Charting a Conditional Approval Pathway for Rare Disease Drugs – A Top Priority for a Revamped FDA?

On April 18, U.S. Food and Drug Administration (FDA) Commissioner Marty Makary **announced plans** to roll-out a new approval pathway for rare disease drugs. Commissioner Makary's comments build on sentiments expressed across both the patient community and industry that rare disease drug development needs greater regulatory flexibility in order to speed access to treatments for patients with no or limited options. This is an initiative that has also been **trumpeted by Janet Woodcock**, former Principal Deputy Commissioner and Acting Commissioner of the FDA, in her work since retiring from the FDA. Prior legislative proposals (including the "Promising Pathway Act" **proposed** in 2024) have attempted to create a time-limited conditional approval pathway in the rare disease space, and Commissioner Makary's remarks may signal a renewed push for action.

In last week's interview, Commissioner Makary emphasized the following potential eligibility factors in how he is thinking about a new "conditional" approval pathway: rare conditions affecting only a small number of people, where a randomized clinical trial has not been conducted and is not feasible, but where a "plausible mechanism" physiologically exists. Commissioner Makary also noted that post-approval monitoring of adverse events and other data may be an important tool to support more flexible regulatory decision making about drug approvals.

Whether *and when* the FDA or Congress will take further steps in outlining a conditional approval pathway, and what form that outline may take (e.g., Agency guidance, expansion of the current accelerated approval authorities, or new legislation), remains unclear at this time. This is an area rare disease researchers and developers should monitor for developments, including any opportunities to provide comments to the FDA on its potential plans.

FDA Publishes Its First Draft Guidance On Use of Artificial Intelligence in the Development of Drugs and Biological Products

On January 7, 2025, the FDA issued a draft guidance called **Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products**. The document clarifies how sponsors, manufacturers, and other industry developers should approach artificial intelligence (AI) to support safe, effective development and marketing of AI-based tools.

The guidance discusses the use of AI models in the nonclinical, clinical, post-marketing, and manufacturing phases of the drug product life cycle, where the specific use of the AI model is to produce information or data to support regulatory decision-making as it relates to safety, efficacy, or the quality of the product. It does not cover AI use in drug discovery or operational efficiencies that do not affect patient safety, drug quality, or study reliability.

Read the full alert **here**.

FDA Platform Technology Draft Guidance Highlights Utility of Obscure Patent Term Extension Provision

As discussed in a **prior Goodwin Alert**, the US Food and Drug Administration (FDA) recently released **Draft Guidance for designating a platform technology for drug development** pursuant to § 560k of the Federal Food, Drug, and Cosmetic Act. The platform technology program was included as part of the PREVENT Pandemics Act "to bring significant efficiencies to the drug development or manufacturing process." Specifically, a platform technology must have the "potential to be incorporated in, or utilized by, m**ore than one drug** without an adverse effect of quality, manufacturing or safety."

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**.

Form FDA 483 Response Best Practices Announced by the FDA

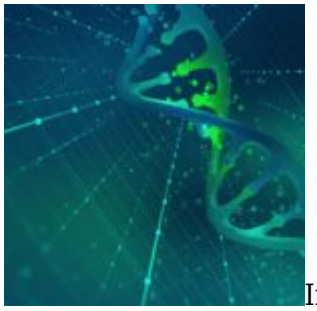
 In Draft Guidance published this week by the U.S. Food and Drug Administration (FDA), **Guidance for Industry – Processes and Practices Applicable to Bioresearch Monitoring Inspections**, the Agency provides some wisdom on best practices for responding to Form FDA 483s, albeit in the context of its Bioresearch 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**.

FDA Finalizes Rule and Sets Course to Phase In Oversight of Laboratory Developed Tests

 On May 6, 2024, following more than a decade of discourse with interested stakeholders on potential approaches to regulation of laboratory developed tests (LDTs), the U.S. Food and Drug Administration (FDA) published its **final rule** setting forth its framework for oversight of LDTs. The final rule and accompanying policy to phase out the agency's general policy of "enforcement discretion" for LDTs comes roughly six months after FDA published its **proposed rule** that outlined the agency's proposed approach to increasing oversight over LDTs. As detailed in our prior analyses of the proposed rule (see **here** and **here**), FDA proposed to implement a **phaseout policy** that would, across five stages and within four years, apply to clinical laboratories offering tests as LDTs the same regulatory requirements applicable to in vitro diagnostics (IVDs).

