PERSPECTIVE

COVID-19: A Catalyst to Accelerate Global Regulatory Transformation

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A global crisis the magnitude of coronavirus disease 2019 (COVID-19) can transform drug development and review. It has exposed vulnerabilities and inadequacies in the global healthcare ecosystem as well as spurred innovation, rapid adaption of novel solutions, and unprecedented collaboration among global regulatory agencies, sponsors, and researchers. For the continued and future benefit of patients, it is imperative that all stakeholders leverage the solutions, learnings, and momentum catalyzed by this crisis to advance regulatory science in the drug development process.

BACKGROUND

Previous public health crises have changed medical product development and regulatory practices. These examples include major legislative amendments and creative application of regulatory paradigms to address HIV, anthrax and other bioterrorism threats, and infectious diseases.[1] To address the threat of COVID-19 and simultaneously ensure continuity of development of non-COVID-19 treatments, regulators are providing significant regulatory flexibility while maintaining the high standards for quality, safety, and effectiveness. As Rasmus Hougaard argued in a recent *Forbes* article, "The heat of a crisis creates a burning platform, propelling organizations and individuals to make pivots and changes that seemed too hard or overwhelming during normal times."[2]

Some of the new policies and procedures allowed regulators to completely reprioritize existing high-priority public health work and reallocate internal resources in unprecedented ways. Arguably, such changes should be reserved for public health emergencies because they are unsustainable in the long run. However, other interim policies have the potential to endure in a "new normal" way of working to better address public health needs (e.g., repurposed drugs and their combinations with novel therapies), while specific risk-based policies to accelerate development of potential COVID-19 therapies and vaccines to an unprecedented level might be applied to other life-threatening diseases. The World Health Organization (WHO) reports, as of August 10, 2020, the total number of global Covid-19 confirmed deaths is approximately 728,000.[3] For perspective, this figure is lower than for other leading causes of death. For example, WHO reported the leading causes of global deaths in 2016 were ischemic heart disease and stroke, which claimed 15.2 million lives, and lung cancers (including trachea and bronchus cancers), which caused 1.7 million deaths.[4] And as the world has witnessed the economic and societal costs associated with COVID-19, other diseases share similar burdens. These data indicate it would be appropriate to apply the same sense of urgency and innovation to areas beyond COVID-19. We are supportive of many of the proposals being discussed by regulators and other groups identifying transformative practices, e.g., use of digital technologies and flexibility in statistical approaches.[5]

Here, we provide an industry regulatory perspective on durable learnings and innovation that may emerge from the COVID-19 experience; they fall into two major categories. First would be innovation in clinical trials and regulatory frameworks, enabled by digital technologies that may

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increase the efficiency and acceptability to both patients and investigators. Second is the application of the same level of regulatory urgency, responsiveness, and flexibility in requirements seen with COVID-19 solutions to other serious life-threatening and/or debilitating diseases that remain major causes of mortality and suffering. These are described in more detail below.

TRANSFORM REGULATORY FRAMEWORKS TO STREAMLINE PROCESSES

First, it is imperative to increase the use of existing electronic-based tools and accelerate modern digital efforts to improve efficiency of operations for both regulators and industry. Outdated technical infrastructure and lack of contemporary digital capabilities present a challenge across many regulatory authorities, regardless of the level of maturity. COVID-19 exposed this shortfall. Faster and better-informed regulatory decisions, coupled with enhanced platforms to enable collaboration and reliance activities among regulators,[6] are critical for success. We discuss the following recommendations, recognizing that certain areas are more practiced, while others require further examination.

Virtual clinical trials and digital health technology

By far, the biggest innovation emerging from the COVID-19 crisis is the virtualization of many aspects of clinical trials by digital enablement. By utilizing various digital health technologies, patients can participate in one or more aspects of a trial without visiting a clinical site as part of "routine" drug development. We commend the regulators for developing much needed guidance during the pandemic, allowing for remote monitoring and other alternatives to help sponsors continue to conduct trials. While decentralized clinical trials and digital health technologies have been critical during the current pandemic, the increased use of telemedicine creates opportunities to reform the clinical trial paradigm by implementing digitally enabled tools in areas such as patient screening, informed consent, telemedicine-facilitated visits, and remote monitoring. The International Council for Harmonization (ICH) is currently revising the E6 Guideline Good Clinical Practice, and we believe this is an ideal opportunity to support the development of a responsive guideline with stakeholders' perspectives and advances in technology.[7]

Alternatives to on-site regulatory inspections

The idea of a virtual regulatory inspection seemed reserved for the next generation of regulatory professionals, until COVID-19. Our experience with remote Good Clinical Practice and pharmacovigilance inspections by regulators during the pandemic has been both positive and encouraging. The challenges of COVID-19 underscore the importance of achieving process efficiency while at the same time ensuring high-quality standards. To date, the remote inspections have demonstrated efficiencies for regulators and sponsors by eliminating travel, enhancing document management systems, and fostering disciplined and focused communications. We recognize the broader practice of virtual inspections is untested, but it's an area worth exploring, where regulatory inspections of investigator sites and sponsors are digitally enabled (e.g., secure video conferencing), allowing inspectors to interview personnel, review procedures, and validate data against source documents.

