

CREATING **CMC** **STRATEGIES** FOR PANDEMICS AND BEYOND

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CREATING CMC STRATEGIES FOR PANDEMICS AND BEYOND

Perspectives on the Impact of COVID-19 Pandemic

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The WCBP 2021 forum, *Special Edition: Creating CMC Strategies for Pandemics and Beyond*, was organized around the many considerations for SARS-CoV-2 virus prevention, diagnosis, and treatment. Speakers and participants grappled with how to manage the needs of the supply chain, repurpose existing drugs, apply prior knowledge, adapt traditional process development paradigms, and carry out technical transfers during unprecedented requirements for speed.

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TRANSLATING INHALED AND NASAL TECHNOLOGIES FOR BIOLOGICS DELIVERY



Mark Parry, Technical Director, Intertek Pharmaceutical Services, discusses the challenges and approaches to translating inhaled and nasal technologies for biologics delivery

Inhaled and nasal biologics continue to grow in importance as the drug development industry continues to expand its focus on the various classes of large molecules from peptides through to gene therapies. The potential for new therapeutic pathways for diseases such as cystic fibrosis, asthma and lung cancer, coupled with the advantages presented both by targeted delivery to the lung and systemic delivery for other diseases or treatment pathways, are driving this increased attention on respiratory delivery across the pharmaceutical industry. Drug delivery via these routes is more convenient and less painful compared with other routes of administration for biologic drugs, which are generally administered intravenously and targeted delivery for respiratory treatments can improve both the performance and cost of these challenging materials.

Development Challenges

In regulatory terms, inhaled and nasal biologics will need to combine the requirements of characterisation as per ICH Q6B, as well as the specific respiratory testing outlined in documents such as the EMA guideline on the pharmaceutical quality of inhalation and nasal products (June 2006) or the US FDA metered dose inhaler (MDI) and dry powder inhaler (DPI) products quality considerations guidance (April 2018). Specific OINDP tests include characterization of DP emission from devices including aerodynamic particle size distribution and emitted-dose/dose uniformity assessments to establish their products' specifications, with device performance a vital part of the overall product performance. Testing programs should aim to both fully

characterise the biological entity and establish whether the device delivery mechanism has adversely affected parameters, including structure, purity (aggregation, fragmentation etc.) and the activity (potency), in line with the ICH Q6B Guidance. Existing nasal and inhalation devices can present challenging environments for biologics and device selection is a key part of early product development.

Formulation and Device Selection

Sophisticated formulation development and device selection are key to developing a stable, efficacious product. Solution and suspension-based sprays are inexpensive and can facilitate biologics administration, however, some devices do not tolerate freeze-thaw cycles, which raises fill-finish concerns. Reconstitution of drug product (DP) close to administration or careful device screening and design can circumvent that problem and can also address drug product stability challenges where lyophilisation can be used to extend the shelf life.

Pressurized metered-dose inhalers (pMDIs) present significant formulation challenges for biologics and so the focus is primarily on aqueous and solid formulations for pulmonary delivery of biologics where particle engineering must be carefully considered for solid or suspension-based products. A nebulizer solution does not require significant particle engineering and is a common target for development for treatment of paediatric, elderly, ventilated and sedated patients. In response to COVID-19, there has been an increased focus on inhaled and nasal delivery of biologics. This includes several examples in clinical trials or being developed to address coronaviruses, including SARS-CoV-2, such as nebulized delivery of IFN-beta-1a.¹

Beyond this, some biologics developers are looking at dry-powder formulations, which can increase drug product stability and longevity but do bring in new particle engineering challenges. This may however bring both performance and commercial benefits for the finished product that can offset the potential increase in development work.

Reference:

1. Inhaled interferon-beta launches into the fight against the Covid-19 pandemic, Pharmaceutical Technology, MARCH 2020



Total Quality Assurance

We have over 30 years of experience in supporting clients' orally inhaled & nasal drug product development, from early-stage development, through to in-process control and product release assays.

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- Cell based potency assays
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- Device Screening
- Quality by Design (QbD) Studies
- ICH and Accelerated Stability Studies
- Clinical Trials Materials Manufacturing
- Product Characterisation Studies
- *In-Vitro* Bioequivalence Studies for Generic Products

Meet our Expert Mark Parry

Mark has nearly 20 years' experience working within the pharmaceutical analysis and formulation development industry, with a particular focus on product and formulation development for novel and generic products, as well as method development and validation, stability studies, pharmaceutical development activities, and clinical trial manufacturing.



Online resources

- Repurposing Vaccines for Intranasal Development
- Nebulised Drug Development Considerations
- Overcoming Challenges to Inhaled Biologic Development
- Repurposing Products for Inhaled Delivery - Rapid Response Strategies

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The challenges to biopharmaceutical development presented by the COVID-19 pandemic have been unprecedented. As a scientific community focused on the technical challenges of producing safe and effective treatments, regulators, academics, and industry are collaborating in new and innovative ways. Our collective experience of the COVID-19 pandemic is a call to action to create effective chemistry, manufacturing, and controls (CMC) strategies that will transform the course of drug development.

This bold topic was the premise of the WCBP 2021 forum, *Special Edition: Creating CMC Strategies for Pandemics and Beyond*. The forum was held virtually on 25–28 January and 1–4 February 2021. The eight-day pandemic-focused event was organized around many considerations for SARS-CoV-2 virus prevention, diagnosis, and treatment. Attending were 500 people (among which were ~100 regulators) from more than 100 companies representing more than fifteen countries. In addition to a primary focus on vaccines, topics included diagnostic testing, biotherapeutics, and the impact of the collective experience on future drug development. The forum grappled with how to manage the needs of the supply chain, repurpose existing drugs, apply prior knowledge, adapt traditional process development paradigms, and carry out technical transfers amid unprecedented requirements for speed.

