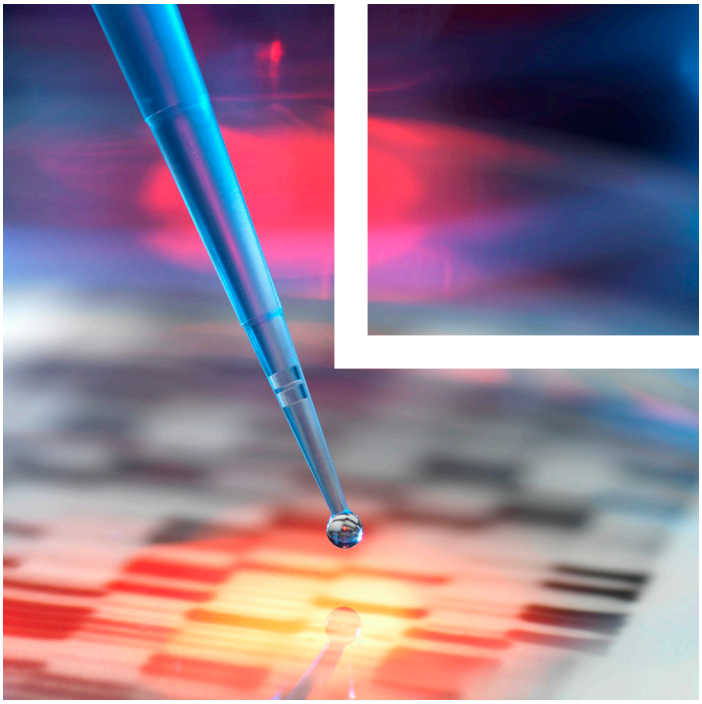
FDA Regulatory & Compliance Monthly Recap
January 2021



FDA issues guidance regarding resumption of bioequivalence testing for generics during COVID-19 pandemic

The FDA issued a guidance providing recommendations for resuming or initiating bioequivalence (BE) studies for generic drugs during the ongoing COVID-19 pandemic. The guidance calls on generics developers to take steps to ensure the scientific validity of the data generated by the studies affected by the public health crisis. To that end, the document provides recommendations designed to protect study participants, including examples of potential infection mitigation models for study visits.

In regard to participant safety, the guidance recommends developers consider the prevalence of COVID-19 and the availability of diagnostic testing in a particular area when determining inclusion criteria. Furthermore, the agency suggests developers consider relevant comorbidities, such as history of significant cardiovascular and respiratory conditions and/or history of other medical conditions, when determining exclusion criteria.

The FDA also recommends that prior to resumption or initiation of BE studies, developers should alter their screening, admission and conduct procedures to mitigate exposure to COVID-19. The standard operating procedures for study sites should include consideration of methods to limit the amount of time spent by participants at the study site and any interactions with other participants and staff. These considerations include electronic informed consent forms or alternative methods of obtaining informed consent other than face-to-face interviews. Such alternative forms should allow for the adequate exchange of information and documentation as well as ensure the signer of the consent form is the individual planning to enroll in the BE study. Additionally, the guidance provides two examples of infection mitigation models to minimize the risks of COVID-19 transmission. These are:

- Confinement (Bubble) Design, in which participants and possibly site staff are confined to the facility for the duration of the study with no ambulatory visits. Sites following such a method would implement regular screening for COVID-19 symptoms and ensure that appropriate personal protective equipment is worn by both participants and staff.
- Non-Confinement (Ambulatory) Design, in which participants are not confined to the facility but instead use select time points for pharmacokinetic sampling, allowing for travel to and from the site each day. This method minimizes potential infections from within the facility. Sites adhering to this method would implement symptom screening for each ambulatory visit and ensure that one participant's visit does not overlap with another's.

FDA issues guidance on COVID-19 considerations for CGT manufacturing

The FDA issued guidance providing pandemic-related manufacturing considerations for both licensed and investigational cell and gene therapy (CGT). The guidance was intended to supplement the recommendations provided in the agency's Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing; Guidance for Industry, issued in June. The document discusses several issues specific to the sector, including cells and tissues recovered from donors and the methods through which a CGT product will be manufactured. The recommendations outlined in the guidance apply to CGT products regulated as drugs and biologics products but not to medical devices or human cells, tissues, or cellular-based products.

The guidance recommends CGT manufacturers perform risk assessments to identify, evaluate and mitigate certain factors that could allow for the transmission of COVID-19 through their products. A description of any such strategies should be included in the necessary FDA submissions, including new drug investigational applications, biologics license applications and master files.

In regard to donor assessments, the FDA notes that there are already established screening measures in place for evaluating clinical evidence of infection in allogenic human cells, tissues, and cellular- and tissue-based products (HCT/Ps). In addition, the FDA recommends that manufacturers consider routine screening measures for autologous HCT/P donors due to the potential expansion of SARS-CoV-2 during the manufacturing process. However, the agency does not recommend using laboratory tests to screen asymptomatic HCT/P donors for SARS-CoV-2 because it has not been declared a relevant communicable disease agent under the Federal Food, Drug, and Cosmetic Act. The FDA also recommends against screening for or deferring HCT/P donors who have been vaccinated against COVID-19 with nonreplicating, inactivated or RNA-based COVID-19 vaccines.

As to cellular or tissue source material, the guidance recommends manufacturers consider known characteristics of coronaviruses in addition to the ability of SARS-CoV-2 to infect and replicate in source cells and tissues. Manufacturers should also consider whether SARS-CoV-2 can infect and propagate in cells or tissues during certain manufacturing processes, such as cell/tissue cultures. Additionally, manufacturers should consider the risk of infection of the specific organ system.

