COVID-19 VACCINE SAFETY BRIEFING REPORT

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WHAT HAPPENS AFTER A COVID-19 VACCINE TRIAL SUCCEEDS?

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Vaccine Safety Briefing Report

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1. Introduction (Current state)

As of November 2020, the world has seen upward of 57 million cases and more than 1 million deaths due to the coronavirus pandemic. While cases continue to surge globally, with the United States, India, Brazil, Russia and Colombia reporting the highest cumulative number of cases, all eyes are on the race for a vaccine.

There are multiple large vaccine trials being conducted and approved by regulatory agencies in record time to expedite the process of manufacturing and successfully bringing a COVID-19 vaccine to market. While research and development have primarily been focused on developing an effective vaccine, it's important to remember that safety cannot be compromised. Hence, the long-term safety follow-up of vaccine trial participants and post-marketing surveillance becomes crucial.

In November, Pfizer and BioNTech announced a successful vaccine candidate against COVID-19 based on results from a first interim analysis of their phase 3 study. A recent final analysis showed that the vaccine was 95% effective in preventing infections, even in older adults. Emergency Use Authorization (EUA) to the U.S. Food and Drug Administration (FDA) was submitted in the third week of November, and conditional marketing authorization to the European Medicines Agency (EMA) was submitted in December.

Alongside Pfizer and BioNTech, Moderna announced a successful vaccine candidate with their interim phase 3 analysis, citing their vaccine was also 95% effective in preventing disease. Moderna plans to submit for EUA to the FDA in the coming weeks.

Globally, two vaccines, Sputnik V and EpiVacCorona, were approved by the Ministry of Health of the Russian Federation, but they have not yet entered phase 3, meaning that the vaccines were approved without any clinical trials for safety evaluation.

The World Health Organization (WHO) aims to enroll more than 280,000 participants from at least 470 different sites in 34 countries for vaccine candidates. In looking at these candidates, it's likely that two doses of a vaccine will be required, meaning that at least 16 billion doses will be needed to meet global demand.

The safe production and equitable distribution of a COVID-19 vaccine will present unprecedented challenges to the life sciences industry. From logistical challenges, like keeping the Pfizer vaccine at minus 75 degrees Celsius (minus 103 degrees Fahrenheit), to considerations around insurance coverage and out-of-pocket costs, the mass distribution of a vaccine will be a serious undertaking, requiring agility, collaboration and speed.

2. U.S. and Global Regulatory Requirements

Below is a brief overview of the regulatory guidelines issued by the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA) and the Central Drugs Standard Control Organization (CDSCO) in India.

2.1 U.S. Food and Drug Administration (FDA):

In June 2020, the FDA released guidance that they would approve a vaccine with less than 50% efficacy, but no such short cuts are accepted in safety evaluation. The FDA revised their guidance in October, as summarized below.

The FDA issued the "Emergency Use Authorization (EUA) for Vaccines to Prevent COVID-19" under section 564 of the FD&C Act (21 U.S.C. 360bbb-3), which allows for rapid and widespread deployment of the vaccine for administration to millions of individuals. With assurance of adequate manufacturing information to ensure quality and consistency with issuance of an EUA, the FDA determined that the vaccine benefits outweigh its risks based on data and a well-designed phase 3 clinical trial.

The FDA's routine vaccine reporting requirements (CDC programs included below):

- Healthcare providers are required to report vaccine-related adverse events (AE) via VAERS.
- Adverse events listed by the vaccine manufacturer are a contradiction to further doses of the vaccine.

2.2 European Medicines Agency (EMA):

The EMA has set up the multidisciplinary COVID-19 Task Force (ETF), bringing together key experts from across the European medicines regulatory network to ensure a fast and coordinated response to the pandemic and to reduce the review timelines to provide approvals (e.g., 20 days instead of 120 days for vaccine manufacturers by EMA).

2.3 Central Drugs Standard Control Organization (CDSCO):

The regulatory authority of India, CDSCO, released draft guidance on 21 Sep 2020. This guideline covers development, manufacturing, efficacy and safety requirements of COVID-19 vaccines. The guidance is summarized below.

