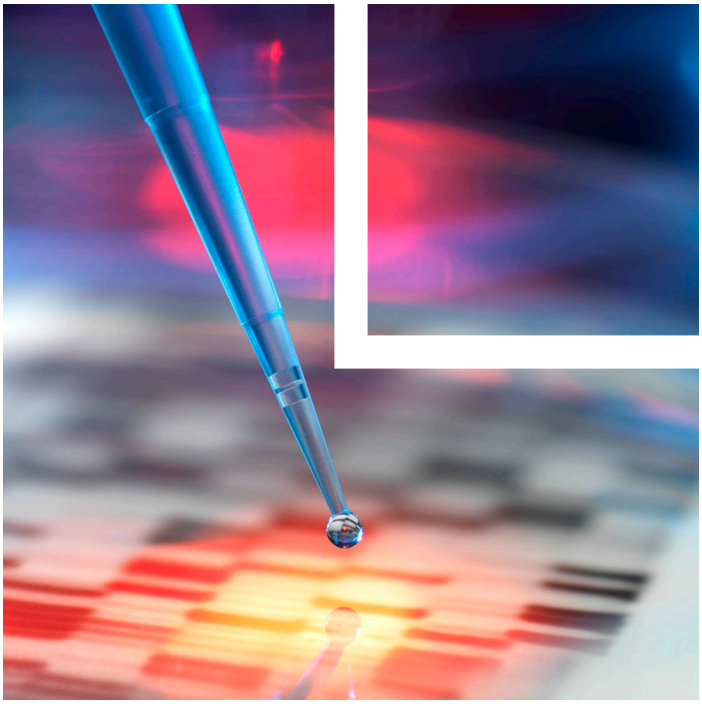
FDA Regulatory & Compliance Monthly Recap
August 2020



FDA issues FAQ guidance regarding inspections and manufacturing, supply chain issues during COVID-19 pandemic

The FDA issued a guidance providing answers to frequently asked questions about regulatory and policy issues relating to inspections, manufacturing and supply chain issues during the ongoing COVID-19 pandemic. The agency recognizes that the outbreak is impacting not just public health but also the drug development and manufacturing process, as well as the FDA's ability to conduct inspections, so it developed the guidance to answer any questions that sponsors and applicants may have regarding these issues.

The guidance first covers common questions in regard to how the FDA plans to handle inspections during the pandemic. Earlier this year, the FDA announced that it would postpone temporarily all domestic and foreign routine surveillance facility inspections, as well as routine surveillance inspections in support of the Bioresearch Monitoring (BIMO) program. As per the guidance, the FDA will continue to conduct only "mission-critical" inspections or, where possible to do so safely, the agency will resume prioritized domestic inspections, which include preapproval and surveillance inspections. Foreign preapproval and for-cause inspections not deemed "mission-critical" will continue to be temporarily postponed. The FDA will base its assessment of whether an inspection is deemed mission-critical on a number of factors, including whether the product has received breakthrough therapy or regenerative medicine advanced therapy designation and whether the product is used to diagnose, treat or otherwise prevent a serious disease or medical condition for which there are no other therapies available.

In regard to manufacturing and supply chain requests, the guidance answers common questions related to changes in manufacturing facilities for approved pharmaceutical products. The guidance notes that if a drug application or biologics license application (BLA) relates to the treatment or prevention of COVID-19 or is

a drug on the FDA's drug shortage list, the cover letter for submissions should clearly state "Priority Review Requested" and include all relevant information in support of the request. In order to accelerate the implementation of manufacturing changes to an ANDA, NDA or BLA for drugs or biological products needed during the COVID-19 pandemic, the FDA may consider available information and methods to mitigate the risk to product quality related to the requested changes to support usage of a lower reporting category than would normally be appropriate for certain supplements. Furthermore, the agency is willing to consider requests from applicants to submit certain changes using a lower reporting category based on risk-mitigation information for drug applications or BLAs related to the treatment and prevention of COVID-19 or to drugs in shortage. Per the guidance, prior to submitting a supplement with a lower reporting category, applicants should contact the FDA for feedback and should include on the application their rationale and supporting data for requesting the lower category, as well as any risk-mitigation information.

The processes outlined in the guidance will remain in effect only for the duration of the COVID-19 public health emergency.

FDA issues final guidance on preparation, submission of pediatric study plans

The FDA issued a final guidance providing sponsors with a framework for the preparation and submission of pediatric study plans. The framework builds off existing regulations and laws implemented in the late 1990s and early 2000s that address the dearth of pediatric data in new drug development. Specifically, the guidance provides recommendations to sponsors regarding the submission of an initial pediatric study plan (iPSP).

Under the guidance, sponsors planning to submit a marketing application—or a supplement to an application—for a new active ingredient, new indication, new dosage form or regimen, or new route of administration must submit an iPSP. The only exception to this rule is for drugs that are for an indication that is already granted orphan designation. Additionally, any sponsor planning to submit an original application for a new active ingredient subject to the molecularly targeted cancer drug provision of the Pediatric Research Equity Act (PREA) must also submit an iPSP. Sponsors must submit their iPSPs before the date on which they submit the required assessments or investigation and no later than either 60 calendar days after the date of the end-of-phase-2 meeting or any specified time agreed upon between the FDA and the sponsor. The iPSP should be submitted to the relevant drug's IND for review by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research as appropriate. If the sponsor has no active IND for the drug but expects to open one for the initial phase 3 study, it should submit the iPSP as a pre-IND submission.