Danielle R. Miller (session speaker from Roche Diagnostics) shared a powerful and personal story about her mother: Eleanor Amelia Miller passed away from COVID-19 on 6 January 2021 (only a week before the forum was held). Speakers and attendees noted that they are motivated by a shared commitment to advance meaningful treatments for patients and their families and spoke about the impact of COVID-19 on their family and colleagues. This was and is personal.

Perspectives from industry, regulatory agencies, and academia addressed several key areas: challenges of drug development at a pandemic pace; applying prior knowledge, capabilities (platform technology), and investment; CMC strategies for accelerated development; partnerships among companies, health authorities, universities, and other government and nonprofit agencies; innovation and new technologies; and lessons learned.

CHALLENGES OF DRUG DEVELOPMENT AT A PANDEMIC PACE

Because the conference occurred in early 2021, it was important for the speakers to review what progress had been made up to that point and to align this event's discussions on current and predicted challenges. The sheer scale of those challenges has upended conventional paradigms for drug discovery and development in the scientific community.

“Cost” Beyond Money: Although early monetary investment in support of COVID-19 vaccines and therapeutics was critical to their accelerated development, the rapid pace of that development

WELCOME FROM THE SYMPOSIUM COCHAIR

2021 will be remembered as one of the most disruptive and challenging years for the biopharmaceutical industry. The COVID-19 pandemic presented academics, regulators, and the industry with unique challenges for delivering the medicines needed to fight what has seemed to be a constantly changing battle against the pandemic. This special edition of WCBP 2021, “Creating CMC Strategies for Pandemics and Beyond,” was developed, planned, and produced to address key questions that biopharmaceutical industry professionals were facing in both their professional and personal lives. Amid the pandemic, innovation, speed, and science have come together like never before — but also with the repercussions of burnout, fatigue, and frustration.

This eBook provides a written digest of proceedings from that special WCBP event. It provides us with a further opportunity to reflect on our “new normal” and how to apply what we are learning from a pandemic that continues to reshape our industry.

—Julia Edwards (Genentech, a Member of the Roche Group),
WCBP 2021 Symposium Cochair

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came with additional costs that are less easily quantified. To enable and maintain the speed of development, industry colleagues and regulators have devoted their time and energy in heroic ways. Many people have worked nights, weekends, and holidays to support this pace of development. It is a truly exceptional effort by both industry representatives and regulators motivated by the promise to deliver meaningful therapies to patients. However, that effort also is disruptive, because resources are diverted to support COVID-19 vaccines and treatments at the expense of frequent delays or postponements of other projects. Additionally, maintaining the rapid pace of reviews to support clinical studies and emergency use authorization (EUA) is a grueling and unsustainable effort for regulators.

Supply Chain and Manufacturing Capacity: The challenges of maintaining complex supply-chain continuity increase exponentially during a global pandemic. The workforce is increasingly working from home and has shown increased absenteeism due to illness and managing caregiving demands. As borders closed and travel quarantines were initiated, there have been and continue to be transportation disruptions. A global surge in clinical manufacturing of vaccines and other COVID-19 therapeutics resulted in increased demands for and limited supplies of raw materials, processing equipment, primary packaging materials, and consumables. Global distribution of clinical drug products to facilitate testing and treatment across many countries and patient populations required extensive coordination, especially for those cold-chain products requiring refrigerated and/or frozen storage conditions.

Equity and Access: Because of the worldwide spread of the virus and a lack of equity within healthcare systems, fair access to testing and therapy was a critical topic of exploration. Many people have asked when vaccination will become available in developing countries. Initial estimates and reports have stated that many such countries may need to wait until 2023 or 2024. To reduce the long wait times, the industry must address issues that include regulatory systems, product delivery, and cost. CMC development teams are tasked with identifying innovative ways to enable increased access such as by introducing new formulations and less-invasive dosing methods.

Testing: Diagnostic testing for active SARS-CoV-2 — both to test for past infection and to analyze potential vaccines — is a critical enabler of treatment, understanding, and control of the virus. Regulators are challenged to review emergency use applications for in vitro diagnostic tests, which then delays regulatory attention to other potentially lifesaving in vitro diagnostics (IVDs). In the early days of the pandemic there were challenges to access virus specimens and to assure accuracy of and access to a comparator (CDC test). Those technical challenges were coupled with moving targets and lack of clarity in regulations such as for laboratory-developed tests (LDTs) and disparities in access to testing.

Developing vaccines
in <1 year is a
“**STUNNING** scientific
accomplishment.”

—Dan Barouch, Center for
Virology and Vaccine Research,
Beth Israel Deaconess Medical
Center

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Finding the Right Approach to Vaccine Development:

Multiple simultaneous approaches to COVID-19 vaccine development were initiated. A single vaccine is not sufficient to address global patient needs. The use of vaccines already was a political issue among some segments of the public with historical concerns about vaccine safety — despite decades of scientific evidence demonstrating vaccine safety and efficacy. The pressure facing companies that were developing vaccines, biotherapeutics, and diagnostics has been immense from both public scrutiny and the desire for rapid testing results. In a supply chain increasingly overwhelmed by the global need for therapeutics, to expend manufacturing resources on a suboptimal candidate will compromise the ability to manufacture other, potentially more effective vaccines.

