



New Approaches to Regulatory Innovation Emerging During the Crucible of COVID-19

In Responding to a Global Health Crisis, Industry is Discovering New, Efficient Ways of Meeting Objectives

Max Wegner¹

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Abstract

The urgency and impact of the ongoing COVID-19 pandemic are changing global drug development and regulatory processes. The need for speed to understand the virus and develop new vaccines, medicines, and therapies for patients has provided unprecedented learning opportunities and revealed how the pharmaceutical industry can improve upon traditional processes. To stay competitive while remaining compliant with agency regulations and guidance, companies need to implement new process/tools that allow for more flexible work models, consider expanding the use of decentralized/hybrid trials, and capitalize on the use of real-world evidence (RWE) and cloud-based data systems. In addition, regulatory agencies should retain the agility exhibited during current reviews of potential new therapies, applying this momentum to other areas of unmet medical need. Further, agencies should consider a globally acceptable application platform. This article, by the Pharmaceuticals' Head of Regulatory Affairs at Bayer AG, examines how impacts of the COVID-19 crisis will continue beyond the pandemic period to the benefit of patients, drug developers, regulators, clinicians, and caregivers.

Keywords Coronavirus pandemic · Regulatory policy · Decentralized trials · Cloud-based systems · Remote work

Overnight, the coronavirus pandemic struck the intricately configured and widely distributed network of international drug development. Pre-clinical, clinical research, regulatory affairs, and manufacturing were all profoundly disrupted—travel restrictions, mandates for social distancing, a shift in priorities, increased demand on resources, etc.

In response, global health authorities and the pharmaceutical industry have worked to simultaneously maintain continuity of ongoing clinical research while accelerating the development of new diagnostics, treatments, and vaccines for COVID-19. As of July 17, 2020, there are more than 100 vaccine candidates in development worldwide and more than 600 clinical trials underway [1].

As the world has mobilized to fight the virus, we have learned lessons that could offer benefits to the biopharmaceutical industry and to patients well beyond the pandemic

period—and we are now asking questions that could reshape the future of drug development.

Learning New Ways of Working

Working from Home

An ongoing debate has raged around whether productivity and performance suffer when people work from home [2]. During the pandemic period, regulatory professionals responded to sudden stay-at-home orders by transforming their homes into workplaces. They did so despite many difficulties: children and spouses, unable to attend daycare/school/the office, extended stays by visiting family unable to return home, the pop-up “offices” made from the living room couch and coffee table, and the strain on internet bandwidth shared among household members. Yet NordVPN data show that people are working more, not less [3].

✉ Max Wegner
max.wegner@bayer.com

¹ Bayer AG, Wuppertal, Germany

At Bayer, for example, regulatory teams have continued to deliver results, maintaining compliance targets and on-time submission of regulatory dossiers, despite the sudden transition to remote work. Regulators have kept pace as well [4], although a recent FDA Guidance acknowledges the possibility of slipped review times going forward [5]. Unexpected efficiency gains have been realized, but what has been lost? Personal interactions, such as impromptu conversations over coffee machines and water coolers should not be underestimated for fostering creativity, strengthening working relationships, and boosting morale.

While it is hard to predict what the “new normal” will look like, it should incorporate the “best of all worlds.” As companies begin to bring employees back to the office, protecting employee health while keeping the business running can help guide experimentation with more flexible, hybrid work models in which, for example, employees may alternate between working at home and from their offices, while leveraging increased use of digital tools such as video-conferencing and collaborative online workspaces.

Regulatory Agility

The COVID-19 crisis prompted many regulatory agencies to introduce accelerated reviews of COVID-19 research proposals, consistent with their public health missions and mandates. For example, as of July 14, 2020, the FDA reported that there are 510 development programs of potential therapies for COVID-19 in the planning stages, and the agency has reviewed more than 230 trials of potential therapies [6]. At least a quarter of the world’s regulatory agencies have issued COVID-19 guidance documents, expediting standard review, and approval processes [7]. As regulators review and make decisions about submissions for potential new coronavirus diagnostics, therapies, and vaccines much faster than standard packages, it raises a question: Can the innovation, creativity, and speed applied to COVID-19-related submissions be applied to other chronic, life-threatening, and rare diseases to make drug development more efficient?

To be sure, the mission of regulatory agencies to protect and promote public health remains unchanged. Regulatory decision making must continue to be based on scientific data and evidence supporting benefit-risk assessment. High regulatory standards and timely assessments are not incompatible [8]. Benefit-risk decision making should continue to rely on transparent, rigorous methodology, and science. Meanwhile, companies should continue to explore and expand collaborations that could anticipate and leverage the following regulatory changes:

- Maximized clinical trial capacity, avoiding use of the same patients, and utilizing trial networks

- Harmonized regulatory processes and mutual reliance to avoid duplication
- Clinical evaluations via joint reviews or shared working models
- Use of artificial intelligence, combined with human support and input, to advance regulatory review and post-marketing surveillance processes, and improve adaptive clinical trial designs, real-world data methodologies, and use of biomarkers [9]

Mobile Tools and Technologies

The uses of mobile tools and digital technologies, from basic tele- and video-conferencing software to more sophisticated collaboration and analytic technologies, have been amplified and accelerated during the pandemic, benefiting patients and increasing acceptance of these tools within the clinical research setting (including decentralized and remote clinical trials).

