A MULTI-PRODUCT CELL THERAPY FACILITY

A conversation with Stephen Judd, Arcadis/DPS Group

ABOUT

Stephen Judd, process SME – Biologics and Cell Therapy, at facility design and engineering organisation Arcadis/DPS Group. Moderator Ben Locwin is a healthcare executive with quantitative and qualitative analytics expertise. He works with senior managers at biopharmaceutical, vaccine, and medical device companies to market at higher velocity and with higher quality.

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Ben Locwin: What are the differences between an autologous and allogeneic cell therapy facility? What might be different in terms of technical requirements and what are the different design considerations?

Stephen Judd: If we start with an autologous facility. So an autologous therapy is a personalized medicine, one batch equals one patient. That's not going to change. If you want to increase manufacturing capacity at your facility it means scaling out rather than up, so you can have multiple patient batches manufactured in parallel.

Scaling out versus scaling up typically means that you need a greater manufacturing footprint. So even though autologous therapy production is a small scale operation using benchtop pieces of equipment, you still need to be able to operate everything in an ergonomic fashion. Everything still needs to be neat. You still need to be able to move around the equipment to be able to set up the kits in a in an effective manner.

At the same time, in autologous therapy production, one of the key factors is ensuring chain of identity and avoiding mix-ups and the layout of the facility needs to reflect that. You need to look at ways you can optimize the layout and footprint by potentially stacking pieces of equipment but then you also need to ensure you have the ability to be able to reach the equipment you're working on. [Continues...}

SJ: Ballroom Suites are a common solution for companies that need to scale out. In these setups you have multiple patient batches in one open plan area, so a key factor there is early engagement with the regulatory authorities because they are going to question how you avoid mix-ups.

Also, with the ballroom approach, from a facility design standpoint you want to have as much equipment as possible in an open area as opposed to having to segregate between different areas. So again, early engagement with regulatory authorities and being able to bring them along through the design process is important. You really want to avoid issues that would otherwise adversely affect the regulatory review process and impact your speed to market when it comes to gaining approval for that facility.

When you look at the comparison then with an allogeneic therapy manufacturing process, there you have the potential for scale-up.

You can manufacture a much greater number of batches for a much smaller footprint. You have less variability. Yes there is variability from donor cell to donor cell, but you can characterize the material better because it's coming from healthy people.

Also you don't have the same chain of identity and mix-up considerations as you do with autologous therapies because your aim is to produce an off-the-shelf medicine that is that is going to be available to multiple people.

BL: Are there any other considerations autologous cell therapy developers should keep in mind?

SJ: Another factor impacting autologous therapy facility design is variability of patient material, because working with cells that differ patient to patient is not the same as working with cells from a healthy donor. Such variability impacts all parts of the process with expansion being a good example. If you do a cell expansion step you're looking for a target cell density and that depends very much on the material. So where you have healthier material that obviously achieves the cell density in a shorter period of time.

From a facility design perspective, the longer the expansion phase, the more pieces of equipment you require in order to achieve a certain throughput compared to you having shorter periods where you can turn over the equipment more quickly.

One of the challenges is ensuring you implement the right number of pieces of equipment in order to achieve your throughput. One way to do this is to model your facility using statistical analysis associated with those expansion periods in order to effectively determine how many pieces of equipment you need. You don't want to be too conservative because that adds cost and expands foot print. Equally, you don't want to underestimate because then you won't achieve your desired throughput.

BL: We have a question on this subject from our audience - Do manufacturers need to consider the modularity of the equipment when designing a facility?

SJ: If we look at autologous manufacturing there are different platforms and advances in equipment which allow multiple process steps to be performed on single pieces of equipment versus other processes which involve individual pieces of kit for each individual step. So with processes becoming more closed, they're becoming more automated which makes it easier to efficiently set those pieces of equipment out in a ballroom area.

BL: What is the value of the closed process and what sorts of operational challenges arise when trying to establish them?

SJ: So a closed process is one that is protected from the environment and from other unit operations. From a facility design perspective they allow for segregation to be minimized. You are able to install multiple pieces of equipment in the same ballroom suite compared to having small rooms.

This is an advantage because any increase in ballroom area minimizes overall footprint. It reduces the number of rooms, the number of air locks, so it reduces the construction materials required. In general, these designs streamline set up schedules and can help increase in speed to market. The other major factor in closed processing is that it minimizes clean room grade requirements. So one of the things I would like to talk about here is the difference between the Grade B and Grade C manufacturing environments and their impact on facility design.

In a lot of facilities, Grade B suites are used for multiple manufacturing operations to protect the product. Also Grade B suites are preferred because there is a perception that the multiple manipulations required in small scale production are more straightforward in safety cabinets than isolators. And then there's the other factor which is speed to market. Often during product development the focus is to get it to market as quickly as possible which means changing the process as little as possible as you come through clinical trials and then maybe optimizing the process when you get to commercialization.

BL: Does reducing clean room grade requirement have any knock on impact? Any benefits from a facility design standpoint?

SJ: Sustainability is a key factor in all new facility designs and in fact it is a specific requirement certainly in Europe that when you're designing a new facility you need to show that you're minimizing energy consumption. Also lot of facilities also look at things like LEED and BREEAM which are sustainability models with clear energy use reduction goals.

