Regulatory Response to Accelerate COVID-19 Drug Development

PEER REVIEWED

Citing concerns of both the alarming levels of spread and severity, and the distressing levels of inaction, the World Health Organization (WHO) declared that COVID-19 could be characterised as a pandemic on 11 March 2020. In response to this, various regulatory bodies – including the Federal Drug Administration (FDA) and European Medicines Agency (EMA) – have issued novel and streamlined guidance, operational processes and best practices designed to accelerate drug product development at this crucial time, given that there is no currently authorised treatment or vaccine.

At the time of writing this, April 10, the FDA has created a special emergency programme for therapeutics known as the Coronavirus Treatment Acceleration Program (CTAP)[1]. This programme attempts to utilise all available methods to shepherd new treatments rapidly along the drug development pathway in an effort to ensure that promising drug products reach patients as quickly as possible, but concurrently ensuring that both efficacy and safety are evaluated as rigorously as possible. The goal of CTAP is to immediately triage upon receipt any requests from drug developers wanting to develop new drug and biologic therapies by connecting them with essential FDA staff, often within a single day. FDA staff will then provide ultra-rapid and iterative input on the development plan with interactions prioritised based on scientific merit, stage of development, and identification as a priority product. This includes an ultra-rapid protocol review that typically occurs within 24 hours of submission. Single patient expanded access requests are also reviewed around-the-clock and generally completed within three hours. Additionally, the FDA will work closely with drug developers and other regulatory agencies to expedite quality assessments for drug products and to transfer manufacturing to alternative or novel locations to avoid any supply disruptions that may occur due to the pandemic.

This heightened support and ultra-fast turnaround times are made possible by the redeployment of medical and regulatory staff to review teams dedicated to COVID-19 therapies. This includes medical, operations, and policy staff to support the overall effort, as well as oversight by senior management. The FDA has also made it easier for healthcare providers and researchers to submit emergency requests to use investigational products for patients with COVID-19, given there has been a huge corresponding increase in the number of emergency use applications and ongoing trials. The FDA remains committed to both enhancing and expanding the CTAP programme and pledges to post summary statistics and link to public information about ongoing clinical trials, in an effort to keep the public updated and to provide summaries of drugs in clinical and preclinical development when legally possible pending confidentiality concerns.

Being acutely aware that many hospitals and academic institutions had already begun initiating studies locally or treating patients as matter of urgency under compassionate use or similar emergency protocols, the EMA has also offered guidance designed to generate robust and interpretable evidence regarding safety and efficacy for drug products designed for the treatment of COVID-19[2]. In a "call to pool EU research resources into large-scale, multi-centre, multi-arm clinical trials against COVID-19", the EMA suggested that randomised controlled trials with a control arm without antivirals or other experimental agents (as none have proven efficacy yet) would supply data that could lead to timely regulatory decisions and best guide clinicians in determining treatment options for patients with COVID-19.

The EMA have also established a task force to take quick and coordinated regulatory action related to COVID-19 medicines[3] that will assist EU Member States and the European Commission in dealing with the development, authorisation and safety monitoring of therapeutics and vaccines intended for treatment or prevention of COVID-19. The main purpose of the COVID-ETF is to draw on the expertise of the European medicines regulatory network and ensure a fast and coordinated response to the COVID-19 pandemic.

Unfortunately, a cursory review of the ever burgeoning number of studies that have recently launched, as seen on clinical trial registries such as https://clinicaltrials.gov/ and other websites such as Covid Trials Tracker[4] and Oxford COVID-19 Evidence Server[5], suggests that many of these studies do not meet these criteria. This is because they have relatively small sample sizes, no control arm without antivirals or experimental agents, or are forms of compassionate use and therefore, are not as likely to be able to generate the required level of evidence to permit sound regulatory and clinical commendations.

The EMA and WHO posit that such studies that are unable to generate an acceptable level of evidence to allow clear-cut recommendations and are not in the best interests of patients. Rather, it is the multi-arm clinical trials investigating several agents simultaneously that have the potential to deliver results quickly across a range of therapeutic options according to the same evaluation criteria. Ideally, all EU countries would be considered for inclusion in such trials and adolescent subjects would at least be considered for inclusion in the large adult clinical trials. Studies of adequate size to assess safety and pharmacokinetics in the paediatric population would also be required.

It is acknowledged that a more coordinated approach across regions is needed to ensure appropriate efforts are geared towards larger multi-country randomised clinical trials that have the potential to generate this level of confirmatory evidence. To answer this call, many drug developers have partnered with private and public agencies/governments to launch large international trials. In fact, four COVID-19 multinational adaptive trials are already underway; one starting with the investigational agent remdesivir, and two with the HIV drug combination of lopinavir-ritonavir. The fourth, known as the Solidarity trial, will compare four treatment options against standard of care in one setting, in order to assess their relative effectiveness of remdesivir, chloroquine or hydroxychloroquine, lopinavir with ritonavir and lopinavir with ritonavir plus interferon beta-1a. Importantly, other drugs can be added based on emerging evidence. By enrolling patients across multiple countries, including Argentina, Bahrain, Canada, France,

Iran, Norway, South Africa, Spain, Switzerland and Thailand thus far, the Solidarity trial aims to discover as rapidly as possible whether any of the drugs slow disease progression or improve survival.

These massive trials demand herculean effort and resources and don't typically permit much flexibility. It may also be possible to gain much-needed information by simultaneously launching new studies that permit the evaluation of multiple drugs (and most are combinations) in a single but relatively smaller study that does not use a factorial type approach to randomisation or analysis. The goal of these types of trials would be to utilise a more efficient and adaptive design that would enhance drug developers' abilities to make comparative decisions very quickly regarding one drug or one combination over another. For example, utilising platform trials should enable drug developers to discover beneficial treatments and combinations with fewer patients, fewer patient failures, less time, and with greater probability of success than a traditional randomised controlled trial which doesn't allow researchers to adapt to the results they are seeing throughout the study[6].

Platform trials can be designed utilising an open master protocol which permits multiple treatments to enter or exit the trial over the course of the study, depending upon ongoing data – thus providing drug developers a chance to adapt to results that are observed throughout the course of the study. This heightened level of flexibility enables developers to drop treatments for futility, to assert certain treatments as superior to others, or add new treatments or combinations of treatments for assessment during a trial as they become available. This also allows developers to better meet the needs of patients within a study.

Another complementary strategy is to utilise various statistical methodologies that permit comparisons amongst studies that do not provide head-to-head evidence from a statistical point of view[7]. According to Kim *et al.*, naïve direct comparisons are in most instances inappropriate and should only be used for exploratory purposes and when no other options are possible. However, adjusted indirect comparisons such as mixed treatment comparisons using Bayesian statistical models to incorporate all available data for a drug can reduce uncertainty. Unfortunately, these techniques have not yet been widely recognised by researchers, or drug regulatory authorities. However this should not discourage drug developers from utilising already known (and if necessary, creating) novel and innovative clinical trial designs and analytic techniques that are efficient, flexible and robust enough in order to address this ongoing crisis in a rigorous and timely manner.

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