



From Drug Discovery to Commercialization: Industry Collaboration in the Age of COVID-19 and Beyond

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ABSTRACT

The pharmaceutical industry has been under tremendous pressure to produce novel life-saving therapies and to accelerate their development in partnership with regulatory agencies. The global public health emergency due to the COVID-19 pandemic that started in early 2020 has highlighted these challenges. In these times, the medical needs are enormous and addressing them requires unprecedented innovation as well as collaboration across international borders among manufacturers and regulators. The global ramifications on the speed of development and approvals both for preventative and curative treatments are far-reaching. The resulting operating efficiencies in many cases have the potential to extend beyond the immediate application to COVID-19 therapies.

With these considerations in mind, companies in the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium or IQ) have been working in a collaborative manner on approaches to facilitate efficiencies during the development and lifecycle management of drugs in the age of COVID-19 and beyond. The nine topics summarized in this paper span the development lifecycle including pre-clinical and clinical research, product development, shelf-life projections, and post-approval life cycle management. The reports all converge on one central theme that not only focuses on the science of how we bring important medicines to patients but how these can be brought to patients with speed, efficiency, and continued patient safety as the drivers. These efforts provide an important framework and foundation that will prepare the industry to effectively apply the lessons learned from drug discovery and development during COVID-19 to support future pandemic or unmet medical needs for the patients we serve.

INTRODUCTION

The global public health emergency due to the COVID-19 pandemic that started in early 2020 has undoubtedly been the watershed event for the pharmaceutical industry in recent memory. Even prior to this crisis, the industry was under tremendous pressure to produce novel life-saving therapies and to accelerate their development in partnership with regulatory agencies. In these times, the medical needs are enormous and addressing them requires unprecedented innovation as well as collaboration across international borders among manufacturers and regulators. The global ramifications on the speed of development and approvals both for preventative and curative treatments are far-reaching. The resulting operating efficiencies in many cases have the potential to extend beyond the immediate application to COVID-19 therapies.

With these considerations in mind, companies in the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium or IQ) have been working in a collaborative manner on approaches to facilitate efficiencies during the development and lifecycle management of drugs in the age of COVID-19 and beyond. This white paper describes these approaches with a focus on what can be learned from the current IQ initiatives and how those lessons can be applied in the future using science and risk-based methodologies. It will highlight examples in the IQ portfolio where technical and scientific foundation and expertise is leveraged for pandemic response programs that need to be accelerated for patients. Additionally, it will discuss technical issues that have not yet been explored but have potential future applicability. The aim is to continue to strengthen collaboration among industry participants and to provide opportunities to shape the external environment including encouragement of continued regulatory harmonization and mutual recognition (1).

Thus, the authors of this white paper took a holistic look at the IQ project portfolio of existing projects and those projects initiated to address specific challenges resulting from the COVID-19 pandemic. The paper describes completed, ongoing, and planned IQ working group efforts that cover topics including preclinical aspects, clinical trial considerations and patient-centric sampling, as well as chemistry, manufacturing, and controls (CMC). Approaches to innovation in development of continuous manufacturing technologies for both drug substance and drug product are described (2). Streamlining complex global supply chains will require the creation and maintenance of appropriate manufacturing capacity throughout the lifecycle of the product even with an increase in the number and geographic distribution of various sites. Harmonization of the regulatory control strategy and post-approval change management of the product will be essential to avoid unnecessary bureaucracy and duplication of efforts while still meeting high standards of quality. Regulatory considerations for CMC aspects of accelerated development, including alternate approaches to evaluate stability data and assign shelf life will also be critical.

Collaboration is at the core of IQ's mission to advance science and technology. Engagement, surveys, and publications are the tools driving collaboration within the IQ Leadership Groups (LGs) and Working Groups (WGs) (Figure 1). Critically, the IQ framework supports pre-competitive discussion and collaboration in many forms: within the individual Working Groups, through academic seminar series, and through external symposia.

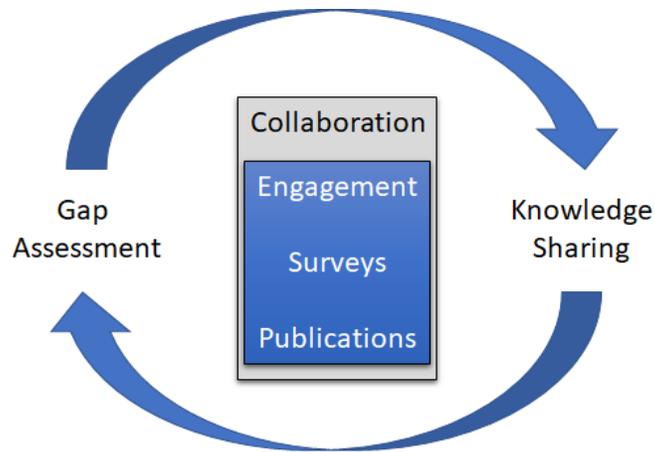


Figure 1: The role of collaboration within the IQ Consortium.

The following sections highlight technical aspects of IQ Working Group activities that could be enablers during the current COVID-19 pandemic, future pandemics, and potentially accelerated development programs. Each section describes the challenge, the objectives and approaches of the IQ Working Groups, the results, and the potential impact of identified solutions. The identified solutions highlight that the acceptance of new technology, focusing on science and risk-based approaches, are critical to the pharmaceutical industry’s ability to respond expeditiously to new and unexpected challenges. Global acceptance, harmonization and recognition from industry and regulators is even more important now than ever and should be considered “the new normal”.

