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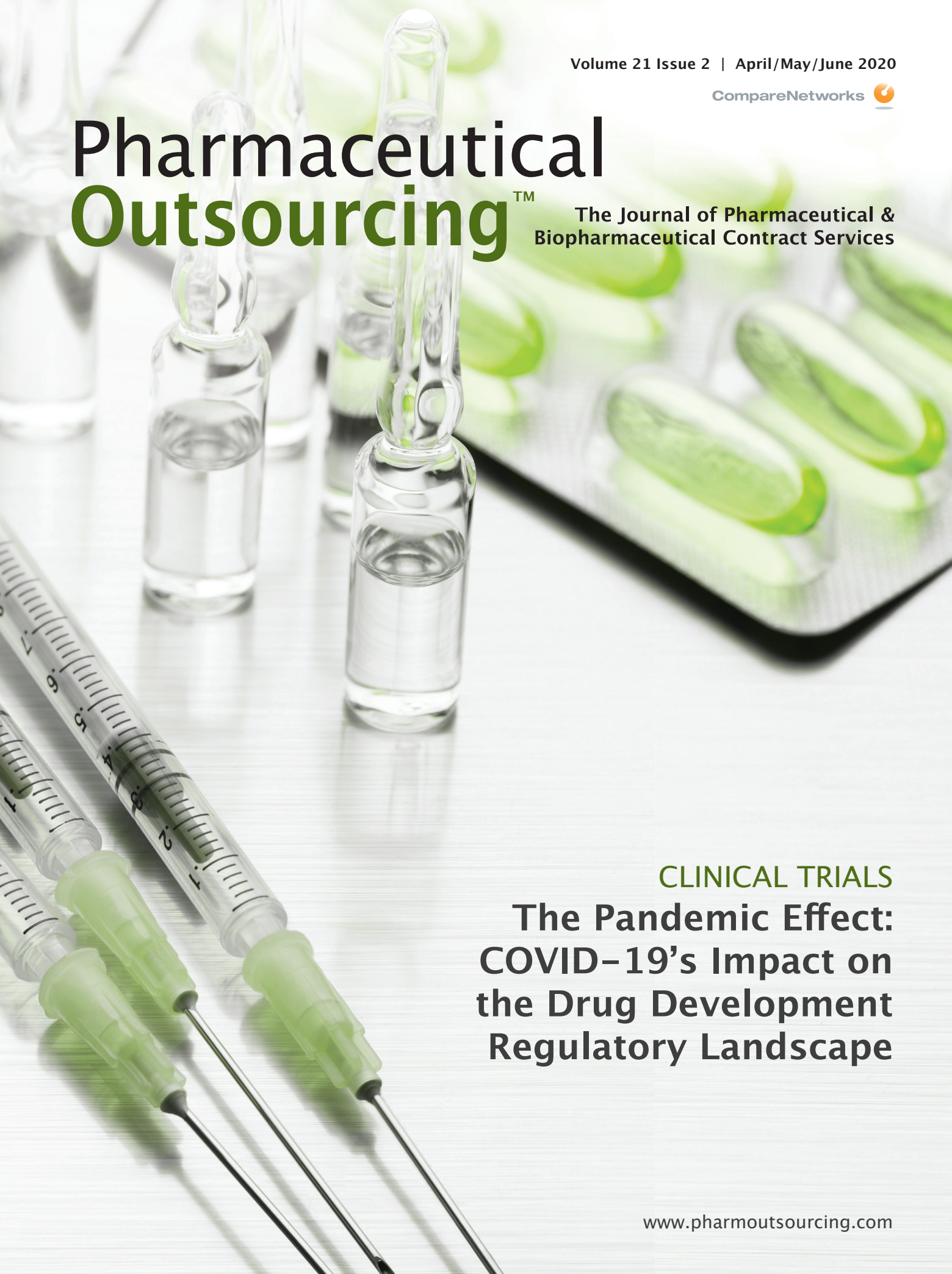

CLINICAL TRIALS

The Pandemic Effect: COVID-19's Impact on the Drug Development Regulatory Landscape

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The Pandemic Effect: COVID-19's Impact on the Drug Development Regulatory Landscape

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With the emergence of the COVID-19 pandemic, the clinical research space has been hit by a "black swan" event.[1] In the financial world, that term indicates a rare, unpredictable event with severe impact. The coronavirus health crisis meets all three criteria and has brought attention to global regulatory challenges impacting drug development.

Perhaps foremost among the challenges highlighted by the pandemic is the dearth of harmonization between global regions. Although attempts at standardization have been made by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), even ICH permits inconsistencies. Members are allowed to layer "add-on" requirements to various guidelines, for example. COVID-19 simply reveals how disorganized the coordination of research communities is at the global level.

