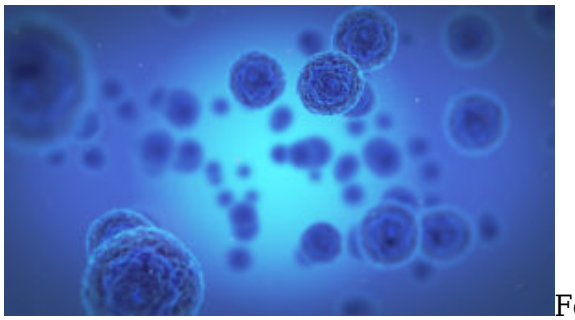
Field Alert Reporting: Supplier Contracting Implications for Drug Developers

 For emerging companies establishing their first supply chains, ensuring notification requirements in supply agreements for when commercial-stage manufacturing issues arise may not be top of mind. However, it is important for drug developers whose contracts enable continuation of a supply arrangement into the commercial-stage to be familiar with the U.S. Food and Drug Administration's (FDA's) field alert reporting (FAR) requirements for new drug application (NDA) and abbreviated new drug application (ANDA) holders to ensure adequate communication between developers and their suppliers.

By way of background, the FAR regulations at 21 C.F.R. §§ 314.81(b)(1) and 314.98(b) require NDA and ANDA holders to notify their FDA field office (using an Form FDA 3331a) within three business days of "receipt" of: (1) information concerning any incident that causes a distributed drug product or its labeling to be mistaken for, or applied to, another article; or (2) information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in its approved application. In brief, timely notification by suppliers really *does matter* here and should not extend past one business day if at all possible.

This past summer, the FDA issued **final guidance** clarifying reporting timelines and the facts and circumstances that trigger submission of FARs. Amongst other things, the FDA clarified that the FAR requirements apply to *all* products marketed under an NDA or ANDA, including positron emission tomography drugs, designated medical gases, and combination products containing a drug constituent part. However, products that are only marketed abroad pursuant to a foreign approval with non-U.S. labeling are not subject to FDA's FAR requirements. FDA also clarified that report-triggering events are not limited to active ingredient issues but can also include issues related to inactive ingredients, processing aids, and packaging.

Additional key takeaways include:

- FARs are required even when a problem is identified and corrected within the three business day reporting window.
- FARs are required even when a problem is identified beyond the three business day reporting window; however, a Form FDA 483 finding can result from the failure to submit timely FARs.
- Day "0" for calculation of the three business day reporting window is the day information triggering the report was received, *even if received by a third-party contractor or supplier*.
- Follow-up or final FARs are recommended but not required if significant new information is received.

- Separate initial FARs are required for a problem impacting drug products covered by multiple applications, but if conducting a single investigation into the issue after submitting the initial FARs, any follow-up can be provided in a single follow-up or final FAR.
- Investigations into issues identified with undistributed products should consider whether those issues may exist in distributed products, triggering a FAR.
- Possible changes or deterioration in distributed products triggering FARs include contamination by bacteria, yeast, mold, virus or other microorganisms.
- Issues leading to recalls do not release an NDA or ANDA holder from FAR reporting responsibility.

Overall, FDA's FAR requirements necessitate prompt or immediate notification of any information discovered by suppliers that could trigger a FAR for NDA and ANDA holders. For supplier agreement negotiations, requiring prompt or immediate notification of issues in clinical-stage agreements positions a developer well to require the same in the commercial stage when FAR requirements apply. Additionally, in the commercial stage, FARs can prompt unannounced FDA for cause inspections and can also lead to expensive product recalls, so early notification, investigation, and remediation of issues warranting a FAR submission can help minimize potential liability and resource expenditure to remedy any issues that arise.

List of Artificial Intelligence and Machine Learning (AI/ML)-enabled Devices Available on FDA's Website

The U.S. Food and Drug Administration (FDA) now provides a list of **Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices** that are legally marketed in the United States. These include devices (1) cleared via 510(k) premarket notifications, (2) authorized pursuant to De Novo requests, and (3) approved via premarket approval applications, or PMAs. FDA explains that the list, developed by FDA's Digital Health Center of Excellence, while not exhaustive or comprehensive, is intended to increase transparency and access to information on these devices that span across medical disciplines.

