipulate the body's mechanisms via gene or cell therapy to correct defective genes or activate the body's immune system to identify and kill cancers.

From a process perspective, if we go back a hundred years to the birth of the pharmaceutical industry, we used chemical synthesis: A+B = C, and we used that pharmaceutical for headaches, pain relief, etc. We moved to the next level with antibiotics and vaccines. Then came recombinant proteins, whereby we are replacing a protein in the body or adding more to the body to correct a certain condition. Now we're to the point where we're able correct defective genes, or enable the body's internal mechanisms to fight cancer and other diseases. To me, that's tremendously exciting.

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