

[Seven Tips for Healthcare & Life Sciences Companies Engaging Independent Monitors and Compliance Experts](#)



For a healthcare or life sciences company settling a government enforcement action, the prospect of being subject to an independent monitor, independent review organization (IRO), or other government-mandated compliance expert may become a reality. (We collectively refer to all of these individuals and entities as monitors throughout this update.) Hiring an independent monitor is a sensitive topic, as a company subject to a monitorship is required to open up its records and files, financial information, proprietary and confidential materials, IT assets, and employees to a third party — often at frequent and regular intervals, and often for a period of five years — not to mention the potential multimillion-dollar expense associated with the engagement.

Read the client alert [here](#).

[FDA’s Final Q&A Guidance on Risk-Based Monitoring of Clinical Trials Provides Additional Recommendations for Sponsors](#)



The U.S. Food and Drug Administration (FDA) recently finalized its guidance, “[A Risk-Based Approach to Monitoring of Clinical Investigations](#)” (the “2023 RBM Guidance”) which follows up on the Agency’s March 2019 draft guidance (the “Draft Guidance”) of the same name and expands on (but does not supersede) the FDA’s August 2013 guidance, “[Oversight of Clinical](#)

Investigations - A Risk-Based Approach to Monitoring” (the “2013 RBM Guidance”), with new recommendations summarized below to aid sponsors in implementing an effective and efficient risk-based approach to monitoring both risks to participants and to data integrity throughout all stages of clinical investigations of human drug and biological products, medical devices, and combination products.

(1) Approach: Identify, assess and re-assess risks. Create a plan to manage, mitigate, and/or eliminate those risks, including those risks that are newly identified or may not have been anticipated.

- Risk assessments should inform clinical trial protocol design, investigational plans, and monitoring plans and should be reevaluated and revised throughout the investigation. The monitoring plan should be comprehensive in highlighting identified risks, even those less likely to occur but that could have a significant impact on trial quality or subject safety, and should note how risks will be managed, mitigated, or eliminated.
- Consider how easily detectable the identified risks are, and the severity and consequences of those risks to human subject welfare and data quality if not detected and addressed.
- Assess systemic risks, as well as site-specific risks, and consider whether site-specific risks have the potential to become systemic risks.
- Determine an approach to on-site monitoring visits by taking into account the risks identified and the complexity and intensity of a clinical investigation. Monitoring activities should evolve based on risks identified during trials and should be proportionate to the risks to participants’ rights or safety or to data integrity.
- Implement a centralized monitoring approach to help minimize missing data and protocol deviations in real-time, such as through the use of electronic data capture systems.
- The risk assessment should guide how and to what extent source data verification (SDV) will be utilized during on-site monitoring visits.
- Establish processes to ensure appropriate blinding is maintained. Identify and monitor deviations which could result in unintentional unblinding.
- Be prepared during an FDA inspection to furnish documentation of the sponsor’s initial risk assessment, if requested.

(2) Content: Components of the monitoring plan should help explain how the sponsor intends to address the risks that could affect the investigation.

- Include the following components (in addition to those recommended in the 2013 RBM Guidance) in the monitoring plan:
 - Overall investigation design, including blinding and randomization procedures and processes for confirming randomization is performed according to the protocol and investigational plan
 - Sample plan(s), including rationale for, and approach to, identifying the records and data that will be monitored
 - Description of particular issues that would trigger immediate escalation
 - Approach for assessing and addressing a site issue that could escalate into a systemic issue that may warrant protocol or investigation plan changes
- Reference other clinical investigation management plans in the monitoring plan rather than repeating the information in the current monitoring plan to avoid inconsistencies.

(3) Communicate: Promptly address and communicate monitoring results to the appropriate parties to mitigate and eliminate risk.

- Perform monitoring in accordance with the pre-established monitoring plan and address issues

as the monitor identifies them, including escalation, if needed.

- Perform a root-cause analysis of issues and promptly implement corrective and preventive actions (CAPAs).
- Consider amendments or revisions to the protocol or the investigational plan.
- Communicate and document significant issues to the relevant parties involved at the sponsor and site level, which may also include institutional review boards, data monitoring committees, and/or regulatory agencies, such as the FDA.
- Provide reports of monitoring activities in a timely manner to the site and discuss the findings with the clinical investigator and site staff. Reports should follow the 2013 RBM Guidance.