The proposed rule received more than **6,500 comments**, and while FDA did not change its amendments to the regulation or meaningfully modify the phaseout timeline, FDA has significantly modified its phaseout policy to extend full or partial enforcement discretion to additional categories of LDTs, creating a framework whereby the agency intends to take a more targeted enforcement approach, particularly in the near-term, to addressing LDTs.

You can read our more in our **Insight**, where **Steven Tjoe**, **Matt Wetzel**, and **Sukrti Thonse** highlight the key features of the final rule and five-stage phaseout policy. Be sure to bookmark our dedicated **LDT Resource Page** to stay informed on the latest news and analyses on LDTs.

Master(ing) Protocols for Randomized Umbrella and Platform Trials

 The U.S. Food and Drug Administration (FDA) recently issued a draft guidance, "**Master Protocols for Drug and Biological Product Development**", that echoes and builds on principles that the Agency previously set forth in guidance for **COVID-19 master protocols (2019)**, **master protocols in oncology (2022)** and **clinical trials for multiple versions of cellular or gene therapy products (2022)**. The draft guidance offers numerous (and at times *very* detailed) recommendations to facilitate the design, efficient analysis of data, and regulatory review of clinical trials conducted under such master protocols.

As a starting point, this draft guidance defines several key terms, including the types of trials that can be conducted under a master protocol:

Master Protocol	a protocol designed with multiple substudies, which may have different objectives and involve coordinated efforts to evaluate one or more medical products in one or more diseases or conditions within the overall study structure.
Umbrella Trial	evaluates multiple medical products concurrently for a single disease or condition
Platform Trial	evaluates multiple medical products for a disease or condition in an ongoing manner, with medical products entering or leaving the platform
Basket Trial	evaluates a medical product for multiple diseases, conditions, or disease subtypes

Master protocols offer sponsors the ability to streamline drug development through shared control groups, study infrastructure and oversight. However, these protocols also involve increased complexities and design challenges that generally require a higher degree of coordination. Here, we highlight some key design and analysis considerations addressed in the draft guidance:

Randomization

Sponsors should consider allocating more subjects to control arms than for each individual drug arm to increase power and reduce the risk of a poorly or highly performing control arm. For a platform trial, a sponsor should create a plan for changes to the randomization ratios that can occur as products enter and exit a platform trial. In umbrella or platform trials comparing different drugs, the sponsor should ensure that the randomization process prevents subjects from being randomized to

drugs they are not eligible to receive given each drug's exclusion criteria.

Informed Consent

Sponsors should cover all treatment arms in their informed consent and obtain consent prior to randomization. In a platform trial where drugs are entering and exiting the study, consent forms should be modified accordingly to reflect the drugs currently under evaluation. FDA also recommends the use of a central IRB to review informed consent forms, the protocol, and other relevant documents for monitoring of a trial conducted under a master protocol.

Blinding

Given the potential for different administration methods for various drugs included in umbrella or platform trials, unique blinding challenges may arise and sponsors should discuss their proposed approach to blinding with FDA early in the planning stage.

Safety Data

Safety data from a master protocol can be considered part of overall safety database but data from other sources may be needed to support approval. The type of master protocol and the drugs being evaluated will impact the approach to safety data collection. FDA also recommends that a data monitoring committee (DMC) or other independent, external entity review accumulating safety and efficacy data to minimize inadvertent dissemination of information that could pose risks to trial integrity.

Regulatory Review Considerations

Each master protocol should be submitted as a new IND, and FDA recommends that the sponsor request a pre-IND meeting to discuss the protocol and other IND submission details. Given the potentially rapid pace of changes in a master protocol, the draft guidance recommends specific procedures for protocol amendments, including cover letters for each protocol amendment that update on the status of each drug and notifying the RPM at least 48 hours before submitting any protocol amendment that could substantively affect the master protocol. The IND should also include a well-designed communication plan to facilitate timely and effective communication between multiple stakeholders, including rapid communication of serious safety information and protocol amendments to investigators and FDA.

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Comments on this draft guidance are due February 22, 2024. Please contact the authors or your Goodwin attorney with any questions or if you would like to submit a comment.

2023 State Drug Transparency Law Development Update

 In October 2021, we **reported** on an uptick in the passage of state drug price transparency legislation. As an update to that report, as of October 2023, approximately 22 states have now passed drug price transparency laws creating new requirements for drug manufacturers.

