Seamless COVID-19 Vaccine Development & Clinical Trials - Regulatory Recommendations & Relaxations

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"The SARS-CoV-2 pandemic has caused unprecedented morbidity, mortality, and economic disruption. Safe, effective, and deployable SARS-CoV-2 vaccines are urgently needed to mitigate the consequences of the pandemic and protect from future outbreaks"[1]. Regulatory agencies United States Food and Drug Administration (US FDA), European Medicines Agency (EMA) and World Health Organization (WHO) have taken steps to facilitate the timely development of safe and effective vaccine and have issued guidance for the industry with respect to the development of COVID-19 vaccine, and conduct of its clinical trials. These guidances and recommendations, also suggest some ways or relaxations which are expected to help the industry in reducing the development & trial time and will facilitate the timely launch of the COVID-19 vaccine.

On June 15, WHO had published a report by the WHO Advisory Group on Human Challenge Studies entitled "Feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental COVID-19 infection and illness in healthy young adult volunteers". This is a draft document and currently open for public comments[2]. Once the final document is published the document is expected to provide detailed guidance on various aspects of conducting clinical trials for the COVID-19 vaccine. In this document "The World Health Organization (WHO) has set forth essential criteria for conducting SARS-CoV-2 challenge studies. Minimizing risk to participants, staff, and the community and ensuring robust scientific and clinical standards are critical considerations"[2]. Last week only, on July 7, WHO also published the "Draft landscape of COVID-19 candidate vaccines" which provides a list of 21 candidate vaccines in clinical evaluation and 139 candidate vaccines in preclinical evaluation stage[3].

In a similar recommendation, the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Vaccines Working Group of National Institute of Health, USA has also proposed CHIMs (Controlled Human Immunization Model) as a strategy for accelerating SARS-CoV-2 vaccine development. However, they have also expressed concern about its applicability because "Currently, we lack sufficient knowledge of SARS-CoV-2 pathogenesis to inform inclusion and exclusion criteria for a SARS-CoV-2 CHIM"[1].

As per another recent document, published by CBER on June 30, entitled "Development and Licensure of Vaccines to Prevent COVID-19 – Guidance for Industry", the US FDA has taken important actions to help facilitate the timely development of safe and effective COVID-19 vaccine by providing guidance with recommendations for those developing COVID-19 vaccines for the ultimate purpose of licensure. "The recommendations described in the guidance are expected to assist the Agency and sponsors in the clinical development and licensure of vaccines for the prevention of COVID-19 and reflect the Agency's current thinking on this issue"[4].

This US FDA guidance[4], provides an overview of the key considerations for regulatory requirements as given in the investigational new drug application (IND) regulations (21 CFR Part 312) and licensing regulations (21 CFR Part 601) with regards to chemistry, manufacturing, and controls (CMC), and nonclinical and clinical data through development and licensure, and for post-licensure safety evaluation of COVID-19 preventive vaccines.

The 160 vaccines[2] currently in the different phases of clinical trials are mostly based on 7 platforms i.e. inactivated, live attenuated vaccine, non-replicating viral vector, RNA, DNA, protein subunits and virus like protein. With regards to the vaccine development the US FDA guidance[4] states that "COVID-19 vaccine development may be accelerated based on knowledge gained from similar products manufactured with the same well-characterized platform technology, to the extent legally and scientifically permissible". These seven platforms, which are already well developed with several vaccines in the market, have formed the basis for development of these 160 vaccines currently in the various phases of clinical trials. This US FDA guidance is likely to ease their process of approval for market authorization proper data regarding the same is submitted.

In terms of manufacturing process data, the guidance states that "Validation data from the manufacture of platform-related products may provide useful supportive information, particularly in the identification of critical parameters". However, there is hardly any change or relaxation in the manufacturing data requirement, to be

submitted in Biologics License Application (BLA) as well as requirement of manufacturing site inspections. With respect to the inspections the document states that "During the COVID-19 public health emergency, FDA is utilizing all available tools & sources of information to support regulatory decisions on applications that include sites impacted by FDA's ability to inspect due to COVID-19"[4].