Public Health Burden of Reemerging and Emerging

Viruses: Our collective experience with traditional approaches to combating viruses — such as licensed vaccines and antibiotics, passive surveillance, contact tracing, and quarantine — was reconsidered in the early days of addressing COVID-19. However, COVID-19 quickly outstripped those traditional approaches by presenting an unmet need on an unprecedented scale and presenting a growing number of fast-changing variants, which in turn interrupt the development, authorization, and access to other vaccines. Currently, 120 viruses are known to infect humans, with potential for an increasing number of viruses that exhibit human-to-human transmission and virulence. Thirty distinct viral families and subfamilies are known to infect humans, and 12 of those virus families lack a representative vaccine. The risk of emerging infectious diseases that can spread easily in a globalized economy remains a threat to our global public health (1).

PRIOR KNOWLEDGE, PLATFORM CAPABILITY, AND PRIOR INVESTMENT

The race for vaccine development to address the global spread of SARS-CoV-2 infections and the need for rapid development of diagnostics and treatments for patients with severe disease resulted in an accelerated pace of pharmaceutical development and at a scale never before seen in the industry. The remarkable timelines achieved that allowed US Food and Drug Administration (US FDA) EUA of multiple novel vaccines and therapies under a year after lead molecule identification and initiation of first-in-human studies were facilitated in several important ways. Early acquisition of the coronavirus genome provided academic, industry, and regulatory laboratories with the ability to develop a framework of multiple vaccine platforms. Previous research on coronaviruses and knowledge gained from recent experiences with severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and Ebola viruses helped support rapid initiation and spurred parallel development for a multitude of preventative and treatment options. Product development, manufacturing, and

“It’s about **PEOPLE**,
not numbers.”

—Danielle R. Miller, JD
(Roche Diagnostics)

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analytical platforms for different types of vaccine and therapeutic proteins were in place, ready to be used for rapid development and testing of new products. Advanced technologies, notably the use of modified mRNA for vaccines, were poised to replace current burdensome and time-consuming approaches to vaccine development.

Platform technologies historically have been established within the biopharmaceutical industry to accelerate and streamline development efficiency. Such approaches rely on using defined strategies for candidate selection, followed by an array of process- and product-development activities. Those are performed according to a well-defined framework that has been established specifically for a target modality based on prior knowledge and experience. In addition, successful implementation of a platform approach requires availability of a set of robust analytical methods capable of reliably monitoring the relevant critical quality attributes (CQAs) of different development candidates within a modality class, thus requiring minimal development and simplifying qualification and/or validation efforts. Finally, end-to-end coordination and alignment across the various groups involved in a development cycle, a robust information technology (IT) infrastructure, and consistent equipment and facility design are critical to enable rapid development and prevent delays. To date, several companies have shortened the development timeline significantly for vaccines and therapeutics using platform technologies. As a result, a diverse array of candidates is progressing through the development pipeline, ranging from adenoviruses, adenoassociated viruses (AAVs), mRNA therapeutics, and protein-based vaccines, to therapeutics based on monoclonal antibodies (MAbs), indicating that platform approaches are generally applicable.

A specific example from Hanne Bak (Regeneron Pharmaceuticals, Inc.) discussed the use of a rapid-response protocol — modeled after previous experience with Ebola, MERS, and respiratory syncytial virus (RSV) clinical programs — to identify potent neutralizing, noninterfering MAbs against the SARS-CoV-2 spike protein for use both as a prophylactic against and as a treatment for active COVID illness. With Regeneron's VelocImmune transgenic mouse platform and human convalescent plasma, the development team quickly generated a catalog of high-affinity chimeric MAb candidates. In conjunction with precise analytical screening tools, the selected divalent antibody cocktail was characterized for its potential to prevent viral escape and neutralize spike protein variants. Regeneron's well-characterized production cell line, purification, and formulation processes, along with its established analytical characterization and control strategy, then were leveraged to generate the final product for clinical studies.

While platform technologies were playing a critical role in accelerating the development of vaccine candidates and COVID therapeutics, prior knowledge of coronavirus biology allowed for the

“We need to work quickly and easily . . . **QUICKLY** is the easy part, but **EASILY** is another question.”

—Kenneth Miller,
AstraZeneca, WCBP
conference chat

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targeting precision necessary for efficacy. As keynote speaker Barney Graham (deputy director of the Vaccine Research Center at the US National Institutes of Health) emphasized during his talk, both “precision and speed” were required to address this public health crisis. Basic research and understanding of coronavirus structural biology initiated decades earlier and reinforced following the SARS and MERS outbreaks were instrumental in identifying not only the correct antigen sequence, but also the correct antigen conformation for targeting. It is important to emphasize that without prior investment and funding of that research and basic understanding of the coronavirus and structural biology of its almost uniformly targeted spike protein, the speed and success of vaccine development and development of neutralizing antibody therapeutics probably would not have been possible.

In addition to prior knowledge built over the years from viral research, understanding of the mechanisms of action (MoAs) for existing drugs also has helped facilitate the accelerated development of potential COVID-19 treatments. With COVID-19 considered to be a dysregulated immune-mediated disease, finding existing drugs to repurpose its treatment was thought to present a more straightforward process than targeting novel therapeutic targets, and speed-to-patient/market can be gained with established CMC and manufacturing packages. The presentations given in the session on repurposing drugs provided examples of late-phase to commercial products that faced different CMC challenges when they were evaluated for COVID-19 treatment, with some lessons learned that may be applicable both within and outside of a pandemic situation.

