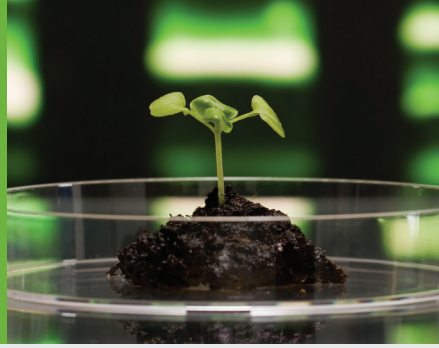
FDA Regulatory and Compliance Monthly Recap



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FDA publishes draft guidance on demonstrating substantial evidence of effectiveness for drugs, biological products

The FDA published draft guidance detailing what evidence is needed for applicants to show effectiveness for NDAs, BLAs and supplemental applications. The document reflects efforts to add some flexibility regarding what qualifies as "substantial evidence" for demonstrating effectiveness, especially as it pertains to emerging programs studying diseases that lack effective treatments or rare disease or disease subsets.

The FDA issued draft guidance stipulating what evidence needs to be provided to demonstrate effectiveness for new drug applications (NDAs), biologics license applications (BLAs) and supplemental applications. The draft builds on guidance issued in 1998 to address provisions under the Food and Drug Administration Modernization Act of 1997 that added some flexibility as to what evidence was needed to support effectiveness. The draft clarifies that the substantial evidence requirement for effectiveness could be met by a single trial along with confirmatory evidence instead of requiring two adequate and well-controlled trials.

The draft discusses other characteristics of the evidence supporting effectiveness that can vary, including trial designs, endpoints and statistical methodology. While the FDA's evidentiary standard for effectiveness hasn't changed, the guidance is meant to address the evolution of drug development and science by allowing for some flexibility in the amount and type of evidence needed to meet the substantial evidence standard in a given development program. It references emerging programs studying serious diseases that lack effective treatments, as well as programs targeting rare diseases or disease subsets. The draft indicates that additional FDA guidance is needed on flexibility in the amount and type of evidence needed to meet the substantial evidence standard in these circumstances.

The guidance says the "substantial evidence" of effectiveness standard refers to both the quality and the quantity of the evidence. It explains that the quality of clinical evidence to establish effectiveness is impacted by the type of trial design, trial endpoints and statistical considerations. It states that all clinical investigations supporting effectiveness should be of high quality and appropriate design (i.e., adequate and well controlled). The FDA notes that a finding of substantial evidence of effectiveness is insufficient for approval, as an approval decision also necessitates a determination that the drug is safe for its intended use. Assessing whether a drug is "safe" involves considering whether its benefits outweigh its risks under the conditions of use defined in the labeling.

The draft also expands the 1998 guidance's discussion around the types of mechanistic and pharmacologic evidence and nonclinical evidence that can amount to confirmatory evidence. The 1998 guidance's examples of the types of evidence considered confirmatory focused on adequate and well-controlled trials of the test agent in related populations or indications, as well as illustrations of a well-controlled trial supported by evidence of the drug's mechanism of action in treating a disease or condition. The guidance details the quantity of evidence required in a given development program, such as providing two adequate and well-controlled trials, providing one adequate and well-controlled trial coupled with confirmatory evidence, or using a previous finding of effectiveness of an approved drug when legally allowed and scientifically justified. It also expands on the 1998 guidance's discussion on the types of pharmacologic, mechanistic and nonclinical evidence that can be considered confirmatory evidence.

To help sponsors understand which trial design will be considered acceptable in various development programs, the guidance details what designs are considered adequate and well controlled and under what circumstances a given design may be appropriate. The draft also describes how the clinical endpoints studied are a critical aspect of evidence quality. For traditional approval, such clinical endpoints include those that reflect patient benefits or those that have been shown to predict a specific clinical benefit. Accelerated approval can be based on a demonstrated effect on a surrogate endpoint likely to predict a clinical benefit, but where there's insufficient data to show that it's a validated surrogate endpoint. Accelerated approval can also be based on the effects on intermediate clinical endpoints. Drugs granted accelerated approval are required by the FDA to undergo post-approval trials to verify the predicted clinical benefits.