The guidance also recommends manufacturers consider starting materials and manufacturing processes used to control viral spread and contamination risk during manufacturing as ways to mitigate the potential for SARS-CoV-2 in CGT products and the unintended expansion and transmission to facility personnel. Furthermore, to ensure Current Good Manufacturing Practice compliance, manufacturers must ensure that employees practice adequate sanitation and health habits.

Finally, the guidance notes that the FDA has no specific recommendations in regard to testing HCT/P material, cell banks, in-process intermediates, final CGT products or other relevant raw materials for SARS-CoV-2. However, the agency also states that manufacturers can include such testing as a risk mitigation strategy.

FDA issues draft guidance on gene therapies for neurodegenerative diseases

The FDA issued a draft guidance regarding the development, testing and trial design for human gene therapies (GTs) for neurodegenerative diseases. The guidance is intended to apply to products designed to treat both adult and pediatric populations and highlights the importance of early communication with the agency prior to the submission of investigational new drug applications (INDs). The document also outlines a list of objectives sponsors should focus on when developing preclinical studies for such products.

The guidance recommends sponsors developing products for neurodegenerative diseases contact the FDA's Office of Tissues and Advanced Therapies prior to submitting an IND, as well as during development, to discuss product-specific considerations, including product design and drug purity and potency, product strength, and the effect of manufacturing processes changes on critical quality attributes. Additionally, the FDA recommends that sponsors discuss pharmaceutical quality development plans early in the process, such as at the pre-IND meeting and throughout the process in general.

The guidance also offers considerations for sponsors in regard to preclinical studies. The document outlines elements that are key for the development of preclinical programs. These include, but are not limited to:

- Preclinical in vitro and in vivo proof-of-concept studies to establish the product's feasibility and to support the scientific rationale for administration of the GT product.
- Biodistribution studies to assess the distribution, persistence and clearance of the vector and possibly the expressed transgene product from the site of administration to target and nontarget tissues.
- Toxicology studies, which should incorporate elements of the planned clinical trial, such as dose range, dosing schedule and evaluation endpoints.

Additionally, in an effort to support product development, the agency encourages sponsors to discuss clinical development plans with the FDA, including elements such as:

- **Study Design**: Sponsors should conduct randomized, concurrent-controlled, double-blind clinical trials whenever possible. Crossover trials may be considered when disease progression can be clearly identified.
- **Study Population**: For GT clinical trials, sponsors should confirm the presence of genetic mutation prior to enrollment. If a reliable genetic diagnostic test is not available, a companion diagnostic test may be required to appropriately select study participants.
- **Dose Selection**: The FDA encourages significant dose exploration throughout clinical trials to identify potentially safe and therapeutic doses for a broad range of subjects. This is also important because some participants may have only one opportunity to receive the product.
- **Safety Considerations**: To monitor systemic immune reactions, sponsors should conduct immunoassays to measure the cellular and humoral immune responses to both the vector and the transgene-encoded protein.
- **Study Endpoints**: The agency encourages sponsors to consider a wide range of endpoints to assess the preliminary safety, activity and effectiveness of a GT product in early-phase trials. These endpoints should allow for assessment of potential clinical benefits and biomarkers, which will guide future clinical development.

FDA issues final guidance on Safer Technologies Program for Medical Devices

The FDA issued a final guidance regarding its Safer Technologies Program for Medical Devices (STeP), which is designed to allow developers of safer devices and diagnostics targeting diseases not included in the agency's Breakthrough Devices Program to take advantage of prioritized review and improved communications. The document provides a breakdown of inclusion criteria for the program as well as examples of the types of devices that would qualify.

As per the guidance, to become eligible for the program, the FDA will evaluate which constituent part of the device is being proposed as a safety improvement. For general eligibility requirements, the agency will consider including products in the program only if the safety improvements are made to the device's constituent parts. The FDA will also consider whether the product should be reasonably expected to substantially improve the benefit-risk profile of an existing treatment or diagnostic through significant safety innovations that provide for one or more factors, including:

- Reduction in serious adverse event occurrences
- Reduction in device failure occurrences
- Reduction in known-use-related hazard occurrences
- Improvement in the safety of another device or intervention

However, the agency will not consider devices already eligible for the Breakthrough Devices Program, due to the less serious nature of the disease or condition being treated, diagnosed or prevented by the product. Additionally, the FDA will consider whether the device's planned marketing pathway is a premarket approval application, De Novo request or premarket notification.

The guidance also outlines the process for withdrawing or disqualifying a device from the program. In the event a sponsor wishes to withdraw from STeP, it should submit the request in writing to the FDA as a withdrawal amendment to the Q-submission number under which the original inclusion request was made. In regard to disqualifications, the agency noted that it does not intend to disqualify a device based on other STeP devices intended to address the same issues. However, the agency may disqualify a device at any time if it is determined that the device is no longer eligible for the program based on available data. A device can also be disqualified if the information supporting a STeP inclusion request contained any untrue statements of material fact or omitted material information.

In regard to development feedback, the agency offers a number of options for sponsors to communicate with the FDA. In the event a sponsor needs timely resolution of a nonclinical or clinical evaluation, the agency is offering "sprint" discussions, with the intent of reaching mutual agreement on a particular issue within a set time period. In addition, sponsors can also request coordination with the FDA in regard to Data Development Plan reviews. Finally, the sponsor and the FDA can also agree to regular status updates beyond the formal regulatory submissions. In these interactions, the sponsor may discuss the general progress of the device's development and next steps. These updates provide opportunities too for a high-level overview of the project and the ability to identify potential hurdles.

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