Regulatory Affairs & Chemistry, Manufacturing and Control

Insights from the Industry

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CHEMISTRYMANUFACTURINGCONTROL

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 Regulatory Affairs and CMC

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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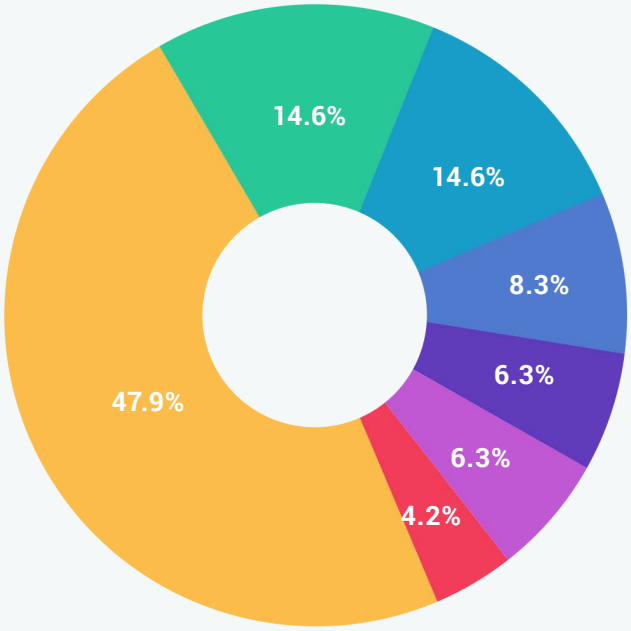