While the guidance admits that randomized superiority trials with a placebo- or active-control design generally provide the soundest evidence of effectiveness, it addresses circumstances under which trials not using a placebo control, superiority design or randomization may be acceptable. This includes instances when the disease is life-threatening or severely debilitating and where there's an unmet medical need. It can also apply to rare diseases. The guidance also discusses situations in which human efficacy trials aren't ethical or feasible and where the animal rule may be applied.

Draft guidance outlines process for soliciting FDA feedback on combination products

The FDA released draft guidance explaining how sponsors of combination products can receive feedback for regulatory and scientific questions. It explains best practices for the agency to employ with sponsors during such interactions, which include formal meetings with the CDER or CBER, the centers' pre-submission processes or through Combination Product Agreement Meetings.

The FDA issued draft guidance outlining how sponsors of combination products can receive agency feedback on scientific and regulatory

questions. The guidance also discusses best practices for the FDA and sponsors on such interactions, which can take place through formal meetings with the Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER), via application-based mechanisms such as the Center for Devices and Radiological Health (CDRH) and CBER's pre-submission processes, or through Combination Product Agreement Meetings (CPAMs).

Under 21 CFR 3.2(e) of the Federal Food, Drug, and Cosmetic Act, a combination product includes:

- A product comprising of two or more regulated components, such as drug/device, biologic/device, drug/biologic or drug/device/biologic.
- Two or more separate products packaged together in a single package or as a unit.
- A drug, biological or device packaged separately that is intended for use only with an individually specified drug, device or biological product where both are required for the intended use, indication or effect.
- Any investigational drug, biological or device packaged separately that, per its proposed labeling, is for use only with another individually specified product where both are required to achieve the intended use, indication or effect.

The guidance was released as part of the FDA's mandate under the Cures Act to establish a structured process for managing pre-submission interactions with sponsors of combination products and to describe how CPAMs relate to other FDA meeting types. The guidance establishes three key attributes to ensure interactions between the FDA and sponsors are efficient and productive:

1. Appropriate product identification and processing: Submissions should be made to the appropriate lead center. Sponsors that make a request for a CPAM or use application-based mechanisms need to clearly identify their product as a combination product.
2. Timely use of appropriate communication procedures: Communications should be timely and made through mechanisms specified in the guidance.
3. Clear, comprehensive information-sharing: To reduce redundant interactions on the same questions and facilitate timely FDA feedback, communications should be clear and comprehensive.

In addition to those best practices, the guidance communicates sponsor-specific best practices to ensure interactions with the FDA are efficient and productive. These include posing clear and appropriate questions, providing comprehensive rationale and supporting information, and communicating through the identified FDA point of contact (POC). The guidance also details best practices for the FDA to consider, such as notifying a sponsor of its FDA POC, engaging appropriate expertise from other medical product centers and the Office of Combination Products, consolidating and aligning feedback to provide comprehensive responses, and providing reliable advice to the sponsor.

FDA updates compliance guide for preapproval inspections

The FDA updated its compliance guidance on preapproval inspections of drug manufacturing facilities to ensure that facilities named in drug applications are capable of manufacturing the drugs while following CGMP requirements and submitting accurate and complete data. The guidance explains the coordination that takes place within the CDER and ORA, and details the agency's field reporting requirements and objectives for such inspections.

The FDA amended its compliance guide on preapproval inspections (PAIs) to ensure that

the drug manufacturing facility named in a drug application is able to manufacture a drug in conformance with Current Good Manufacturing Practice (CGMP) requirements and that the data submitted is accurate and complete. The update, which will take effect Sept. 16, 2022, aims to provide companies with better guidance to potentially avoid Form 483s.

The guide explains that the compliance program was revised to describe the potential Official Action Indicated reporting responsibilities and to align with the Center for Drug Evaluation and Research (CDER) and Office of Regulatory Affairs' (ORA) efforts to integrate facility inspections for human drugs. The document details redefined collaborations and shared responsibilities between the CDER and ORA for determining and undertaking an inspection. It also updates field reporting requirements and outlines the following three objectives:

1. Readiness for Commercial Manufacturing—Determining whether the establishment has a quality system that is designed to achieve adequate control over the facility and commercial manufacturing operation.

2. Conformance to application—Verifying that the formulation, manufacturing or processing methods; analytical (or examination) methods; and batch records align with descriptions contained in the chemistry, manufacturing and controls section of the application.