While the FDA's regulations require sponsors to monitor the conduct and progress of their clinical investigations, there are no specifics on *how* sponsors are to conduct such monitoring. FDA's guidance provides helpful direction on clinical trial monitoring while recognizing that a monitoring approach should evolve over the course of a trial as risk assessments evolve. Sponsors with upcoming or ongoing clinical trials should consider FDA's recommendations in monitoring plan development and execution of monitoring activities throughout a trial.

Leveraging Investigator-Initiated Trials in Rare Disease Drug Development

Investigators interested in rare disease treatment development have the opportunity to approach drug and biologic developers to obtain investigational drug supply for trials in which the investigators, typically at academic institutions, act as sponsor-investigators. Similarly, companies open to extending their product development pipelines can look to investigator-initiated trials as a mechanism to better understand the overall safety profile for their product candidates while exploring the potential therapeutic utility of their product candidates in diseases where unmet medical needs remain. So often, those needs exist in rare diseases where populations are small and investment returns are difficult to project. Drug developers deciding whether to supply investigational products to sponsor-investigators looking to explore therapeutic potential in areas of their research interests should evaluate what level of involvement to exercise over the investigator-initiated trial. We highlight some of these considerations below.

Company Considerations for Level of Involvement in Investigator-Initiated Trials

- Availability of resources to support the trial
 - Amount of investigational product
 - Funding for conduct of trial
 - Other trial support (e.g., administrative, monitoring plan, data management, regulatory submission assistance, training, recruitment, etc.)
- Relationship-building between Company and Investigator and Investigator's Institution
 - Establish a relationship that may lead to future collaboration opportunities for Company-sponsored trials
- Opportunity to utilize trial data to support additional Company INDs, to evaluate potential for expanding product indications (in the case of approved products), etc.
- Desire to have:
 - Input on proposed trial design and later amendments thereto
 - Access, where possible, to emerging data
 - Ability to publish data from the trial
 - Ownership rights in the trial data
 - Inventorship and other intellectual property rights that may arise from the trial
 - Termination rights



Ultimately, drug developers hold the decision-making power over whether to allow investigator-initiated research for their product candidates. Thereafter, the contracting process around the setup of an investigator-initiated trial and clinical supply agreement provides drug developers the opportunity to negotiate their level of involvement in the research of their candidates. In negotiating the setup of investigator-initiated research supply, drug developers often balance their support of research into what are often unmet needs with limited company resources, limited supply that may be available and any potential risks that may flow from trial learnings in the proposed disease space. As an upside, investigator-initiated trials afford developers the opportunity to extend their research reach and product development pipelines, so any interest by investigators to conduct research with industry candidates warrants consideration.

[Understanding Data Monitoring Committee Conflict of Interest Limitations](#)



For sponsors utilizing a data monitoring committee in their trial designs to monitor for emerging safety signals, lack of effect, and/or futility of treatment, understanding data monitoring committee conflict of interest limitations is important to ensuring an

objective view of the data from a trial. Where we see these conflict of interest considerations put to the test most often is in rare disease trials where the available pool of informed experts can be just as small as the patient populations under study. As explained in FDA's final [guidance](#) for industry on this topic, core considerations for avoiding potential conflicts of interest in data monitoring committee member selection include:

- **Financial interests.** Here, careful consideration must be given to whether any prospective committee member holds ownership interests in the sponsor entity or stands in a position to benefit financially from the outcome of the trial. This can include equity or stock interests, employee or temporary employee status, paid consulting or advisory board relationships with the sponsor, prior research funding from an institution involved in the study, whose product is being evaluated in the study or competes with a product being evaluated in the study, among other things. FDA generally recommends against appointing any committee members with *ongoing* financial relationships to the trial's sponsor.
- **Other roles in the trial.** Those individuals entering subjects into and conducting a trial stand in a considerable conflict position given their knowledge of interim data emerging from subjects at their trial site which could influence the recruitment or monitoring trends of those individuals for the trial. As such, FDA generally recommends against appointing any committee member who is serving as an investigator in the trial the data monitoring committee would oversee. Additionally, FDA disfavors appointment of any members that have had input into the design of the trial or are involved in the conduct of the trial in any other role for similar reasons.
- **Intellectual conflicts.** Perhaps most challenging to evaluate and navigate in rare disease trials is the risk to objectivity that strongly held views of prospective data monitoring committee members could play in their ability to review the data in a fully objective manner. This could include prospective committee members with strong views on the relative merits of the intervention under study vs. others under development. Additionally, FDA recommends against appointing committee members with strong relationships to or personal differences with trial investigators or to sponsor employees which are likely to cloud their objectivity.

