CELL & GENE THERAPY INSIGHTS

INTERVIEW

INTERVIEW with:
Emily Thompson, Process Engineer, CRB

"You need a flexible facility so you can use that space when required, but you can also use it to manufacture other products when you don't."

Multi-modal cell and gene therapy facilities: future-proofing with flexible design

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Q Could you tell me about your current work at CRB?

ET: I am a process engineering lead, and an advanced therapy medicine product (ATMP) SME. I focus primarily on ATMP (cell and gene therapy) projects for a number of different clients

across the country, and I work with them to design, optimize, and construct their facilities for new therapies they are bringing to market.

Q What are the key considerations and requirements you hear from companies in the cell and gene therapy space? What do they consider to be the most crucial aspects of facility design?

> "...a lot of the products in the ATMP space are awaiting approval. This means companies are building facilities at risk."

ET: For the clients I am working with, this is often their first time bringing their product to market, so up until now, they have been doing a bit of commercial and clinical manufacturing in more of a lab-like setting. A lot of these companies are very small startups, so they might not have the manufacturing experience that larger pharmaceutical and biotechnology companies do. For these reasons, process is key – they really want us to learn and understand their process, and help them translate it into a process that is suitable for commercial manufacture.

Another key consideration is contamination. Everyone is worried about this issue; especially cross-contamination for autologous cell therapy where you have multiple patient batches in the same manufacturing space. This encompasses everything about your facility design including logistics and how you approach chain of custody through bar coding and tracking each patient's therapy from vein to vein.

These facilities are almost always single use, again because of cross-contamination concerns. With larger biotechnology companies you may have a dedicated facility, but for these smaller organizations, they typically want to go for maximum flexibility. They do not know what products are going to come through, so right from the beginning it must be a flexible, nimble facility.

Finally, in the ATMP space, the manufacturers are typically a very conservative group. They often come to us for help understanding the regulatory requirements to ensure they comply with FDA and EMA regulatory guidelines.

Q What are the benefits and the drawbacks of a dedicated manufacturing facility?

ET: If you have enough demand for a product there are benefits to having a dedicated manufacturing facility, because it is custom for that product. If it is well designed, it can be very efficient.

It is also easier from a manufacturing perspective. Your operators know the process: they have learned it, they come in every day and know what they are doing. It makes supply chain considerations easier as you know what product you are making, so you know what materials need to be ordered and how quickly you use them up.

However, things can change. Perhaps your patent expires, another competitor turns up, or for some reason you start having adverse side effects from your product. Now you have this very

expensive custom facility that you have built, and you have to figure out what to do with it. It may be difficult to retrofit, particularly if it is a stainless steel facility that has complicated piping and custom equipment.

> "...we are seeing a lot of interest in having multiple different types of products in the same facility."

Dedicated facilities can also take longer to build from the beginning, especially if it is a very large-scale stainless facility. You may hear about facilities that take 12 or 18 months to complete start-to-finish, but this is not the reality for most dedicated manufacturing facilities. From design, build, to completing commissioning and validation, creating a traditional stainless steel facility could take up to five years.

Q Have you worked with many clients in that scenario, where they have had to retrofit and repurpose a facility?

ET: I started with CRB 18 years ago, and when I joined, I worked for one client for my first 4 years. They had built a very large stainless steel manufacturing facility, and over the last 18 years I have followed that facility. During that time, at least half a dozen new products have been introduced, and every time they have had to retrofit the facility. Each time, it requires an investment in cost, engineering scope, and construction management. It is a significant undertaking that requires money and time – but it can be done.

Q In contrast, what do you see as the biggest benefits of multimodal ATMP manufacturing facilities, and have you started to see a trend towards more multimodal manufacturing facilities in the sector?

ET: There are several benefits. Currently, a lot of the products in the ATMP space are awaiting approval. This means companies are building facilities at risk. If they are not approved, then having a flexible space you can repurpose for other products in your pipeline or to provide capacity to contract manufacture other companies' products is the best way to build since it keeps the investment profitable.

Regarding multimodal facilities, we are seeing a lot of interest in having multiple different types of products in the same facility. This is mainly because companies have been outsourcing to multiple contract manufacturing organizations (CMOs), which can be difficult to manage. Companies are looking at bringing everything in-house in order to have control of their supply chain. They want to have reliable supply and control of their process and facility.

When using a CMO, it is a relationship that must be managed. For example, sometimes when working with a CMO who is using a proprietary manufacturing process, the client is not even fully aware of how their product is being manufactured. This can create issues with technology transfer or with increasing capacity. Companies are realizing that they need to own their manufacturing process and ensure they have capacity to make their products.

Q What do you think are the biggest challenges that companies might face when looking to move from a dedicated manufacturing facility to a more flexible multimodal approach? Are there any instances where this type of facility wouldn't be compatible with the different manufacturing needs a company faces?

ET: When you are moving from a dedicated to a more flexible approach, it is a shift for your operators. Before, they may have known how to run one process on one set of equipment. Or if it is a monoclonal antibody (mAb) facility where they are running a number of different mAb products through that facility, those processes are still broadly similar, share many of the same unit operations, and take the same general approach from start to finish.

