Biomanufacturing & Cell and Gene Therapy

Insights from the Industry

BIOMANUFACTURING

CELLANDGENETHERAPY

PROVENTA INTERNATIONAL

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Introduction

There are few years in living memory as disruptive and uncertain as 2020 has been. While this is true of almost every sector, the events field has seen unprecedented change in how events are held and how operations will be conducted in the future.

Proventa International was among the companies spearheading this innovation, utilising its trademark versatility to ensure that none of its important meetings were cancelled and its mission was carried out. Moving fully online, Proventa was able to facilitate connections and host expert, sector-critical discussions that would otherwise have been missed.

Despite the unforeseen challenges 2020 brought, Proventa's meetings were as successful as always, bringing together top-tier industry experts to talk through challenges and innovations with one another, make new connections and take back brand new information to their companies. Whatever challenges the rest of the year brings, those who attended the online meetings will be able to face them fully prepared and as informed as possible.

The Future of Biomanufacturing and CGT

While not quite as affected by the recent pandemic as some areas - for example clinical trials - manufacturing is currently entering a fascinating new era of technological growth and change. The roundtables held by Proventa this year took advantage of this, discussing among other things the use of the Internet of Things to minimise waste and maximise productivity; moving from early to late-stage development in cell therapies; and leveraging digital solutions to ensure QMS requirements are met.

From continuous manufacturing to CGT vectors to single-use technologies, Proventa's 2020 event looked at some of the most relevant and important changes in the field today, with leading experts offering their insights and thoughts to those who were there.

This report will look at some of the highlights of the recent Biomanufacturing and Cell and Gene Therapy events, but will also go further: it will explore what delegates are investing in right now, and look ahead to the next five years in the field: how Biomanufacturing and CGT will change as the years roll on, and how delegates are being affected by the turbulence of Covid-19.

We hope you enjoy this report, and look forward to seeing you at our events next year,

Joshua Neil, ***Editor***
Proventa International

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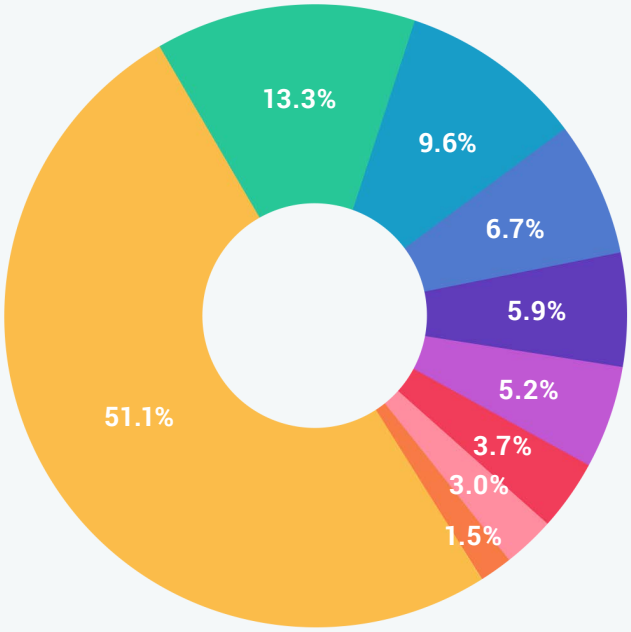