FDA recognizes the tension that sponsors must navigate between placing a high value on independence and avoidance of conflicts of interest in the composition of its data monitoring committees, on the one hand, and understanding the importance of a well-informed data monitoring committee to the effective oversight of emerging data from a trial, on the other. While there is no one-size-fits all approach, data monitoring committee charters and sponsor conflict of interest policies can be helpful in this regard to establish and document the sponsor's limitations on engagement and interaction with the committee and vice versa. The more interconnected the sponsor-developer and investigator communities become, the more challenging it may become for sponsors, particularly those in the rare disease space, to ensure the objectivity of its data monitoring committees.

[Avoiding Misbranding: Words Matter When](#)

[Describing the Regulatory Status of 510\(k\) Cleared Devices and Registered Device Establishments](#)



When it comes to discussing medical devices regulated by the U.S. Food and Drug Administration (FDA), words such as “approved” and “cleared” cannot be used interchangeably as these terms carry a particular meaning. Similarly, creating an impression of approval of a device establishment or its devices because the establishment is registered with FDA also is prohibited. Long-standing regulatory provisions, [21 C.F.R. § 807.97](#) and [21 C.F.R. § 807.39](#), set forth, respectively, the FDA’s position that approval and clearance are not interchangeable and that device establishment registration does not denote approval of the establishment or its devices. Importantly, these provisions also highlight the consequences to industry for misusing terms when discussing the regulatory status of a device or a device establishment.

When seeking to market a new device for which a premarket notification must be submitted to the FDA demonstrating that the device to be marketed is substantially equivalent to a legally marketed device, the submitter must obtain an order of substantial equivalence from the FDA, which is commonly referred to as a 510(k) *clearance*. Conversely, to market a new device for which a premarket approval application must be submitted to the FDA, the applicant must obtain FDA’s *approval* of the application. While FDA review and FDA action occur for both types of medical devices, the outcomes of clearance and approval are distinctly different and carry legal consequences. Specifically, 21 C.F.R. § 807.97 states that “[a]ny representation that creates an impression of official approval of a device because of complying with the premarket notification regulations is misleading and constitutes misbranding.” Additionally, 21 C.F.R. § 807.39 states that “[a]ny representation that creates an impression of official approval because of registration or possession of a registration number is misleading and constitutes misbranding.”

We researched Warning Letters in [FDA’s Warning Letter Database](#) and found that FDA issued four Warning Letters citing violations of § 807.97 since 2017 and thirteen Warning Letters citing violations of § 807.39 since 2017.

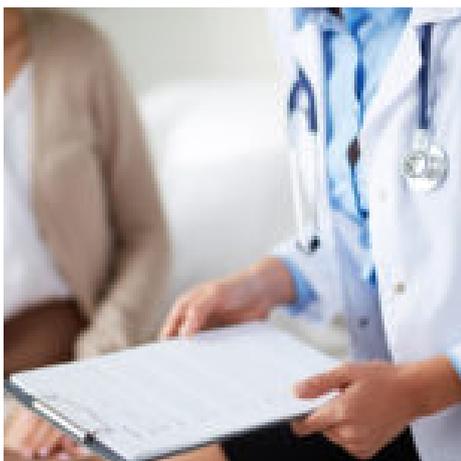
Many of the representations that FDA found to be misleading under § 807.97 were straightforward violations, such as language on product websites stating that cleared devices are “FDA approved,” or listings of device clearances under the heading “FDA Approvals.” In one instance, FDA found the website to be misleading under both § 807.39 and § 807.97 because the company claimed the device had been cleared by the FDA, when in fact it was marketing a 510(k) exempt device for an indication that would require a de novo authorization which the company had not obtained, and the website claimed the company maintained an active listing, which was hyperlinked to the company’s FDA Establishment Registration and Device Listing for only the 510(k) exempt device.

In response to the COVID-19 public health emergency, FDA issued twelve Warning Letters related to representations regarding masks and antibody tests that were found to be misleading under § 807.39. In virtually all of these instances, company websites displayed unofficial “certificates of FDA registration” issued by third parties which claimed to certify that the manufacturer had completed FDA Establishment Registration and Device Listing. These certificates often incorporated unauthorized reproductions of FDA’s logo and motifs of the U.S. flag, giving the impression of official government documents. FDA consistently found the display of these certificates to be misleading, even when they included ostensible “disclaimer” language stating that the certificates did not denote FDA endorsement or approval. FDA repeatedly found that these disclaimers did not adequately limit or otherwise mitigate the misleading impression of the certificates because they were phrased, designed, and placed in a manner where they could be easily overlooked.

