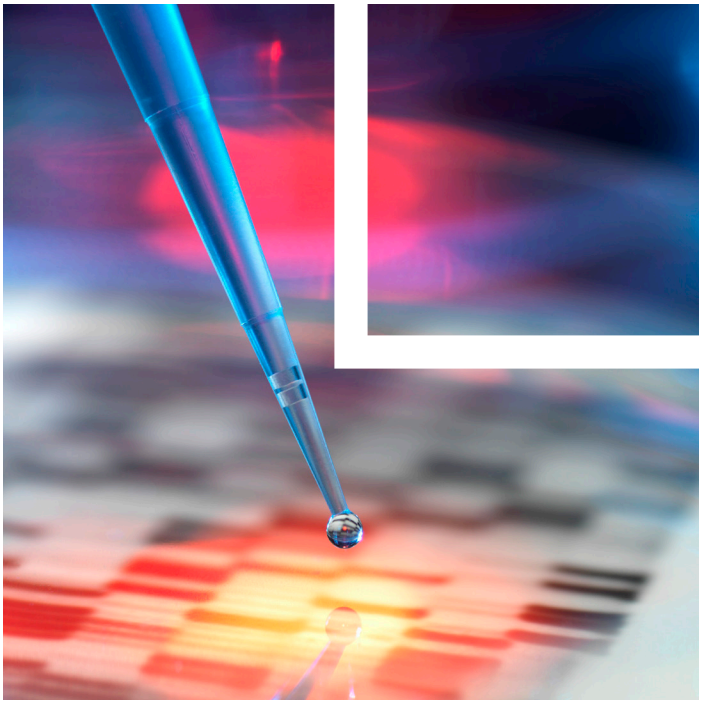
FDA Regulatory & Compliance Monthly Recap
October 2020



FDA issues guidance on EUAs for COVID-19 vaccines

The FDA issued a guidance providing recommendations to sponsors requesting Emergency Use Authorization (EUA) for COVID-19 vaccines. The document offers recommendations regarding the data and information required to support an EUA issuance for a COVID-19 vaccine. Additionally, the guidance provides recommendations regarding critical information and data submitted on an investigational new drug application (IND) or cross-referenced master file before EUA submission. Finally, the guidance explores the agency's current position regarding the appropriate circumstances under which a COVID-19 vaccine would receive an EUA.

According to the guidance, sponsors seeking an EUA for a COVID-19 vaccine should contact the Center for Biologics Evaluation and Research's (CBER) Office of Vaccines Research and Review (OVRR) as early in the development process as possible to discuss expectations and considerations for that sponsor's potential vaccine. Prior to submitting an EUA request, sponsors should provide the FDA with a detailed description of the chemistry, manufacturing and controls information, and data should be submitted to a relevant IND or cross-reference master file a minimum of one month prior to an EUA request. The agency also strongly urges sponsors to provide it with notice 24 hours after completing any interim analysis upon which the EUA submission request is based.

The EUA request should include a description of the product and its intended use, safety and effectiveness information, a risks and benefits discussion, a listing of any approved alternative products and their availability, a description of the product's FDA approval status, and supply chain information. The EUA request should include information and data on chemistry, manufacturing and controls, as well as a list of each site where the product is or would be manufactured. This information includes a minimum of three process performance qualification lots per manufacturing facility, as well as validation of critical process parameters and in-process controls of specific unit operations. Evidence that all drug substance and drug product manufacturing sites have been properly validated is also required.

The EUA request should also include safety and effectiveness information, including the diagnostic bioassays used to assess study endpoints for clinical studies in support of the EUA. In addition, a list of nonclinical studies in support of the vaccine should also be included, along with timelines for study completion and final study reports, as well as a final study report for a developmental and reproductive toxicology study, if available. The FDA is also requiring the inclusion of Phase 3 clinical studies, which should include a median follow-up duration of at least two months after completion. Safety and COVID-19 outcomes in individuals with prior SARS-CoV-2 infection who may have been asymptomatic are also vital because it is unlikely that screening for prior infection would occur before administration of COVID-19 vaccines under EUA.