51.1% Director level

13.3% Department Head

9.6% President / VP

6.7% Other

5.9% Scientist

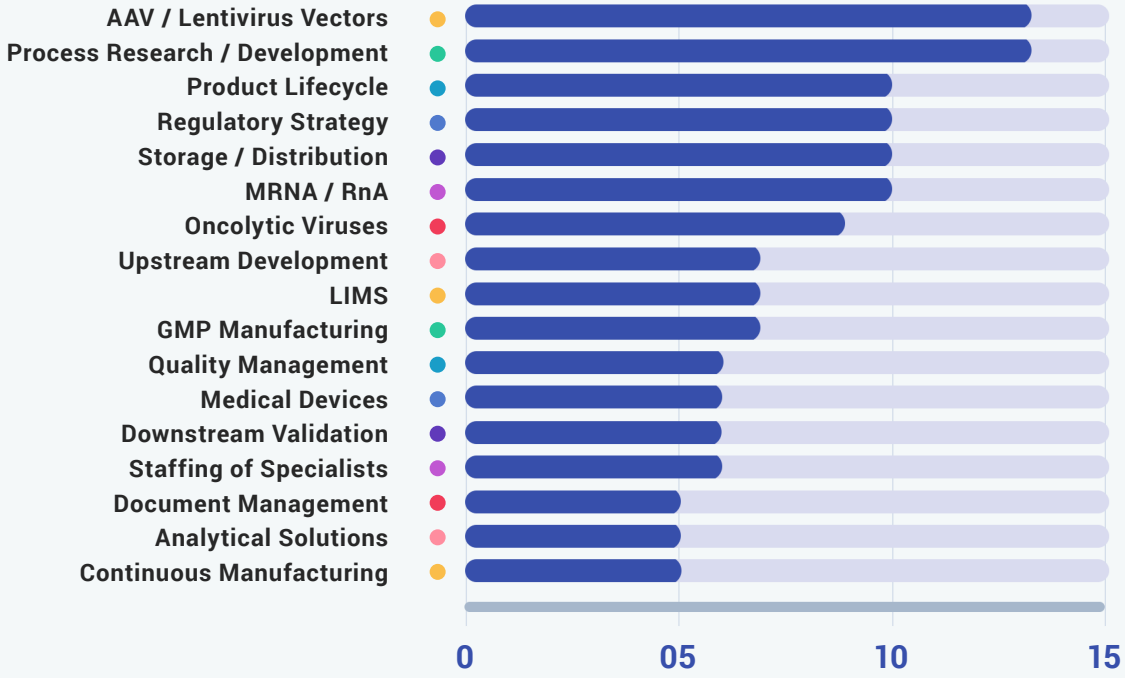
5.2% Manager

3.7% C-Level

3.0% Team Lead

1.5% Chairman

Key Investments



2020 Event Highlights

BIOMANUFACTURING

Challenges for Point-of-Care Manufacturing

Michael Lotze, Vice Chair Department of Surgery, University of Pittsburgh, delivered a fascinating discussion in the morning session for Proventa's CGT track, talking about the challenges of moving to more point-of-care manufacturing.

Dr Lotze showed the delegates a typical CGT manufacturing chain - in it, two major shipping steps occurred, one after the infusion bag was prepared and delivered to the patient, and another when the tumour has been excised and is shipped to be dissected. Dr Lotze asked whether it was possible to cut out the two shipment processes and move manufacturing closer to the patient.

In order to do this, technology would need to co-evolve with groups trying to pioneer this 'bedside manufacturing', for example G.E. and Miltenyi Biotec. The fundamental notion of this change, he said, particularly for CAR-T cells, was to take apheresis, put in the CAR-T cell, expand it and infuse it back into the patient, as is done with solid organ or bone marrow transplant.

There is already substantial literature for this, alongside a recent consortium announced between Wilson Wolf, Bio-techne and Fresenius-Kabi that will try and create this bedside manufacturing not by using equipment such as Miltenyi's Prodigy, but with lower-priced disposable culture vessels and materials that will allow delivery to where the patient is.

He then pointed out some of the problems of cryopreserved cells being transported from patient to hospital was the need for a complex network of people moving these goods, with tracking always providing an issue. While new technologies providing constant, reliable tracking, it is still a burden on CGT companies to ensure constant tracking and security of product.

The roundtable then opened up to audience questions. One delegate pointed out the final question asked - what is right for the moment? They thought that a medication which costs 500,000 euros was a medication at all, at least not for everyone.

