COVID-19 vaccines and treatments: When speed is necessary and not enough

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INTRODUCTION

The infectivity and severity of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) pandemic (coronavirus disease 2019 [COVID-19]) has fostered the need for speed in the work to make progress against the virus. However, speed alone—without proper direction and control—can have dangerous, unintended consequences. This commentary describes ways COVID-19 has disrupted business as usual for industry and regulatory agencies. We highlight critical implications in global health and community engagement as well as opportunities to address long-standing challenges to accelerating biopharmaceutical innovation.

INDUSTRY

Industry has demonstrated the ability to accelerate the research and development (R&D) life cycle, including the execution of clinical trials. As of January 2021, the World Health Organization (WHO) reports that there are 237 vaccine candidates from a broad range of technology platforms, 64 of which are in clinical development.1

The urgency of the search for treatments and vaccines has intensified the level of collaboration across the biopharmaceutical, academic, and regulatory sectors. This collaboration has already yielded precompetitive efforts to standardize the methods and models for testing candidate vaccines, the coordination of clinical trials, standardization of end points, and achieved emergency use authorization (EUA) in the United States for two vaccines, with other candidates quickly following suit.2

Although enhanced collaboration across the biopharmaceutical, academic, and regulatory sectors has catalyzed the development of new or repurposed treatments and vaccines, competition and lack of coordination has led to a plethora of similar clinical trials as well as vaccines. In particular, the duplication of effort has plagued COVID-19 efforts, especially clinical trials; with, for example, 343 reported clinical trials of hydroxychloroquine as of the end of November 2020.3 Moreover, across a range of drugs, many of the trials have been too small or poorly designed to answer rigorous questions—with too few being blinded, randomized, controlled trials—and a large proportion of the completed trials have not reported on ClinicalTrials.gov or in the academic literature (1516 of 3754 completed trials, 40.4%).4 The large number of vaccine candidates in clinical development is extraordinary, and although some of those multiple efforts are undoubtedly important to ensure success—and reflect an understandable urge to respond quickly to the pandemic—competitive forces have probably driven this number too high, resulting in a potential waste of effort and resources.

Industry’s greater openness to a new speed and scope of data sharing is a promising sign of collaborative progress. The willingness to share diverse databases, including experimental...
conditions, patient risk factors, and outcomes, coupled with standardization and coordination of research methods and end points may, in turn, support faster and more useful insights from emerging artificial intelligence technologies.\(^5\)

**REGULATORY AGENCIES**

The public has come to expect that the sense of urgency amongst scientists in R&D will manifest itself in faster regulatory decision making timelines and more rapid deployment of successful candidates; in turn creating new tensions—for example, around the dosing schedules of the approved vaccines. As the ongoing clinical trials of the vaccine candidates prove successful, sponsors have already begun to seek EUA through US, UK, or European authorities. Reviewing the safety and efficacy data and inspecting manufacturing facilities for good manufacturing practice compliance will entail an enormous global effort. What will the reviews performed under the emergency authorization procedure look like? Will the reviews be adequate to ensure confidence and trust in the outcome?

A coordinated cohort of globally distributed, interdisciplinary teams, with representation from commercial, scientific, public, and regulatory interests, including a diverse range of expertise will be required to manage the influx of dossiers. The teams will be required to not only increase the speed, but also enhance the scope, agility, and utility of the question-based reviews, and to balance the inter-related strategic, technical, operational, and impact factors.

Further, as we have seen with collaboration among researchers, collaboration among the global regulatory agencies will be critical and can build on the successful history of collaboration via the International Council on Harmonization.

Effective collaboration will require sharing not only the final reviews, but also the work products and thinking behind the reviews. The combination of data, reviews, and work products could allow the teams to develop and consider systematically a range of best-case and worst-case scenarios from different perspectives and allow for timely exploration of mitigation strategies.

There is longstanding recognition of the importance of enabling collaboration and reliance activities among regulators that has been heightened by the global impact of COVID-19. Regulatory sharing, specifically work products, including assessment reports and inspection reports, depends on industry permission, and where the industry will draw the line on asserting proprietary rights to confidentiality for the COVID-19 vaccine remains to be seen.