Decentralized trials (executed by telemedicine and mobile/local healthcare providers only) and hybrid trials (combining remote and traditional processes) reduce participant and research staff burden. By learning from experiences during the coronavirus pandemic, participants could more readily take part in trials from their homes, utilizing telemedicine and direct shipment of study medicines to patients’ homes, among other adaptations. These approaches allow for a more real-time collection of data that are more reflective of what is occurring in a real-world setting, and from a broader set of participants (due to fewer limitations) to support product safety and efficacy with evidence more relevant to patients’ real lives.

What is Becoming Even More Possible for the Future?

Real-World Evidence Supporting Regulatory Approval

The use of real-world data (RWD) and real-world evidence (RWE) can help in the fight against a pandemic like COVID-19, provided that the appropriate data sources are identified, and strict methodologies for surveillance and analysis are applied in real time. Real-time access to data, real-time analysis of what it means, and new technologies with standards for interoperability could truly bring clinical research into the twenty-first century.

The use of RWE in drug development is still maturing and evolving. To increase the use of RWE derived from RWD, regulators, Health Technology Assessment (HTA) agencies, and industry should convene to standardize datasets, data capture, and data analytics. That will take time. RWE offers

immediate utility for companies in helping to identify and select appropriate study participants, potentially resulting in a safer, more efficient clinical study. For example, today, sponsors could use RWE to help determine unmet medical need or identify differential benefits/risks in subsets of serious and life-threatening diseases without adequate treatment options or small patient populations, such as in oncology.

Recent learnings from high-profile studies of COVID-19 therapies (some of which were retracted) also highlight the risks of RWE [10]. As such, this evidence must be gathered and analyzed rigorously. Its value is dependent on quality data, transparency, and correct analyses—and companies must refine their ability to handle RWE properly. The RWE vision is compelling; getting there will require a stepwise application of sound science.

Regulatory reviews via a globally accessible cloud platform: 25 years ago, new drug applications were submitted using trucks loaded full of binders stuffed with paper documents. If the application was to be filed in another country(ies), an additional, nearly identically massive paper dossier was sent to each of the regulatory agencies around the world. Across major regions of the world, industry and regulatory agencies now make use of electronic submissions based on a common technical document. In some instances, this is achieved through an electronic gateway; in other instances, this still may require submission by a physical DVD loaded with terabytes of data; and some countries still require paper submissions.

In this moment, new approaches to digital and electronic submissions and reporting could leapfrog older, less efficient ones, leading to: broader adoption of electronic Common Technical Documents (eCTDs); the use of electronic product labels; reforms to the Certificate of a Pharmaceutical Product (CPP) paradigm, and the discarding of the antiquated requirement for “wet signatures” on documents (e.g., Vietnam, Ukraine, Philippines, India, and several countries in middle Africa).

In the future, all data could reside in the cloud and be more readily exchanged between and among regulatory agencies across different geographies [11]. Companies would send an email to the relevant regulatory agency once a product dossier is ready for review. Agencies (including both Regulatory and HTA agencies) could then access and analyze the data from a structured cloud environment (divided into discrete, protected sections for companies, agencies, and agency–company interactions). This, of course, would require broad acceptance and adoption of such a cloud-based approach by regulatory agencies around the world. Legal considerations and data security issues remain stumbling blocks, but stakeholders are beginning to focus on overcoming them.

Use of a cloud-based solution for regulatory submissions would enable a dynamic and more fluid exchange of

information between industry and regulators, speeding the response to public health emergencies such as COVID-19. For example, to approve a clinical trial, regulatory agencies are now reviewing COVID-19 research protocols in seven days, versus thirty. If data were in a cloud-based system, with accessible analytics applications, reviews could go even faster.

To enhance efficiency, industry and regulatory agencies need to come together to align an approach for cloud-based data systems that could support large dataset submissions and facilitate coordinated global regulatory reviews that proceed simultaneously instead of country by country. The cloud could promote faster and more streamlined interactions between companies and regulators and empower agencies to perform more sophisticated analyses across disparate studies, applications, and reviews. If industry and regulatory agencies could more readily share fast-evolving datasets through a cloud-based system, we could learn about new diseases faster by exchanging data in real time.

As New Habits Form, Some Will Stick

While much of the world continues to combat and adjust to the ongoing challenges stemming from the coronavirus pandemic, there is also hope that the current crisis will inspire positive and long-needed improvements in drug development, review, and pharmacovigilance. Operational efficiencies and flexibilities realized during the pandemic period could benefit biopharmaceutical companies and regulatory agencies well beyond the current crisis. Remote monitoring and home nursing, for example, offer the potential to strengthen clinical research and lessen burdens on patients around the world. The current context has made clear that patient centricity is not an aspiration; it is imperative.

If we internalize these lessons, if we do not revert to ingrained and increasingly obsolete ways of working, the promise of future drug development and innovation could be realized, delivering medicines faster to people who need them. This will only be possible if we maintain the same sense of urgency, then we now feel well beyond the current COVID-19 pandemic. And that would be wise for everyone.

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