The guidance also outlines what information should be included in an iPSP, including:

- Overview of the Disease/Condition in the Pediatric Population
- Overview of the Drug or Biological Product
- Overview of Planned Extrapolation to Specific Pediatric Populations
- Planned Request for Drug-Specific Waiver(s)
- Planned Request for Deferral(s) of Pediatric Studies
- Tabular Summary of Planned Nonclinical and Clinical Development
- Age-Appropriate Formulation Development
- Nonclinical Studies
- Clinical Data to Support Design and/or Initiation of Studies in Pediatric Patients
- Planned Pediatric Clinical Studies
- Timeline of the Pediatric Development Plan
- Agreements for Pediatric Studies With Other Regulatory Authorities

Additionally, when a deferral of pediatric studies is requested for NDAs, BLAs or supplemental applications subject to PREA, sponsors must include an agreed-upon iPSP in the application. In such an instance, the iPSP fulfills the requirement of the sponsor to submit a pediatric study plan. Sponsors can also request an amendment of the iPSP at any time and should include support for the requested change, a copy of the agreed-upon iPSP with the requested changes clearly identified, and a clean copy of the proposed amended iPSP.

Finally, if the sponsor and the FDA cannot reach an agreement on an iPSP by the end of the 210-day review period, the agency will issue a letter stating that the iPSP is considered non-agreed. As there is no established timeline for the review and agreement of non-agreed iPSPs, the FDA strongly encourages sponsors to work with the agency to reach agreement during the initial 210-day review period.

FDA finalizes guidance on multiple function device products

The FDA issued a final guidance intending to assist sponsors on agency reviews of medical products containing both medical and nonmedical functions. The guidance addresses provisions of the Cures Act that excluded certain software applications from being considered medical devices under the FDCA. The document also clarifies a draft guidance issued in 2018 regarding how and when the FDA will consider the impact of other functions of a product that are not subject to premarket approval.

In regard to premarket reviews, the guidance reveals that the FDA does not plan to review a device function already subject to an enforcement discretion policy simply because it's part of a multifunction device. The agency instead plans to review only device functions for which approval is being sought. In such a case, the FDA's decision to clear or approve would apply only to the functions being reviewed. The agency encourages manufacturers to determine whether an "other function" affects the safety or effectiveness of the device function-under-review and include such information in its premarket submission information. Furthermore, manufacturers should include this information only if the impacts of the "other function" could negatively impact the device function-under-review or if there is a positive impact that will be disclosed in the device's labeling.

In the event that an "other function" has a positive impact on the device function-under-review, and the device sponsor would like the FDA to consider that impact in its assessment, the sponsor should include the following information regarding the "other function" in its premarket submissions:

- Indications for use
- Description of the functions
- Labeling
- Architecture and design
- Device hazard analysis
- Requirements and specifications
- Performance testing
- Submission summary

The guidance also outlines additional considerations for a multifunction device function-under-review. Whenever possible, the device function-under-review should be separated from "other functions" in design and implementation. According to the FDA, the higher the degree of separation, the easier it will be to independently review the safety and effectiveness of the device function-under-review. Additionally, separation will increase the likelihood that the device function-under-review is not reliant on the "other functions" in a product. Manufacturers should also consider the effect these "other functions" will have on the device function-under-review's performance, as well as potential limitations caused by use of the "other function." Manufacturers should also develop appropriate hardware and software resource specifications for multifunction devices to ensure that any impact caused by "other functions" is mitigated as much as possible. Other considerations include how to ensure that end users take appropriate actions when using the device function-under-review and identifying and mitigating any additional risks when the device function-under-review is used in conjunction with "other functions."

FDA issues guidance regarding bioavailability, bioequivalence sample retention

The FDA issued a guidance regarding its policy on retention of reserve samples of test articles and reference standards used in an in vivo bioavailability (BA) and in vivo bioequivalence (BE) study. Additionally, the guidance provides conditions under which the FDA does not plan to take enforcement action against organizations retaining less than the required amount of reserve samples.

The guidance was intended to address the agency's requirements under 21 CFR 320.38(c) to retain reserve samples of enough quantity to allow the FDA to perform at least five times the release tests in an application or supplemental application. However, since the final rule was issued in 1993, there have been numerous technological advances, which have led to less destructive and more sensitive testing methods. The new methods allow the FDA to detect the identity and composition of the test article and reference standard with a smaller volume of samples. As a result, the agency does not intend to take enforcement action for violations of 21 CFR 320.38(c) if the quantity retained is sufficient for the FDA to complete all its testing.

For drug products manufactured in single-dose units, the FDA will not require a sufficient quantity of sample to perform five times the release tests, so long as (i) the minimum quantity retained is 30 units of the test article and (ii) 30 units of the reference standard from each shipment are retained. For drug products manufactured in multidose units, the FDA will not require a sufficient quantity of sample to perform five times the release tests, as long as the minimum quantities of three units of the test article and three units of the reference standard from each shipment are retained.

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