IQ CONSORTIUM EFFORTS

COVID-19 PANDEMIC ANIMAL RESEARCH PROGRAMS EXPERIENCES AND RESPONSES¹

THE CHALLENGE

The COVID-19 pandemic has impacted animal care and use programs and requires consideration and implementation of novel and creative approaches to continue to provide high quality animal care and meet preclinical study needs in the face of a range of limitations and disruptions of undetermined length. Programs have instituted their existing business continuity plans and continue to refine and modify operations in this dynamic situation, while providing the preclinical needs of drug discovery and development projects as well as participation in the larger societal response to the pandemic.

¹ **WG/LG:** COVID-19 Pandemic Animal Research Programs Experiences and Responses/3Rs TPS LG
Working Group leads and affiliations: Sean Maguire (GlaxoSmithKline) and Jerry Polling (Lilly)

OBJECTIVES & APPROACH

IQ members met virtually to rapidly and efficiently identify common challenges and share best practices in order to apply them to maintain our commitment to the animals in our charge, our care and research community, and societal good. A survey on the practices instituted as a result of the pandemic has been developed and we are currently receiving responses. This survey includes detailed questions to gather feedback on staff safety and emotional impact that has been created as part of the ongoing pandemic. In addition to the drug discovery science and relevant staff aspects, our programs deal with animal use that has additional ethical, welfare and regulatory considerations, as well as other internal resource requirements. As the pandemic continues, the survey will help diagnose how institutions are functioning throughout the pandemic including the return back to work if operations have paused, what sort of new processes were put into place, and new programs to ensure staff safety and well-being as the pandemic continues.

RESULTS

The COVID-19 Pandemic Animal Research Programs Experiences and Responses Working Group is focused on the operation of animal research programs (as opposed to specific research outcomes). The value of the survey results will guide users on how to manage future disruptions and aid in the development of processes for returning to a focused preclinical animal research environment.

Ongoing Working Group discussions included aspects where quick action and decisions were appropriate along with a revision of those decisions as our knowledge and experience matured. Dealing with the challenge of how we continue operations that are an essential preclinical step for improving human health raised many questions about priorities, responsibilities, and commitments. The requested survey questions took into consideration our staff, animals, local community, and the greater society.

Areas of focus included supply chains, personnel safety including mental resilience and work/life balance, research impacts and mitigation plans, transition plans and updates to business continuity plans (Figure 2).

IMPACT

This global pandemic has resulted in diverse challenges for animal research programs, spanning ethical, practical, and regulatory concerns (Figure 2). There has been a wide range of plans to deal with personnel safety, ranging from increased personal protective equipment to animal depopulation and pausing animal research. The business continuity programs are integral to the response to meet the ongoing need for new medicines. Developing ways to protect the health and safety of the staff as well as the animals are paramount to early molecule development.

The survey results and these learning will be summarized in a future manuscript to facilitate greater effective and efficient responses as this situation evolves.



Figure 2. Summary of preclinical research stakeholders, challenges faced during COVID-19 and plans required to address them.

NONCLINICAL SAFETY PRACTICES AND STRATEGIES FOR COVID-19 PROGRAMS AND APPLICATION TO OTHER SEVERELY DEBILITATING OR LIFE-THREATENING (SDLT) INDICATIONS²

THE CHALLENGE

Severely debilitating or life-threatening (SDLT) indications include conditions in which life expectancy is short or quality of life is greatly diminished despite available therapies. As such, the medical context for SDLT indications is comparable to advanced cancer and the benefit versus risk assessment and development of SDLT therapeutics should be modeled on those used for advanced cancer therapeutics. A streamlined development approach would allow patients with SDLT indications earlier and continued access to new, potentially beneficial therapeutics (3), (4). While there are regulatory guidelines for advanced cancer therapies and for therapies for rare diseases (which include some, but not all, SDLT indications), as well as regulatory programs

²WG/LG: Nonclinical Safety Strategies and Practices for COVID-19 Programs/DruSafe

Working Group leads and affiliations: Maggie Liu (Pfizer) and Judith Prescott (Merck & Co., Inc., Kenilworth, NJ, USA)

primarily employed to expedite late development for serious conditions (5), (6), (7), (8), (9), (10), (11), (12), (13), there is minimal, and no global, guidance to facilitate early development and availability of SDLT therapeutics for patients with limited therapeutic options. In light of this high unmet need, a global guideline is needed to facilitate streamlined development of non-oncology SDLT therapeutics. While much of this is focused on therapeutics for SDLT conditions, it should be noted that the development of vaccines for SDLT indications with urgent medical need and no adequate preventatives should similarly apply a streamlined development approach.

COVID-19 may be characterized as an SDLT indication (e.g. hospitalized COVID-19 patients) based on the life-threatening nature of the disease and potential for long-term debilitating pulmonary and extra-pulmonary complications requiring rehabilitation (14), (15). Although the long-term consequences require further study (e.g. long COVID), there appears to be the possibility of debilitating morbidity even in less severely affected patients. Given the unprecedented nature of the COVID-19 pandemic, high unmet medical need and global health crisis, industry and regulatory authorities have adopted innovative strategies and practices to expedite drug and vaccine development for treatment and prevention of COVID-19 (16). It is therefore imperative to understand and document these experiences and “lessons-learned” so that these may be applied to ongoing efforts for COVID-19, potential future pandemics, and, as appropriate, more broadly to other SDLT indications.

OBJECTIVES & APPROACH

The DruSafe leadership group has formed this Working Group to understand and document learnings related to nonclinical development for COVID-19 drugs and vaccines, discuss whether and by what means these learnings may be applied broadly across SDLT indications in all therapeutic areas, and consider how these learnings may be embedded as a globally accepted approach. This includes an assessment of:

- Innovative nonclinical strategies (e.g. streamlined nonclinical safety packages) to expedite availability of promising drugs to patients and vaccines to high-risk, healthy subjects for indications with high unmet medical need;
- Best practices for expediting conduct and delivery of nonclinical safety studies (e.g., internal practices, working with Contract Research Organizations, etc.); and
- Regulatory interactions (e.g., regulatory acceptance of more streamlined nonclinical safety packages, consistency across regulatory agencies, etc.).

