

[New Momentum for a Time-Limited Conditional Approval Pathway for Rare Disease Drugs](#)



On October 4, 2024, a US House version of the revised Promising Pathway Act (PPA) 2.0 was introduced, sponsored by Rep. Bruce Westerman (R-AR). The bill ([H.R.9938](#)) mirrors a US Senate version that was introduced in May 2024 ([S.4426](#)) that would authorize the US Food and Drug Administration (FDA) to grant time-limited conditional approval to drugs for rapidly progressive, terminal diseases with substantial unmet need for treatments that are eligible for the Orphan Drug Act and result in a substantially shortened lifespan, substantial reduction in quality of life, or other substantial adverse health effects.

Read the full insight [here](#).

[Common FDA Bioresearch Monitoring \(BIMO\) Violations: Updates from FY 2023 to Now](#)



The Bioresearch Monitoring (BIMO) Program, operated by the U.S. Food and Drug Administration (FDA), conducts on-site inspections and data audits in order to effectively monitor the compliance of all FDA-regulated research.

As a follow up to our [July 2023 post](#), we highlight the most common violations identified in Fiscal Year (FY) 2023, in addition to those observed thus far in FY 2024. BIMO conducted **1073** inspections in FY 2023. The majority of these inspections (approximately 79%) were of drug,

biologic, or medical device study clinical investigators, institutional review boards (IRBs), sponsors, clinical research organizations (CROs), and sponsor-investigators. Some of the most common inspection outcomes are highlighted in our alert linked below. Our methodology included a search of FDA's Warning Letter database for FY 2023 and 2024, to date, for letters issued by BIMO and the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health to IRBs, CROs, clinical investigators, sponsors, and sponsor-investigators.

Read the full alert [here](#).

FDA Issues Overdue Draft Guidance on Clinical Trial Diversity Action Plans



Yesterday, the U.S. Food and Drug Administration (FDA) released its long-awaited [draft guidance](#) on Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies. This draft guidance replaces the agency's similarly-titled April 2022 [draft guidance](#) and has been issued to satisfy a requirement under the [Food and Drug Omnibus Reform Act of 2022](#) (FDORA) that the agency update or issue new draft guidance on the format and content of Diversity Action Plans. Under FDORA, Diversity Action Plans will be required for Phase 3 or other pivotal trials for drugs and for most device clinical trials, although some Diversity Action Plans for device trials can be first submitted with a marketing application such as a premarket notification where an investigational device exemption (IDE) is not required for the trial.

Read the full insight [here](#).

Form FDA 483 Response Best Practices Announced by the FDA



In Draft Guidance published this week by the U.S. Food and Drug Administration (FDA), [Guidance for Industry - Processes and Practices Applicable to Bioresearch Monitoring Inspections](#), the Agency provides some wisdom on best practices for responding to Form FDA 483s, albeit in the context of its Bioresearch Monitoring (BIMO) program inspections, but very much translatable to *any* Form FDA 483 response. FDA notes the following best practices:

A response should demonstrate the establishment's acknowledgment and understanding of FDA's observations. It should also demonstrate the establishment's commitment to address the observations, including a commitment from senior leadership.

Responses should be well-organized and structured to:

- Address each observation separately
- Note whether the establishment agree(s) or disagree(s), and why
- Provide both corrective and preventive actions and timelines for completion
- Provide both completed and planned actions and related timelines
- Provide a method of verifying or monitoring the effectiveness of the actions
- Submit documentation (e.g., training, Standard Operating Procedures (SOPs), corrective action plans, records, etc.)

Importantly, FDA also states that timely Form FDA 483 responses that include "appropriate corrective and preventive actions could impact FDA's determination of the need for subsequent Agency action." FDA encourages responses within 15 business days after the end of an inspection and, helpfully, notes that any responses received within that window "will be considered before further Agency action or decision." Interested stakeholders may submit comments [here](#) on FDA's Draft Guidance until August 5, 2024.

Please contact [Julie Tibbets](#) or any member of our [Life Sciences Regulatory & Compliance practice](#) with questions on FDA's Draft Guidance or on responding to Form FDA 483s.

