

# Front & Center

## COVID-19 Highlights Need for More Agility, New Paradigms in Drug Development

The rapid spread of COVID-19 across the globe highlights the absolute need for preparedness in the face of pandemics in order to reduce and eliminate the emergence of new cases and quickly create treatment options for emerging illnesses and diseases. As it stands now, the sluggish response to the current crisis combined with the slow, rigid development process for therapies have been extremely inefficient and ineffective at handling the current crisis, thus signaling the need for faster, more agile paradigms.

In mid-March, *Pharmaceutical Executive* spoke with three industry leaders who have broad experience in technology, research and clinical approaches to epidemic disease:

- o Srinivas (Srin) Shankar, Senior Vice President and Global Head of Life Sciences at Cognizant
- o Ulo Palm, MD, PhD, Senior Vice President of Digital Sciences at Allergan
- o Thomas A. Bock, MD, MBA, Founder and past CEO of HeritX; Chair of the Columbia Business School Healthcare Advisory Board; and former Senior Vice President, Global Head of Medical Affairs at Alexion Pharmaceuticals.

They believe the medical community, life sciences industry, health institutions, governments and regulatory bodies must act with a sense of urgency to examine any and all recommendations that bear a promise to delay or stop the spread of global pandemics such as COVID-19.

### Urgency to Act

In just three months, COVID-19 mushroomed from a local outbreak of atypical pneumonia in Wuhan, China, to a global pandemic spread of SARS-CoV-2, a novel zoonotic coronavirus. Retrospective analysis suggests the disease was circulating in China as early as November 17, 2019, although the first case was not announced until December 8. The first case outside China was identified in Thailand on January 13, 2020 and the first US case was identified on January 21. As of March 19, 2020, more than 200,000 cases of COVID-19 had been confirmed worldwide and more than 9,950 deaths occurred as the pace of infection continued to climb.

“We have to solve these kinds of rapidly escalating problems, which potentially can kill millions of people if they are not managed quickly,” Dr. Bock said. “We must act with two critical concerns in mind: what is best for the patient and how to develop treatments and vaccines as fast as possible. Technology today gives us the tools that allow us to move ahead much more aggressively.”

But current technologies and tools are not being applied broadly. In early March, South Korea, a secondary epicenter of COVID-19, was testing 3,692

people per million population. Meanwhile, the United States was testing a mere 23 people per million.

“We do not have the sense of urgency needed,” Dr. Palm said. “We need to be able to act fast to save our patients. We have to think and to act at the speed of viral replication. If we don’t keep up with the virus, we will pay a very high price.”

### Combining RCTs with Accelerated RWE Studies and Real-Time Clinical Analysis

Reliance on established procedures is hampering the rapid development and deployment of novel therapies for COVID-19. Traditional drug development relies on randomized controlled trials (RCTs), a framework developed in the 1940s. RCTs have a proven track record, Srin Shankar said, but are time-consuming to execute. It can take months to create a study protocol and receive approval, several more months to set up studies, and still more months for recruiting and randomizing patients, collecting data and analyzing it. All told, RCTs often take several years to complete.

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Srini Shankar suggested that in addition to needing to operate in an “emergency mode” for clinical trials, the gold-standard placebo-controlled model is inappropriate for finding treatments to combat current pandemics. “Is it even ethical to use a placebo given the mortality risk? We have an absolute need to think outside the box with non-traditional, unconventional trial designs. RCTs must be complemented with a different approach to bringing therapies to market based on the urgency of the situation,” he stated.

One approach is to adapt existing technologies to drug development using real-time, real-world evidence (RWE) and adaptive biostatistical models to evaluate experimental agents in real patients.

“Using real-world data to guide key operational decisions is an established reality in the commercial world,” Srini Shankar noted. “RWE can just as readily be applied to individual patients and populations to track drug response, disease progression, safety and other clinical factors in real time.”

He feels accelerated studies should happen under the umbrella of a simplified pragmatic RWE study, in which the data is collected—preferably on an existing drug in the development pipeline with some demonstrated efficacy and tolerable safety profile based on preclinical studies. The clinical data should then be continuously monitored and analyzed, almost in real time, leveraging existing EHR/EMR networks. Data would be analyzed with statistical approaches that are different from what is employed in RCTs, allowing us to react quickly on a large scale, balancing the vital needs of individual patients with the need to collect scientific data about efficacy and safety.

A precedent for this approach already occurred in Germany. The 2011 outbreak of Shiga toxin-producing *E. coli* hemolytic uremic syndrome quickly overwhelmed

hospitals, clinics, dialysis units and other healthcare resources. There were no approved therapies, but an Alexion agent, eculizumab, had a favorable therapeutic profile and acceptable safety.

A coalition of industry, government, researchers, regulators and clinicians created an emergency treatment protocol that began to enroll patients within 24 hours and provide drugs within 48 hours using then-current data collection and analysis techniques, according to Dr. Bock, who led the Alexion team. At the same time, a formal regulatory approved study was prepared. After its initiation in six weeks, the study was back-loaded with accrued patient data and updated daily. Working outside the accepted industry norms and using an experimental agent under controlled, but not randomized, conditions allowed clinicians to curtail and end the crisis in two months.

“Government and regulatory bodies must be included in this kind of program, and the top leadership of the companies be involved because there is a different risk posture than a typical drug development program,” Dr. Bock said.

There have been fragmented attempts to use existing antiviral agents against COVID-19 in places like China, but no coherent global, or even national, experimental use programs. It is possible that existing agents such as Remdesivir (Gilead Sciences), a broad-spectrum antiviral developed to treat Ebola, could be trialed in real time. The National Institutes of Health initiated a randomized clinical trial of Remdesivir in February, but the conventional RCT is not taking advantage of current technology.

#### **Leveraging Technology for Accelerating Therapies to Patients**

“If it is ethical to move ahead in a clinical trial, why isn’t it ethical in an emergency to use that same agent in patients and be very transparent about it?” Dr.

Bock asked. “Technology today gives us the tools that allow us to move ahead and track outcomes in real time.”

One specific technological advancement that might be useful while exploring treatments for vaccines are Patient Reported Outcomes (PROs). In the case of COVID-19, it is believed that the majority of afflicted individuals exhibit mild symptoms and be under self-quarantine. While they may be unable to visit clinics and record clinical data, they can easily use mobile apps for reporting clinical outcomes such as the severity of cough and temperature measurements. Remote monitoring can be orchestrated to support them through this real-time data collection, providing vital data streams for clinical analysis, avoiding the draw site activation and traditional patient recruitment. Mobile apps can be deployed and updated within days, thereby even rendering the RWE study “adaptive,” in addition to real time.

Srini Shankar also believes that a virtual “visual command center” should be created, possibly at the CDC, where data streams from EMR systems and electronic Clinical Outcome Assessment (eCOA) platforms come together from across the globe to provide a real-time assessment of how the infected patient population is reacting to emerging investigational treatments. “Umbrella designs, where new treatments are seamlessly added while ineffective ones are removed, allows you to determine safety and efficacy in real time,” Srini Shankar adds.

#### **Final Thoughts**

As an industry, Srini Shankar, Dr. Palm, and Dr. Bock say we are nowhere near exhausting what’s possible and the boundaries of human imagination in dealing with a crisis of this magnitude and velocity. The answers are within our reach and we have an obligation to act now.