RESULTS

DruSafe conducted a preliminary industry survey of IQ member companies on nonclinical development of COVID-19 drugs and vaccines. These initial survey results were presented at the American College of Toxicology (ACT) annual conference in November 2020 (17). This Working Group is developing a more in-depth industry survey to inform on ways in which nonclinical safety development experiences for COVID-19 may be applied broadly across all SDLT indications and embedded as a globally accepted approach.

IMPACT

The desired impact of this initiative includes application of learnings from the COVID-19 experiences to other SDLT indications, thus expediting availability of safe and efficacious drugs and vaccines to address high unmet medical needs.

ACCELERATING DRUG DEVELOPMENT³

THE CHALLENGE

Health authorities (e.g. FDA and EMA) provide multiple regulatory pathways to accelerate the approval of drugs, such as Breakthrough Therapy Designation (BTD), Priority Medicines (PRIME), and Regenerative Medicine Advanced Therapy (RMAT) designation. However, acceleration of drug development can be challenging with limited knowledge and using the current framework for development, manufacturing, supply, regulatory submission, and post approval changes.

OBJECTIVES & APPROACH

The Accelerated Drug Development (ADD) Working Group aims to identify CMC opportunities and challenges in accelerating drug product development with considerations of risks, benefits, and value to our industry and the patients we serve. The ADD Working Group plans to accomplish this aim through: (a) an industry survey to benchmark industry best practices and attain collective understanding of the current landscape; (b) publication of a white paper to review the strategies for the development of drugs through the accelerated pathways; and (c) organizing a workshop to stimulate discussion and alignment of strategies to accelerate drug development with primary stakeholders. The scope of these endeavors will encompass various pathways of accelerated drug development including drugs or vaccines developed for COVID-19. Recent experience from the development of drugs and vaccines for COVID-19 will be collated for lessons learned. This is a continuing effort and the results are still being gathered.

IMPACT

The collective experience of ADD Working Group members will provide valuable inputs to the industry survey, white paper, and workshop. The lessons learned from these endeavors will benefit the development of on-going COVID-19 drugs and vaccines. The strategies and tools developed through these endeavors will enable stakeholders to accelerate drug development for future pandemic or unmet medical needs for the patients we serve.

³ **WG/LG:** Accelerated Drug Development (ADD) Working Group/DPLG

Working Group leads and affiliations: Cheng Thiam “David” Tan (AbbVie Inc.), Nicole Buist (Merck & Co., Inc., Kenilworth, NJ, USA), Clarice Hutchens (Pfizer), and George Chen (Daiichi Sankyo Inc.)

ADVANCEMENT OF CONTINUOUS MANUFACTURING FOR DRUG SUBSTANCE AND DRUG PRODUCT THROUGH COLLABORATIONS⁴

THE CHALLENGE

Continuous manufacturing (CM) and other such disruptive technologies have the potential to play an important role in accelerated development of medicines and major public health needs in the future. There are recent examples of commercial implementation of CM across the pharmaceutical industry. Both drug substance (DS) and drug product (DP) manufacture benefit from the reduced manufacturing footprint, production efficiency, agility in response to market demand, and potential for advanced quality and control owing to the inclusion of advanced analytical technologies. Despite these clear advantages, the adoption of continuous manufacturing within the pharmaceutical sector has been slower than other industries due to the complexity of integrating a diverse set of unit operations and the regulatory hurdles associated with novel manufacturing technologies. In addition, many companies have existing batch capacity for drug substance and drug product manufacturing in dedicated plants (Figure 3A). To date, the focus of the continuous manufacturing Working Groups has been synthetic small-molecule drug substance and drug product continuous manufacturing as independent processes (Figure 3B). Summarized here are the approaches taken by the continuous manufacturing Working Groups to drive the advancement of this compelling manufacturing technology through periodic gap assessments, knowledge sharing, collaboration with IQ members, and engagement with external thought leaders as companies move towards the goal of realizing fully-integrated drug substance and drug product manufacturing at a single site with Real Time Release (Figure 3C).

⁴ **WG/LG:** Continuous Manufacturing Drug Product and Continuous Manufacturing Drug Substance/DSL and DPLG
Working Group leads and affiliations: Matthew G. Beaver (Amgen Inc.), Gabriella Dahlgren (Janssen Pharmaceutical), and Suzanne M. Opalka (Biogen Inc.)