Finally, the guidance notes that the availability of a COVID-19 vaccine under EUA was not grounds for stopping blinded follow-up in ongoing clinical trials. EUA requests should include potential strategies to ensure ongoing clinical trials are able to assess long-term safety and efficacy. Such strategies should explore how ongoing trials will deal with the loss of follow-up information for study participants choosing to withdraw from the study.

FDA issues guidance on postmarketing requirements for drug, biologic manufacturers

The FDA issued a draft guidance regarding its postmarketing requirements (PMRs) and commitments. The guidance outlines the ways in which drug and biologic marketers can use forms FDA 3988 and 3989 for submitting annual status reports and other postmarketing information online. These forms allow applicants to report to the agency the status of PMRs and postmarketing clinical trials (PMCs). Additionally, the document provides information on how to include the forms in the electronic common technical document (eCTD) for new drug applications, biologics license applications, investigational new drug applications and abbreviated new drug applications.

The guidance provides marketers with instructions on when and how to use both Forms FDA 3988 and FDA 3989. According to the FDA, Form FDA 3988 should accompany each PMR/PMC-related submission, including, but not limited to, any submission related to PMR and PMC draft and final protocols, interim reports, final reports, general correspondence, requests for Pediatric Research Equity Act deferral extensions, responses to information requests, and revised milestone requests. When submitted, the form should be included on the eCTD in the "Forms" section or, if the applicant's eCTD publishing tool does not include such a section, in the "Cover Letter" section.

Form FDA 3989 can be used to replace the Status of Postmarketing Study Commitments and Requirements content in the eCTD. Additionally, the annual submission of Form FDA 3989 will meet the reporting requirements for postmarketing studies or clinical trials described in Section 506B of the FDCA. If an applicant chooses to use the form, the applicant should submit it instead of adding a company-derived status update document in the eCTD. Additionally, if opting to submit Form FDA 3989, applicants must complete Form FDA 2252 as well.

The FDA noted that while the use of these forms is entirely optional, applicants must submit them electronically if they choose to use them. Furthermore, the agency stressed that providing complete and accurate information on the forms will help expedite routing of submission for FDA review and any follow-up.

FDA issues guidance regarding endpoint considerations for OUD treatments

The FDA issued a final guidance regarding endpoints for new medications designed to treat opioid use disorder. The document was intended to assist sponsors developing drugs for the treatment of OUD and address critical endpoints considered by the agency to be acceptable for demonstrating the effectiveness of those treatments. The guidance also provides general considerations for selecting study populations, and outlines desirable endpoints for study. Also included are considerations for designing trials using a patient-reported outcome instrument.

The guidance highlights a number of possibilities for sponsors to use as critical endpoints for medications to treat OUD. Sponsors may study several of these endpoints in the same trial while selecting one as the primary endpoint or by selecting one or more as secondary endpoints. Additionally, sponsors can combine outcomes into a composite endpoint. These include:

- **Reduction in adverse outcomes**: These can include overdose mortality and overall mortality, as well as need for emergency medical interventions and hepatitis C virus infections or reinfection. Sponsors can also propose other adverse outcomes and use them as either primary or secondary endpoints.
- **Change in disease status using diagnostic criteria for OUD**: If all trial patients meet the criteria for moderate to severe OUD outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), at baseline, sponsors can use the proportion of patients meeting the DSM-5 criteria for remission at the end of the trial as a primary or secondary efficacy endpoint.
- **Change in drug use pattern**: This is the most commonly used endpoint in registration trials for OUD treatment drugs in development. The agency recommends sponsors compare percentage of responders rather than group means when determining patterns. Abstinence is a commonly used definition for a responder, but sponsors may employ other drug use patterns to define OUD treatment response. When proposing other drug use patterns to define clinical response, sponsors should specify how they intend to measure the change in drug use patterns.
- **Patient-reported outcomes**: Sponsors can develop a patient-reported outcome instrument to evaluate a direct effect on how patients feel or function, such as improvements in sleep or mood. Sponsors can also use this approach to develop a means to measure the intensity of the urge to use opioids. Such outcomes could be used as a secondary endpoint in trials that focus on behavioral changes as a primary endpoint.