[Designating a Platform Technology: FDA's Long-Awaited Draft Guidance](#)



In newly released [Draft Guidance](#) from the U.S. Food and Drug Administration (FDA) entitled, *Platform Technology Designation Program for Drug Development*, the FDA addresses its new designation program for platform technologies, which is intended to bring efficiencies to drug development, manufacturing, and review processes for applications that incorporate designated platform technologies.

Read the full alert [here](#).

[Common FDA Bioresearch Monitoring Violations: Updates from FY 2022 to Now](#)



The Bioresearch Monitoring (BIMO) Program, operated by the U.S. Food and Drug Administration (FDA), conducts on-site inspections and data audits in order to effectively monitor the compliance of all FDA-regulated research.

As a follow up to our [June 2022 post](#), we highlight the most common violations identified in Fiscal Year (FY) 2022, in addition to those observed thus far in FY 2023. BIMO conducted 766 inspections in FY 2022. The majority of these inspections (approximately 79%) were of drug, biologic, or medical device study clinical investigators, institutional review boards (IRBs), sponsors, clinical research organizations (CROs), and sponsor-investigators. Some of the most common inspection outcomes are highlighted below. Our methodology included a search of FDA's Warning Letter database for FY 2022 and 2023, to date, for letters issued by BIMO and the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health to IRBs, CROs, clinical investigators, sponsors, and sponsor-investigators.

FY 2022:

BIMO conducted 504 inspections of clinical investigators (468 of which were assigned to FDA's drug, biologic, and device Centers), making up over half of BIMO's inspections conducted in FY

2022. Inspections of IRBs, sponsors, CROs, and sponsor-investigators assigned to FDA's drug, biologic, and device Centers comprised another 138 inspections in FY 2022. Of the 504 clinical investigator inspections, only 9 resulted in a classification of "Official Action Indicated" (OAI) and 87 resulted in a classification of "Voluntary Action Indicated" (VAI). The most common inspection observations included: (1) failure to comply with Form FDA 1572 requirements and protocol compliance; (2) failure to follow the investigational plan and protocol deviations; (3) inadequate and/or inaccurate case history records and inadequate study records; (4) inadequate accountability and/or control of the investigational product; (5) safety reporting and failure to report and/or record adverse events; and (6) inadequate subject protection and informed consent issues.

Of the Warning Letters that were issued in FY 2022 to clinical investigators, the most common observations were:

- **Failure to ensure that a clinical investigation was conducted according to its investigational plan.** This finding in various Warning Letters included failure to properly consent participants, failure to properly randomize participants, and/or failure to properly screen potential participants to ensure they met a protocol's inclusion and exclusion criteria prior to enrollment in an investigational plan. For example, in one [Warning Letter](#), an investigator did not ensure that subjects randomized to a specific intervention group received the assigned investigational drug for that intervention group and did not adhere to the blinding protocol.
- **Failure to submit an IND application for the conduct of a clinical investigation with an investigational new drug.** For example (and similar to trends observed in FY 2021), the FDA noted that one [clinical investigator](#) failed to submit an IND for the use of a product that was determined by the FDA to be a drug. The study design demonstrated that the investigational product was intended to cure, mitigate, and/or treat a disease or condition and therefore, an IND application should have been submitted to the FDA prior to commencing any research activities. Another [Warning Letter](#) included a finding that a protocol comprised of a combination product (a drug and device component) required an IND application.

BIMO conducted 81 inspections of sponsors and CROs in FY 2022 (all but one were assigned to FDA's drug, biologic, and device Centers). Of these, 0 resulted in a finding of OAI, though 15 were classified as VAI. The most common inspection observations included: (1) failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan; (2) failure to meet the abbreviated requirements for investigational device exemptions (IDEs); (3) failure to maintain and/or retain adequate records in accordance with 21 CFR 312.57; (4) accountability for the investigational product; (5) failure to comply with Form FDA 1572 requirements; (6) financial disclosures; (7) failure to submit an Investigational New Drug (IND) application and IND safety reports; and (8) failure to submit current list of all participating investigators to FDA at the six-month interval after FDA approval of the study.