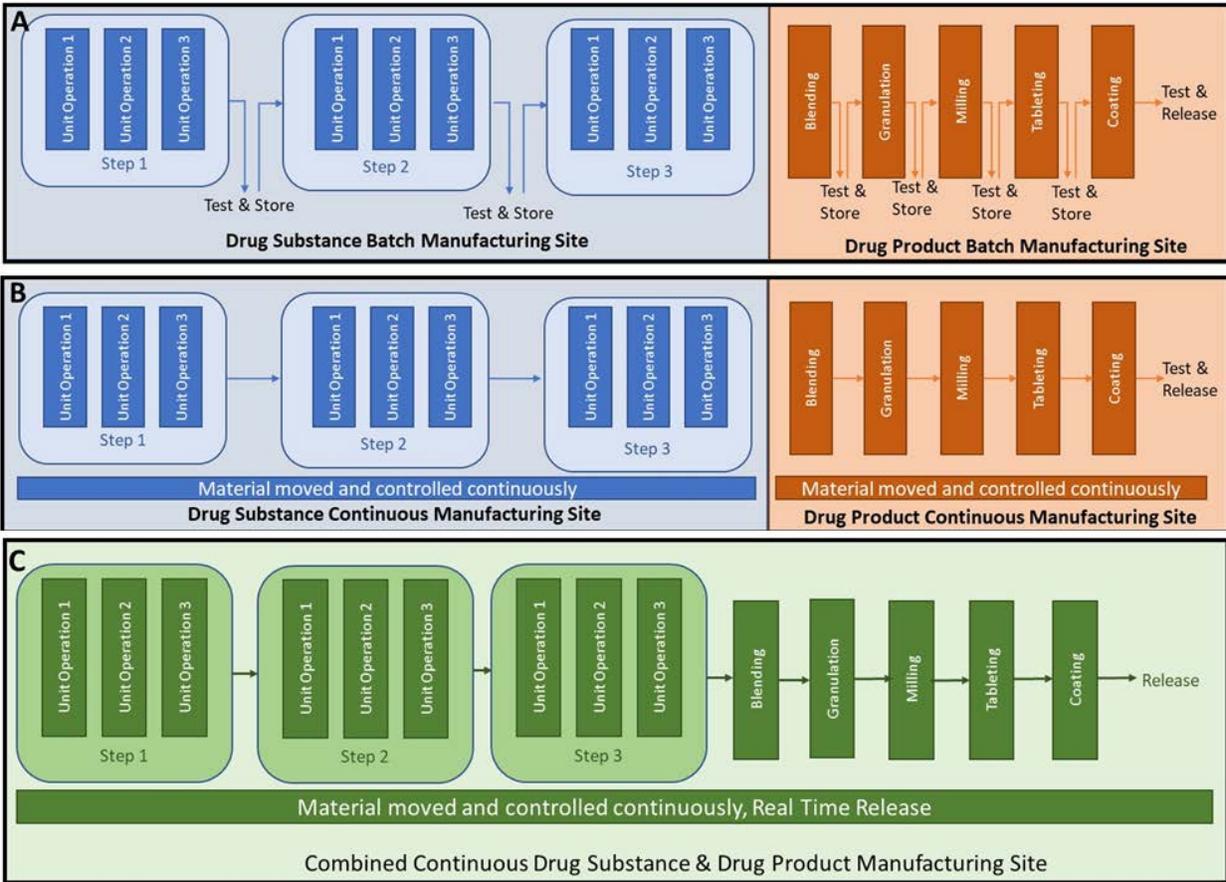


Figure 3: A) Traditional approach to batch manufacturing at separate and dedicated sites; B) Continuous Drug Substance (DS) or Drug Product (DP) Manufacturing at separate sites; C) Future state – Fully-integrated DS/DP manufacturing with Real Time Release (critical to quality attributes (CQAs) evaluated as part of manufacturing and released as soon as manufacturing is completed).

OBJECTIVES & APPROACH

The continuous manufacturing drug substance (CMDS) and continuous manufacturing drug product (CMDP) Working Groups used engagement within the working groups, surveys within and outside IQ, and publications to:

- Drive the definition of technical, procedural, and regulatory gaps in a cross-functional manner;
- Support the holistic review and alignment on best practices; and
- Provide a platform for the broad dissemination of outcomes and lessons learned.

RESULTS

The CMDS Working Group conducted an extensive survey focused around personnel, equipment, chemistry, processing, analytical, regulatory, and factors impacting adoption with 25 contract

manufacturing organizations and 10 IQ member companies responding. The output of this survey was a publication comparing these findings and identifying the drivers and barriers to continuous manufacturing implementation (18). Given the side-by-side comparison of capabilities present in both member companies and the external contract network, this information can help organizations identify areas for internal investment versus relying on vendor networks.

After identifying the broad strategies and areas explored by member companies on continuous manufacturing, additional surveys on equipment such as pumps for liquid and slurry transfer, aqueous work-up and extraction modules, crystallization and distillation platforms, process analytical technologies (PAT), and emerging technology platforms including photochemistry and electrochemistry were assessed. These topics were further categorized into lab-scale and plant-scale categories, which speaks to the maturity of each platform. Currently, the outputs for these surveys are available to member companies on our internal portal allowing members to access information when a specific area of expertise is needed.

The CMDP Working Group also used a survey to benchmark the current state of continuous manufacturing implementation in 2019 with a focus on oral solid dosage forms, which is the most mature pharmaceutical continuous manufacturing process to date given that a few companies already obtained regulatory approvals. The survey was given to IQ member companies and included a wide range of topics such as development strategy, identification of challenges with current technology to regulatory strategy and communication. Given the wide range of topics, the survey allowed for an in-depth understanding of the current state of continuous manufacturing across member companies. It provided an overview of the current pain points, benefits of continuous manufacturing, and identification of differences and similarities in the approach to continuous manufacturing across companies. The survey results were published to share the information more broadly beyond IQ companies (19). One of the most common pain points identified was how to manage PAT methods through the full product lifecycle as regulatory guidance is unclear. As a direct action, the CMDP Working Group incorporated members from the IQ PAT team into their regular discussion. This collaboration resulted in the submission of a manuscript focused on lifecycle management of spectroscopic methods as part of the overall quality management system.

The CMDP Working Group early on identified an unmet need in the inherent differences in how to develop a control strategy for continuous versus batch manufacturing processes. The major shift is the need for a more holistic approach to allow for an appropriate control strategy of a continuous manufacturing line, including the manufacturing equipment, process design and any monitoring tools needed to ensure product quality. Therefore, the Working Group's first paper focused on direct compression, the most widely implemented continuous manufacturing process to date for DP – to demonstrate assurance of control (20). It also captures the need of a risk-based approach as the control strategy evolves through the product development lifecycle and defined several concepts novel to continuous manufacturing such as “state of control”, natural process fluctuations, and start-up and shutdown.

Similar critical needs were identified by the CMDS Working Group, who are in the process of finalizing a manuscript detailing six case studies across industry for how to manage transitional

material during start-up and shutdown. This paper will also illustrate that due to equipment variations and process constraints a uniform strategy is not possible but that product quality can be ensured through a range of approaches while common concepts are defined (21).