47.9% Director level

14.6% Department Head

14.6% Manager

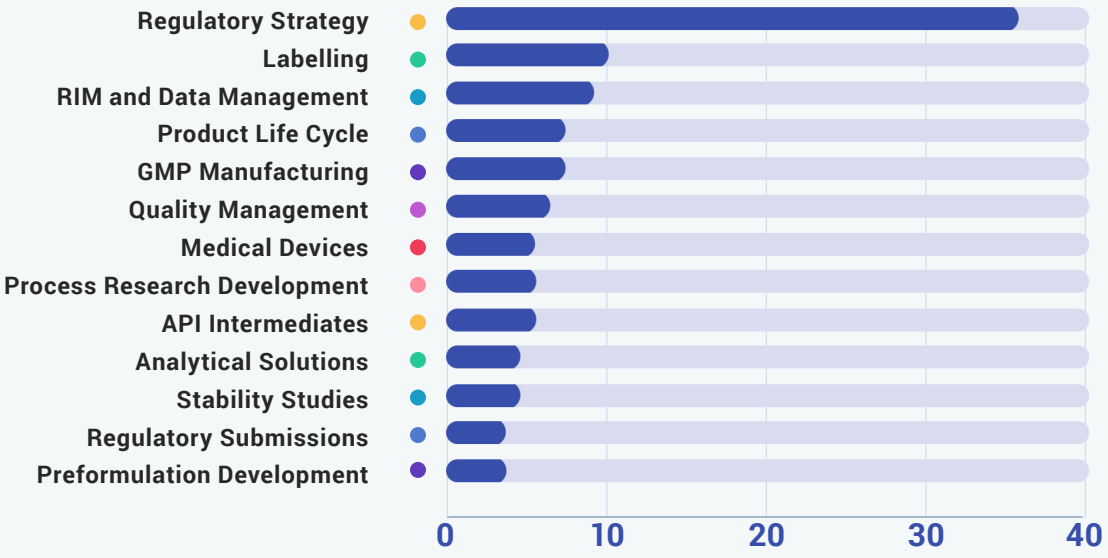
8.3% Scientist

6.3% Team Lead

6.3% Reg Affairs Assoc

4.2% President / VP

Key Investments



2020 Delegate Breakdown

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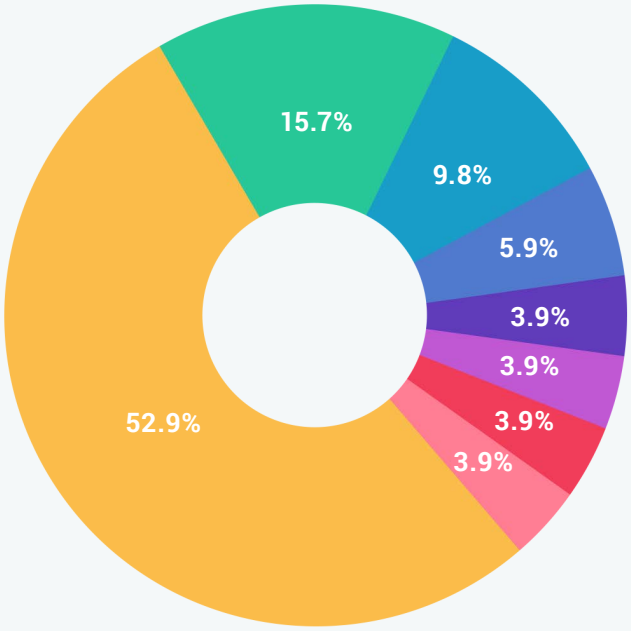
2020 Attendee Breakdown



52.9% Director level

15.7% Department Head

9.8% Scientist

5.9% President / VP

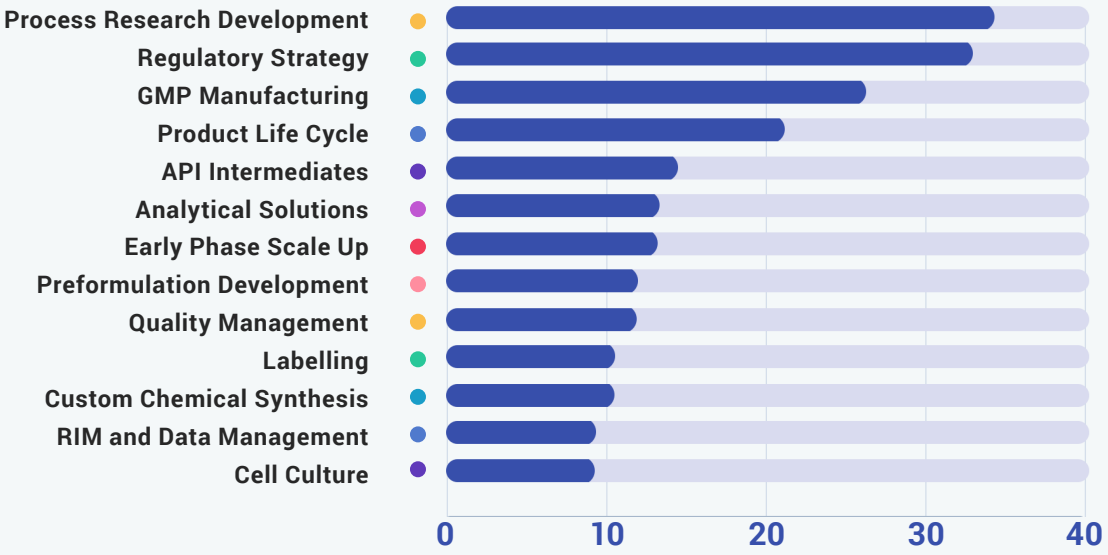
3.9% Other

3.9% Team Lead

3.9% C-level

3.9% Manager

Key Investments



2020 Event Highlights

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Impact of Covid-19 on Development, Registration and Post Approval Lifecycle Management of Parenteral Combination Products: A Regulatory Overview

One of the most interesting discussions during the Regulatory Affairs event related to how COVID-19 has affected parenteral combination products, given largely from a regulatory overview. This was led by **Yogita Bahl, Director and Team Lead for Regulatory Affairs and CMC at Daiichi Sankyo, and S. Prasad Peri, Senior Director of Regulatory Affairs and CMC at Teva Pharmaceuticals**.

The discussion began with an introduction to the topic: Yogita began by noting that COVID-19 has created a number of challenges in pharma, from ensuring new drugs reach patients to ensuring a robust supply chain: she pointed to current regulatory guidance around COVID-19, from manufacturing operations to inspections and clinical trial operations.

A question then arose asking which areas had been most impacted around the manufacturing, distribution and approval of approved products.

One delegate pointed out that the first impact was entirely operational: working from home etc. Otherwise, there were no delays noticed in lifecycle management. He said there was a lot of work for clinical trials, in regulatory terms, as many needed to be halted as patients could not reach hospitals. Inspections, however, were fine.