Moreover, there is no single approach to "tell the story" to regulators regarding product risk/benefit ratios. There are varying ways to show safety and efficacy data, and the risk/benefit analysis is different for every drug, every indication and every patient population - as it should be. A drug being trialed as a treatment for late stage oncology patients should be scrutinized differently than a potential over the counter treatment for young headache sufferers.

What all of this means is that for years, sponsors have had to work through many longstanding, time-intensive regulatory procedures to get treatments to market. COVID-19 has exposed just how slow-moving those processes have been; even "expedited" pathways cannot enable what consumers would deem "swift" responses, especially in the case of an expeditious global pandemic.

Thus, COVID-19 offers the entire industry - sponsors, regulators and others - a chance to examine opportunities to mitigate regulatory hurdles and expedite drug development pathways. It offers us a rare global impetus to begin to think in different ways.

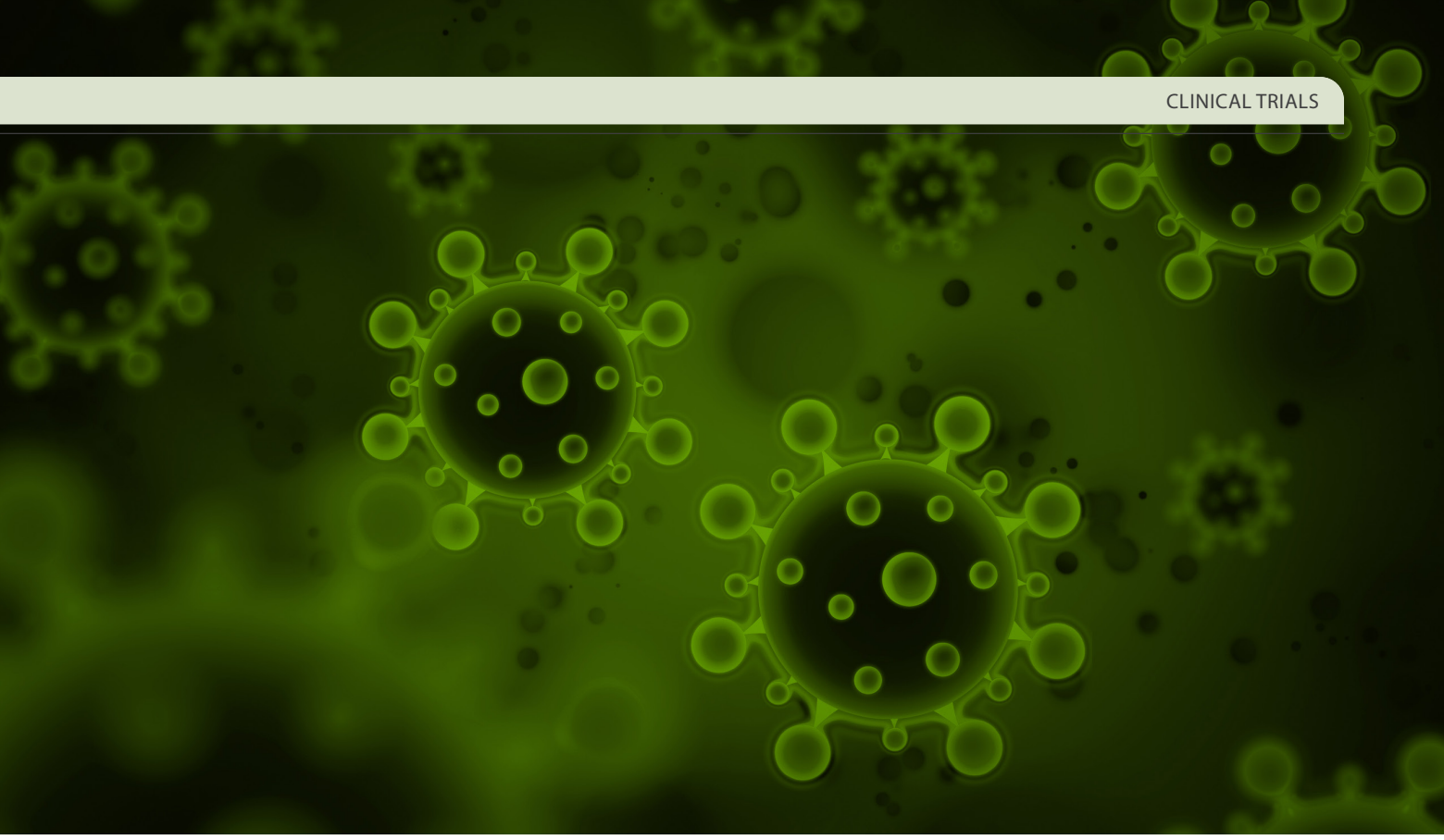
Trends Spotlighted by COVID-19

Examining the effects of COVID-19 on the current regulatory landscape presents a prime opportunity to see where regulatory trends may be headed.

