CONSIDERATIONS FOR CLINICAL SAFETY EVALUATIONS OF NEW COVID-19 VACCINES

Rebecca Reindel, M.D.
Acting Senior Advisor
FDA-CBER-OVRR-DVRPA
My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.
Timeline for Adverse Event Assessments

After each dose:
- Day 0
- Day 7/14
- Day 21/28

Solicited local and systemic adverse events

Unsolicited adverse events

After last dose:
- Month 6
- Year 1+

Serious and other medically attended adverse events (including severe COVID-19 as long as feasible, ideally 1-2 years)

Longer safety monitoring may be warranted for certain vaccine platforms (e.g., those that include novel adjuvants)

Pregnancy outcomes, including pregnancy loss, stillbirth, and congenital anomalies
Safety Analysis Populations

Pre-licensure safety database of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure

- Solicited local and systemic adverse events: Adequate number of study participants to characterize reactogenicity (including at least a subset of participants in late phase efficacy trials)
- Unsolicited adverse events: All participants
- Serious and other medically attended adverse events
- Pregnancy outcomes: At a minimum, pregnancies with conception prior to vaccination or within 30 days after vaccination
For novel adjuvants or novel adjuvant-antigen combinations, we request collection of MAAEs through 12 months or longer following the last study vaccination, due to the theoretical potential for induction of autoimmune or auto-inflammatory diseases. We also request that analyses of these events include a MedDRA query using the Immune-mediated/Autoimmune disorders Standard MedDRA Query (SMQ).

- COVID-19 vaccine-associated enhanced disease (VAED)
  - Evidence to date with Spike antigen-based vaccines has not corroborated this concern, but more experience is needed to assess whether VAED would be a risk associated with vaccines based on (or including) other antigens
  - Ongoing safety analyses and hold criteria for imbalances in severe disease
  - Use of an independent data safety monitoring board (DSMB) for vaccine-associated enhanced disease and other safety signal monitoring, especially during later stage development
- Safety assessments in subgroups with prior infection
## Pediatric considerations

### Size of safety database and duration of monitoring
- Overall safety database should be at least ~3,000 vaccine recipients
- Adequate representation across age groups (e.g., 12 to <18 years, 6 to <12 years, 2 to <6 years, and 6 months to <2 years)
- Supplemented with available safety data from clinical trials and post-marketing use in older age groups
- Duration of safety monitoring similar to that for adults

### Age-specific risks
Type, severity, and frequency of adverse reactions may differ across age groups

### COVID-19 specific
- COVID-19 vaccine-associated enhanced respiratory disease (ERD)
  - Similar concerns as for adults
  - Monitoring for MIS-C
Follow Up Duration Considerations for EUA

Median follow up duration of at least 2 months after completion of the vaccine(s).

High proportion of the safety population (>3,000 vaccine recipients) followed for at least one month after completion of the vaccination regimen.
Post-marketing surveillance

Post-authorization/marketing active and passive safety surveillance required to further characterize safety profile

- Post-licensure/authorization studies conducted by:
  - the manufacturer as requirements or commitments
  - public health authorities
- Ongoing monitoring and surveillance of post-marketing safety databases

Robust post-marketing surveillance led to rapid identification of infrequent serious risks
(e.g., GBS, TTS, and ITP for adenoviral-vectored COVID-19 vaccines and myocarditis for mRNA COVID-19 vaccines)