FY 2023 Trends (to date):

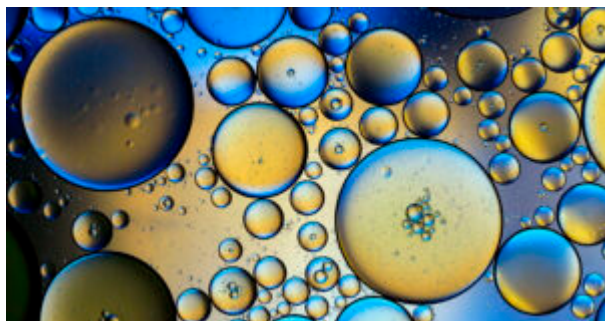
In 2023, we have already observed six Form FDA 483 Warning Letters issued to clinical investigators and IRBs, three involving the failure to submit an IND for the conduct of a clinical investigation with an investigational new drug, two involving failure to follow the clinical investigation according to its investigational plan, and one involving overall lack of IRB oversight and IRB compliance. For example, in a 2023 [Warning Letter](#) issued to an IRB, the FDA noted that the IRB: (a) failed to review proposed research at convened meetings at which a majority of IRB members were present; (b) failed to maintain adequate documentation of IRB activities, including keeping an active list of active IRB members; and (c) failed to ensure that information provided to study subjects as part of the informed consent process was done in accordance with applicable FDA

regulations. Although sponsors may often make the decision to utilize a central IRB to oversee the conduct of a clinical investigation, some participating sites may be required to utilize their own local IRB, and it is important to remember that any IRB which does not adhere to FDA's requirements can introduce a compliance risk for studies it is engaged to oversee.

Sponsors, clinical investigators, CROs, and IRBs should review the FDA's [BIMO Compliance Program Guidance Manuals](#) regularly to ensure that they understand their responsibilities when carrying out clinical research involving human subjects. Sponsors, clinical investigators, CROs, and IRBs should ensure inspection readiness at all times while bioresearch is ongoing and following completion of bioresearch that may support marketing applications submitted to the FDA. Ensuring diligence in the research site selection process, careful monitoring during clinical trials, and corrective actions when deviations occur can help manage the risk of inspection findings of noncompliance or Warning Letters issued by the FDA. The Goodwin Life Sciences Regulatory & Compliance team provides regulatory counseling on FDA's Good Clinical Practice requirements and the resolution of BIMO inspection findings and Warning Letters when they occur.

[Contact](#) our team to learn more.

[Psychedelics & Drug Development – Key Considerations for Healthcare Industry and Life Sciences Companies as Congress Seeks to Tap Into Psychedelics' Therapeutic Potential](#)



Based on recent regulatory changes at the state and local level and the efforts by the federal government and certain foreign agencies, investors, clinical trial sponsors, life sciences companies, and investigators operating in the psychedelics industry may have reason to be optimistic about the future regulatory landscape for therapeutic psychedelic product candidate development, approval, and commercialization. The proposed Breakthrough Therapies Act is one such reason.

On March 8, 2023, US Sens. Cory Booker (D-NJ) and Rand Paul (R-KY) **introduced** an **updated version** of the Breakthrough Therapies Act. If passed, the bipartisan bill would amend the federal Controlled Substances Act (CSA) to enable the Drug Enforcement Administration (DEA) to reclassify from Schedule I to Schedule II drugs and biologics, including therapeutic psychedelics, that receive breakthrough therapy designation or are authorized for expanded access by the US Food and Drug Administration (FDA). Therapeutic psychedelics are Schedule I substances and include LSD, MDMA, and psilocybin. According to the bill's sponsors, the "legislation [would] remove regulatory hurdles that inhibit research and compassionate use access to potentially lifesaving treatments that are heavily restricted by Schedule I of the [CSA]."

The bipartisan effort behind the Breakthrough Therapies Act signals the federal government's evolving position on psychedelic substances, their therapeutic potential, and access. This evolution, discussed in greater detail in our Client Alert, presents an important opportunity for investors, clinical trial sponsors, life sciences companies, and investigators.