**GLOBAL HEALTH AND EDUCATION**

Successful deployment of new vaccines for COVID-19 will depend not only on public acceptance of regulatory endorsements of the vaccine, but also on how the evidence for safety and efficacy is interrogated and transparently communicated to the global community. Equally critical is acceptance by the procurement, payors, legal, and insurance components of the community who will need to develop flexible and agile strategies for iterative payment and liability schemes that can adjust as greater assuredness regarding a vaccine benefit-to-risk profile is established.

The question-based review for COVID-19 clinical trial data, while focused on efficacy and safety, must also consider the impact of externalities, such as societal, environmental, economic, and political factors on vaccine response and uptake. Vaccine candidate sponsors have made significant efforts to increase the diversity of subjects enrolled in clinical trials, but little data has been generated from subjects in low and middle income countries (LMICs). Cold chain requirements and logistical feasibility of deployment have already emerged as a potential differentiator in vaccine selection. Other issues, such as the impact of malnutrition, micronutrient deficiency, and diseases, such as HIV, malaria, and tuberculosis, on vaccine response remain to be discerned from future trials.\(^6\)

The potential for the global release of multiple versions of COVID-19 vaccines, including those based on novel technologies, both increases the scale of the risks and compresses the timeline to the potential emergence of those risks. How will differences in vaccine response, particularly across multiple versions of the vaccine, affect our ability to develop an effective long-term immunization strategy against the disease? These factors will increase the requirements for rigorous pharmacovigilance studies, particularly in LMICs, that not only monitor for safety concerns but also the extent and duration of immunity.\(^7\)

Unfortunately, the infrastructure for safety monitoring is poor to nonexistent in many LMICs, heightening the risk of never truly identifying if these products are indeed safe and effective in these populations.

The front-line health and social workers are a high priority group for vaccination in order to interrupt the infection-transmission cycle. They are also the group who will be most likely amenable to participate fully in pharmacovigilance efforts and will play a vital role in broadly communicating and educating the public on the safety (or not) of the vaccines, including via word-of-mouth and social media.

**BACK TO THE FUTURE – RECOMMENDATIONS**

It has been nearly 25 years since Lewis Sheiner published his landmark paper on the learn and confirm paradigm in pharmaceutical drug development.\(^8\) These ideas had
a transformative effect on the practice of science and innovation in the biopharmaceutical industry and remain relevant today, pointing to critical next steps in our current moment of transition. See Table 1 for a summary of recommendations.

**Accelerate learning**

It is imperative that we work to systematically accelerate and plan for incorporation of learning as well as maximize the diversity and utility of our knowledge. From a research program perspective, the rapidly evolving information and experience that emerges during a global health threat, such as the COVID-19 pandemic, requires a continual review of action plans. The prioritization of new candidates for development or selection of drugs for repurposing might be based, for example, on pharmacologic first principles, yet these may ultimately prove inadequate and misleading as an expanded sense of the determinants for effectiveness or safety emerges. Continually questioning the relevance and appropriateness of research plans by systematically considering emerging knowledge can help to reduce the risk of overlooked opportunities and misdirected time and resources.

One promising way to support faster and sufficiently diverse and rigorous learning is to underpin the question-based review with explicit, interlacing conceptual schemes that formalize the knowledge, and identify gaps in the knowledge, from multiple perspectives. Systems pharmacology schemes for inflammation and its effects in target organs, including the lungs, brain, heart, and kidneys, can be interrogated and refined by incorporating emerging COVID-19–specific knowledge.

These conceptual schemes provide a foundation for multidisciplinary dialogue, generate promising heuristics for artificial intelligence-based analyses, and may also serve as a basis for the development of probability models that incorporate exposure-response and prognostic data to predict outcomes in counterfactual scenarios. See Figure 1 for an illustration of an iterative process for accelerating learning and its application.

**Accelerate sharing**

Sharing in the work of critical knowledge creation while avoiding unnecessary and wasteful duplication of efforts does not have to end with the pandemic. A willingness of direct competitors to join forces by sharing proprietary information, R&D capabilities, and other resources can result in sustainable models for process improvement, data sharing, accelerated learning, and complementary drug development.