Following the successful publication of the direct compression paper the focus of the CMDP Working Group shifted to what is needed to facilitate further expansion of continuous manufacturing to a broader drug product portfolio, resulting in an article focused on twin screw wet granulation, which has significant benefit since for currently marketed products there is roughly a 50:50 split between direct compression and wet granulation (22). Wet granulation can improve tabletability or stability of pharmaceutical products that cannot be manufactured by direct compression. Again, the focus was on the control strategy including expanding on how the use of PAT tools and automation approaches can aid in process control.

IMPACT

The surveys and publications highlighted technical approaches and solutions with the outcome being: (a) increased understanding of available approaches by each member company; (b) helped eliminate some of the hurdles for new companies to enter the continuous manufacturing space; (c) helped shape the practical definitions of various continuous manufacturing terms as it moves towards a more established pharmaceutical manufacturing process.

To date the CMDS and CMDP Working Groups have been successful in knowledge sharing to drive increased adoption of continuous manufacturing across the drug substance and drug product space within the member companies and to outside audiences through collaborations, surveys, publications, seminars, and conference session. As shown in the concept paper for a new International Council for Harmonization (ICH) guideline, ICH Q13 “Continuous Manufacturing of Drug Substances and Drug Products” (23), the approach towards drug substance and drug product continuous manufacturing should not be considered in silos, but under a harmonized set of guidelines. We envision closer collaboration between CMDS and CMDP Working Groups to align with this mindset moving forward. Additionally, these collaborations should extend to other pharmaceutical entities that may consider adding continuous manufacturing focus groups (such as Biologics). As the technology becomes more mature, other aspects of the end-to-end drug product lifecycle beyond the technical focus will be evaluated such as collaborations with Quality and other IQ groups. Additionally, the overall impact of IQ can be further increased by broadening the participants in these focus group to other departments (technical, quality, and regulatory) to allow for cross-functional representation and ensure that diversity of thought is captured. These holistic collaborations will help drive towards a future state of a fully continuous process with advanced release strategies (Figure 3C).

Moving forward, the teams will continue to embrace all forms of externalization opportunities such as Webinars, short courses, and blog posts to reach the largest possible audience to help drive continuous manufacturing forward and increase active membership expanding the pool of experts.

The next chapter of continuous manufacturing will build on and include stronger collaboration between the drug substance and drug product Working Groups, inclusion of biologics and quality

representation, and continued interactions with academic and regulatory leaders in this new and exciting space, which can deliver pharmaceuticals to patients faster in a more controlled and environmentally sustainable manner.

ALTERNATIVE APPROACHES FOR DEMONSTRATING PRODUCT SHELF-LIFE⁵

THE CHALLENGE

The collection of long-term stability data can be the rate-limiting step to filing a drug application for marketing approval. ICH stability guidelines clearly articulate expectations for long-term stability data at the time of submission. The well-defined expectation for 12 months of long-term stability data for initial approval may limit the ability of companies to leverage current technologies and alternative approaches to support a viable shelf life for launch.

OBJECTIVES & APPROACH

The Science and Risk Based Stability (SRBS) Working Group aims to enable the application, approval and launch of critical therapies to occur earlier with robust alternative data, as opposed to, waiting for the recommended long-term stability data. The SRBS Working Group has taken a multi-pronged approach to achieving this objective. Papers are published or in development that outline the utility of Risk-Based Predictive Stability (RBPS) tools and Stability Risk Assessments (SRAs) to support setting retest period or shelf-life.

These tools enable a more holistic approach to developing stability understanding and enable science-based approaches throughout development and product lifecycle. The Working Group is currently drafting our recommendations for incorporating science and risk-based stability strategies into ICH Q1 and Q5C. Recommendations include guidance on how to use RBPS tools and present data in submissions and how to use SRAs to leverage supporting data, prior knowledge, and/or data from bridging strategies. These strategies could enable faster submission and approval for breakthrough therapies, including those for COVID-19.

RESULTS

The SRBS Working Group has published a review paper detailing industry's experience with the utilization of risk-based predictive stability within regulatory submissions (24) and a paper of case studies that focus on the use of the right stability data to substantiate a shelf-life or support a change, rather than defaulting to a standard protocol (25).

IMPACT

The approach taken by the SRBS Working Group includes many components that will work together to provide companies the tools and references needed to implement scientific strategies that are not clearly laid out in current regulatory guidance. The approach will support

⁵ **WG/LG:** Science and Risk Based Stability Working Group/ALG

Working Group leads and affiliations: Brian P. Regler (Boehringer Ingelheim) and Megan McMahon (Pfizer)

any science and risk-based stability strategy from early development through marketed product lifecycle changes. Importantly, the work can be directly applied to move medically necessary therapies, such as COVID-19 therapies, to market without the ICH recommended 12 months of primary stability data to set shelf life. Additionally, the work done should help drive global harmonization by highlighting for Health Authorities across the world examples of scientific based stability strategies that have been deemed acceptable by regulatory authorities. Finally, this work has the potential to impact patients by enabling registration and launch of medically necessary therapies more efficiently.

GLOBAL HARMONIZATION OF CONTROL STRATEGY⁶

THE CHALLENGE

Industries develop a single core control strategy to supply therapeutics to the market globally. While the same data set is submitted to multiple markets, the data set is interpreted differently and may lead to country specific control strategies and a customized Module 3 for a new drug application. Instead of having a truly harmonized global dossier, localized interpretations of ICH guidance have resulted in different technical requirements and is most impactful where divergence leads to modification to control strategies. Market divergence not only increases the regulatory burden, supply chain complexity, and potential risks of drug shortage, divergence has become one of the newest risks to innovation.