Accordingly, we have identified and answered 8 key questions that stakeholders should consider as they develop and innovate in the psychedelic space:

- What Is the Difference Between a Schedule I and a Schedule II Drug?
- What Diseases and Conditions Can Potentially Benefit From Therapeutic Psychedelics?
- What Are the Key Provisions of the Proposed Breakthrough Therapies Act?
- How Does a Drug or Biologic Obtain Breakthrough Therapy Designation From FDA?
- What Is Expanded Access?
- What Are Some Key Limitations in the Proposed Breakthrough Therapies Act?
- What Is the Status of Therapeutic Psychedelics at the State and Local Level?
- What Regulatory Changes Are on the Horizon for Therapeutic Psychedelics?

Read the full client alert [here](#).

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.

Clinical Trial Diversity Plans and Rare Diseases



Clinical trial diversity is not a new concept—the U.S. Food and Drug Administration (FDA) issued a [draft guidance](#) providing specific recommendations to industry on how to improve diversity in clinical trials in April 2022 which we blogged about [here](#)—but the passage of the Food and Drug Omnibus Reform Act, or FDORA, highlighted that the FDA will continue pushing sponsors to make progress on this front. Sponsors of rare disease trials, in particular, know that the act of *increasing* clinical trial diversity is not an easy undertaking, especially when working with already limited rare disease populations. However, the FDA’s focus on ensuring diversity among trial participants may present new opportunities for designing and executing clinical trials in rare disease indications.

Under [FDORA](#), sponsors of new investigational drugs will be required, unless waived by the FDA, to submit a “diversity action plan” for all Phase 3 clinical trials or, as appropriate, another pivotal study in support of a future marketing application (there is also a similar requirement for sponsors of medical devices where a trial is conducted under an investigational device exemption). Under FDORA, this plan is required to include the sponsor’s goals for enrollment in the study, the rationale for those goals, and an explanation of how the sponsor intends to meet those goals. While FDORA requires these elements to be included and that FDA issue guidance on the form and format of diversity plans, FDORA does not expressly restrict a sponsor from providing additional information with its description of goals. For rare diseases, some education and background on the disease population may be warranted in submission of sponsor diversity plan goals.

Under FDORA, sponsors must submit their plan no later than when they submit their Phase 3 or other pivotal trial protocol, and the FDA has the authority to modify the plan or to waive the requirement for a plan altogether in certain circumstances, such as if conducting a clinical trial in accordance with a diversity action plan would otherwise be impracticable.

During FDA’s Rare Disease Day 2023, agency officials noted that the FDA has long encouraged diversity, including through guidances issued prior to the April 2022 draft guidance, but the passage of FDORA marks the first time that addressing diversity with a prospective plan is a *requirement* in the development process. With that in mind, speakers pointed out that developing a candidate in a

rare indication is all the more reason to develop a strategy to enroll as many eligible patients as possible.

Sponsors in the rare disease space should consider the following strategies to increase diversity in their trials, where feasible:

- Engage advocacy groups and community health groups (early and often), as these groups deeply understand their populations' specific barriers to research participation and the types of accommodations that should be considered when designing trials to minimize burdens and maximize participation;
- Create more inclusivity at the study design stage, such as by widening eligibility criteria, re-enrolling early phase participants in later phase studies, where possible, or conducting cross-over extension trials, which could make a significant difference in a patient's willingness to participate;
- Simplify the complexity of trials and minimize burdens to patients to participate, where possible, such as through the use of local laboratories for testing, or consolidating assessments to be done at a smaller number of in-person visits during the trial;
- Adopt as part of the trial design access to telemedicine and technology-driven solutions, which can help promote more inclusiveness with respect to socioeconomic, travel/location, and language barriers; and
- If using a contract research organization, or CRO, partner with a CRO, or other third-party vendor, that can demonstrate experience supporting and achieving diverse population enrollment and a community-first approach.

We anticipate that the FDA's specific recommendations for sponsors will continue to evolve, as FDORA requires the FDA to issue new draft guidance or update existing draft guidance within 12 months of the enactment of FDORA. At this stage, however, sponsors have an opportunity to propose creative and innovative approaches to designing, recruiting patients for, and conducting their Phase 3 and pivotal clinical trials, even in the rare disease space.