For example, narsoplimab has been developed for treatment of endothelial injury due to stem cell transplant and is under review as an orphan drug. It is now being evaluated as a COVID-19 treatment because its MoA includes inhibition of the lectin pathway — the same pathway for damage caused by SARS-CoV-2. Because narsoplimab originally was designed for an orphan indication, CMC challenges faced in extending its use for COVID-19 include limited manufacturing capacity and scattered manufacturing locations (all outside of the United States). Simultaneous process validation and comparability at multiple locations also present further difficulties.

By contrast, the repurposing of Orencia (abatacept) seems more straightforward. CMC concerns for the product are minimal because an existing package already is in place, including an appropriate control strategy and a manufacturing and supply chain. Abatacept is a CTLA4-IgG1 fusion protein that has been shown to reduce cytokine release syndrome after hematopoietic cell transplant and myocarditis, similar to the immune dysregulation associated with influenza and COVID. Prior knowledge of the MoA helps to position abatacept in multiple ongoing phase 3 trials as a potential COVID treatment.

“The desire to **RAPIDLY** deploy the first vaccine should not keep us from finding the **RIGHT** vaccine.”

—World Health Organization,
11–12 February 2020, Geneva

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ACCELERATED DEVELOPMENT STRATEGIES

Traditional CMC timelines are no longer the norm for most products in drug development, but the COVID-19 pandemic sent even the most rapid development activities into hyperspeed. During the forum, several CMC strategies to accelerate development and patient access were shared. Those included performing technology transfer to support manufacturing capacity requirements, leveraging supply-chain strategies to manage the complexity of global patient supply needs, validating and demonstrating comparability robustly and efficiently, mitigating raw material and component shortages, and applying process and product understanding (using quality by design, QbD) to enable acceleration.

Technology Transfer: Ralf Altenburger (global head of cell and gene therapy and of pharmaceutical technical regulatory at F. Hoffmann-La Roche Ltd) shared a case study to discuss how it approached technology transfers. Actemra (tocilizumab) is an anti-IL6 antibody with an MoA that suppresses the cytokine storm induced by hyperactivation of T cells. At the onset of the pandemic, off-label use of tocilizumab for COVID treatment resulted in a >500% increase in projected demand above the 2019 baseline, and imminent stock-outs were projected. In addition, a previously planned transfer of drug-substance and drug-product manufacturing already had been underway, with new sites under review with the US FDA and the European Medicines Agency (EMA). Various operational issues associated with the new sites and supply issues related to packaging materials were encountered. Proactive dialogs held with the FDA and EMA during the technical transfers leveraged historical data for risk mitigation, leading to acceptance of expedited batch release concurrent with process verification and stability studies. Batch-specific biologics license application (BLA) amendments for release were accepted by the US FDA. A prior approval supplement (PAS) was filed in June 2020 on a long-term supply strategy protocol, and a changes-being-effected supplement (CBE-30) was filed in November 2020 following data availability.

Prior knowledge is a powerful tool for accelerating development. By using well-characterized MAb production processes in conjunction with understanding of the role of coronavirus spike proteins, sponsors can accelerate development and introduction of neutralizing antibody treatments against COVID-19. JR Dobbins (Eli Lilly and Company) presented lessons learned and regulatory perspectives from his company's journey toward developing bamlanivimab, a neutralizing MAb against the spike protein. Using a stable bulk-production cell line and sterile mobile units for drug product fills, the team generated clinical material for first-in-human studies. Receiving EUA for the treatment of mild-to-moderate COVID-19 symptoms, the team approached the US FDA early on to develop a supply plan, devised investigational new drug (IND) application content and strategy

“Collaboration and cooperation can

COEXIST.”

—Attendee Comment,
Therapeutic Proteins, Day 3

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(including demonstration of process consistency and control), and proposed commitments to transition to traditional cell-line and drug product manufacturing processes. A comprehensive process-comparability approach used ICH Q5E concepts, an overarching analytical characterization and control strategy, and prospective protocols for technology transfer and stability programs.

Supply Chain Strategies: The challenge facing drug manufacturers is not limited to making a product. The delivery of vaccines, therapeutics, and diagnostics posed additional obstacles. During the forum, companies shared innovative strategies to supply the products around the globe reliably while maintaining high quality standards. A vaccine distribution model involves many factors including quality and compliance, supply and distribution trade channels, agility to accommodate alternative distribution models, and internal and external quality controls. The current mRNA vaccines require frozen storage conditions, and rapid delivery of a frozen product is not an easy accomplishment. Existing processes for packaging configuration and flexible storage and distribution options have been adapted and improved. Engineers were motivated to ensure equitable access to vaccines in hard-to-reach areas. At the time of the forum, one case study noted that a vaccine had been delivered to more than 63 countries with over 4,600 unique destinations. Those impressive numbers now have been surpassed, but at that time were accomplished with 99% delivery within one to four days and 99% quality success rates.

A case study outlined the vaccine test distribution from a Belgian manufacturing site to patients in Malaysia. Tracking the shipments required tracking an express parcel service and monitoring the controls of a thermal shipper and logger. The manufacturer used integrated dashboarding to aggregate multiple data streams to provide real-time monitoring of both product and shipper. The product was shipped to several different locations within the countries including interim storage facilities from which product was distributed by truck, stored at mass vaccination facilities, and then stored at point-of-use sites, including hospitals and clinics. Many of those sites were in development in parallel with the development of the shippers and transport logistics. To account for different conditions at the vaccine-distribution sites, more robust thermal shippers were designed to reduce the risks of product loss if a shipper was not managed as required. The ability to re-ice a thermal shipper every five days was a strategy that allowed the teams to overcome many of those difficulties.