Each state has its own unique set of requirements, but reporting is often completed via an online portal administered by the state's implementing agency. Generally, these laws require manufacturers to report pricing and other information related to the cost, development, and sale of drugs to the state or state-affiliated entities. Some states will use this data to produce public reports about the cost of prescription drugs with the goal of creating pricing transparency for drug manufacturers as well as to educate the state legislature and public about the drug pricing process.

Read the full alert **here**.

How to Get Your SIUU Out: FDA Provides Long-Awaited Update for Industry on Communicating Off-Label Information

 On October 23, 2023, FDA announced the availability of a revised draft guidance titled "Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products." The draft guidance supersedes the agency's 2014 draft guidance, "Distributing Scientific and Medical Publications on Unapproved New Uses," and it provides more direction for industry on how information regarding unapproved uses of approved/cleared medical products can appropriately be shared with healthcare providers (HCPs).

The draft guidance coins a new acronym, SIUU, for scientific information on unapproved uses of an approved/cleared medical product, and provides recommendations for how to communicate SIUU in a "truthful, non-misleading, factual, and unbiased" manner. FDA explains that HCPs can prescribe medical products for unapproved uses when they determine that an unapproved use is medically appropriate for a given patient, but it is critical that company communications about unapproved

uses include all of the information necessary for HCPs to evaluate the strengths, weaknesses, validity, and utility of the information about the unapproved use to make these determinations.

The revised draft guidance is organized in a question and answer format and addresses: (1) what firms should consider when determining whether a source publication is appropriate to be the basis for an SIUU communication; (2) what information should be included as part of an SIUU communication; (3) how SIUU communications should be presented (e.g., the format and accompanying disclosures); and (4) recommendations for specific types of materials (including reprints, clinical reference resources, and firm-generated presentations of scientific information from an accompanying reprint).

For industry stakeholders looking to understand what is new and/or different about these recommendations relative to the 2014 draft guidance, we note that the agency continues to recommend providing disclosures about how the information in these communications compares with the FDA-approved labeling, and that such communications be non-promotional in nature. However, the revised draft guidance provides more insight into what studies or analyses are "scientifically sound" and provide "clinically relevant information," such that they could be the basis for SIUU communications. Scientifically sound studies or analyses should "meet generally accepted design and other methodological standards for the particular type of study or analysis performed, taking into account established scientific principles and existing scientific knowledge." Clinically relevant information is information that is pertinent to HCPs when making clinical practice decisions for an individual patient. FDA notes that while randomized, double-blind, controlled trials are the most likely to provide scientifically sound and clinically relevant information, other types of well-designed and well-conducted trials, or even analyses of real-world data, could also generate this type of information. In contrast, studies that lack detail to permit scientific evaluation, communications that "distort" studies, and data from early stages of development that are not borne out in later studies are examples of information that may not be appropriate as the basis of SIUU communications.

Another clear theme in the revised draft guidance is the need to separate SIUU communications from promotional communications. FDA explains that the use of "persuasive marketing techniques" (such as celebrity endorsers, premium offers, and gifts) suggests a firm may be trying to convince an HCP to prescribe or use a product for an unapproved use, not merely presenting scientific content to help an HCP make an informed clinical practice decision, and thus would fall outside the scope of the enforcement policy outlined in the revised draft guidance. FDA also recommends several ways to separate SIUU communications from promotional communications, including using "dedicated vehicles, channels, and venues" for SIUU communications that are separate from those used for promotional communications—such as distinct web pages that do not directly link to each other, sharing the types of information via separate email messages, and dividing booth space to separate the presentation of these types of information at medical and scientific meetings. In addition, FDA advises that if a media platform has features (such as character limits) that do not allow a company to provide the disclosures recommended for an SIUU communication, then that platform should not be used to disseminate SIUU, but could be used to direct HCPs to an SIUU communication (e.g., via a link to a website).

Companies may already be following many of the recommendations in the revised draft guidance, but the updates and clarifications throughout reflect FDA's continued emphasis on ways to appropriately share accurate, scientifically sound data with HCPs to inform clinical practice decisions. In line with the agency's 2018 guidances on **communicating information that is consistent with product labeling** and **communicating with payors, formulary committees and similar entities**, this draft guidance acknowledges the evolving realities of medical product communications and provides guardrails for companies to assess whether and how to communicate

product information that is not included in its FDA-required labeling, while at the same time reminding the industry that there are “multiple important government interests” served by statutory requirements for premarket review and the prohibition on introducing a misbranded product into interstate commerce.

Comments on the draft guidance are due December 24, 2023, and can be submitted to the docket available **here**. Please contact any of the authors or your Goodwin attorney if you have any questions about this revised draft guidance.