> "If you are transitioning to a multi-modal approach, your operators must be a lot more flexible..."

If you are transitioning to a multi-modal approach, your operators must be a lot more flexible, and they have to learn a number of different processes. It can also add complication from a segregation perspective; for example, if you are working in one suite and then you would like to work in another suite you are going to have to exit the first processing suite, go back to the locker rooms, complete a shower, re-gown, and only then are you allowed to enter the second manufacturing suite, to avoid cross-contamination. There is definitely some training that needs to occur, as you require a different mindset when running multiple different products in the same facility.

Support operations are also going to change. If you are supporting one type of product, your warehousing will look different than if you are supporting five different types of product. With single use, companies are very concerned about being able to get their consumables, so they stockpile three to six months of consumables in their warehouse. You will need a very large warehouse if you are running multiple different products and trying to ensure sufficient inventory.

The quality assurance/quality control (QA/QC) requirements for multi-modal manufacturing spaces grow. You have multiple different products, and they do not share the same analytical methods. Additionally, if you have an autologous cell therapy, each patient that comes in is a different batch and each batch must be tested. It is very different to have 2,000 one liter batches, versus one 2,000 liter batch. You are treating the same number of patients, but your QC and QA testing just increased dramatically to accommodate that. From a logistical standpoint, these facilities are simply much more complicated to run. You have much more going on, and you really have to manage those flows to prevent cross-contamination and to avoid mix-ups.

One limitation for multi-modal facilities is an increase in scale. We often have clients who are running a 500 liter viral vector scale currently, but might want to do 2,000 liter scale in the future. As you push towards those larger volumes, a multi-modal suite may or may not be able to support that, especially in regards to equipment sizes and ceiling height limitations.

Another process that does not work well in a multi-modal space is oligonucleotide manufacturing, which typically uses a solvent manufacturing process to manufacture RNA products.

Due to the code requirements associated with solvent processing, this is a process that we would want to design for upfront as it is difficult to retrofit into an existing facility in the future.

Q Why is future-proofing manufacturing and maintaining flexibility important for the cell and gene therapy space in particular?

ET: One of the reasons we touched upon already, is that the products are not to market yet, they are still in clinical trials. We don't know what is going to happen, so retaining that flexibility is important. With this approach, if for some reason the product does not come to market, that space can be used for something else.

For a lot of these therapies, there are several players in the field. For one treatment there may be three or four different companies trying to develop the same gene therapy, and they will not know which one is going to get to market first. It benefits them to have a flexible facility for that reason, too.

Additionally, the patient populations for some of these gene therapies are extremely small, as there has been a focus on unique orphan-type therapies. It does not make sense to have a dedicated manufacturing facility when only a handful of patients might be treated every year. You need a flexible facility so you can use that space when required, but you can also use it to manufacture other products when you don't.

Q With the uncertainty that the Covid-19 pandemic has brought to many businesses, and the need for social distancing currently at the forefront of everyone's minds, many companies and organizations are using their current facilities in very different ways, or even repurposing them. Do you think the pandemic is going to have a significant long-term impact on the facility design of the future?

ET: I think it will have some impact. What we are seeing now is if you are not an essential employee, there is more of an acceptance of working from home. At CRB, we are considering whether we need more office space, and questioning if instead we can just utilize what we have better and give employees the option to work from home when they need it.

I believe there has been a shift in the way people think. Everyone has realized that with video conferencing and other tools available for remote teamwork, there may not be a need to spend as much time in the office. On the other hand, there are essential people that do need to be on-site. There was a trend towards open cubicles and open office layouts, but with the emergence of COVID, businesses are realizing that these may not be the best idea.

When we design facilities, we look at the office space as well. Usually our clients have in mind that they need seating for a given number of people. I do think that is going to change as we move forward – possibly they will not need as much space, and the space utilization may be different.

> "One limitation for multi-modal facilities is an increase in scale."

And of course, we are talking about flexible facilities. At the moment, it seems like everyone has jumped into the effort to develop a COVID-19 vaccine. I do not think anybody has had time to build a dedicated facility for a COVID-19 vaccine, so manufacturers are taking the facilities they have, and retrofitting them. It goes back to the same theme – you want to have a space that is flexible, where you can set up a new process and roll with it, with minimal constraints in the way.

Q If you were to put your psychic hat on and predict what a cell or gene therapy facility would look like in 10 to 15 years, what trends would you expect to see?

ET: Right now, especially with autologous cell therapy, the processes we are seeing are very manual. But any time you have operators performing critical manual steps, it increases the chance of error, mix-up, or contamination. The best way to mitigate these risks is to reduce manual intervention and incorporate more automated equipment. I think it is going to be equipment that we have not seen yet, or that is just coming onto the market now, that is very specialized to this industry.

