FDA Regulatory & Compliance Monthly Recap
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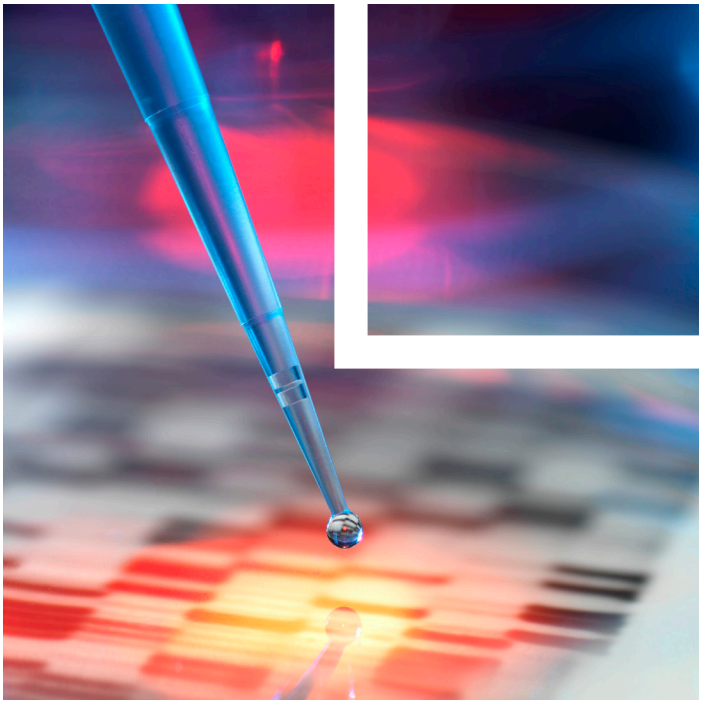

FDA finalizes first guidance as part of patient-focused drug development initiative

The guidance, published as a draft in June 2018, discusses the collection of comprehensive and representative patient input. It outlines a stepwise approach through which stakeholders can collect and submit patient experience data for medical product development and regulatory decision-making.

As part of its efforts to make drug development and review more patient-centered, the FDA finalized the first in a series of four guidances as part of its Patient-Focused Drug Development (PFDD) initiative. The guidance documents, which are part of the FDA's mandate under the Prescription Drug User Fee Act VI, will provide input on methods that may be used to solicit patient perspectives. The first guidance document outlines sampling methods that may be used to collect information on patient experience that is representative of the intended population, as well as methods to operationalize and standardize the collection, analysis and dissemination of such data.

The guidance defines patient experience data as data about the experiences, perspectives, needs and priorities of patients related to the signs and symptoms of a disease; the course of a disease over time; treatments; potential disease or treatment outcomes; the impact of the disease, treatment and outcomes; and potential trade-offs between outcomes and treatment benefits and risks. In the context of medical product development, the patient experience incorporates the patient journey through the course of their disease, including views, feelings, needs, actions, preferences and interactions related to the disease and its treatment. As such, patient experience data may be collected throughout product development, from early development to the precompetitive setting. The guidance notes that patient experience data needs to not only be relevant, objective and accurate but also representative of the target population. It outlines factors to consider to ensure sufficient representation, including socioeconomic and demographic background, cultural background

and spoken language, literacy and health literacy, and clinical characteristics such as severity of disease and comorbidities.

Different methodological approaches, including qualitative, quantitative and mixed methods, may be appropriate for collecting robust and meaningful patient experience data. Since the level of rigor needed may vary across studies, the guidance recommends that stakeholders engage with the FDA early to determine which approach should be used. The FDA cautions that sponsors need to carefully design study enrollment criteria to properly select the target patient population. For the collection of patient experience data, the agency recommends direct reports from patients unless they are not able to reliably report on the concept of interest. In instances in which direct reports from patients may be limited, alternatives to patient-reported outcome measures may be needed. The guidance also notes that depending on the type of patient experience data, different content and formats may be needed to submit data. At a minimum, the FDA expects sponsors to provide a study report and protocol when submitting patient experience data, along with information about the primary data capture.

Other guidance documents in the PFDD series will address:

1. Methods for gathering information from patients about their symptoms, impacts of their disease and other issues important to them, including best practices for qualitative research, such as interviews and surveys. It will also address what to ask patients and how to do so in a nonleading way.
2. What should be measured in medical product development programs to demonstrate clinical benefits and how to identify and develop fit-for-purpose clinical outcome assessments (COAs) to investigate outcomes important to patients.
3. The development and interpretation of COA-related end points. It will also address the incorporation of COA tools into defined clinical study end points.

FDA issues guidance on statistical considerations for clinical trials impacted by COVID-19

The guidance discusses statistical considerations for proposed changes to trial conduct to ensure interpretable findings with correct statistical quantification of uncertainty. The guidance recommends that sponsors engage with relevant FDA review divisions when considering protocol changes and modifications to the statistical analysis plan that may impact the analysis and interpretation of end points.

Recognizing that the COVID-19 public health emergency may impact the ability to collect data, the FDA issued guidance on statistical considerations to mitigate the impact of the pandemic on meeting clinical trial objectives. The FDA outlines considerations for the statistical analysis of primary and key secondary end points to ensure results are interpretable and have the proper statistical quantification of uncertainty.

The guidance calls on sponsors to proactively plan to address the impact of COVID-19 on the ability to meet trial objectives. When considering changes to the trial to mitigate the impact of the pandemic, the FDA cautions that modifications should not be proposed based on data that may introduce bias into the interpretation of trial findings. The guidance explains that any trial modifications, including original planned analyses, should not be based on data that reveals information on the treatment effect. The guidance explains that appropriate participant data to consider when making changes to the trial includes:

- Summaries pooled over treatment arms, including information on missing data
- Participant treatment discontinuation or interruption
- Participant trial withdrawal
- End points

In addition, sponsors may consider information not specific to individual participants, such as site closures or a disruption in the supply of the investigational product.