The single biggest energy use in a manufacturing facility is the HVAC system, which is what conditions your air and maintains the environment within clean rooms, and how these operate differs for Grade B and Grade C. For example, usually in Grade B there are 65 air changes per hour versus 35 changes per hour at grade C. So there's a massive difference in the energy consumption associated with operating those facilities.

BL: What happens if a human operator has to been involved in a specific production process?

SJ: Operations that can't be fully closed such as when you are working with adherent cells, cells stacks or filling operations can be effectively carried out in isolator. There are examples of cell therapy cell processing isolator offerings from certain vendors and then small-scale filling systems that can be effectively operated in an isolator which allow those isolators to be installed in a Grade C environment and that minimizes the clean room grade.

The other thing associated with Grade B clean rooms is that they are very challenging to maintain and onerous to work in especially if you look at the sanitization requirements associated with bringing material into those suites and the risk that that creates to environmental contamination of the area.

BL: You have a case study Stephen that looked at a multi-product autologous CAR-T facility in Europe. Would you mind jumping into that?

SJ: One of the main considerations associated with ATMP regulations in Europe - and I think they are the same with the FDA - is that once a product undergoes a genetic modification it needs to be segregated but prior to that it does not.

So when you're looking at a multi-product facility it's important to break it down into the different areas and establish which operations prior to the transduction step can be put into a common area. This allows you to have a common ballroom space where you have operations associated with multiple products being carried out.

And then once you move into operations where the transduction step has been carried out - once you introduce the viral Vector - you need separate suites for each product. How you manage those operations and split up your operations so you can use ballroom areas and best lay out your facility is the big question.

The case study also emphasised the importance of having unidirectional flow through manufacturing suites to prevent the cross-contamination associated with people entering and leaving a manufacturing area. Equally it's important to separate your products and waste flows but all of that can be contained within a suite as long as you ensure everything is properly sanitized before you move it out of the manufacturing areas.

Then having bi-directional circulation spaces can help to streamline your overall space as opposed to having supply and return corridors which can lead to a greater footprint. If your operational procedures are effective then you are able to streamline those areas. In the case study, the majority of the clean rooms in the facility were reduced to Grade C because there was effective process closure of single-use systems.

BL: What are the other on-site logistical considerations manufacturers should keep in mind?

SJ: Warehousing, cold chain and freezer chain can be a challenge for autologous therapies in terms of facility design. You have small scale equipment but you have a lot of units operating in parallel in order to achieve the throughput, so your management of your single use strategy is very important.

You have to ask yourself what is your business case for the quantities of single-use consumables you keep on site? Do you engage a third-party logistics company to get an extra two or three months of storage? This is a particular issue because single-use consumable lead times are going through the roof at the moment.

Then there are the consumables. You have that specialist piece of equipment, which is your cell therapy system but you also have things like bags and connectors that come from other vendors. For efficient operation these elements need to be combine into kits ahead of time so they available for the operator. So an efficient means of managing how each kit is assembled as well as an efficient means of managing how all that is sanitized is very important.

Again, from a facility design perspective, one good approach is to have a dedicated kitting area that is the same grade as the manufacturing suite. This strategy allows you to pre-sanitize everything and minimize what you need to do when you're actually bringing it into the suite.

BL: Cold chain and cold storage are also important cell therapy manufacturing. How do those needs shape facility design?

SJ: When it comes to cold chains and freezer chains one of the challenges is you may have extended a periods of product release. As a result your QC product release testing may take between two and four weeks and during that time you have a lot of other material within the facility which is backing up and needs to be staged in freezes. So freezer capacity is a critical consideration.

My advice is that you also look at different freezer design. You have new advances in freezer technology that have automated retrieval which gives you an improved safety because people don't have to actually go into the freezer and improved chain of identity because everything is automated.

However, those freezes have a lower capacity than the manually operated freezers so it's a trade-off and you need to look at space that is associated with being able to set those out.
So that is definitely a critical Factor when it comes to setting out that area and ensuring that you have enough space for all the freezers that you needed.

BL: How do you build these intricacies like the longer supply chain lead times for single use or changes in freezer technologies into your facility designs?

SJ: Well the statistical analysis for the variation in the batch process step times comes from the client. As designers we need to get the best available information and to build that into the model but it just quickly.

One thing to consider with the way the outsourced manufacturing services and supply market is going, is that a lot of supply chains are getting very pressurized. They're getting longer lead times, higher costs so I think if a company can bring things in-house it is ultimately going to reduce the cost of goods for the overall process.

You could look at, for example, E coli based fermentation for plasmid production followed by a mammalian cell culture based process for antiviral vector manufacturing. Provided you have the right level of segregation there's no reason why you can't have those defined manufacturing facilities at the same site. So this these are definitely things that need to be considered because they are things which can significantly impact the ability to supply that medicine to the market.

This case study was originally presented at Evaluating Biopharma's Cell therapy strategies online and interactive event

You can watch Stephen's case study in full and on demand here.
Details of future Evaluating Biopharma events can be found here.

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