INTERVIEW

Planning for Commercial-Scale Production: Tools & Technologies of the Future

DAVID JAMES David is an experienced international Executive who has spent nearly 30 years commercializing innovative technologies. His broad industry experience and balanced technical and commercial perspective have helped launch several market leading instruments, consumables and manufacturing systems for Cell Therapy and Diagnostics. David is a regular conference speaker, guest lecturer for the Department of Chemical and Bio-molecular Engineering (University of Melbourne) and author of multiple papers and articles

Q What are the key cost drivers associated with the manufacture of autologous cell and gene therapies?

DJ If we consider what happens within the manufacturing facility using a typical manual approach, which is what most companies start out with, then you have around 50-70% of the cost of goods attributable to your consumables. Of this, reagents are the largest cost. The remainder of your cost is typically spread across labor, (~20%), facilities (~10%), quality control (~10%) and then equipment.

The fact that most of your costs are for reagents and consumables is something that I don't feel many people have a real appreciation of. There's a lot of expectation that automation will reduce costs, but actually automation typically does little to reduce reagent usage. So, for me, bringing down the cost of reagents and consumables would certainly have a big impact on lowering cost of goods of these products.

Q Is that one of the things people have been most surprised by when you talk this through with them?

DJ Unfortunately I think many people are still fairly naïve to what the real costs are. In addition, there's a common misconception that you can introduce automation at any stage, to solve a cost of goods problem. But if you think about it, reagents are fundamental to your products and are defined at the very beginning of your process development. So, in fact most of your costs are actually locked in very early and can't be changed significantly through the introduction automation.

Q When should companies be investing in manufacturing processes that are going to be amenable to moving to commercial scale production downstream?

DJ If you asked a regulatory Consultant (which I'm not) they would probably tell you that you can make changes pretty much at any time providing you prove it's comparable, perhaps with a bridging study. But, I look at it differently. From an engineering perspective, the simplistic answer is the earlier the better. However, in reality it's a lot more difficult to do than you would think.

Very early on in your product's development you actually don't know a lot about the process – what's important and what isn't. So you often can't really define the process sufficiently well to automate. In addition, you typically don't have sufficient funds to do what you would like to do early on. Therefore, whilst from a comparability perspective it's an ideal scenario to invest in integration and automation as early as possible, in reality it's often just not practical.

For many years I felt that Phase 2 was probably the sweet spot, because you should have enough clinical data to justify the investment and it's before you start your Phase 3. But, I've actually revised that position in more recent times, especially looking at the accelerated development programmes that a lot of companies are pursuing. A perfect example of that is Japan, where basically you can get market approval on Phase 1-2 data, including approval of the process you have used. So, if anything, Phase 2 is too late.

My current thoughts are that Phase 1 is the time when you really are locking down the majority of your process, and making the fundamental decisions on what technology to go with. Unfortunately this is much earlier than most people realize. My advice therefore is that for someone in R&D

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or Phase 1, they should be choosing processes and platforms that are scalable and closed – that's imperative. If you're already in Phase 2 or beyond, then you should be extremely careful about using any process that wasn't used to generate the clinical data to date.

Q Where do you see the biggest opportunities to reduce cost of goods by moving to closed and automated systems?

DJ The very simple answer is moving out of the expensive Class B cleaning rooms. They're expensive to build and operate. By closing up the process you can reduce the demand on the clean rooms, but there are some other side benefits which are actually quite significant. One of the difficulties with open processing is you need to sterilize the area before you introduce a new batch. Apart from the cost of cleaning, you also have to validate that it is in fact clean before you start. So, you end up with a fairly poor up-time on your facilities as a consequence. There's another hidden cost with operating Class B-type cleanrooms: it's much more difficult to move people in and out. Again, that impacts the efficiency of the facility and the efficiency of the staff you employ to work in it. There's actually more hidden costs in operating these higher-end clean rooms than people imagine and therefore if you can close up your processes you achieve savings across the board.

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Whilst cost is clearly a key consideration, in my view, one of the biggest benefits to closing the system is actually quality improvements and the security of knowing the system you're using is sterile.

Q There's been a great deal of interest in your article published last year. Has it altered the conversations you've had with people in the industry?

DJ Yes and no. If I reflect back on the last 15 years, I was one of the lone voices in the wilderness talking about scale-up and cost of manufacture, so

it's great to see this now come to the forefront of discussions in the sector. Today, we have trade shows and conferences dedicated to the topic, which is a reflection of the increased awareness and the information out there.

Where I've been quite surprised is that the talk isn't necessarily turning into the sort of actions I would have expected. We still see a reluctance to embrace new technologies. Whilst people might want to change, there are certain barriers that make it difficult. You still have the commercial pressures of getting to the next clinical milestone with limited funds and you've still got lack of certainty about what the process is. And you've still got a lack of awareness of exactly what capabilities and technologies are available. Those fundamentals haven't changed. So despite the increased awareness, people are still by and large making the same decisions they were making. I think we're seeing a change, but it's not as rapid as I expected it would be.

> "We still see a reluctance to embrace the technologies that are available, or becoming available."

Q How do you think we can catalyze that change?