Table 1 Regulatory Requirements – Case study

	Pre-market authorization requirements	Post-market authorization requirements
FDA (US)	Safety Data required at submission: • Discussion of risks and benefits with any steps taken to mitigate risk or optimize benefits • Recommended restrictions to ensure safe use (if applicable) • Situations when product should not be used (contradictions) • A plan for active follow-up for safety • Data from phase 3 studies should include a median follow-up duration of at least 2 months after completion of full vaccination regimen • SAEs and events of special interest followed at least 1 month after full vaccination regimen	• Expanded safety monitoring systems have been developed by the CDC for all vaccines. • A SmartPhone app (V-Safe) has been developed for post-vaccine health. The app will connect with vaccine recipients to track health problems following COVID vaccination.
EU	Core RMP requirements for COVID-19 vaccines are required (coreRMP19). • Comparisons of reactogenicity of the vaccine vs. the control group • Considerations for antibody-dependent enhancement • High reactogenicity and subgroups of the "frail" and risk of flares in patients with chronic inflammatory conditions • Differences in reactogenicity with a second (or subsequent) dose should be discussed • Formulation and preparation of the vaccine should be discussed when they may increase the risk of ADRs (e.g., a formulation where a diluent for reconstitution needs to be added may affect sterility, leading to clinical reactions such as increased local reactions) • In case two (or more) doses are recommended, the risk of vaccine drop-out (e.g., due to reactogenicity) should be evaluated as well as the risk of disease enhancement • Any early signal from clinical trials should be adequately documented and discussed in this section • The relevance of the long-term follow-up should be discussed, and adequate pharmacovigilance activities should be considered	• For COVID-19 vaccines, MAHs will be expected to submit monthly summary safety reports in addition to regular PSURs/PBRERs. These will include, among others, information on reported suspected adverse reactions, including adverse events of special interest (AESIs), and sales data. • A timely availability of aggregated exposure data for each COVID-19 vaccine will be essential for several pharmacovigilance activities, including observed-to-expected analyses, ensuring to collect information on individual vaccinations. • Post-authorization studies (PASS) will be considered routine activities. • The ACCESS project (vACcine covid-19 monitoring readinESS) - focuses on data sources and epidemiological methods to monitor safety, effectiveness and coverage of COVID-19 vaccines. The project involves 22 research centers throughout Europe. • Management of signals for COVID-19 vaccines may be shortened for discussion at PRAC meetings.
CDSCO (INDIA)	Adequate data, including data to inform the potential risk of vaccine-associated Enhanced Respiratory Disease (ERD) will be needed. • Unsolicited adverse events in all study participants for at least 21–28 days after each study vaccination • Serious and other medically attended adverse events in all study participants for at least 6 months after completion of all study vaccinations • All pregnancies in study participants for which the date of conception is prior to vaccination or within 30 days after vaccination should be followed for pregnancy outcomes, including pregnancy loss, stillbirth and congenital anomalies	• Solicit local and systemic adverse events for at least 7 days after each study vaccination in an adequate number of study participants. • Longer safety monitoring is warranted.

3. Treatments Currently in Use: Approved and Unapproved

Treatments that are available for COVID-19 are also under observation for safety and efficacy, as the approvals were given based on limited data considering the pandemic situation.

The treatment is focused on symptomatic management.

Approved treatment	Unapproved (Off-label use)
EMA and FDA have approved one drug, remdesivir, for COVID-19 in adults and children who are age 12 and older.	Corticosteroids, Vitamin C, Dexamethosone in mild/ moderate COVID-19, any other vitamins
EMA is endorsing the use of dexamethasone in adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy.	Hydroxychloroquine and chloroquine
• To manage symptoms like any viral respiratory infection – acetaminophen, oxygen, fluids for dehydration. Supplemental oxygen and mechanical ventilatory support in severe cases.	Lopinavir, ritonavir favipiravir and merimepodib
• Blood plasma from people who've recovered from COVID-19 in order to help patients with severe or life-threatening cases. • Bamlanivimab.	Mesenchymal stem cells and monoclonal antibodies – tocilizumab

4. Challenges to Address:

Pre-market authorization challenges	Post-market authorization challenges
Supply and logistics of delivering doses (e.g., see below): 1. Maintaining the cold chain necessary for vaccine supply and distribution 2. Affordability	Operational considerations for long-term monitoring (e.g., see below): 1. Collecting data via virtual modes post-vaccination, VSafe app, telephonic follow-up 2. Analysis of data at faster speeds for real-time decisions for safety purposes 3. Communication of safety concerns to patient, healthcare professionals in timely manner and in effective way (virtual mode-online webinar, social media vs HCP letters, seminars in past)
Operational considerations for long-term monitoring of clinical trials from recruiting and monitoring considering managing with remote/virtual and social distance rules in place.	Data collection for vaccines can vary based on vaccine type for collecting information (e.g., see below): 1. type of vaccine, injection dates 2. onset of AEs (if any), type of AE (MedDRA coding) 3. immunological responses that would need in-depth expertise
Market access/availability (e.g., see below): • How to comply with the government/regulatory requirements for distribution and eventual administration	Compliance: • Monitoring safety data in real time (as it is received) for signal/trending analysis and taking action to communicate and mitigate this signals/risks

Possible Approaches and Solutions

Key to the success of COVID vaccine safety will be the speed and accuracy of the collection and analysis of the volume of safety data that will be coming in post-authorization for the expected risk management requirements to the regulatory authorities.

Considerations across data collection and analysis include:

Data Collection/Processing

5.1 Enabling technology to ensure faster, effective and cost-beneficial analysis of data.

- Possibility of app development for patient reporting of AEs specifically for COVID vaccine

5.2 Providing call center support for medical information for patients and healthcare providers to ensure collection of post-marketing data.

5.3 Possibility of patient registries for long-term safety and efficacy follow-up.

5.4 Providing support for pharmacovigilance end-to-end case processing of long-term follow-up.

5.5 Compliance:

- Excellent understanding of regulatory compliance requirement from pre-clinical to post-marketing
- Timeline adherence despite large volumes of data

5.6 Quality-driven processing for patient safety needs and real-time data analysis to enable actions to change vaccine safety communication content to HCP and patients.

Data Analysis

5.7 End-to-end vaccine development to distribution support including post-marketing surveillance and analysis to monitor/mitigate safety risks.

5.8 Signal detection activities to monitor and develop mitigation strategies for identified signals.

5.9 Consider advanced signal analysis via data analytics approach that utilizes external data sources such as electronic health records and/or claims data, and possibly even genomic data, for a risk mitigation approach of potential adverse events.

5.10 Aggregate report writing to comply to regulatory requirements and to ensure these activities provide an additional layer to identify signals.

5.11 Clinical documents to ensure faster and effective data for analysis and approval of vaccines.

- As close to real-time data analytics and subsequent analysis of safety data by demographics (age, gender, co-morbidities, concomitant medications).

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