The FDA explains that multiple strategies may be needed to address the impact of the pandemic on evaluating primary and secondary end points. As such, sponsors should discuss design and analysis strategies with the

relevant FDA review divisions. The guidance warns that a major consideration for sponsors considering stopping a trial and conducting a final analysis is the loss of statistical power. Halting a trial earlier than anticipated or adding interim analyses to the trial may impact the statistical inference. The FDA explains that adjustments to the definition and ascertainment of trial end points may be warranted to address the impact of the pandemic on trial integrity. However, the impact of any change in end point or ascertainment should be carefully assessed in sensitivity analyses and should be discussed with the FDA.

The guidance will remain in effect for the duration of the public health emergency.

FDA implements new compliance program for CDER-/CDRH-led combination product inspections

The new program outlines the FDA's approach to inspections of Center for Drug Evaluation and Research (CDER)- and Center for Devices and Radiological Health (CDRH)-led combination products, with an emphasis on single-entity and copackaged products with drug and device or biological and device constituent parts. The guidance addresses the use of a streamlined compliance approach leveraging specific "called-out provisions."

The FDA implemented a new compliance program to guide its inspections of CDER- and CDRH-led combination products under which combination product makers may demonstrate compliance with Current Good Manufacturing Practice (CGMP) regulations using a streamlined approach. The compliance program focuses on single-entity combination products, in which the constituent parts are physically or chemically combined, and on copackaged combination products, in which the constituent parts are packaged together. The compliance program applies to pre- and post-approval inspections, as well as to surveillance, for cause and other risk-based inspections. It does not apply to Center for Biologics Evaluation and Research-led combination products, nor to facilities that make only one type of constituent part or that manufacture only device components.

Combination product makers may demonstrate compliance with CGMP requirements in one of two ways: 1) by complying with all applicable CGMP regulations for each constituent part or 2) by using a streamlined approach by demonstrating compliance with either the drug CGMP or the device Quality System Regulation, in addition to specific called-out provisions from the other set of requirements. The compliance program delineates the specific called-out provisions for both drug- and device-led combination products that manufacturers must adhere to when using the streamlined approach. For cross-labeled combination products manufactured at the same facility, the FDA does not intend to object to the use of a streamlined CGMP operating system rather than distinct systems for each constituent part. Irrespective of whether a streamlined approach is used, makers of combination products that include a biological product must demonstrate compliance with all applicable CGMP requirements for biological products.

Under the compliance program, inspectional and administrative practices of the lead center and base compliance program will serve as the foundation of a combination product inspection, though commodity-specific compliance programs based on the constituent parts will also be used to guide the conduct of inspections. When appropriate, the lead center will communicate any specific products for coverage or focus for the inspection. A single establishment inspection report (EIR) and Form FDA 483, when applicable, should be used for all observations during an inspection of a combination product manufacturer. Documentation of the inspection should align with the reporting requirements of the base compliance program. The EIR should also include information on the CGMP operating system in use for the combination product, a description of the manufacturing activities, and evidence and samples needed to support each observation.

The FDA acknowledges that certain audit and inspection programs, including third-party audits or the medical device single audit program, may impact implementation of the compliance program.

FDA publishes guidance on IRB review for expanded access requests during COVID-19

The guidance provides direction to institutional review boards (IRBs) during the COVID-19 outbreak in response to the increase in the number of requests by physicians looking to treat patients with investigational drugs under the FDA's individual patient expanded access (EA) pathway. It is intended to provide clarity to IRBs on key factors and procedures to consider when reviewing individual patient EA submissions.

In response to the notable increase of individual patient EA requests for COVID-19 investigational drugs, the FDA issued guidance for IRBs to provide clarity on key factors and procedures to consider when reviewing such submissions. Under current FDA regulations, there are three categories of EA investigational new drug applications (INDs) available: individual patient INDs, including for use in emergencies; intermediate-size INDs; and "treatment" INDs for larger populations. This guidance does not address IRB reviews of intermediate- or treatment-sized populations and is intended to address only individual INDs. The reason is that larger-sized EA requests generally focus on potential risks and benefits to an entire population of patients rather than the potential risks and benefits to an individual patient.

Individual patient EA requests are submitted to the FDA by a licensed physician after they have been reviewed and approved by an IRB. When reviewing an EA request for an individual patient, the IRB should focus on key factors needed to assess the risks and benefits of treatment for the specific patient involved. The guidance recommends that IRBs implement procedures for a single member to review an EA submission for an individual patient if a physician requests a waiver of a full review. These procedures should reflect information deemed by the IRB as relevant for a single-member review and should include procedures designed to ensure that the decision is properly documented.

The guidance also outlines key factors that should be considered by an IRB when reviewing an EA request, including:

- The proposed daily dose, route and frequency of administration; duration of planned treatment; criteria for discontinuation of treatment; and planned dose modifications for adverse events
- The planned monitoring for adverse events, response to treatment and changes in clinical status, as well as proposed modifications to the treatment plan to mitigate risks to patients, if appropriate
- Key details of the patient's history, including diagnosis and summary of prior therapy (including response to such therapy), as well as information regarding a patient's relevant clinical characteristics (such as comorbid conditions and concomitant medications) that are necessary to assess the potential for increased risks of the drug
- A summary of the known risks of the drug

The guidance will remain in effect until the end of the ongoing COVID-19 public health emergency.

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