DJ What we're seeing is an injection of capital coming into the industry to support some really robust clinical results and that typically ends up flowing through to technology and innovation. We're also starting to better understand what it takes to get there and that people are becoming more comfortable with how much money is required to do things properly. Over time, once more products get to market, the pressures to manufacture efficiently will start to take centre stage and catalyze innovation, with the required funding behind it. We are starting to see this gradual shift already, but it takes time.

Q Do you think there are sufficient advances in terms of solutions and tools and technologies?

DJ We are starting to see a shift in terms of new tools being developed specifically for our market. Naturally it follows that as funds start to flow into the industry, then the tools companies will feel more inclined to invest and do the things they need to do to support it because ultimately they have a business case they have to make as well.

Most of the major players, if not all, are now making strategic investments in the industry. But, it has really lagged behind and that's one of the

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reasons companies are having to use technologies that perhaps are 'good enough' for their product development but far from optimal for commercial scale manufacture.

Recently there have been several developments, particularly in the cell expansion area, with new technologies being introduced into the cell therapy space from small batch bioprocessing. These are the kind of technologies that can make a big difference. There's also lot of talk around dealing with frozen product, and what can be done to achieve better control of the supply chain.

Another key change is that we're seeing a big shift away from the fully integrated, fully automated approaches, into a more modular, flexible approach. For me that's a very healthy change because it gives people the ability to really customise a process to suit their products.

Q What do you see as the key challenges of really moving to this modular approach?

DJ We don't have to imagine too hard what they're going to be because other industries have dealt with this in the past. The current situation of "islands of automation" is typical of a new industry where you have technologies being developed by different people in different places at different times. You don't see a rapid convergence on even standard things such as the way you might physically connect with another instrument.

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There are some initiatives within the industry to try to tackle this very issue and I know that the Alliance for Regenerative Medicine (ARM), amongst others, are trying to do just that.

Whilst some level of standardization could be helpful, you also want people to be creative and to innovate, without being stifled by putting too many boundaries around them.

There's another gap that a lot of people again underestimate, which is that if you're to close a system that's made of different modules from different suppliers, inevitably there are points in that process where it's not entirely seamless, and where you can't naturally go from one closed system to another. These interface issues can represent a significant challenge, again when you're designing a process and selecting technologies, and is

a common area where people come undone. Again, I think we'll start to see that standardise over time, as people realize how these systems work together.

Q Where do you see the real opportunities to develop step-changing technologies for the cell and gene therapy sector?

DJ I feel that small batch processing and having technologies that are optimized for small volumes is a key area for development. Whilst it has been a common belief that autologous therapies could not be commercially viable because of the scale up issues, they now represent over 50% of the market for cell and gene therapies. However, because of this "belief", development of small batch processing technologies has really lagged behind, and it does need some fairly unique solutions for these processes to become viable.

I think the cell therapy industry has been underserved with optimized manufacturing technologies as a whole, but the autologous space in particular. With autologous therapy, you don't get a chance necessarily to get another sample from the patient, so every cell is critical. It's therefore not just a cost of goods issue. It's "do I have enough or any product to treat the patient?". Batch failure in autologous therapies can also literally mean a death sentence for the patient.

One process in particular is the cell wash and concentrate step, where companies are often working with 30% losses on an autologous product because you have a technology that's really not up to the job. To me this is something that has to be addressed. Whilst there are technologies that deal with small volume, they're not often scalable and they're not suitable for GMP production. So, there are still some significant gaps in terms of the technology you might want to use in the autologous space.

Scinogy was formed with the intention of plugging some of these holes and to be honest, we were spoiled for choice in terms of the areas we might look at. Quality control (QC) is a space where I think there's still significant work to be done. One important QC challenge is trying to get process controls happening closer to real time and without breaching the closed system. So, one of the things that Scinogy has been doing is making sure that we include the QC functionality in these systems where possible.

Another area we've chosen to focus on has been in the cell wash and concentrate space, particularly for small batch processing where yields are typically so poor. We've been fortunate to be involved in counter-flow centrifugation

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for the last 10 years and therefore recognised the potential of the technology, but what we didn't see was a version capable of dealing with the small volumes needed for autologous products. This led to us developing ROTEA, a new device based on the principle of counter-flow centrifugation but specifically designed for small batch handling.

Rotea had its first big public outing at the Cell and Gene Therapy World Forum this year. It's a closed process which is critical to any system you would introduce to the cell therapy space and the counter-flow centrifugation technology delivers outstanding live cell recovery and viability, focused on small volume processing – both small volume going in and small volume coming out. Many of the existing technologies for this process step struggle to deliver the very small doses you're dealing with, often sub 5 mL. Because with autologous therapies, the cells you are handling are precious, we've made sure that the Rotea system delivers those very small volumes of product.

We've achieved some outstanding results to date, for example, upwards of 98% live cell recovery, which is a considerable improvement on existing technologies. We've also placed a lot of importance on making the device as user-friendly as possible, reducing the possibility of manual errors. Crucially, for a technology to be adopted by the industry, it needs to be implemented during the early research phase and clinical trials. So, we've made sure it's absolutely suited to that part of the market, but will also seamlessly translate into a GMP environment when the need arises.

Overall, it was an ambitious undertaking, but we are delighted with the outcome and we're certainly excited to finally be out there.

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