OBJECTIVES & APPROACH

The Control Strategy Global Harmonization (CSGH) Working Group is seeking to bring awareness, by both regulators and manufacturers, on the significance of divergence and to facilitate opportunities for improved global harmonization that would advance manufacturing processes and enhance product quality. The CSGH Working Group is gathering examples from registration products, both small molecules and biologics, where interpretations have varied amongst ICH members and observers. The CSGH Working Group is focused on fundamental differences that impact the global dossier and quality control strategies such as the identification and justification of an active pharmaceutical ingredient (API) starting material, manufacturing process controls (e.g. criticality of parameters, in-process controls, set point parameters/ranges), and specifications. Harmonization is essential when supplying therapeutics to the global market and bringing awareness may streamline localize interpretations of ICH guidance.

RESULTS

The CSGH Working Group intends to share their findings through publications and presentations that will be used in workshops and delivered to ICH.

⁶ **WG/LG:** Control Strategy Global Harmonization Working Group/QLG

Author names and affiliations: Greg Rullo (AstraZeneca), KeAndra Robinson (Biogen), Timothy Watson (Pfizer)

IMPACT

Diversion in control strategies typically require additional controls that increases the regulatory burden associated with maintaining document compliance, increases the supply chain complexity and may result in temporary drug shortage in some markets. Applying country specific control strategies and customizing Module 3 of a new drug application to satisfy localized interpretation of ICH guideline delays patients' access to new medicines and does not necessarily offer more assurance of quality. Through the compilation of agencies' queries and dossier impact assessments, industries can share their experiences collectively and facilitate opportunities for improved global harmonization.

COVID-19 AND PATIENT-CENTRIC SAMPLING⁷

THE CHALLENGE

Clinical trials are essential to the discovery and development of new, safe, and efficacious medicines, and usually involve regular hospital or clinic visits which include collection of biological samples (e.g., blood) from patients. During the COVID-19 pandemic, clinical trial visits were curtailed to protect patients and health care staff, and these staff and facilities were reassigned for COVID-19 care. This disrupted ongoing trials and delayed initiating new ones. One company reported stopping the development of a new drug for acute myeloid leukemia citing COVID-19 (26). As such, the medical and pharmaceutical industries were challenged to find new ways to continue and initiate trials including how to collect biological samples when onsite clinic visits were limited or impossible.

OBJECTIVES & APPROACH

Remote clinical trials with in-home sample collection has been recognized for some time as potentially a more efficient and patient centric way to conduct studies. Prior to the COVID-19 pandemic patient-centric sampling (PCS) approaches, such as at-home blood collection or novel devices enabling smaller volume and less painful collection, were gradually gaining wider acceptance, but the adoption was slowed by validation and regulatory concerns. The pandemic propelled PCS into the mainstream for COVID-19 diagnostic testing and disease tracking (27) due to the necessity of scale and the need to protect patients and health care staff.

Due to the time needed to meet validation requirements for novel collection approaches for pharmacokinetic or biomarker samples, remote phlebotomy was instituted to keep trials moving. Though limited, case studies usually involving COVID-19 testing are emerging where trial participant blood samples were collected at home and mailed to the bioanalytical laboratory (28).

⁷ **WG/LG:** Patient Centric Sampling Working Group/TALG

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RESULTS

Through the IQ consortium, experts across the pharmaceutical industry have discussed how to advance adoption of novel biological sampling approaches. Key barriers to adopting new devices include acceptance of novel approaches in traditional clinical trials, bioanalytical challenges, and regulatory considerations. The pandemic has necessitated a shift from site-centric to patient-centric approach to clinical trials and could be the catalyst to change how biological samples are collected in future. To increase awareness and adoption of patient-centric sampling approaches beyond mobile phlebotomy, the IQ consortium has conducted multiple webinars, presented at scientific conferences, drafted a publication, and co-hosted a roundtable with the FDA on this topic (29), (30), (31). Interest is growing and pharmaceutical companies and device manufactures are partnering to enable ease of adoption of patient-centric sample approaches into clinical trials with the goal of easing patient burden in clinical trials both during a pandemic and beyond.

IMPACT

The challenges brought up by the COVID-19 pandemic highlight the importance of PCS (32). When hospitals are overwhelmed, remote testing locations offer a viable alternative for robust testing. When clinical sites are shut down for planned study visits, at home study nurse visits and sample collections offer a lifeline to keep trials going. The impact of PCS is hard to overestimate during this special time and gives some insight to what may be feasible when the pandemic is over. PCS adoption also affords the benefit for inclusion of vulnerable or geographically dispersed trial participants, painless sample collection methods, and minimizing blood volume. Sponsors may reduce enrollment times and enhance retention in clinical trials. The ability to obtain clinical samples outside of the clinic, may also provide critical data on biological response. PCS approaches will benefit all who engage in clinical trials with the greatest impact being realized by the trial participants.

FACING THE CHALLENGE OF COVID-19 PANDEMIC ON CLINICAL TRIALS FROM A CLINICAL PHARMACOLOGY PERSPECTIVE⁸

THE CHALLENGE

The COVID-19 pandemic has disrupted clinical trial conduct across the globe. Concerns related to participant safety, access to medical facilities and travel restrictions during this public health emergency are causing protocol deviations and missing pharmacokinetic (PK) and pharmacodynamic (PD) data. While several health authorities have issued guidelines to assist sponsors with ensuring trial participant safety and maintaining quality and compliance (33), (34), there has been little guidance on how to handle the challenges of collecting PK and PD samples

⁸ **WG/LG:** CPLG COVID-19 and Clinical Trials Working Group/CPLG

Working Group leads and affiliations: Tong Zhu (Astellas), Sandhya Girish (Gilead), Amita Datta-Mannan (Eli Lilly), Silpa Nuthalapati (AbbVie), Ferdous Gheyas (Merck & Co., Inc., Kenilworth, NJ, USA), Jitendra Kanodia (Theravance Biopharma US, Inc.), Lee Naga o (Faegre Drinker Biddle & Reath), Mohamad-Eslam F. Mohamad (AbbVie), and Amit Desai (Astellas)

during the pandemic, and how to assess the impact of missing data on trial results or to communicate pandemic-impacted trial results to regulatory authorities.