### Table 1: Summary of recommendations

| Recommendation                      | Goals                                                                 | Examples                                                                 |
|-------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------|
| **Accelerate learning**             | • Ensure coherence across strategic, technical, operational, and impact dimensions of innovation<br>• Perform continued assessment of development plans to assess the impact of emerging knowledge | • Performing multidisciplinary question-based reviews paired with evolving conceptual schemes (including systems pharmacology)<br>• Revisiting action plans to reflect emerging insights and gaps |
| **Accelerate sharing**             | • Standardization and coordination of research methods and end points<br>• Implement systematic curation, communication, and collaboration strategies | • Regulatory collaboration and reliance activities<br>• Industry-regulatory process improvements<br>• Data portals and platforms, including Vivli,a ICODA,b IDDO,c and ISARICd |
| **Avoid unnecessary duplication**  | • Systematic research mapping and strategic profiling<br>• Repurpose duplicate trials to study priority risk factors not yet adequately studied in clinical trial settings | • Precompetitive collaboration<br>• Overarching, authoritative repository of funded research projects |
| **Future applications of accelerated R&D** | • Perform benefit-to-risk profiling to determine eligibility for acceleration status | • Globally relevant, multidisciplinary approach to an enhanced clinical utility index |

Abbreviations: COVID-19, coronavirus disease 2019; R&D, research and development.

aVivli: https://vivli.org/.
bICODA, International COVID-19 Data Alliance: https://icoda-research.org/data-sharing-for-covid-19/.
cIDDO, Infectious Diseases Data Observatory: https://www.iddo.org.
dISARIC, International Severe Acute Respiratory and Emerging Infection Consortium: https://isaric.org; https://www.iddo.org/news/iddo-and-isaric-partner-support-data-collection-and-analysis-covid-19.
The COVID-19 pandemic has spawned a number of data platforms to capture emerging data, including ICODA, Vivli, IDDO, and ISARIC (see Table 1). These platforms along with funding initiatives to support innovative analyses play a crucial role in generating clinical and research insights beyond the primary outcomes of clinical trials.

Avoid unnecessary duplication

Precompetitive collaboration to address critical gaps in knowledge while avoiding unnecessary and wasteful duplication of efforts should be paramount. Centralized tabulation of funded research projects can serve as an important source to help both funders and researchers to prioritize resources to underfunded areas where there is greatest research need and facilitate further strategic collaboration.

Future applications of accelerated R&D

From a wider societal perspective, the speed and urgency of the COVID-19 R&D effort is severely stressing the existing process of providing checks and balances to industry-regulator-global health interests. This new faster paradigm can only realistically be imagined for other serious and life-threatening diseases for which there are not adequate current therapies or preventatives, and, even so, requires diligent prioritization. As with the pandemic, this is more likely to be for exceptional cases when the community is willing to commit the needed excess human and financial resources, and when the community is willing to tolerate a greater risk of the unknown about the product (i.e., accept a less complete data base at the time of significant usage in the population outside the consented clinical trial setting). A sustainable approach to assigning such an accelerated status to new therapeutics, and perhaps building on the existing US Food and Drug Administration (FDA) Priority Review designation under the Prescription Drug User Act, will be required. This designation will require a globally relevant and multidisciplinary approach to developing an enhanced clinical utility index that can be used as a practical multi-attribute approach to awarding this distinction.

CONCLUSIONS

The global nature of the pandemic has disrupted business as usual and highlighted the inevitable changes occurring in industry, regulatory agencies, and diverse community stakeholders. This disruption offers the opportunity to gain a new perspective on what is possible as a global society with motivation and shift in mindset.

In some cases, the shift marks a revisiting of familiar pathways with renewed interest in ensuring operational success. In other cases, the shifts will require recognizing and developing the latent advantages offered by new technologies to secure the inherent value. In all cases, the pandemic presents a generational opportunity to instantiate the lessons learned during this pandemic for the widest public good.

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