Comparability and Validation: In highly accelerated product development that encompasses multiple parallel activities, efficient evaluation of comparability is essential. Such evaluation includes batch-to-batch considerations that require an analytical marathon to keep pace with changes to support patient delivery needs.

To scale production and use multiple manufacturing sites successfully, developers are considering using disposable

“Challenging conventional thinking has brought us **SUCCESS** during this pandemic. There are more challenges and decisions ahead.”

—Dr. Barney S. Graham, MD, PhD
(Vaccine Research Center,
NIAID, NIH)

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equipment, for which they need to factor in time for facility qualification and related activities. The inherent variability of biological processes presents challenges for the evolution of control strategies in parallel with manufacturing. Companies mitigate such challenges by investing in process understanding and developing robust comparability strategies and protocols to evaluate changes to a product and process. A major difficulty lies in the need to leverage clinical data: If a company cannot demonstrate an analytical link back to those results, then requests for additional clinical data are likely to delay patient access to that needed therapy.

During the panel discussion, Nancy Green (Health Canada) offered some suggestions for accelerating validation. Those included generating a large process validation data package by producing smaller batches instead of combining data from multiple bioreactors or purification cycles and deferring testing to stability timepoints based on QbD and development data at hand rather than at release.

Raw Material and Component Strategies: Raw materials and strategies for dual/alternative sourcing are of critical importance and concern. To address shortage of drug product components in the case of tocilizumab technical transfer, a different vial, stopper, and colored-cap types were adopted along with secondary packaging that used components already approved at the new drug-product (DP) site. In addition, the compounding procedure approved for another product at the new site was adapted similarly.

Process Controls and link to QbD: QbD principles are useful in support of control strategy development. Evaluating where testing can be carried out (whether in-process or at release) and linking attribute-based controls to patient treatments were the subjects of key discussions related to developing COVID-19 vaccines. With a limited data set, companies were identifying ways to leverage prior knowledge and risk assessments to justify their approaches. To realize a future state in which predictive models could be leveraged in lieu of traditional testing, companies and regulators will need to align on the overall risk assessment and potential impact to safety and efficacy.

PARTNERSHIPS

Developing one or more safe and effective COVID-19 vaccines has been one of the most complex challenges of our time. Unlike with past vaccine development, scaling up manufacturing and completion of human trials for vaccine candidates must happen in parallel. Even with accelerated investment in manufacturing and the completion of trials to ensure safety and efficacy, the speakers anticipated no scenario in which supply over the next 18 months could exceed demand.

Partnerships between biopharmaceutical companies and regulatory agencies during the pandemic have expedited patient access to new therapeutics and vaccines and also have shed light

Partnerships between biopharmaceutical companies and regulatory agencies during the pandemic have **EXPEDITED** patient access to new therapeutics and vaccines and have also **SHED LIGHT** on novel CMC approaches to accelerate manufacturing and testing.

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on novel CMC approaches to accelerate manufacturing and testing. The COVID-19 health emergency has fostered unprecedented cross-industry collaboration to identify and address common issues, coordinate interaction with regulators, and partner to develop and supply therapy and testing. Cross-company partnership is indispensable for fast and equitable supply of vaccines. To address COVID-19 meaningfully on a global scale, several vaccines from different manufacturers are needed to ensure sufficient supply.

The WCBP program highlighted a number of examples of such partnerships:

- Covax (the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator) co-led by the global vaccine alliance (Gavi), the Coalition for Epidemic Preparedness Innovations (CEPI), and the World Health Organization (WHO)
- the CMC/GDMP COVID task force operated through Vaccines Europe (VE) and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
- partnerships between research institutions and industry such as between the Vaccine Research Center (VRC) and Moderna
- collaborations between contract manufacturing organizations (CMOs) and suppliers
- sharing of manufacturing capacity
- and partnerships between industry and regulators.

Covax is a global solution for equitable access to vaccines: Through portfolio diversification, pooling of financial and scientific resources, and economies of scale, participating governments and regional blocs can hedge the risk of backing unsuccessful candidates. Similarly, governments with limited or no ability to finance their own bilateral procurements can be assured access to lifesaving vaccines that otherwise would have been beyond their reach (2).

The scientists, physicians, funders, and manufacturers who form that international collaboration, coordinated by WHO, are working to speed availability of a vaccine against COVID-19. They recognized that a vaccine for general use would be instrumental in controlling the pandemic. Members of the collaboration applauded implementation of community intervention measures to reduce spread of the virus and protect people, including vulnerable populations, and pledged to use the time gained by the widespread adoption of such measures to develop a vaccine as rapidly as possible. Their efforts continue to strengthen the unprecedented worldwide collaboration, cooperation, and sharing of data already underway. Covax works to reduce inefficiencies and duplication of effort toward the goal of making one or more safe and effective vaccines available to all (3).

The Access to COVID-19 Tools (ACT) Accelerator is co-led by the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi, and WHO. Their goal is to help end the acute phase of the global pandemic by the end of 2021 through providing access to at least two billion doses of safe and effective COVID-19 vaccines to the

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most vulnerable in all participating economies. If this group succeeds in its goal, through the appropriate allocation of safe and effective doses of vaccines in phases determined by epidemiology and public health to slow and ultimately to stop the pandemic, that could save millions of lives and transform the economic prospects of governments and individuals.