OBJECTIVES & APPROACH

The project aims to identify industry practice for collecting PK and PD data during the pandemic, methodologies for handling the impact of missing data on trial results, and for communicating trial results with regulatory authorities.

Project objectives will be accomplished via two surveys: Survey 1 was completed in July 2020, approximately 4 months into the pandemic. Survey 1 focused on companies' experience with interruptions with dosing or PKPD sampling. A subsequent Survey 2 will focus on the impact of the pandemic on clinical trial design and conduct as well as the impact of missingness on clinical trial results and regulatory decision making in addition to gathering additional case studies.

The Working Group has actively engaged the FDA Office of Clinical Pharmacology (OCP) on scientific discussions as appropriate.

Survey 1 results were shared with member companies and presented at the IQ Webinar.

RESULTS

Survey 1 questions were designed at trial-level. It consisted of two parts, one with multiple-choice questions leading to quantitative study, and the other seeking prose response of case studies. Survey 1 collected responses on 69 non-COVID-19 clinical trials across 11 IQ companies. The response dataset was represented by trials across development phases, treatment modalities, and route of administration.

Quantitative survey results revealed the extent of missed doses and missing PK and PD data and identified the causes of missed doses and missing data as well as common mitigation strategies that trial sponsors have implemented.

Case studies further revealed enrollment challenges especially in vulnerable populations that led to reduced clinical pharmacology data packages, heterogeneity of missingness between groups and over time within a trial, and impact of missing data that varied based on trial objectives, design, types of data, planned analysis.

The Working Group is also preparing a publication in a scientific journal detailing the results.

IMPACT

The completed Survey 1 captured evidence of the challenges of collecting PK and PD data during the pandemic and offered a data-based initial view of the impact of COVID-19 on clinical pharmacology aspects of trials. Through the scientific exchange with FDA OCP, the survey results provide the regulators a view of the impact of the pandemic from a clinical pharmacology perspective, and the possibility of using modeling and simulation as a potential strategy to fill the data gap. However, a case-by-case approach is likely needed to fill the data gap. Survey 2

questions are under preparation to further quantify the impact of missingness on clinical trial results, the impact on regulatory decision-making, and the strategies that companies use to fill the data gap.

LEVERAGING ICH Q12 TOOLS AND CONCEPTS TO ACCELERATE ANALYTICAL METHODS LIFECYCLE MANAGEMENT⁹

THE CHALLENGE

The COVID-19 pandemic has elevated the need for CMC accelerated product development of therapeutics and vaccines. This requires “fit for purpose” analytical methods to enable launch while deferring robustness activities post launch. Post launch activities may involve analytical method changes, which traditionally would delay adoption in various regulatory regions impacting a global supply chain. Ability to manage post approval CMC analytical changes in a more predictable and efficient manner across the ICH regions will enable accelerated CMC development of COVID-19 therapeutics and vaccines.

OBJECTIVES & APPROACH

The ICH Q12 Working Group (Q12 Working Group) objective is to facilitate adoption and implementation of ICH Q12 (35) tools such as Established Conditions (ECs), Product Lifecycle Management (PLCM) document, and Post Approval Change Management Protocols (PACMPs) for analytical methods by industry and regulatory authorities. The current Q12 guidance does not address in detail implementation of ECs for analytical methods; thus, the Working Group is focusing on developing case studies that demonstrate implementation of ECs, PLCMs, and PACMPs. Definition of ECs and use of PACMPs provide opportunities for downgrading regulatory reporting categories, which in turn can accelerate implementation of the change. This would provide industry and regulators a road map for more robust change management that would support an accelerated development strategy for a COVID-19 therapeutic or vaccine.

RESULTS

The EC sub-team will deliver a case study of a chromatography method defining Established Conditions and a corresponding PLCM. Following that exercise they will develop a decision tree to define a framework for EC identification and regulatory reporting category.

The PACMP sub-team will develop a case study using the EC case study output, defining a common change that would be relevant to accelerated develop scenarios. This study would provide an industry approach to content, level of detail, reporting category definition in a PACMP.

The Q12 Working Group intends to engage with cross industry organizations to further collaboration, such as sponsoring a workshop (virtual or face to face as appropriate) inviting regulators, cross industry organizations (e.g. ISPE, BioPhorum) to demonstrate how Q12 tools

⁹ **WG/LG:** ICH Q12 Working Group/QLG

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can impact analytical lifecycle management and support implementation across industry and Health Authorities.

IMPACT

The EC sub-team is taking a cross modality approach to ensure applicability to all modalities. They have partnered with the IQ Analytical Quality by Design (AQbD) Working Group and the Bio LG AQbD Working Group. We envision utilizing these case studies, which propose regulatory change reporting categories using a science- and risk-based approach (36), in communicating industry’s strategy to regulators. These outputs will also support implementation of Q12 and more effective use of resources both within industry and Health Authorities by facilitating the management of post approval CMC method changes in a more predictable and efficient manner across the product lifecycle.

