<u>Common GCP Bioresearch Monitoring</u> <u>Violations</u>



The U.S. Food and Drug Administration's (FDA's) Office of

Bioresearch Monitoring Operations (OBIMO) oversees domestic and foreign agency field inspections for clinical and non-clinical research. In particular, OBIMO manages the Bioresearch Monitoring (BIMO) Program which conducts onsite field inspections and data monitoring to ensure institution and industry compliance with FDA's regulations relating to Good Clinical Practices (GCPs). These inspections can occur as a result of a marketing application submission, for general surveillance during an ongoing clinical trial, or as a result of a "for cause" reason. After an inspection, FDA investigators may issue a Form 483 to communicate any onsite findings of noncompliance with FDA's regulations. BIMO also has authority to issue Warning Letters when the noncompliance FDA identifies is serious.

In the past 5 years, following are the three most common violations found in OBIMO Warning Letters:

- 1. Failure to ensure that the clinical trial was conducted according to the investigational plan. For example, in one Warning Letter, the FDA noted that a clinical investigator failed to adhere to the investigational plan because subjects took less than the required dosing of the study drug, and some subjects may have taken placebo rather than the required study drug, calling into question the validity of the study data.
- 2. Failure to maintain adequate and accurate study records, including the case histories of individual subjects, the disposition of the drug, or signed informed consent forms. For example, in one Warning Letter, the FDA found that a clinical investigator failed to complete diagnosis summary score sheets for multiple subjects, and the same clinical investigator also failed to accurately report the amount of drug dispensed versus the amount of drug taken by the subject.
- 3. **Failure to ensure that proper informed consent was obtained**. In several Warning Letters, the FDA determined that the investigators had failed to obtain proper informed consent from participants, including instances where exculpatory language was used waiving the participants' legal rights, other necessary elements of informed consent were missing, and the form was not specific to the study or approved by the institutional review board.

Sponsors and sites should review **FDA's BIMO Compliance Program Guidance Manuals** to better understand their responsibilities during clinical trials to ensure GCP compliance and to ensure readiness for future FDA BIMO inspections, should they occur. Anyone who has run a clinical trial will tell you that no trial is perfectly executed; deviations can and will occur, so preparedness is necessary. An effective monitoring program is critical to sponsors ultimately ensuring the integrity of their clinical trial records and data set. The Goodwin FDA Regulatory team works closely with sponsors on managing GCP issues when they arise during clinical trials.

<u>Connect</u> with our Goodwin FDA team to learn more.

*Madeline Fuller, a 2021 summer associate in Goodwin's Washington, D.C. office, contributed to this post.

<u>Navigating the New Normal:</u> <u>Biomanufacturing Goes Local</u>



The pandemic has spared no industry. The life sciences industry knows this well and perhaps learned this lesson the hardest way during the pandemic when overseas supply shipments were delayed or, worse, when overseas manufacturing facilities were shut down because of government-mandated quarantines. Producing novel biologics is, unfortunately, not so easy to pick up and relocate, especially during a pandemic and even moreso when there are not enough domestic producers to begin with. As the life sciences industry continues to rapidly grow and mature in the U.S., life sciences clusters are growing and expanding into the next phase: biomanufacturing onsite and building their own self-sustaining supply operations. Learn more about the expansion of the domestic supply chain here.

Read the **<u>full insight</u>**.

<u>FDA Answers New Questions on Foreign Trial</u> <u>Sites Operating Under INDs</u>



On May 19, 2021, the U.S. Food and Drug Administration (FDA) released an **updated guidance** in draft form on how to complete the Statement of Investigator form (Form FDA 1572). The guidance addresses frequently asked questions from sponsors, clinical investigators, and institutional review boards (IRBs), and it provides new information on waivers of the Form FDA 1572 signature requirement, which is particularly relevant for sponsors of clinical trials that include sites located outside the U.S.

Form 1572 is an agreement signed by an investigator to provide certain information to the sponsor and comply with FDA regulations on conducting a clinical investigation of an investigational drug or biologic, and under 21 CFR Part 312, an investigator must sign this agreement before participating in a trial. FDA's **previous guidance** on the Form 1572 requirements and process, issued in 2010, touches briefly on the responsibilities of investigators conducting foreign studies under an investigational new drug application (IND) in the U.S., but it does not go into detail on how sponsors should proceed when an ex-U.S. investigator cannot or will not sign the 1572 (e.g., because the commitments for investigators on the Form 1572 extend beyond or conflict with what local law requires).

Under the updated guidance, FDA provides detailed steps for sponsors to request a waiver of the Form 1572 signature requirement for foreign investigators. A Form 1572 waiver allows a trial at a foreign site to take place under an IND even when the investigator cannot or will not sign the Form 1572, as noted above. When requesting a waiver, the sponsor should propose an alternative course of action to adequately satisfy the purpose of a signed Form 1572, and the sponsor must request and receive a 1572 waiver for an investigator before the study is initiated at the investigator's site. Importantly, the guidance provides examples of sponsor and investigator commitment statements that would satisfy FDA's guidelines for granting a waiver, and FDA recommends using these templates to enable FDA's efficient review of a waiver request.