As processes become more automated and in turn, more closed, this translates into a change in facility environmental requirements. Currently if you are performing manipulations in a biosafety cabinet, you need a Grade B background. If you move to a fully automated and closed system, you might be able to go down to a Grade C or Grade D background depending upon regulatory requirements of the intended market. This in turn changes our facility design because air locking and HVAC requirements are reduced. This decreases facility size and operational expenses but increases upfront capital expenditure. I think this is something we will see as the industry matures and has more product successes. Currently, most of the companies in this space don't have a huge amount of capital funding, so they choose to use more manual processes, because it is more cost efficient to build a larger space that has biosafety cabinets rather than to build a facility with more automation.

My other prediction is that there will be improvements in testing. With current QA/QC testing, there is a wait time to get results, and often the product lot is released to the patient even though all the testing is not complete. We are going to see a push for more rapid on-line and at-line testing of the product, so we have completed results prior to patient administration.

Q In terms of automation, do you liaise directly with technology developers to stay up to date on how these developments impact facility design?

ET: Yes – pre-COVID, this often occurred during an exhibition or a trade show. CRB would meet with vendors and find out more about their technology. More commonly now, CRB reaches out to vendors to explore options for our clients. There are definitely a few established players on the market, and more are always emerging. We work with vendors and give them feedback, although this varies, as some are very secretive and don't want to talk about their

product. We always strive to find our clients the best solution, whether that be an off the shelf option or a custom solution tailored to meet their needs.

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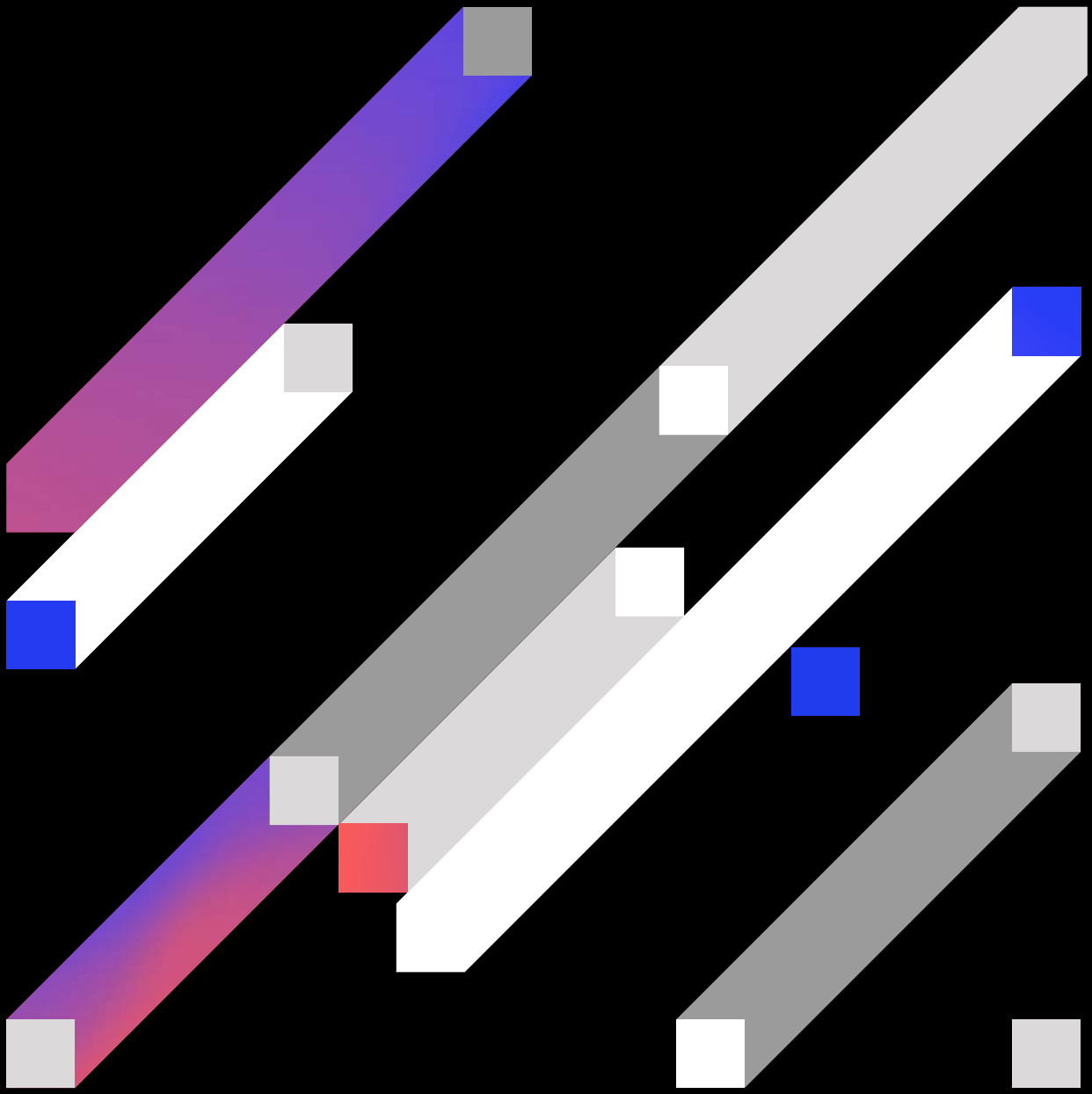

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