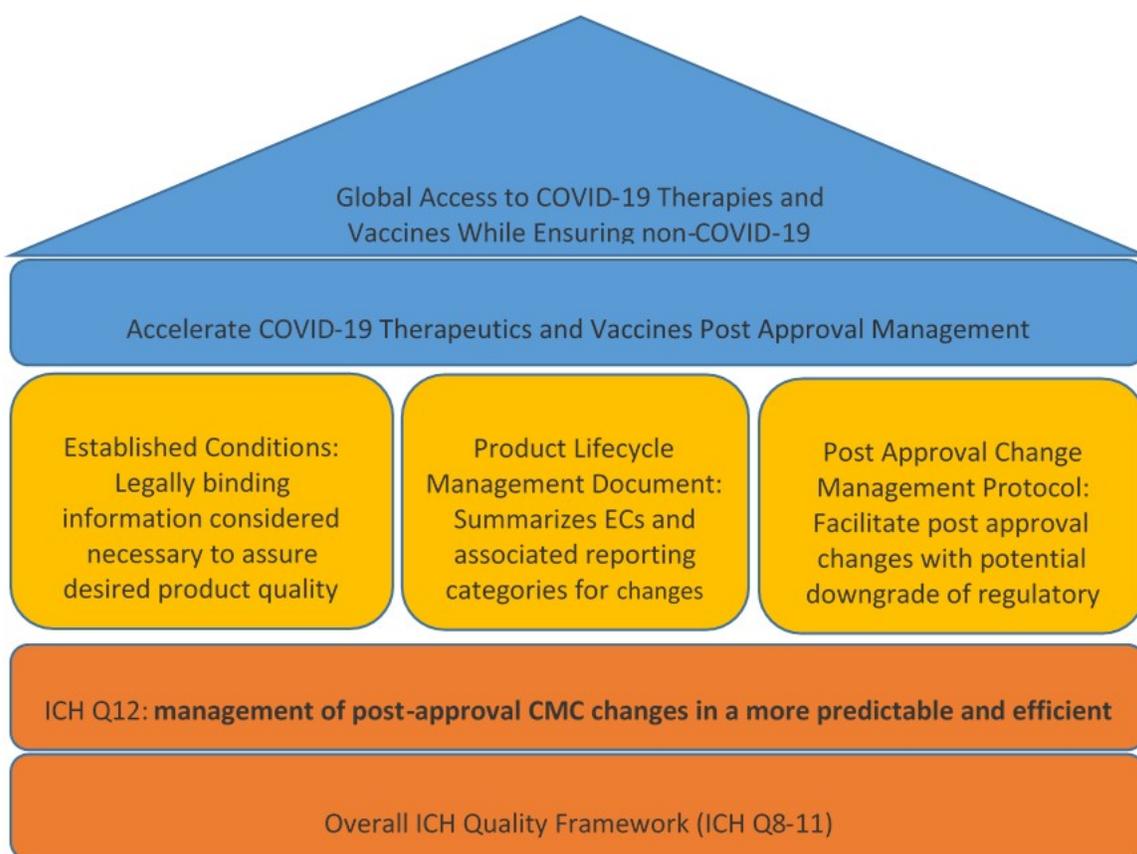


Figure 4: Relationship of how Established Conditions and PACMPs can facilitate analytical lifecycle management to accelerate COVID-19 therapeutics development and post approval management to deliver a global supply chain.

DISCUSSION

As stated previously, the COVID-19 pandemic has undoubtedly been a watershed event for the pharmaceutical industry. How industry and regulators respond to this event and what lessons will emerge will impact the pharmaceutical industry tremendously in the future. The IQ Consortium is focused on science and risk-based approaches, believing these are critical to the pharmaceutical industry's ability to respond expeditiously to new and unexpected challenges and to provide regulatory agencies with the appropriate scientific and technical information to accept novel (e.g., cloud-based regulatory global submissions) and alternative approaches to drug development.

The nine reports summarized above span the development lifecycle including pre-clinical and clinical research, product development, shelf-life projections, and post-approval life cycle management. The reports presented above all converge on one central theme, which not only focuses on the science of how we bring important medicines to patients, but how these can be brought with speed, efficiency, and continued patient safety as the drivers. These risk-based novel and alternative approaches address:

- (a) Diverse challenges for animal research programs, spanning ethical, practical, and regulatory concerns and emphasizes the importance of developing ways to protect the health and safety of the staff as well as the animals that are paramount to early molecule development;
- (b) How experiences gained during COVID-19 from non-clinical safety strategies and practices will be applied to other severely debilitating or life-threatening indications, thus expediting availability of drugs and vaccines;
- (c) How the strategies and tools developed by the ADD Working Group will enable stakeholders to accelerate drug development for future pandemic or unmet medical needs for the patients we serve;
- (d) How continuous manufacturing has emerged as a disruptive technology across the pharmaceutical industry and will play an increasing role in our ability to deliver pharmaceuticals to patients faster and in a more controlled and environmentally sustainable manner;
- (e) How to submit regulatory filings without the ICH recommended 12 months of primary stability data and to set shelf life for programs such as COVID-19 therapies; drive global harmonization by highlighting for Health Authorities across the world examples of scientifically-based stability strategies that have been deemed acceptable in the US and EU; and by using these scientifically-based stability strategies enable registration and launch of medically necessary therapies more efficiently;

- (f) How through the compilation of regulatory agencies' queries and dossier impact assessments industries can share their experiences collectively and facilitate opportunities for improved global harmonization of control strategies;
- (g) How Patient Centric Sampling benefits the inclusion of vulnerable or geographically dispersed trial participants, painless sample collection methods, and minimizing blood volume thus providing the greatest impact to the trial participants;
- (h) How PK/PD modeling and simulation methodologies could help connect trial design, nature of the missing data, and utilization of simulated results in regulatory decision making; and
- (i) How the management of post approval CMC method changes in a more predictable and efficient manner across the product lifecycle using ICH Q12 will enable effective utilization of resources both within the industry and Health Authorities.

Overall, the work summarized in this white paper shows the strengths of collaboration and highlights one of IQ's strategic pillars "these concepts are advanced in a collaborative group setting better than through individual efforts". These efforts provide an important framework and foundation that will prepare the industry to effectively apply the lessons learned from drug discovery and development during COVID-19 to support future pandemic or unmet medical needs for the patients we serve.

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