In regards to the requirement of nonclinical data, the US FDA guidance states that "The extent of nonclinical data required to support proceeding to first in human (FIH) clinical trials depends on the vaccine construct, the supportive data available for the construct and data from closely related vaccines". It also states that in some cases, it may not be necessary to perform nonclinical safety studies prior to FIH clinical trials for which a reasonable rationale must be provided to support the study. Further, to facilitate the vaccine approval, FDA states that "Data from toxicity studies may be submitted as unaudited final draft toxicologic reports to accelerate proceeding to FIH clinical trials with COVID-19 vaccine candidates. The final, fully quality-assured reports should be available to FDA within 120 days of the start of the FIH clinical trial" 4. In addition, the document also provides guidance regarding characterization of the immune response in animal models and studies to address the potential for vaccine-associated enhanced respiratory disease (ERD).

FDA recommends adoption of adaptive and/or seamless clinical trial design in order to expedite clinical development program for COVID-19. In addition to providing guidance regarding conducting trials in emergency conditions, trial population and their safety, trial design, efficacy considerations, safety considerations and statistical considerations the FDA has offered to provide an "early advice, and potentially concurrence in principle, on plans for expedited/ seamless clinical development. However, sponsors should plan to submit summaries of data available at each development milestone for FDA review and concurrence prior to advancing to the next phase of development".

Just a couple of days ago, EMA, on July 9, posted a press release entitled "International regulators align positions on phase 3 COVID-19 vaccine trials" after a meeting of Medical Authorities around the world who met under the umbrella of International Coalition of Medicines Regulatory Authorities (ICMRA)[5] and published a report on "ICMRA SARS-CoV-2 Vaccines Workshop #2"[6]. This workshop was held by teleconference on June 22 and was jointly convened by EMA and US FDA under the auspices of ICMRA. In this workshop, the Medical Authorities of the various countries discussed preclinical and clinical data requirements to support proceeding to Phase 3 clinical trials with SARS-CoV-2 vaccine candidates. In addition, participants discussed concepts of trial design for these studies including trial population, endpoints and statistical considerations.

In the ICMRA report, the key points discussed for Preclinical and clinical data required to support proceeding to Phase 3 clinical trials include requirement of nonclinical safety data, need for inclusion of immune markers of potential enhanced respiratory disease (ERD) outcomes, postvaccination challenge data derived from non-human primates and clinical data of immune response in different age groups. The postvaccination data requirements have been termed desirable and also accepts that this data may not be available at the time of initiation of Phase 3 trials. It is also mentioned that "Proceeding into Phase 3 clinical trials will be determined on a case-by-case basis and depends on the specific SARS-CoV-2 vaccine construct, and the totality of preclinical and clinical data available for this construct. Data from other challenge models, e.g. hamsters, ferrets, transgenic mice, could provide valuable supportive evidence"[6].

Further it is also mentioned that "because pre-vaccination screening for prior infection is unlikely to occur in practice with licensed COVID-19 vaccines, safety and efficacy data in individuals with prior SARS- CoV-2 infection should be collected as well." It can be derived from these statements that the authorities understand that in order to support and facilitate the timely development of vaccine some deficiencies in the clinical data have to be allowed. Therefore, unlike other vaccines, well designed and conceived nonclinical studies are most likely to form the basis for Phase 3 clinical studies for SARS-CoV-2 vaccine which can be seen as a kind of relaxation to facilitate the development of vaccine.

In addition, the study design for Phase 3 clinical trials was also discussed in the meeting and the key considerations have also been outlined. In this teleconference, "It was agreed that the primary analysis for efficacy would be conducted in SARS-CoV-2 naïve subjects". It was also acknowledged that the "Phase 3 studies should be powered to assess the overall vaccine efficacy across subgroups enrolled. It was acknowledged that trials will not be powered to demonstrate vaccine efficacy by subgroup, e.g., age." Further, it was also "acknowledged that initial licensure of SARS-CoV-2 vaccines would likely be in adults". However, the participants agreed that "stringent success criteria to ensure that SARS-CoV-2 vaccines have adequate efficacy should be specified in initial clinical efficacy trials[6].

After going through these recently published documents by

WHO, US FDA and EMA it can be concluded that even though the acceleration of the process of approval and facilitation of development of COVID-19 vaccine is in the thought process but there is no gross relaxation and the authorities are in no mood to compromise in the efficacy of the vaccine and quality of a clinical trial. It has always been conveyed that the patient safety is and will always remain as the prime concern for all regulatory authorities as well as for all the sponsors who look for market authorization of their products. Time will actually tell how much the approval process has actually been eased out and has actually helped in the reducing the trial and approval time for a COVID-19 vaccine. However, the entire WORLD is eagerly WAITING for a COVID-19 vaccine.

References

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