3. Data integrity audit—Auditing and verifying raw data at the facility that is associated with the product. The guide highlights some indicators of possible lab data integrity problems, such as an alteration of raw, original data and records; discrepancies between material used in a biostudy and reserve samples; or backdating stability test results in order to meet required commitments. In instances of unreliable data, the guidance notes that an inspector can expand the inspection's scope to marketed products under the compliance program for drug manufacturing inspections, or the FDA can invoke the Application Integrity Policy, which is the FDA's policy for the integrity of data submitted in an application.

In conducting preapproval facility evaluations, the CDER and ORA look at information about each facility named in a marketing application, the drug being manufactured and other information to determine whether a PAI is needed before an application can be approved from a quality perspective. For PAIs, the CDER and ORA analyze the manufacturing processes and control strategies to ensure the commercial product's quality and its conformance to application, facility and CGMP requirements. The CDER uses information from the inspection in conjunction with other information to determine whether to approve a drug application. The compliance program also provides risk-based strategies for the scope of inspectional coverage and clarifies roles to establish efficient communication. During the PAI, if systemic CGMP deficiencies are discovered, the FDA can expand the scope of the inspection.

The revised compliance program reinforces the agency's risk-based approach to determine whether inspections are needed using information contained in applications and that the FDA may have regarding the facilities. When a sponsor submits a marketing application, the CDER launches the preapproval facility evaluation by convening an integrated quality assessment (IQA) team to conduct the quality assessment. The team offers patient-focused and risk-based quality recommendations as they relate to the drug product, including recommendations for facilities that manufacture, process, package, or hold and test the product. During the quality assessment, the IQA team determines a facility's need for PAIs by assessing product risk, manufacturing risk and the accuracy and reliability of the information contained in the application.

FDA finalizes guidance on annual reports for PMAs

The FDA finalized guidance detailing the type of information medical device companies need to include when submitting annual reports for devices subject to premarket approval. It shares a recommended format to detail annual reportable changes, offers examples of rationales for changes to devices, and discusses instances in which the FDA may necessitate post-approval studies and periodic reporting on a device's safety, effectiveness and reliability.

The FDA issued final guidance describing the information required for medical device companies submitting annual reports for medical devices subject to premarket approval (PMA) under section 515 of the Federal Food, Drug, and Cosmetic Act. The guidance, initially issued as a draft in 2014, offers a recommended format for the table of annual reportable changes that includes columns for device manufacturers to explain the type of change, provide a description of the change, detail other related changes and explain why a change doesn't affect a device's safety and effectiveness.

The final guidance includes examples of rationales for changes to devices, such as the result of a device improvement or enhancement; the result of an adverse event or device defect; in response to a customer complaint or suggestion; in association with a recall or corrective action; related to an FDA safety alert; or in relation to a public disclosure from the applicant. The guidance explains how the FDA requires companies to make available data about the number of devices shipped or sold within the reporting period.

Per the guidance, the FDA aims to complete its review of annual reports within 90 days, after which it will acknowledge completion of the review, request additional information, and/or notify the applicant via letter that a PMA supplement or 30-day notice is needed for certain changes. The guidance also explains instances in which the agency may require post-approval studies and periodic reporting on the safety, effectiveness and reliability of the device for its intended use. It advises companies to send their annual reports and post-approval study reports separately, even if they are due at the same time, and to indicate in the annual report the date that the post-approval study report was submitted.

This guidance also details the steps FDA staff generally take in reviewing annual reports, along with the resources at their disposal for such reviews and potential actions they may recommend after reviewing the reports. Their review memorandum to the applicant will summarize the changes described in the annual report along with their evaluation of those changes. They will also detail the agency's understanding of the applicant's rationale for the changes along with their assessment of that rationale. The guidance aims to ensure that annual reports are complete and that the actions taken by Center for Devices and Radiological Health and Center for Biologics Evaluation and Research staff are consistent.

In the PMA approval orders, the FDA typically specifies that applicants submit a report one year from the date of approval of the original PMA, and every subsequent year thereafter. Per the guidance, there may be instances in which the agency requests more frequent periodic reports that provide the same information contained in the annual reports. The guidance explains that its approval order will describe the purpose of such studies and the frequency with which post-approval study reports need to be submitted.

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