Another delegate added that they were impacted across most of the topics under discussion, including health authority interactions, product approvals, inspections and post-approval change submissions. Some products, such as essential products and those related to COVID, actually accelerated in approval, however.

A third noted that none of his studies had been cancelled purely due to COVID-19 concerns: the rationale was more clinically driven, and was determined by where staff could revise study designs.

The next question related to the impact of COVID-19 on the key areas of trial activity. One delegate said that their clinical trials had been entirely affected, and that it was a tremendous activity to roll out all trial activities post-COVID-19 without risking patient or hospital safety. He said regulatory guidance had been a tremendous help. Clinical site inspections were almost all delayed or stopped.

The final question related to the experience companies had had with novel approaches taken by health authorities for inspections and GMP status post-Covid. The answer, delegates agreed, depended on the criticality and complexity of the manufacturing process, as some candidates had a new biologic products site submitted to the FDA and it was not accepted, while others saw the opposite reaction.

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How much can we rely on the technology transfer from multiple sources in multiple locations to have the same QbD principles?

Thomas Sauer, VP, Head of Biologics Projects, CMC New Products Program at Sanofi, facilitated a fascinating roundtable during the CMC event around QbD principles in technology transfer.

Thomas began by discussing the importance of good technology transfer practices: ensuring the project is feasible in the pre-project phase; creating the proposal and organising the transfer; the planning stage; agreeing on the process and procedures (including agreeing on the end goals); full implementation and qualification; and closing the project and post-transfer monitoring.

Delegates discussed the typical timeline for this process, which was largely agreed to be anywhere between 3 and 18 months, depending on whether the platform must be established on the receiving side.

One delegate questioned how others ensure incoming CMO data quality is sufficient. One answered that this depends on a process transfer or analytical transfer, and to compare that with one's own data. This data can then be compared with the data produced by a CMO.

This was followed up with a question about the criteria that should be used to choose a site. Delegates responded to this by stating it is highly dependent on what is being done on the other side: it will depend on the pipeline. Another delegate answered that it is hard to find a CMO who can excel at everything, and on the area in question.

One expert mentioned that many CMOs can be found to help a company through the first stages of tech transfer, so would be okay for initial phase 1/phase 2/clinical supply, but not always for further stages. Another suggested an initial audit to ensure the CMO had full expertise and equipment necessary.

Moving back to capturing incoming data and picking a CMO around this, one delegate said they have a documentation system where all supporting study documentation was uploaded so that it can be found at any point during the study, to understand rationale of how critical process parameters were chosen etc.

One delegate then asked how others ensure, when interacting with other companies, that they use the right data system. Another expert replied that their own internal data system was used for data capture, and was not shared with CMOs.

The discussion then moved on to whether companies embed a professional into the CMO plant during the process. One delegate noted it is important to send experts to observe the site, as it helps understand what is going on immediately. It also helps to minimise deviation by communicating any problems with CDMO operators on what to pay attention to.

One delegate questioned if Google Glasses were being used, but others pointed out that there are several legal issues around this subject, so for many it is only a theoretical option. Another mentioned it has been used, but only in the U.S.

Key Delegate Challenges - 2020 and Beyond

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Regulation

Regulatory challenges were the main challenge for CMC professionals surveyed. Those who took part during Proventa's event gave a wide range of issues they were facing within this area, including meeting global regulatory requirements, understanding the regulation process and how to implement it in order to keep a continuous manufacturing process, and the regulatory aspects of innovation.

Partnerships and Outsourcing

Partnerships and outsourcing were two more areas with a considerable number of challenges for CMC delegates. Specific issues cited by those surveyed included finding the right CDMO, outsourcing manufacturing and the management of contract manufacturers.

Funding and Resources

The twin issues of cost and resources were another challenge delegates mentioned as ongoing. Specific difficulties that will continue to dog the sector include limited equipment, a lack of technical resources, and general costs.

Supply Chain

Managing efficient and effective supply chains for outsourced manufacturing, supply chain logistics and diversity in the supply chain were some of the challenges mentioned by CMC experts as being a continuing problem that will remain potentially unsolved in the near future.

