Regulatory Affairs & Chemistry Manufacturing Control

Insights from the Industry

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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 CMC and Regulatory Affairs

The clinical sphere was arguably the area most hard-hit by Covid-19. With patient-facing roles and clinical interactions commonplace, experts here had to adapt and change far more than those in R&D, and possibly more than in manufacturing too. Whole projects and processes had to be rapidly altered to limit face-to-face interactions, and the problem of patient retention became a genuine fear.

But this year brought benefits, too. Decentralised trials, for a long time largely a hypothetical scenario, have been brought wholly to the fore as their utility skyrocketed. Hygiene and patient safety measures have become much more important. And brand new means of increasing patient engagement and retention have been deployed to ensure fear of contamination does not put patients off contributing to science.

This report will look at some of the highlights of the recent CMC and Reg Affairs event, 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 clinical trials and PV 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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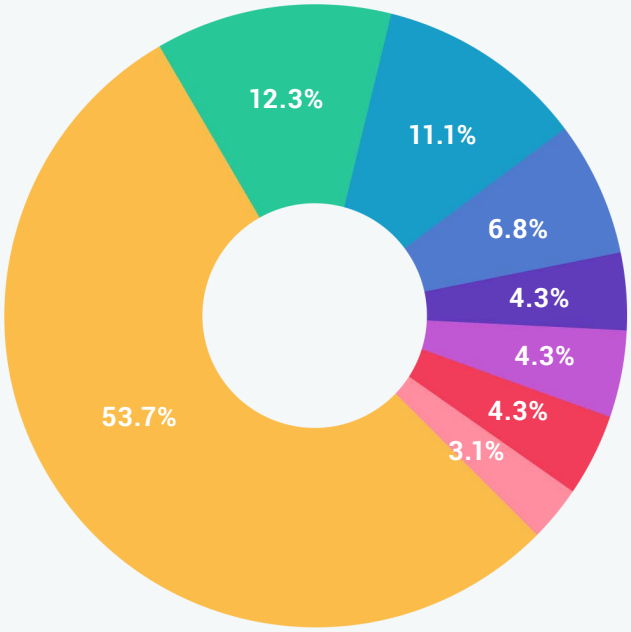

53.7% Director level

12.3% President / VP

11.1% Department Head

6.8% Team Lead

4.3% Manager

4.3% Other

4.3% Scientist

3.1% C-Level

Key Investments

2020 Event Highlights

REGULATORYAFFAIRS

Regulatory Challenges and Opportunities for the Global Development of Gene Therapies

One of the most fascinating sessions in the **Regulatory Affairs** meeting was held by **Dr. Daniela Drago, Senior Director of Regulatory Sciences at Biogen**. Speaking about regulatory challenges and potential in global gene therapy development, Dr. Drago led with her thoughts on major challenges surrounding the global development of gene therapies. These included:

- While the regulatory framework worldwide is changing, many countries lack specific regulations
- Regulatory requirements and specific advice vary across regions
- There are different timelines, pathways and document requirements across regions
- A burdensome and lengthy GMO review process could hinder or prevent development

From there, the session was opened up to delegates to discuss their own challenges and difficulties.

One expert pointed out that with increasing compression of program cycles, some shortening from seven years down to three, keeping up with regulatory requirements was becoming an increasing challenge. Several delegates expressed concerns about keeping up with changing therapies, staying abreast of the regulatory situation and keeping patients safe. Another delegate questioned how someone could have fully-characterised processes with these sped-up times.

Another delegate noted that often they came across issues where it was not clear what regulatory expectations were. It was noted that it is important to have very solid, clear internal standards, so that in such a situation the company would be able to demonstrate to regulators that standards remained high even if regulation was not clear. This was found to be particularly true around early-phase trials, where companies might not yet have the formulation they desire.

Using non-GMP cleared IMPs or other technologies in trials is a difficult situation, and could lead visiting regulators to determining that site handling is poor, even though there are no regulations stating how the situation should be handled.

Another concern was the difference in feedback provided from the FDA and EMA, and a follow-up that asked whether it was worth conducting joint activities or procedures with the FDA and EMA. One general answer to working across regulators in different areas was to focus on the quicker side first, especially if there was more prior experience with that regulator. In the example given, the FDA was generally swift to review CAR-T therapies, and would be approached first for approval. The delegate then said they'd go to their overseas partner to approach their local agency, given their greater presumed experience there. A bonus to this approach was that sometimes as the second regulator was being approached, data was already available from the first country, providing evidence to better convince them of safety and efficacy whereas otherwise they may have fought back.

Another delegate mentioned relying on previous advice and guidance for support where regulations were lacking, as it could well point in the right direction. They noted it was important not to rely on just one individual's interpretation of that advice, however, as that could steer companies wrong as they navigated the regulatory maze.