He noted experts should focus on safety of therapy, but each addition to a CAR-T therapy only made it more expensive: after safety, cost reduction should be focused on.

Another delegate then moved on to discuss the near future of cell therapy manufacturing. He pointed out that between preclinical mouse models and phase 3 studies, few products succeeded: he attributed this to a form of overexcitement in preclinical studies, which then saw products rushed into phase 1 before they were ready. He said the community seemed more focused on the design and therapeutic molecules without understanding the models they were being tested in.

A number of delegates agreed from this that to use mouse models was wrong: and that despite this having been known for many years, most companies still used them. Speaking about the potential for point-of-care therapy in the near future, one delegate said that there are certainly challenges to be overcome before this could be a reality: first, building the necessary infrastructure and building the right resources, and difficulty of holding multi-centre trials in this situation.

To make this point-of-care manufacturing a reality, delegates concluded by noting that automation would be key, including to standardise product standardisation and have a smaller footprint. Another said that microbiome would be key, helping to stratify patients and determine who should and shouldn't receive immune-based therapies.

Current processes and future considerations for Upstream and Downstream Viral Vector Production

On the event's biomanufacturing side, a fascinating roundtable was chaired by **Blair McNeill, VP, Head of Biologics and Gene Therapy at Sumitovant Biopharma**, on current and future considerations for both upstream and downstream production of viral vectors.

The talk was an in-depth and knowledgeable debate between several experts in the field, and covered a wide range of issues within the area. In particular, the processing of viral vectors and a focus on upstream processes were explored by those present.

The discussion began with delegates noting the positives of using transient transfection to manufacture viral vectors. Most agreed that development is much quicker with transient transfection. Compared with stable transfection, however, transient compared poorly in terms of consistency, and required more DNA preparation. Transient transfection is also not as scaleable, meaning greater challenge when making DNA complex at higher scales. The biggest drawback to transient, one delegate concluded, was a commercial factor: there is a long plasmid DNA supply chain before the vector can be manufactured. Controlling this was a major difficulty.

After briefly discussing the regulatory implications of transferring from a transiently-expressed vector to a non-transient one, the delegates moved onto comparability studies when switching from transient to stable transfection as compared with holding out to use only stable transfection.

A delegate answered that they decision here centres on where to focus a company's effort. If they proceed with a transient system and want to change, comparability studies will take longer then the delay of waiting for a stable transfection would be.

The decision is simply how a company wants to progress, and whether it has the time to put a full comparability set together at a later stage.

The roundtable then moved to a discussion about general appetite for a move towards more defined media to help with expression, as seen in the protein therapeutic and vaccine fields. The answer was that before this could be discussed, most companies are currently focused on recovery of viral vectors from produced titers, that are lost easily in this process. Sometimes, only 1% of the vector made has the required qualities. Delegates noted that this is currently more important than media, though some companies are starting to look at media and strategies post-transfection.

One delegate concluded on this that as used platforms mature, there will be more opportunities for performing metabolic studies and looking to see what's currently missing from media, when media exhaustion occurs etc, and where supplements can be added. But right now, there are not enough mature processes where yield can be gained. It was noted that downstream, AAVs are much easier to purify, with lentiviruses generally worse. Some delegates said they often lose half a stock through sterilising and filtering.

The roundtable concluded with a question about the biggest downstream issues with lentiviruses. Delegates agreed that the lack of homogeneity is one of the biggest, due to the broad size range that often sees variations between 50 and 200 angstroms, with no proof of which is functional when viewed. Delegates finished by noting that in this field, confidence is built only by developing processes - with little that can be done before those processes begin.

Key Delegate Challenges - 2020 and Beyond

Time and Resource Management

The challenge most delegates suggested would be an issue over the next few years related to time and resource management, with a number of professionals suggesting their greatest difficulty related to strict timelines and limited resources. Particular challenges cited included resource prioritisation and capacity management; sourcing raw materials; time to clinic; and general funding issues.