When selecting an endpoint to demonstrate the efficacy of a particular product, sponsors should be aware that a product's demonstrated benefit will be evaluated against its risks under the FDA's approval standards. Furthermore, if the product itself has abuse potential, the agency will consider the public health effects of the drug, such as risk of diversion and the potential effects on risks to both patients and nonpatients. These risks can include those related to misuse, abuse, OUD, overdose and accidental exposures.

FDA updates guidance on conducting clinical trials during COVID-19 pandemic

The FDA issued an updated guidance on conducting clinical trials of medical products during the COVID-19 public health emergency. Despite the increased volume of investigational new drug (IND) safety reports during the pandemic, the guidance states the review of safety reports remains a vital part of the investigator's role in clinical trials' safe conduct. In all cases, IND safety reports must go to the FDA and to all investigators if it is determined an adverse event (AE) is serious and unexpected and there is a possibility the drug caused the event. Further, when deciding whether an AE should be reported, investigators should consider whether the event constituted an unanticipated problem that involves risk to human subjects or others. Additionally, if serious AEs meet the criteria for safety reporting for an IND-exempt bioavailability/bioequivalence study, they generally will meet the threshold of unanticipated problems involving risk to human subjects or others and should immediately be reported to the internal review board (IRB).

The guidance is in response to the unique threat posed by COVID-19 and is intended to ensure the testing of medical products continues to be conducted in a timely, rigorous and safe fashion during the public health emergency. The FDA acknowledges the pandemic will have a negative impact on clinical trials, with issues like quarantines, site closures, travel limitations and interruptions to supply chains likely to occur. To counter this and to provide sponsors with flexibility to conduct trials whose protocols may need to be modified because of COVID-19-related impacts, the FDA outlined recommendations that fall under considerations for ongoing trials, both in general and if policies and procedures are not already in place for applicable trials, as well as for all trials that are impacted by the COVID-19 public health emergency.

Under the guise of ensuring the continued safety of participants during clinical trials, the FDA explains that during ongoing trials, sponsors should be cognizant that specific circumstances could lead to modifications to trial recruitment, trial continuance or patient monitoring protocols. Whatever decisions are made, it is paramount to inform participants of any change to the trial. The decision-making process should include input from the sponsor, IRBs and independent ethics committees (IECs) and will likely be dependent on factors like the investigational product, safety monitoring, the potential impact of the circumstances on the investigational product supply chain, and the nature of the disease under study. In the absence of on-site monitoring or dosing, the FDA says sponsors will need to implement alternative safety protocols that could include remote technology or the use of off-site labs or imaging centers. Sponsors also must consider whether in-person visits are necessary to continue the access and use of the investigational product and whether safety monitoring should continue even if the decision is made to discontinue access to the investigational product.

The FDA states sponsors need not report COVID-19 screening procedures mandated by health care systems hosting trials as an amendment to the protocol unless the data collected is part of a new research objective. While it is desirable for sponsors to consult with the IRBs, IECs and/or FDA before modifying trial protocols, the FDA admits that may not be practicable to safeguard participants and directs sponsors to report on any deviations. Changes attributable to COVID-19 should be documented, including any impacts to design and participants, with a listing of contingencies that were enacted and their rationales in a clinical study report or in a separate study-specific document. Specific missing data relating to COVID-19-related disruptions to the trial should be included in the case report form. If changes in the protocol lead to amended data management and/or statistical analysis plans, sponsors should address how protocol deviations related to COVID-19 will be accounted for in the final analysis. In devising protocols for new investigational product trials, sponsors, clinical investigators and IRBs should develop modifications to policies and procedures that could be implemented to mitigate possible effects of COVID-19 on the trial and its participants. Changes to the informed consent process, data collection, monitoring, and AE reporting related to travel restrictions, quarantining or the outbreak itself should be anticipated.

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