One delegate finished by summarising their approach to approaching agencies. They said that in their experience, agencies are more open to new therapies if they are presented with a package which demonstrates that the method used is appropriate. In the delegate's case, they often started with a longer method, and then made a goal to create a method with a shorter time-period associated with it. Additional samples will then be collected, often while simultaneously running clinical studies. Data will be collected on the samples until there's a large enough sample size for a package to be submitted to an agency. This submission is often not discussed in advance for the sake of timing, the company remaining conservative until approval for the new method is received. He added that good justification is also often needed, so small companies should think of working with external providers who have experience in suggesting what can go into a package and the approach to be used.

How to Ensure Clarity and Communication of Goals and Expectations for Successful Technology Transfer During Drug Development With Your CDMO

On the **CMC** track, one standout roundtable was headed by **Nick Dunwoody, VP of CMC at Tetraphase Pharmaceuticals**. He began by stating the major concern of the discussion: that the process of moving methodologies around the world can be very difficult at times. Analysts are often assigned a method to transfer at a CDMO. Often transferring this method meets several roadblocks, which the analyst has no power to change.

The initial concern, he said, was to identify key stakeholders. Building relationships and conducting face-to-face meetings are often key in determining who can move on projects for you where an analyst couldn't - especially regarding technological issues.

Another vital point discussed was conducting pre-transfer exercises to solve unexpected issues. Dunwoody noted that even in transfer situations where processes - be they qualified assays or assays yet to be qualified or validated - should work perfectly, unexpected issues can occur. To prevent those situations, ensuring the method is reliable before transfer is extremely useful. Dunwoody mentioned a recent transfer in which the receiving lab was using a certain set-up that was not working properly. After a site visit, it was found that the equipment set-up was the problem.

Dunwoody also noted that with the good standard of regulatory approval at this time, it is important to work closely together with CDMOs and understand the receiving lab, alongside their equipment capacity and scheduling. Often, he added, delays are largely down to scheduling and planning: avoiding leaving workload until the last minute can hugely help the tech transfer process.

At the point that top-line good data is seen in phase 2 trials with patients, Dunwoody said it was time to invest, not to delay and fall short with no methods in place.

As the roundtable was opened up to delegate questions, one asked how different technology transfer would be under the post-Covid regime, particularly in regard to outsourcing to different parts of the world. Dunwoody and others suggested that there would certainly be much more limited travel with colleagues to meet a team: while currently delegates were going every 6-12 months to build rapport and keep relationships operational, there would need to be changes for the future to avoid this - though it was generally agreed that Zoom was, at least for now, working sufficiently. It was also pointed out that having a capable project manager who listened to advice, fed information to the team and could engage in online one-to-ones was hugely helpful in this regard.

A final question raised revolved around the challenge of reconciling information as it passes across multiple vendors: as information is wrongly interpreted the whole process can suffer, becoming a full-time job to correct which in turn reduces the ability to innovate. The delegate asked what technology, if any, could be leveraged to streamline information transfer and facilitate additional knowledge-building. In reply, a number of delegates mentioned cameras in plants as a way to ensure increased understanding of where processes are going wrong; in addition, enabling analysts from vendor A to travel to vendor B is vital to ensure greater understanding between sites and that technology transfer runs smoothly.

Key Delegate Challenges - 2020 and Beyond

Regulatory Challenges and Submissions

This year, delegates suggested that a number of challenges related to regulation and document submissions were collectively the most the biggest difficulty facing CMC and Regulatory Affairs today: answers from delegates included general compliance, GTx regulations, filing strategies for biosimilars and combination products and also FDA approaches for BLA prioritisations.

Outsourcing and Partners

Closely following regulatory complexities as one of the most-picked delegated challenges for 2020 and beyond, matters of outsourcing work, finding partners and selecting CDMOs were frequently mentioned. Specific examples from delegates included finding a large, flexible CMO; determining new modality capability and capacity in the CDMO space; and access to capable CDMOs.

Resource Management (Including Time)

Another major challenge to delegates for the near future is resource management - delegates noted commitments to external spend prior to clinical data, developing cost-effective programs, and meeting aggressive timelines as examples of this difficulty, which affected a large number of attendees.

Commercialisation

Commercial issues were another major factor that will challenge delegates in the years to come. In particular, attendees noted the challenges of commercialising current technologies and a lack of experience in GMP to support commercial needs.

CMC

The area of CMC itself was mentioned as an area of difficulty for the years to come. This included CMC for cell and gene therapies and implementing CMC changes in ongoing clinical development programs.

Key Delegate Challenges - 2020 and Beyond

Supply Chain Management

Managing the supply chain is another difficulty that came up several times in Proventa's survey. Delegates suggested that challenges around this area included diversifying the supply chain for multiple markets, reliability of the chain, and COVID-related disruptions, with potentially severe knock-on results for the coming years.

Moving from Pre-Clinical to Clinical, and Managing Trials

Several delegates suggested that transitioning from one scientific phase to the next was a current burden for them - as was managing the many variables in clinical trials once there. Particular challenges cited included passing clinical phases, co-ordination of nd translation of cell-based therapies into clinics.