Outsourcing and Partners

The next challenge most mentioned by delegates was finding partners and outsourcing work to CDMOs: among other difficulties, experts surveyed suggested that they had trouble with building outsourcing networks, finding vendors for new technology and accessing capable CDMOs, among other things.

Commercialisation and Competition

The third most-mentioned challenge for the coming years related to commercial aspects of biomanufacturing and CGT: delegates noted a lack of experience in GMP to support commercial needs and the need for differentiation from competitors as some of the challenges they are facing at present.

Logistics & Supply Chain

Next, delegates mentioned their supply chain as a source of difficulty for them. Experts surveyed mentioned a lack of agility in the supply chain for facing program demands based on clinical outcomes as one area that presents a challenge for the years ahead.

Hiring and Internal Expertise

Difficulties in finding sufficient talent and suitable internal expertise were more challenges cited by multiple delegates. Among other things, those surveyed said they were facing difficulties with generating expertise on CGT for future projects, acquiring the right talent and increasing their recruitment rate.

Key Delegate Challenges - 2020 and Beyond

Regulations

Regulations were an area many delegates professed struggling with. Some particular challenges in that area included quality/regulatory implementation requirements for new technologies; regulatory filing in general; and anticipating questions from the FDA.

Expansion

A number of delegates mentioned expansion as a difficulty for them: some mentioned global expansion as the challenge they most struggled with, while others noted capacity expansion or looking for excellent target investments as something that have focused on recently.

AAV Gene Therapy / CAR-T / CGT

Several delegates voiced difficulties with particular therapies that looked set to continue into the future. Among other things, several described having issues working with AAV gene therapy, gene and CAR-T therapies, and generating expertise on CGT.

COVID-19

Surprisingly low on the list, COVID-19 came as a further difficulty that looks set to continue for many delegates. This included disruptions to their supply chain due to the new measurements in place while the quarantine continues, and generally developing a business within the COVID environment.

New modalities

Finally, several professionals mentioned new modalities as a difficulty they were working around. Particular points mentioned on this topic included advancing new therapeutic modalities, finding platforms for new modalities to reduce complexity, and establishing internal manufacturing capability for new modalities.

A Look Ahead:
Biomanufacturing and CGT Over the Next 5 Years

While key investments of our leading delegates are a useful indicator of what is most important to industry professionals both now and in the immediate future, their scope and importance only extends so far ahead. To look further - to the next five years in Biomanufacturing and CGT, for instance - Proventa asked its facilitators about their expectations for the near future, and how the field will have changed in the run-up to 2025.

Digitalisation and AI

Perhaps the most discussed topic during the event was, unsurprisingly, AI and the industry digitalisation surrounding that. **Susanne Rommel, Executive Director of Development & Commercial Quality at Gilead Sciences** suggested these new technologies have the potential to significantly impact the pharmaceutical bottom line, compared to other industries, and could have a major impact in the next few years. In particular, she said the near future would see increased efficiencies and further automation with reduced losses stemming from this.

Anthony Colenburg, Director of Quality at Adicet Bio agreed with this assessment of the future, suggesting that reduction of overall manufacturing process timeline through automation and virtual reality integration would have a major impact on the manufacturing field. So too did **Devyn Smith, C.O.O. of Sigilon Therapeutics**, who suggested that full automation for cell/gene therapies would soon be revolutionising the field.

This area was, however, the area where perhaps the most hype was expected: Susanne Rommel noted that misunderstanding what digitalization/ AI is and can do could reflect poorly on unprepared companies, while **Siddhartha Jain, Director / Fellow, Manufacturing Sciences and Operations Innovation Strategy at Sanofi Genzyme** suggested that overall digital transformation has not been well-defined, with benefits that may well be overestimated.