Overall, the guidance provides greater clarity on when a Form 1572 waiver would be needed and how a sponsor can obtain one. Sponsors planning to conduct a clinical study at a foreign site under an IND should review the updated guidance and, if a waiver is needed, factor in time for submission and FDA review of a waiver request before initiating the trial at a foreign site. Additionally, sponsors should ensure that clinical trial agreements with foreign sites contemplate Form 1572 completion and signatures and/or waivers when necessary.

<u>FDA Issues Guidance for Cell and Gene</u> <u>Therapy Manufacturers to Minimize Potential</u>

Transmission of SARS-CoV-2



On January 19, 2021, the FDA issued <u>guidance</u> for licensed and investigational cellular and gene therapy (CGT) manufacturers during the COVID-19 pandemic. This new guidance supplements the recommendations provided in FDA's <u>June 2020 guidance</u> regarding manufacturing controls to prevent contamination in drugs, risk assessment of SARS-CoV-2 as it relates to drug safety and quality, and continuity of manufacturing operations as applied to all drug and biological product manufacturers.

The new guidance provides risk-based recommendations to minimize potential transmission of SARS-CoV-2 to patients and facility personnel with specific considerations relating to, among other things, the assessment of donors, cellular and tissue source materials, manufacturing processes, manufacturing facility control, material testing, and the number of patients that can be treated with the product. While FDA acknowledges in the guidance that is not aware of any CGT products that have been contaminated with SARS-CoV-2 or of information indicating transmission of SARS-CoV-2 via CGT products, FDA notes that "CGT manufacturers are expected to evaluate whether [the virus] poses new risks in the context of their specific products, facilities, processes, and manufacturing controls."

FDA recommends that CGT manufacturers review the current good manufacturing practice requirements and recommendations and perform a risk assessment that identifies, evaluates, and mitigates factors that may allow for transmission of SARS-CoV-2 to patients and facility personnel and include a description of the risk assessment and mitigation strategies in any investigational new drug application (IND), biologics license application (BLA), or master file. Since this is an evolving area, manufacturers should look to scientific literature to provide justification and support for their risk assessment and mitigation strategies.

CGT manufacturers should evaluate their manufacturing operations for SARS-CoV-2 risks and be sure that all risk assessments of production controls, including any follow-up and changes, are approved by their quality unit and appropriately documented within their quality management system.

FDA Announces Temporary Review Timelines for Responses to Facility Assessment-Related Complete Response Letters Due to COVID-19



As follow-up to our October **post** on pre-approval and prelicensure inspections impacting U.S. Food and Drug Administration (FDA) drug and biologic approvals, this blog post discusses FDA's recently announced temporary policy set forth in its **December 2020 guidance** on review timelines for company responses to a Complete Response letter (CRL) for applications requiring the conduct of manufacturing or bioresearch monitoring (BIMO) program site facility inspections prior to approval. This guidance augments FDA's **August 2020 guidance**, which described FDA's intent to issue a CRL or defer action on an application until an inspection can be completed.

FDA acknowledges in its recent guidance that it is "facing difficulties" in conducting inspections during the COVID-19 pandemic. Industry has felt the impact of this with delayed approvals of new therapies in 2020 as a result of these inspection delays. While FDA has sought to use alternative tools to mitigate the need for in-person inspections (*e.g.*, requesting records and other information directly from facilities and requesting existing inspection reports from trusted foreign regulators), FDA indicated in its December 2020 guidance that these inspection-alternatives "can be as resource intensive as inspections, if not more," thereby presenting a challenge to timely completion of required pre-approval and pre-license inspections during the application review period.

To provide greater transparency on expected timeline impacts for company complete responses where FDA issued a CRL either (a) due to its inability to perform a required inspection because of COVID-19, or (b) where the inspection involves the use of time- and resource-intensive alternative tools, the Agency provides the below timeline expectations in its December 2020 guidance for the review of applicant responses to CRLs:

- <u>NDAs & BLAs</u>: Resubmissions of original applications and efficacy supplements for NDAs and BLAs will be subject to a Class 2 review timeline of 6 months, which is "consistent with existing policies and practices when a facility inspection is required."
- <u>Biosimilars & NDA & BLA manufacturing supplements</u>: There will be no changes in the review timelines for resubmissions of original applications, supplements with clinical data, and manufacturing supplements for biosimilars, or for resubmissions of manufacturing supplements for NDAs and BLAs.
- <u>ANDAs</u>: Regardless of whether the CRL contains a major deficiency, amendments to original ANDAs and amendments to prior approval supplements for approved ANDAs will be treated as major amendments, subject to the timelines provided in FDA's <u>July 2018 guidance</u> on Generic Drug User Fee Amendments (GDUFA).