The **Coronavirus Immunotherapy Consortium** (CoVIC, a multidisciplinary partnership of academic, government, and industry experts from four continents) originally formed as a joint enterprise to expedite Ebola virus research. The group's approach consisted of developing analytical tools to aid in the discovery and characterization of neutralizing MAbs against Ebola. They sought to build a database of potential candidates while protecting the intellectual property of the donors. Led by Erica Ollmann Saphire at the La Jolla Institute for Immunology, CoVIC has adopted that framework for surveillance of plasma samples isolated from SARS-CoV2 survivors to find effective antibody treatments for COVID-19. The collaborative nature of this consortium, its use of a standardized panel of assays, and the implementation of well-characterized MAb production processes can help to greatly reduce the costs of manufacturing an effective product and making it available to a wide patient base.

Vaccine development and manufacturing also were accelerated through the use of **existing public-private partnerships** that could be leveraged to accelerate clinical development. For example, Dr. Maria Elena-Bottazi (associate dean, National School of Tropical Medicine, Baylor College of Medicine) mentioned several such existing partnerships involving her institution. They included a partnership with the Walter Reed Army Institute of Research's Pilot Bioproduction Facility (PBF) for vaccine manufacturing; a partnership with PATH (formerly known as the Program for Appropriate Technology in Health) for vaccine development; a partnership with Emory University, which has an established nonhuman primate model; and a partnership with Biological E. Limited for low-cost vaccine production.

Partnerships between health authorities and industry are critical to support access to vaccines, therapeutics, and diagnostics. Health authorities were hampered by their inability to travel to manufacturing sites during the pandemic. Global regulators met the challenges and were supportive partners of product acceleration through paper reviews, acceptance of mutual inspections by other regulatory agencies, virtual inspections, and risk-based approaches for preapproval and prelicense applications (see the "Conditions" box).

INNOVATION AND NEW TECHNOLOGIES

Challenging times commonly spur significant disruptive advancements in technology and innovation. Creative solutions were shared during the forum. The enormity of the scale and the speed at which the industry must move during the pandemic has

BLA CONDITIONS

Dr. Zhihao Peter Qiu referenced relevant sections of the *US Code of Federal Regulations* (CFR) to outline the following Biologics License Application (BLA) conditions.

The facility in which a biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent (PHS Act: Section 351(a)(2)(C)).

The applicant consents to the inspection of the facility that is the subject of the application (PHS Act: Section 351(a)(2)(C)).

A biologics license application shall be approved only upon examination of the product and upon a determination that the product complies with the standards established in the biologics license application and the requirements prescribed in the regulations (21CFR Sec. 601.20(a)).

A biologics license application shall be approved only after inspection of the establishment(s) listed in the biologics license application and upon a determination that the establishment(s) complies with the standards established in the biologics license application and the requirements prescribed in applicable regulations (21 CFR Sec. 601.20(d)).

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accelerated technology and capabilities. Speakers noted that the industry's collective problem-solving ability has improved. Technological advances have been seen in the use of digital technologies, identification of immune biomarkers for use in prognostic and predictive diagnostics, mRNA therapeutics, and viral vectors.

The use of mRNA as a vaccine platform has been many years in the making. It has come to fruition after numerous discoveries led to the understanding that modified synthetic mRNA encapsulated in lipid nanoparticles will provide a sufficiently stable molecule that will not itself be targeted by a patient's immune system. On administration and delivery into cells, the mRNA can escape into their endosomes. Years of investigation into the therapeutic use of mRNA in gene therapy has increased the knowledge base significantly, enabling recent work on an mRNA-based influenza vaccine to be leveraged for SARS-CoV-2 programs.

Use of platform analytical technologies is enabled by the ability to deeply characterize mRNA and the fact that many critical quality attributes (CQAs) of mRNA now are well understood. These vaccines undergo extensive quality control (QC) and characterization testing for both the mRNA and the nanoparticle lipids; high-resolution technologies were selected to assess the CQAs accurately and precisely. One of the enablers for rapid development was partnering across functional groups within a company to introduce new technology and ensure that everything would meet commercial standards from the start. Manufacturing processes for mRNA were found to be robust and scalable, which allowed for investigations into multiple candidates with different modifications and provided a key enabler for performing technology transfers and achieving the scale needed to support control of the pandemic. The speed at which batches of mRNA can be manufactured also simplifies validation strategies; a statistically meaningful number of batches can be made in a short amount of time. Based on both development and manufacturing speed, mRNA vaccines could enable rapid responses to virus variants that are sufficiently different to evade first-generation vaccines; adjusting the mRNA code will be faster than developing and manufacturing new viral vectors and proteins. Although mRNA is significantly less stable than many of the other molecules used for vaccine platforms, its stability is consistent and predictable, which also can enable rapid molecular changes needed to keep pace with viral variants.

The use of viral vectors is less novel, but only a few viral-vectored vaccines have been approved to date. A replication-incompetent adenoviral vector based on human adenovirus type 26 (Ad26) was studied for use as a platform for vaccines against several viral pathogens, including human immunodeficiency virus (HIV), Zika, RSV, and Ebola (for which an Ad26 vaccine has been approved). Those studies not only support proof of concept for the efficacy of Ad26-based vaccines in general, but they also have

Manufacturing processes for mRNA were found to be **ROBUST** and **SCALABLE**, which allowed for investigations into multiple candidates with different modifications and was a key enabler for performing technology transfers and achieving the scale needed to support control of the pandemic.