Continuous Manufacturing and Single Use Technologies

New and innovative processes, such as continuous manufacturing (CM) and single-use technologies, were suggested by some of the delegates as having major importance for the coming years. Siddhartha Jain pointed out that single-use technology provides flexibility of manufacturing, especially in small batch sizes, while Susanne Rommel said the future would see an increase in ballroom concepts (a large manufacturing area with no fixed equipment) and modular manufacturing, disposables, and continuous manufacturing.

Anthony Colenburg added to this, saying that to him one of the most interesting developments in recent years has been the ability to manufacture in closed systems.

Cost of Goods and Quality

The cost of goods and of quality were two issues a number of facilitators spoke about. Susanne Rommel suggested reducing the costs of quality was an important change to be made over the next few years, while Devyn Smith suggested the cost of CGT goods as an important factor in the field today.

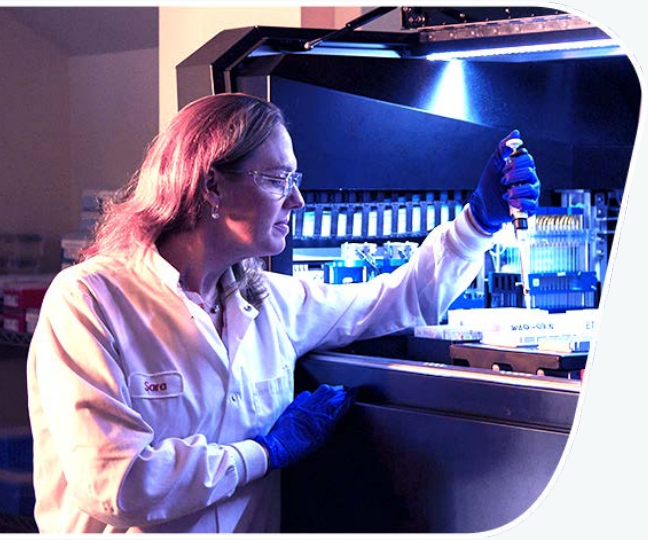
Siddhartha Jain noted that there is a consistent focus on cost of goods reduction due to pricing pressures, while raw material control was another major challenge for the next few years - with raw material complexity increasing, there is an increasing need to understand and control raw material variability and supply robustness.

A Look Ahead:
Biomanufacturing and CGT Over the Next 5 Years

Personalised Medicine

Mukta Gupta, Quality Lead at Takeda suggested the rise of personalised medicine was one of the most important elements of the field right now, particularly within CGT, due to increasing global demand and progressive sustainability requirements. **Darren Dasburg, Biotech Executive at Contango Ventures** agreed, stating particularly that personalized medicine supply chain impacts are a huge issue in the field right now. He said that particularly CRISPR, as the 'holy grail of gene treatments', will soon be revolutionising CGT and manufacturing.

Devyn Smith also suggested that from a clinical perspective the rapid rise of CGTs was one of the most interesting developments in recent years, as was the slower pace of CMC innovations in the space.



New Modalities

Introduction and scale-up of new modalities was an expected element of the coming years, according to some of the facilitators surveyed. Devyn Smith suggested that more approved advanced therapies will change the dynamics of the field, with CDMOs needing to improve their services/ quality or risk companies limiting their outsourcing.

Anthony Colenburg issued a warning in this area, however, noting the potential for over-exaggeration of the potential of new and untested therapeutics.

Vaccines

The development of vaccines is another area set to change considerably over the coming years. Mukta Gupta said that in recent years, products were developed and generated depending on the market need. So while there was a recent decline in the number of vaccine manufacturers in the U.S., Covid-19 has changed the field and grown vaccine manufacturing considerably. She said the current trend to discover a Covid-19 vaccine has bought up the need of vaccine products, awakening a new interest across the industry globally.

Despite this, Darren Dasburg pointed out that the Covid response could well fall short of expectations, with over 620 trials and no more than a dozen likely winners.

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