The December 2020 guidance enables applicants to better plan for approval timeline delay contingencies as they proceed through FDA's review process. Comments on the December 2020 guidance may be submitted to the docket for Agency consideration <u>here</u>.

<u>Are Pre-Approval and Pre-Licensure</u> <u>Inspections Limiting Approvals During</u> <u>COVID-19?</u>



In this post, we discuss FDA's conduct of inspections of manufacturing facilities for new drugs and biologics during the COVID-19 pandemic. These inspections, known as pre-approval and pre-licensure inspections (PAIs/PLIs, respectively), are performed to give FDA assurance that a manufacturing site named in a new drug or biologics license application is capable of manufacturing the product according to current good manufacturing practices (cGMPs) and producing the product at commercial scale.

In July, FDA resumed limited domestic on-site inspections after temporarily postponing all domestic and foreign routine surveillance facility inspections in March. Since June, FDA had conducted only mission-critical domestic inspections. Currently, domestic on-site inspections are pre-announced and are prioritized on a newly developed rating scale that uses real-time data on the number of COVID-19 cases in a local area to qualitatively determine when and where it is safest to conduct inspections. Foreign PAIs/PLIs continue to be temporarily postponed unless deemed missioncritical. FDA may deem an inspection mission-critical based on a variety of factors including, but not limited to, whether the product has received breakthrough therapy or regenerative medicine advanced therapy designation.

In response to COVID-19, FDA has used, on a limited basis, various tools to conduct alternative inspections. These tools include the use of FDA's authority under Section 704(a)(4) of the FD&C Act, which enables the Agency to request records directly from facilities "in advance of or in lieu of" drug inspections. In addition, FDA has indicated that it may also look to records of recent inspections and information shared by foreign regulatory partners through mutual recognition agreements. And while the concept of virtual inspections has been floated, it remains to be seen if video-based or other virtual inspection strategies can be used to fulfill PAI/PLI requirements and how long such proposals may take to implement.

Worryingly, FDA explains in its <u>August 2020 guidance</u> that should the Agency determine that a PAI/PLI is necessary, and such an inspection cannot be completed during the review cycle due to restrictions on travel or other COVID-19-related risks, FDA generally intends to issue a Complete Response letter or may defer action. The guidance, along with a number of concerns raised quietly by sponsors regarding delayed inspections leading or potentially leading to Complete Response letters, paints a potentially ominous picture for drug and biologic approvals and the advancement of the public health over the coming months. Sponsors submitting marketing applications in the near-term would be wise to proactively prepare for discussion of alternative inspection approaches during the review of their applications.

<u>Real-World Evidence: Challenges and</u> <u>Opportunities During COVID-19</u>



The urgent needs of the COVID-19 pandemic have more squarely brought into focus the role realworld evidence (RWE) can play in analyzing and informing product development and clinical and public health decisions. Specifically, the U.S. Food and Drug Administration (FDA) is participating in the COVID-19 **Evidence Accelerator**, in partnership with Friends of Cancer Research and the Reagan-Udall Foundation, to bring leading experts together to share insights and use RWE to help answer the most pressing research questions raised by the pandemic.

The FDA believes that RWE can play an informative role in analyzing potential therapies, vaccines, and diagnostics for COVID-19. At the recent "Establishing a High-Quality Real-World Data Ecosystem" workshop hosted by the Duke Margolis Center for Health Policy, Amy Abernethy, the Principal Deputy Commissioner of Food and Drugs and Acting Chief Information Officer at the FDA, highlighted the work of the Evidence Accelerator initiative, noting that RWE allows the FDA to constantly update its understanding of COVID-19 and recurrently analyze data to address changing needs. Amongst the other presenters, the general discussion focused on the many hurdles industry needs to address to establish a robust and more accurate RWE data ecosystem, including efficient capture of reliable data at the source. While internet access, smartphones, and wearable technology enable consumers and patients to keep meticulous records of their biometric data, the vast amount of collected data does not necessarily lead to efficient or fruitful analysis currently. FDA noted during the workshop that, to be more insightful, RWE stakeholders must narrowly tailor their collection to what is actually useful and relevant to clinical endpoints, fit for purpose, rather than merely what is easily accessible. Eric Perakslis, a Rubenstein Fellow at Duke University, noted that stakeholders must balance the usefulness of RWE collection against the risk of over-surveillance for each data point collected. While not discussed during the workshop, collecting massive data sets must also be weighed against the ever-present risk of data breach. Finally, speakers also discussed patient-generated health data (PGHD) and the need for aligned stakeholders who are motivated to collect this data and understand the process for doing so, including a plan for handling outlier data which is unavoidable with PGHD.

In the context of the COVID-19 pandemic, RWE presents an opportunity for real-time learnings toward quicker identification and development of treatments and vaccines. As a result, the pandemic has only strengthened the importance of RWE in product development and, if deployed well, could help support more efficient and expedited product development plans.

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