Read the **client alert**.

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.

Promotion of Devices Subject to the FDA's COVID-19 Enforcement Policies

The Biden Administration's withdrawal of the Trump Administration's proposal to exempt 84 medical device types from the FDA's premarket notification, or 510(k), requirement, underscores the promotional framework that developers and marketers of these devices are subject to. The Trump Administration proposal included devices critical to combating the COVID-19 public health emergency, ranging from personal protective equipment and ventilators to remote patient monitoring and other types of digital health devices.

Read more about promotional considerations for these devices **here**.

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 Answers New Questions on Foreign Trial Sites Operating Under INDs


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.

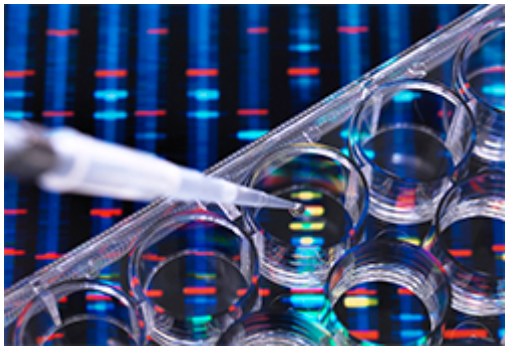
Overall, the guidance provides greater clarity on when a Form 1572 waiver would be needed and how a sponsor can obtain one. Sponsors planning to conduct a clinical study at a foreign site under an IND should review the updated guidance and, if a waiver is needed, factor in time for submission and FDA 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.

Disrupt + Innovate + Transform: Key Regulatory Issues for Digital Health Companies Webinar

Goodwin Life Sciences and Healthcare partner **Roger Cohen** and associate **Anne Brendel** along with Life Sciences and FDA associate **Steven Tjoe** kicked off Goodwin's multi-part webinar series "Disrupt + Innovate + Transform: A Healthcare Webinar Series" with "Key Regulatory Issues for Digital Health Companies" discussing the key regulatory issues affecting digital health, telemedicine and healthcare IT companies. The webinar series will be presented by a cross-disciplinary team of Goodwin lawyers exploring the topics that are most relevant for the healthcare industry today. From ever-changing regulatory guidelines to digital health, women's health and privacy, Goodwin will take attendees through these topics and more and provide guidance to help you navigate the current healthcare landscape.

View the Video:

Goodwin's Clinical Trials Service Offering



Given the breadth of clinical-stage companies that the Goodwin FDA and Healthcare teams advise, our regulatory attorneys together with our commercial contracting, products liability and insurance attorneys play an integral role in counseling clinical-stage companies on matters related to the conduct of clinical trials.

Learn more about our clinical trials service offering **here**.

Moving from the Informed Consent to Approved Labeling: Preparing for Risks in Product Marketing & Use Webinar Recording

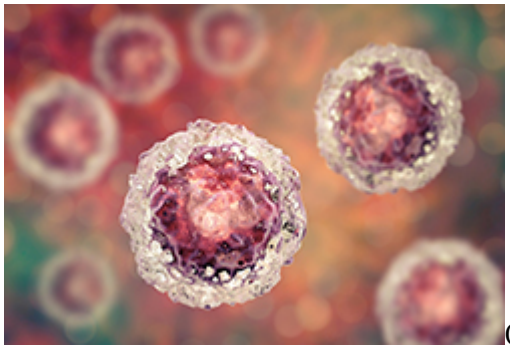
On February 3, 2021 Goodwin FDA Regulatory partner, **Julie Tibbets**, Products Litigation + Counseling partner, **Nilda Isidro**, and Risk Management & Insurance counsel **Brian**

Mukherjee discussed what drug and biologic companies with late-stage product candidates can do to best position their products to mitigate the risks that come with transitioning from clinical trials to marketing and sales.

Our speakers – leaders in life sciences regulatory compliance, product litigation preparedness, risk management, and insurance – highlighted best practices surrounding pharmaceutical promotion, preparing for risks inherent in the marketing and sale of prescription drugs, and the ways in which insurance can help mitigate those risks. This webinar identified key takeaways for companies that are nearing FDA approval and are poised to launch their commercial products.

Click **here** to view the slides and webinar recording.

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.