To begin, it is imperative to recognize that non-COVID-19-related clinical research has significantly slowed. Before the pandemic, there were more than 335,000 ongoing clinical trials worldwide.[2] However, research studies widely are considered elective services, so most sites have suspended all research activity except COVID-19 trials. Even without suspensions, investigators who now are focused on increased patient care demands are not available for research. In addition, sites are restricting visitors - including researchers - to maintain social distancing measures, and participants are unable to travel due to quarantine and shelter-in-place mandates.

Sponsors, therefore, must be flexible and cautious through the duration of the pandemic and the gradual easing up and relaxing of restrictions. The rapid rate of change highlights four key things sponsors should do to protect their research:

- *Monitor requirements and changes daily.* Although the frenetic pace that marked the emergence of COVID-19 may have slowed somewhat, changes remain dramatically dynamic. New developments still arise daily and even hourly.
- *Be conservative in recruitment projections.* COVID-19 *will* affect recruitment and other timelines for non-COVID-19 trials.
- *Educate financial backers on the current landscape.* With recruitment and timelines affected overall, it is prudent to revise projections and educate and update venture capital and other funding resources.



- *Think from the patient perspective even more than before.* Now is the time for sponsors to take advantage of opportunities to use technology to engage patients and advocacy groups. Send patients devices to engage with them while they shelter in place, for example, or create a website landing page to keep them updated. Consider adapting future study designs to incorporate virtual visits instead of site visits where appropriate. Eventually, the pandemic will end; use the time now to engage patients and advocacy groups for stronger recruitment and retention once normal trial activity resumes.

Regulatory agencies, too, have been quick to adapt and help the industry pivot. The U.S. Food and Drug Administration (FDA), the EU's European Medicines Agency (EMA) and the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) all have issued guidance on the impact of COVID-19 on ongoing clinical research.

For example, the FDA has stepped in to help sponsors assess trial viability during the COVID-19 emergency.[3] It includes recommendations about trial suspension, extension or postponement options, as well as the applicability of incorporating phone or telemedicine "virtual visits" into trial protocols and designs.

Regulators' chief responsibility is to protect patients, with rules designed to ensure drug products meet certain levels of safety and efficacy. History indicates it is wise to have regulatory hurdles in place for clinical research. Yet during health crises such as the COVID-19 pandemic, quick response by regulators is required to safeguard both individual patients and the greater good.

That is why regulatory agencies have been a strong voice at the table, guiding the industry on the best ways to speed up the development of potential COVID-19 therapies - including evaluating new technologies and new ways of working.

Particularly noteworthy is regulators' willingness to be flexible and open to changes in protocols and study designs. Virtual visits, for example, increasingly are seen as essential for the sheer fact that trials cannot proceed without access to patients. Furthermore, to accelerate research, agencies are proactively collaborating with sponsors. One illustration of this heightened partnership approach is the FDA's email hotline to fast-track COVID-19-related reviews. During the pandemic, the agency has taken the unprecedented step of helping sponsors determine how best to conduct a trial with rapid response through its Clinicaltrialconduct-COVID19@fda.hhs.gov email address.[4]

Guidance on the design of animal studies and clinical trials for COVID-19 vaccines and treatments has been rapidly forthcoming. The World Health Organization (WHO) has published direction regarding COVID-19 animal models and clinical trials.[5,6] The International Coalition of Medicines Regulatory Authorities (ICMRA) released a report on the pre-clinical data required before moving to first-in-human clinical trials.[7] Indeed, it seems COVID-19 is pushing the industry to embrace the power of technology, computer modeling and artificial intelligence to arrive faster at the data necessary to show drug safety and efficacy. The ICMRA continues to meet and share knowledge on how best to align globally with the added benefit of full transparency.

How to Expedite COVID-19 Drug Development Efforts

Never before has the research industry seen as much regulatory engagement as it is witnessing with COVID-19. Much of what we know about expedited pathways has gone by the wayside for the time being. For sponsors developing COVID-19 vaccines and/or treatments,

a specific expedited pathway is available in the U.S. through the FDA's Coronavirus Treatment Acceleration Program (CTAP).[8]

This "special emergency program" is designed to offer FDA assistance early in clinical development and speed the review of COVID-19 treatment, cure or prevention therapies. The program combines multiple methods to connect sponsor companies with FDA experts quickly. Its all-hands-on-deck approach shortens to about two days the usual 30-day FDA review process prior to clinical trial.