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provided a significant amount of clinical safety data, including experience in pediatric subjects down to the age of six months, which could be critical supportive information for enabling a much-needed rapid response to SARS-CoV-2. There also have been indications that the Ad26 platform could offer the advantages of a single-dose regimen, capability for mass production, and what is very important, greater stability than mRNA, enabling a supply chain that is more amenable to current global capabilities. Janssen was able to take advantage of the vector design for its SARS and MERS vaccine candidates, benefiting from the analytical tool package that it has used for other platform products, process operations based on extensive experience, and comparability strategies developed following previous technology transfers. Risk assessments and product-specific confirmation have supported the rapid development of what is still considered a novel type of vaccine.

Newer adjuvants, such as that used for the Novavax protein-based vaccine, also could offer improvements upon older vaccination strategies. Similar to the mRNA-based vaccines, Novavax's modified-spike-protein vaccine also uses both a specialized nanoparticle technology for delivery and a platform process for manufacturing. The proteins are generated using a platform baculovirus expression system with a purification process enhanced to increase purity of the SARS-CoV-2 antigen. The antigen is based on the company's proprietary Matrix-M saponin adjuvant, which enhances a long-lasting immune response. The adjuvant allows for use of smaller amounts of an antigen, which also provides for the capacity to develop multiple candidates to address virus variants.

Digital Technologies: The pandemic has been a catalyst to advance digital technologies. They address common challenges regarding knowledge management, change management (countering slow adoption of change), and immaturity of systems (along with slow return on investment). Digital technologies enable daily operation and interaction with regulatory agencies. Technologies such as cloud-based submissions can enable real-time access to information and proposed changes to a submission. The pandemic has accelerated the frequency of such changes, but obstacles remain. Among them is a need for data standards and alignment on nomenclature — which will be difficult to accomplish without a collective, cross-industry/agency effort. The security of information and its accessibility in cloud-based files and submissions may be difficult for smaller regulatory authorities to achieve. Reasonable access across the globe should be ensured.

Another obstacle lies in the use of quick-response (QR) codes to support setting product expirations. Omitting an expiry date (when that information is not yet available) enables labeling activities to be carried out at risk and updated based on regulator feedback and/or approval. A WHO guidance outlines this in more detail (4).

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LESSONS LEARNED

Workshop session eight of WCBP 2021 was titled “Lessons Learned from the Pandemic: What Might the Future Bring?” In this session, a diverse group of panelists shared their experiences with how accelerated CMC approaches enabled rapid progression through development and how those experiences might be applied to future pandemics. Panelists were Marco Cavaleri (EMA); Lisa Dunkle (Novavax), Weining Hu (Merck), Steven Kozlowski (US FDA Center for Drug Evaluation and Research, CDER), Celia Lourenco (Health Canada), Wassim Nashabeh (Genentech, a Member of the Roche Group), Philip Pang (Vir Biotechnology), Ann Taylor (AstraZeneca), and Celia Witten (US FDA Center for Biologics Evaluation and Research, CBER).

They discussed the successful accelerated development of COVID-19 vaccines and biotherapeutics in the face of high global demand. Lessons learned from an industry perspective included impediments to accelerating necessary activities and a level of risk coordination never before imagined. An FDA representative stated that speed to clinic is important and that use of stable cell pools could be an important strategy for initial lots, along with use of compounding standards for sterile filling. Greater flexibility for timing of cell bank testing, viral clearance testing, and submission of stability data also is needed. Health Canada’s recommendations were that having a development plan at the start is important for vaccine development and that manufacturing plans should be developed early. Clinical development timelines have been highly condensed, but even though CMC activities often are rate limiting, the science should not be sacrificed.

At the start of the pandemic, clinical trials for nonpandemic medicines slowed down significantly. Essential workers in manufacturing and testing kept the supply chain for lifesaving medicines uninterrupted. A need for diversity of subjects enrolled in clinical trials was recognized early on. Solutions included hiring specialty groups to ensure diversity using social media outreach, ensuring diversity among site investigators, and having appropriate criteria for site selection that include recruitment of minority subjects. In the future, clinical trial participation might be simplified; for example, using subcutaneous delivery routes for nonpandemic medicines can help reduce the need for clinic visits.

Producing billions of doses at lightning speed requires scaling up and out through multiple manufacturing facilities. The US FDA received many requests for site changes and worked on expedited assessments to address future shortages. There is flexibility to demonstrate comparability when timelines are compressed, although alignment with ICH Q5E and well-designed comparability protocols (CPs) are key. Rolling-lot evaluation is an option, as is having early discussions with regulators about technology transfers and test methods. Addressing the timing of submissions for stability and validation requirements and global acceptance of continuous process validation (CPV) also will be important in the

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future. From the FDA standpoint, concurrent validation is possible. For EUA products, extensive process characterization can be used instead of process validations depending on the benefit–risk ratio for that population.

The hyperaccelerated timelines highlighted supply-chain constraints, so increasing manufacturing capacity is critical. Companies are sharing capacity, but rapid technology transfer and scale-up are difficult when those companies have different platforms. Thus, integrated, anonymized information sharing might be ideal. A thorough understanding of bottlenecks and resource constraints is key to development of a sustainable plan. Use of advanced technologies such as continuous and distributed manufacturing should be encouraged to mitigate investment and perceived regulatory costs.