Product Development and Lifecycle

Further down the list of critical challenges for CMC experts, the various stages of product development proved challenging for many. Delegates interviewed spoke of complete process development on short timelines, global product development, and supporting industrial operations for lifecycle management as considerable challenges in this area.

Manufacturing

General manufacturing challenges were next on the list of difficulties faced by CMC professionals. Those surveyed mentioned manufacturing vaccines, identifying a GMP peptide manufacturer, virtual manufacturing and low manufacturing efficiency as challenges to be overcome in the near future.

New Technology / AI

Lower on the list than it was in other pharma areas, new technologies and the integration of AI came next for a number of delegates. Specifically, those surveyed pointed to technological maturity, access to cutting-edge technology and innovations, and digital transformation as challenges they are facing at present.

Staffing and Expertise

The problem of finding expert recruits, providing resources training, hiring CGT experts and creating a talented workpool were all quotes by delegates about the challenges they face within staffing and expertise.

Commercial

Commercial concerns were one of the lower challenges facing delegates. Those surveyed specified the transition to commercial biomanufacturing and the transfer and validation of manufacturing processes from R&D to commercial sites to allow for commercial launch as some of the challenges they will be facing in the years to come.

GMP

Finally, GMP was mentioned as a concern of many delegates. Among other things, delegates specified identifying a good GMP peptide manufacturer, GMP manufacture scale-up and development of current small-scale routes towards GMP-ready routes as challenges to be overcome in the future.

Key Delegate Challenges - 2020 and Beyond

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Product Development / Lifecycle

One of the most pressing challenges for those in regulatory affairs related to product development and lifecycle: among other things, delegates specified speed of development, complete process development on short timelines, and process development / lifecycle management for biologics and ADCs as challenges that must be overcome in the near future.

Funding and Resources

The joint challenges of funding and resources were also a challenge that dogged many delegates surveyed. Several of those attending the Proventa event spoke about resource management, limitation of resources, and budgeting as difficulties they have faced in their day-to-day work.

COVID-19

Naturally, COVID-19 was a major challenge for the years ahead. Delegates surveyed pointed to difficulties including working during the lockdown, travel limitations, post-COVID clinical operations and remote execution during COVID-19 among other challenges.

Globalisation

Globalisation was another difficulty for many delegates. Those surveyed mentioned communication from global to local, global applications, the global post-approval lifecycle and global working model changes accelerated by COVID-19.

Regulatory Strategy

General regulatory strategy was another concern of event experts, with accelerated approval strategies, RIM strategy and efficient management of regulatory strategies under COVID-19 being some of the specific challenges mentioned during the survey.

Staffing and Expertise

The use and hiring of staff was another challenge cited by multiple event attendees. Those who mentioned it spoke specifically about general staffing, resources training and talent acquisition as challenges they faced.

CMC

Accelerated CMC development and timelines, keeping CMC development in pace with clinical development for accelerated approval and global rollout of post-approval CMC changes were some of the challenges faced by delegates who pointed to the CMC arena as a source of challenges for the coming years.

Data

Data was another concern for many experts, though not as high on the list of potential difficulties as it has been in other pharma areas. In particular, delegates mentioned data migration, RWE, data analytics and moving from document to data as difficulties they are facing.

Commercial

Commercial challenges were another area mentioned by delegates. Among the challenges they face in the near future, attendees mentioned the transition to commercial biomanufacturing, market access in the EU and market and product reimbursement.

New Technology and AI

Finally, newer technologies including AI were a challenge for delegates, though much lower on the list than they are for some experts in other areas. In particular, delegates mentioned technological maturity, the impact of digital technologies on regulatory science, and automation of processes and upskilling staff to work with robots and AI as challenges they have faced in the recent past.

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 Regulatory affairs and CMC, 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

One chemistry expert attending the event 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.

Another delegate 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, he 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

One regulatory affairs expert thought that CGTs were one of the most important factors in CMC for the near future. He noted that within CMC, 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 experience is very complicated.

In contrast, another suggested that current RNA targeting therapies are potentially a product of hype. 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 frame that everyone will be able to follow”.

Another expert 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

One delegate 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.

A second individual 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.

Another expert 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

One delegate 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

One expert 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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