These Warning Letters present a cautionary tale to all sponsors intending to market new medical devices. While sponsors may be tempted to claim their devices are approved by the FDA following the agency’s review of a premarket notification or upon completion of FDA Establishment Registration and Device Listing, § 807.97 and § 807.39 make clear that such claims will constitute misbranding. Sponsors can avoid § 807.97- and § 807.39-related Warning Letters and associated liability by carefully reviewing all of the language on their marketing materials and websites to ensure that none of their representations create the impression of official approval based on reference to a premarket notification submission or establishment registration.

Visit the [Goodwin on Medtech hub](#) to stay informed on important developments affecting medtech innovators and investors.

[Common Bioresearch Monitoring Violations: Updates from FY 2021 to Now](#)



The Bioresearch Monitoring Program (BIMO), run by the U.S. Food and Drug Administration (FDA), oversees the conduct of on-site inspections and data audits of FDA-regulated research in support of new product development and marketing approvals. As a follow up to our [July 2021 post](#), we highlight here the most common violations FDA’s BIMO identified in Fiscal Year (FY) 2021 along with those we have seen so far in FY 2022. Our review focuses on BIMO’s clinical investigator, sponsor, and contract research organization (CRO) inspection outcomes across 516 inspections conducted in FY 2021, as these comprised nearly 85 percent of all BIMO inspections.

Amongst these, 81 percent did not result in any findings of noncompliance. Eighteen percent resulted in findings of noncompliance but without recommending regulatory action, and about one percent resulted in findings of noncompliance recommending official regulatory action. In FY 2021, the most common violations leading FDA to issue a Form FDA 483, FDA's official form for documenting noncompliant inspection findings, included:

- **Failure to submit an IND application.** For example, FDA issued several Warning Letters for investigations of dietary supplements or foods determined by the FDA to be drugs. FDA found that the study designs demonstrated the investigational products were intended to cure, mitigate, and/or treat a disease or condition, triggering application of FDA's drug authorities and requiring an Investigational New Drug (IND) application to be in place before conducting the research.
- **Failure to follow the investigational plan and implement corrective or preventive action plans.** For example, in one [Warning Letter](#) resulting from a BIMO inspection, the FDA noted that the investigator failed to exclude subjects according to the study's exclusion criteria and did not identify any procedures in place to prevent future violations.
- **Inadequate or inaccurate recordkeeping (including case histories, study records, and drug disposition records).** For example, in one recent [Warning Letter](#) following a BIMO inspection, the FDA noted that a study site failed to retain necessary documents for 2 years following marketing approval when it could not locate informed consent forms and case report forms, amongst others, from a study for which a Biologics License Application was pending.

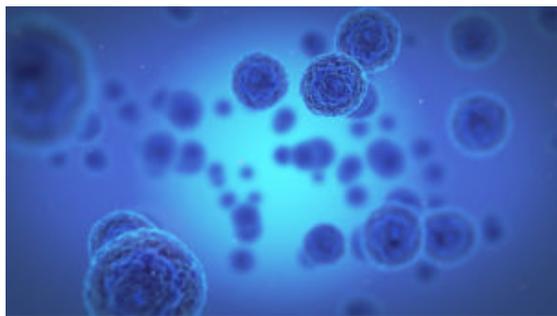
Of note, these continue to be the most frequently cited violations in BIMO Warning Letters issued to date in 2022. To avoid these missteps and better understand the scope of their respective responsibilities before, during, and after a clinical trial, sponsors, CROs and investigators should review [FDA's BIMO Compliance Program Guidance Manuals](#) and ensure adoption of standard operating procedures (SOPs) that provide an infrastructure for regulatory compliance. Sponsors and investigators should also ensure that they understand when an IND application is required, and review the requirements for appropriate recordkeeping during and after a clinical trial. Finally, sponsors and CROs should have mechanisms in place to both promote protocol adherence and promptly respond to any deviations when they inevitably occur. Sponsors receiving BIMO Form FDA 483s should respond with a detailed explanation of their root cause findings, corrective actions, and their plan to prevent similar missteps in the future. The Goodwin FDA team works closely with sponsors to apply FDA's Good Clinical Practice requirements and to resolve BIMO inspection findings when they occur.

[Connect](#) with our Goodwin FDA team to learn more.

*Maura Friedlander, a 2022 summer associate in Goodwin's Washington, D.C. office, contributed to this post.

[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.

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.

[Navigating the New Normal: Biomanufacturing Goes Local](#)



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 [full insight](#).

[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.