CTAP was not created via regulatory statute, therefore it functions more like a pilot program than a newly established long-term pathway. For now, however, it enables interactive FDA input on most development plans, review of clinical protocols within 24 hours, review of single patient expanded access requests within a handful of hours and collaboration on quality assessments and transfer manufacturing.

In the same spirit of partnership, sponsor companies also can seek discussions with the U.S.'s Biomedical Advanced Research and Development Authority (BARDA).[9] These meetings allow companies to talk with U.S. government experts and pursue federal partnership opportunities.

Likewise, the European Medicines Agency (EMA) has developed guidance and a task force (COVID-ETF) to ensure more engagement and collaboration with researchers.[10] The task force pledges scientific support and feedback on development plans, among other assistance. Moreover, the EMA is offering fast-tracked scientific advice free of charge for potential COVID-19 treatments or vaccines.[11]

Other Expedited Pathways to Consider

With so much attention on COVID-specific expedited pathways, it is imperative that sponsors not overlook existing expedited pathways in the U.S. and EU that are available for other indications as well as COVID-19. These include:

- **Emergency Use Authorization (EUA).** The FDA can authorize the emergency use of specific unapproved medical products under specific conditions, when justified by a public health emergency.[12] The FDA must determine: that there are not any "adequate" approved treatments available for the public health emergency; that the drug product "may be effective" in diagnosing, treating or preventing the cause of the public health emergency; and that the product's benefits outweigh its risks (although the normal burden of showing "substantial evidence" of safety and efficacy is not required).
- Products granted EUA are only authorized for use for a specified period of time, after which they may be reauthorized or removed from the market. An example of an EUA specific to COVID-19 is the one that allowed BARDA to provide stockpiled chloroquine phosphate and hydroxychloroquine sulfate to treat COVID-19.
- **Expanded Access (a pre-approval pathway).** This pathway allows FDA to grant either standard or emergency access to an investigational drug on a compassionate basis.[13] Typically, it enables drug access to patients who otherwise would not qualify for a clinical trial due to the extent of their illness; patients must have a serious or life-threatening condition for which there is no approved treatment. Expanded Access does not grant product approval. Rather, sponsors must submit an IND Protocol or Protocol Amendment. Companies may charge for the drug under Expanded Access, but with restrictions.
- **Right-to-Try (a pre-approval pathway).** Similar to Expanded Access, Right-to-Try (RTT) in the U.S. opens access to an investigational drug for patients with a life-threatening illness who have exhausted approved treatments and are not eligible for clinical trial participation.[14] It requires completion of a Phase 1 clinical trial, but does not require review by an Institutional Review Board. Right-to-Try allows companies to charge for the drug and restricts reference to adverse events found during the drug's use during subsequent reviews to obtain approval.
- **Accelerated Approval.** Phase IV confirmatory trials are required under Accelerated Approval, but the FDA will permit the use of surrogate endpoints to help hasten approval for drugs that fill an unmet medical need for serious conditions.[15]
- **Priority Review.** The usual U.S. clinical trial requirements remain unchanged in priority review, but the FDA reduces its application review period to six months from 10 months.[16]
- **Scientific Advice.** In this program, the EMA answers specific questions companies ask about their drug development plan. Companies normally must spend nearly €88,000 and wait 2-3 months to receive scientific advice. However, EMA is expediting answers and waiving the fee for drugs to prevent or treat COVID-19.[17]
- **Priority Medicines (PRIME).** PRIME allows EMA to provide advice and support for products in the early clinical development stage, with a speedier assessment of approval applications.[18]
- **Conditional Marketing Authorization.** Through this pathway, EMA accepts less comprehensive data than normal in situations where the risk of less data is outweighed by the benefit of more immediate drug availability. The EMA grants temporary approval for one year.[19]
- **Accelerated Assessment.** The EMA reviews marketing authorization applications within 150 days instead of the standard 210 days for drugs of major public health interest.[20]

The Long-Term Effects of COVID-19 on Drug Development Regulation

Given the nature of the novel coronavirus transmission, the resulting shelter-in-place and social distancing mandates, a short-term slowdown in clinical research is inevitable during the current pandemic. What researchers need to consider are the potentially positive long-term impacts of COVID-19 on the regulatory landscape.

Regulatory agencies have shown they are willing to be flexible, and the industry is unlikely simply to revert to "business as usual." The primary

role of regulators - to protect patients by ensuring drug safety and efficacy - will remain unchanged going forward. Yet for future clinical studies, faster and more proactive engagement with regulators should continue to be encouraged. Our response to COVID-19 may also help us uncover new ways to leverage computer modeling, artificial intelligence and technology to speed drug development and clinical trials—all while still preserving patient safety.

COVID-19 represents a monumental moment in the history of regulatory agencies. Indeed, it may turn out to be the push the industry needs to revolutionize historically protracted clinical research processes.

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