Common GCP Bioresearch Monitoring Violations

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.

Connect 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.

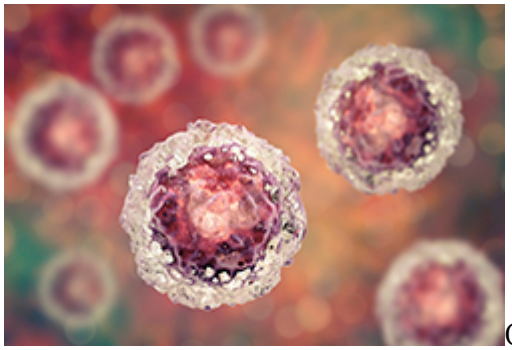
Drug Development Scorecard — A Guide for Companies Navigating the FDA Drug and Biologic Development and Approval Process

Developing a new drug or biologic is a complex process. Based on our extensive experience advising early-stage and clinical-stage companies, the Goodwin FDA team created this "**scorecard**" for companies to use as a guide as they navigate the FDA drug development and approval process. The drug development scorecard (or checklist) can help companies keep track of progress, identify opportunities, and achieve milestones that are appropriate for each stage of development.

If you have product development or approval strategy questions, we encourage you to contact the Goodwin FDA team.

FDA Issues Guidance for Cell and Gene Therapy Manufacturers to Minimize Potential

Transmission of SARS-CoV-2

 On January 19, 2021, the FDA issued **guidance** 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 **June 2020 guidance** 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 pre-licensure 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:

- NDAs & BLAs: 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."
- Biosimilars & NDA & BLA manufacturing supplements: 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.
- ANDAs: 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 **July 2018 guidance** 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 **here**.

Are Pre-Approval and Pre-Licensure Inspections Limiting Approvals During COVID-19?

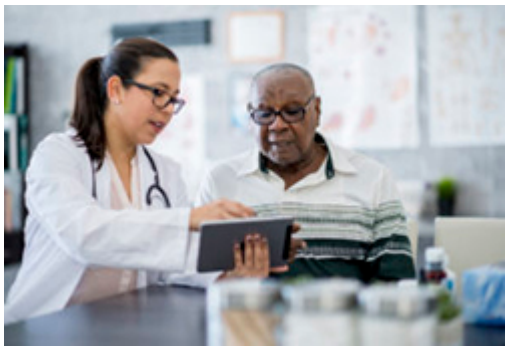
 In this post, we discuss FDA's conduct of inspections of manufacturing facilities for new drugs and biologics during the COVID-19 pandemic. These inspections, known as pre-approval and pre-licensure inspections (PAIs/PLIs, respectively), are performed to give FDA assurance that a manufacturing site named 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 mission-critical. 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 **August 2020 guidance** 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.

What are Clinical Outcome Assessments (COAs) and Can They be Used to Support Approval and/or Labeling Claims?



The patient voice is recognized as one of the most critical sources of data in drug development, and patients play an increasingly important role in these efforts by teaching us about their experience with their condition and its impact. A common way sponsors can leverage the patient experience is by utilizing a clinical outcome assessment (COA). A COA is an assessment that describes or reflects how a patient feels, functions, or survives. Such an assessment can be a patient-reported outcome (PRO) measure, observer-reported outcome (ObsRO) measure, clinician-reported outcome (ClinRO) measure, or a performance outcome (PerfO) measure. **Alexander Varond** chaired a session on this topic in June 2020 at the Drug Information Association's Annual Meeting. Slides from his presentation can be found **here**.

FDA plans to issue a guidance that will provide patient-focused approaches and methods to consider in the selection and/or development of COAs. This future guidance, known as Patient-Focused Drug Development (PFDD) Guidance 3, is one piece of FDA's plan to develop a series of four PFDD-specific guidances for stakeholders on how to collect and utilize patient experience data in drug development. We initially discussed this plan and background on patient experience data **here**. In the meantime, FDA has described a "roadmap to COA selection/development for clinical trials" **here**. This roadmap sets forth how to obtain an understanding of the disease or condition, conceptualize clinical benefit (i.e., how a patient feels, functions and survives), and how to select, develop and modify a COA. In Guidance 4, FDA will discuss how to incorporate COAs into endpoints for regulatory decision-making. FDA issued a discussion document related to the forthcoming Guidance 4 **here**.

As background, a COA may support approval of a product if it is a "well-defined and reliable" assessment (21 CFR § 314.126). FDA interprets this to mean that the COA must have content validity, construct validity, reliability, and the ability to detect change. But COAs can do much more. For example, COAs can be included in labeling claims, as with CRYSVITA (burosumab-twza) for X-linked hypophosphatemia linked **here**, which incorporates both PRO and ClinRO measures. COAs can even lead to a regulatory change in thinking about a particular disease or condition. For example, just over two months after hearing directly from patients with epidermolysis bullosa (EB), a rare disorder that results in serious cutaneous manifestations, at an externally-led PFDD meeting, FDA published a draft guidance for sponsors developing therapies for EB that outlined specific examples of efficacy endpoints that would show the drug provides a clinically meaningful improvement. The finalized guidance can be found **here**.

If you are considering developing or utilizing in your clinical development program a COA, or if have questions about other PFDD initiatives such as PFDD meetings, we encourage you to contact your Goodwin life sciences lawyer for assistance on how to incorporate the patient voice–the real experts on their disease or condition—in drug development.