Regulatory agencies around the world have been challenged by the need to deal with large numbers of submissions and associated review timelines. The EMA has implemented the concept of “rolling reviews” to cut down on review durations following a final submission. Current timelines are not sustainable despite the immense benefits. A Health Canada representative stated that it has had many intensive interactions with sponsors and that the frequency of such interactions is usually a tradeoff between sustainability and prioritization. An FDA representative also stressed the importance of frequent yet efficient regulator–sponsor interactions. Upfront understanding of a sponsor’s overall manufacturing strategy, including sites and comparability protocols, is needed to expedite review of submissions.

Experience with the pandemic highlighted different approaches, expectations, and timelines. Some previous lessons regarding collaboration and partnerships across industry and governments had to be relearned. Regulatory harmonization including work-sharing reliance mechanisms became a central theme during the pandemic, and alignment through the International Coalition of Medicines Regulatory Authorities (ICMRA) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (ICH) can encourage sustainability of good regulatory practices. Having a formal emergency regulatory pathway will be important, and use of remote inspections and mutual recognition agreements will increase efficiency.

The rapid advancement of mRNA vaccine technology has been a game-changer that could revolutionize the future of vaccinology. The larger public needs to develop a comfort level with that technology, and sufficient safety follow-up is needed. The SARS-CoV-2 virus may become endemic; strain changes will occur with some periodicity and need to be dealt with efficiently. There should be alignment among health authorities to address regulatory pathways for variants. The flu vaccine model may not be ideal, so proactive approaches such as looking at advances in epitope discovery are needed. Products designed to address variants should

FURTHER RESOURCES

For more information regarding the conference, presentations, and agenda, please go to <https://www.casss.org/page/WCBP2100>.

Below, is the list of sessions held during the forum:

Developing a Vaccine Manufacturing Process and Control Strategy During the SARS-CoV-2 Pandemic

Diagnostic Testing: A Key Component for Battling the COVID-19 Pandemic

Biotherapeutics Part One: Neutralizing Antibodies and Convalescent Plasma

Research and Advanced Technologies Supporting the Accelerated Development of a COVID-19 Vaccine

Leveraging Platform Technologies to Significantly Accelerate Development of COVID-19 Vaccines and Therapeutics

Biotherapeutics Part Two: Repurposing Drugs

Nuts and Bolts: A Perspective on the Impact of COVID-19 Pandemic for Nonpandemic Biopharmaceutical Products

Lessons Learned from the Pandemic: What Might the Future Bring?

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be viewed as modifications rather than new products, applying the concepts of platform knowledge for CMC attributes (process, cell lines, viral clearance, stability data, and testing methods) as well as for clinical aspects and regulatory reviews.

The panelists shared their views on whether parallel development models and intense collaboration efforts were sustainable. Knowledge of and rules for sharing information that is not a trade secret but will benefit the whole sector are needed. One example is to standardize the way data are presented in regulatory filings to facilitate review. Allocation of critical resources across industry and regulatory agencies might require a centralized body, and collaborations with academia also could help. Sustainable funding is needed for areas that are essential to support public health. A broad surveillance approach to identify lessons learned about infectious diseases, including information about “near misses,” could help to preposition resources in advance of the next crisis. Priorities for both industry and regulators should be focused on preparedness for the next pandemic and development of therapies in advance of actual demand.

LOOKING TO THE FUTURE

Discussions such as those included at this meeting often uncover more questions than provide answers. This is a key element of the excitement of scientific discovery and the shared commitment to keep moving forward. As outlined herein, many key topics will be advanced in future meetings.

At the end of the program, Julia Edwards, the industry chair for WCBP 2021, reflected on knowledge sharing and capacity building. She highlighted stunning scientific accomplishments during the pandemic, noting that the pandemic represents a personal battle for regulators, companies, and for patients and their families. The conference highlighted the importance of vaccines, diagnostics, and therapeutic proteins. She stressed the importance of collaboration as the heart of everything we do as an industry. A keynote address highlighted the fact that the industry needs to challenge conventional thinking. Many more challenges lie ahead, and more than ever before, she said, we need to work quickly and efficiently.

Edwards concluded by posing a number of questions to the audience.

- We have the technology and the know-how, but are we limited in capacity (lacking both people and manufacturing space)? Building capacity takes time and effort. How do we do it more quickly and easily and without burnout?

- An assertive risk-based approach aligned with regulator expectations can accelerate technology transfer. Are we holding ourselves back by using the same old playbook? Can we do more to ask harder questions? Is industry holding itself back by not asking the right questions of regulators?

Julia Edwards, the industry chair for WCBP 2021, highlighted **STUNNING** scientific accomplishments during the pandemic, noting that the pandemic represents a **PERSONAL** battle for regulators, companies, and for patients and their families.

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Steve Hadley (The Bill and Melinda Gates Foundation)
Carmilia Jiménez Ramírez (BioMarin Pharmaceutical Inc.)
Wayne Kelley (GlaxoSmithKline)
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Kevin King (Pfizer, Inc.)
Carol Krantz (Seattle Genetics, Inc.)
Joseph Kutza (AstraZeneca)
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- How can we continue to benefit from improved data analysis (big data combining multiple data inputs) and “assisted intelligence?” What will personalized treatment look like (e.g., profiling immune systems to identify high risk patients)?
- How do we improve access? Many people are shut out of the system (for both testing and treatment).
- Can we build centralized testing, data, and tools that we can leverage for future pandemics?
- The idea of “well-characterized vaccines” was noted in the panel discussion in Day 1. Do we have them now? What are related consequences and future challenges?
- Although our capability has increased, that comes at a cost. What has the pandemic taught us about our weaknesses and where we need to invest further for the future?

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