A global platform to accelerate real-time data and insight sharing

The pandemic has galvanized a renewed call for knowledge and voluntary data sharing as researchers race to find solutions to end the pandemic. While stakeholders are committed to facilitating effective data sharing of COVID-19 research findings, the types of data and the methods of sharing should be harmonized, where appropriate. Forums such as ICH and the International Coalition of Medicines Regulatory Authorities can play an important role in convening stakeholders to navigate the various challenges and avoid the emergence of fragmented, potentially conflicting systems. Beyond data sharing to accelerate development, cloud-based systems have the potential to accelerate and streamline regulatory review and enhance regulatory decision making, encompassing parallel agency review and reliance.[8]

Universal acceptance of electronic regulatory submissions

As noted above, we have seen a wide range of flexibility by regulators to avoid delays in patient access to new and existing treatments. Regulators around the world have permitted electronic files for Certificates of Pharmaceutical Products and Good Manufacturing Practices, and accepted all regulatory filings electronically (e.g., meeting packages and annual reports). This reduction in administrative burden—without reduction in quality of information being provided—has simplified regulatory processes while maintaining compliance, and facilitated more efficient use of resources.

Moreover, COVID-19 has revealed the advantages to having real-time and accurate product information for all countries. Electronic labeling provides the opportunity to immediately share with patients and healthcare providers changes in approved product information. While we recognize many regulators have already taken steps toward implementing electronic labeling, it is important to do so in a consistently accessible manner, seeking standards and interoperable solutions.[9]

ADVANCE MORE RISK-BASED REGULATORY DECISIONS TO ADDRESS OTHER SERIOUS DISEASES

In order to rapidly accelerate the development and manufacturing scale-up of COVID-19 therapeutics, industry and regulators continue to partner in quick fashion to adopt fit-for-purpose regulatory strategies. Similar to how we take such exceptional action for COVID-19 patients, we need to advance regulatory policy for patients with life-limiting autoimmune conditions, late-stage heart failure, or other serious illnesses. Such life-threatening diseases will continue long after COVID-19 is managed, and it will be important not to revert to previous practices and to emerge from the current situation with enduring solutions for the benefit of patients, globally. This objective will challenge each stakeholder to implement processes that enable regulators to prioritize and focus on the most important, unmet needs with the most substantial public health impacts.

Innovative clinical evidence generation

The pandemic has underscored the premium for speed of success and the acceptability by regulators of the use of innovative trial strategies with a quantitative decision-making framework to support regulatory approval. We have seen the benefit of streamlining trial protocols and embracing novel trial designs such as platform approaches to simultaneously test multiple assets in the clinic, using historical data for predictive analyses, or borrowing information on placebo/standard of care from other trials.[10] These mechanisms, together with use of real-world data on external controls and adaptive clinical designs are not new and are increasingly well understood and accepted. They should be leveraged where similar benefit/ risk considerations apply.

Risk-based preclinical safety requirements

The global support for drug and vaccine development, including streamlining nonclinical requirements, has allowed candidates, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) antibodies, to move quickly into the clinic to most efficiently determine if the experimental treatment is effective for patients. The practice of deferring or eliminating certain preclinical studies while there is a degree of uncertainty in the experimental candidate for specific life-threatening illnesses with no effective treatment is not new. ICH S9 Guideline "Nonclinical Evaluation for Anticancer Pharmaceuticals" provides for such regulatory flexibility for advanced oncology indications. We encourage regulators to apply this approach to other life-threatening illnesses across therapeutic areas, and to model a global harmonized approach as ICH. The benefits to society could be significant—by reducing the need to use animals, modernize drug development, and potentially make new therapies available to patients faster.

Fit for purpose and risk-based CMC requirements

As preclinical and clinical phases are streamlined, chemistry and manufacturing controls (CMC) data must equally be fit for purpose. In order to rapidly accelerate the development and manufacturing scale-up of COVID-19 treatments and vaccines, regulators have employed risk-based decisions to defer certain CMC requirements to later stages of development or even post approval. There are long-standing challenges to accelerating manufacturing aspects under expedited programs, and the COVID-19 experience further emphasizes the need for analogous regulatory flexibility. For instance, using judgment-based clinically meaningful specifications or deferring longer-term stability data until the postmarket setting. Moreover, allowing companies to report more postapproval changes within their quality system (vs. submitting for regulatory approval) would allow for more manufacturing flexibility and ability to react to supply challenges globally more quickly, as outlined in ICH Q12 Guideline "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Development."

POTENTIAL CHALLENGES

These proposals are not without their respective challenges. Technological solutions need to account for issues like privacy, security, and platform stability; likewise, expanded training for personnel might also be necessary. Unintended consequences can also result, e.g., the possible development of diverging drug review processes under various global health authorities. But these challenges can be addressed and overcome. Considering the significant benefit these transformative initiatives bring to patients, we support near-term implementation with reviews and future adjustments as necessary.

CONCLUSION

This paper touches on some critical innovations deployed during the crisis. It is not comprehensive, but there is little reason not to immediately begin exploring these initiatives as part of the "new normal." We are committed to working with stakeholders around the world to transform regulatory frameworks using new technologies while maintaining the gold standard of approval.

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CONFLICT OF INTEREST

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