Quality

The need for quality across the range of CMC and Regulatory processes was another oft-cited challenge for professionals in the field. Specific issues around quality included the need for greater data quality; better quality management oversight; the problem of sourcing and variability in product quality from lot to lot; and quality implementation requirements for new technologies.

The Need for Talent / Internal Expertise

A few delegates noted the need for more talent and expertise within their company as one of the big challenges over the next few years. Specifically, they mentioned talent acquisition, a lack of expertise in combination products and generating cell and gene therapy expertise for future projects as particular areas which would need to improve as the company moved forward.

Pipeline development

Finally, the development of the therapeutic pipeline is a difficulty that delegates are facing in the CMC / Regulatory field. Specific examples of this problem included the ever-increasing pipeline when combined with limited resources; advancing pipeline products; and the need for greater enrichment.

A Look Ahead:
CMC and Regulatory Affairs 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 CMC and Regulatory Affairs, 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.

The Evolving Regulatory Landscape

Theodore Martinot, Senior Director of Chemistry / ChemDev at Infinity Pharmaceuticals, said that while quality will always be the most important area of CMC, the changing nature of regulation in the area is almost as key. This is because despite attempts to harmonise regulations and guidance in recent years, every country still has independent requirements for ensuring patient safety.

Stan Russell, VP at Sebela Pharmaceuticals, agreed with the importance of this factor: he argued that maintaining consistency in filing across geographies, given the continued growth of mutual recognition agreements, was something that area decision-makers needed to keep a tight grasp of.

In addition to this, Stan Russell noted the importance of determining what changes must be made, and what must be retained, in terms of requirements and limitations as therapies become more personalised and complex.

Both speakers noted that these issues would continue to be important across the next five years.

Cell and Gene Therapies

Fernando Aleman, Co-founder and CSO at Navega Therapeutics, thought that CMC was one of the most important factors in CGTs for the near future. He noted that within CGTs, the process is the product. As most gene therapies are very different from one another, establishing a CMC of a complex gene therapy is paramount. As CGTs are expensive to produce and part of a continually-improving process, setbacks are frequent and new regulatory reviews are constantly needed.

He also noted that there is currently great difficulty in piggybacking on previous experience, as there are few gene therapies approved by the FDA/EMA compared to small molecules or even antibodies. Thus, the regulatory pathway is different for each product. Because of this and his first point, he added that finding regulatory consultants with the required CGTs experience is complicated.

In contrast, Fernando suggested that current RNA targeting therapies have not delivered the expected results. He pointed out that the first antisense oligonucleotide reached the market in 1998, but that only 7 are now in the market for rare diseases. “The homeostasis of RNA and its adaptation capacity is underestimated, thus overestimating the potential of RNA-targeting therapies.” He pointed out that DNA therapeutics such as CRISPR, however, could also be utilized to modify gene expression without permanent changes in the genome, and as such offers advantages over RNA-targeting approaches.

He hoped that these current issues would not continue into the future, however: “the more gene therapies that reach the market, the better regulatory framework that everyone will be able to follow”.

Stan Russell agreed with this assessment of CGT’s importance. Alongside the technology itself, he also suggested it was important to focus on how well manufacturers are learning what can and cannot scale.

A Look Ahead:
CMC and Regulatory Affairs Over the Next 5 Years

AI and Machine Learning

Stan Russell noted that over the next five years, AI will go from being a 'toy' or speculative risk to more of an essential tool to be understood and embraced, specifically used to accelerate testing and evaluation but also to demonstrate and ensure value proposition.

Theodore Martinot agreed, stating that technology continues to drive improvements in the field as a whole. He thought that balancing high-tech solutions with (sometimes) low-tech manufacturing solutions would move to the forefront in how CMOs are selected and leveraged appropriately.

He did warn, however, that AI and ML were suffering from being 'buzz phrases' right now: while he doesn't doubt their application potential and values investment in the discipline, he said that what many currently see as the potential of AI/L will realise itself (e.g. self-aware learning automata). To fully realise that potential, he thought the sector requires thinkers and visionaries to both bridge the gap and realise the quantum leap to the next discovery.

Stan Russell agreed that AI had the potential to be misused or misunderstood: for those who did not understand their own business, he said, AI would be little more than a toy. However, he suggested that using the models properly - to help more accurately predict future disease states and identify prevention and treatment - could revolutionise the field in the next few years.

Data and Knowledge Management

Theodore Martinot suggested that technologies centered around knowledge management / structured data would soon be revolutionising the CMC/Regulatory affairs fields, as they facilitate rapid decision making and enable CROs / CMOs to become a true extension of the organisation.

Outsourcing and the Business Model

Theodore Martinot also said he found the continuous growth of the Contract Research / Manufacturing Industry, in parallel with the sustainable virtual business model of biopharm, a fascinating and important development, if not a recent one. He added that in the context of the current health crisis, it will be interesting to see whether this business model will change geographically or strategically.

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