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The U.S. Food and Drug Administration (FDA) recently issued a draft guidance, "**Master Protocols for Drug and Biological Product Development**", that echoes and builds on principles that the Agency previously set forth in guidance for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 The draft guidance offers numerous (and at times *very* detailed) recommendations to facilitate the design, efficient analysis of data, and regulatory review of clinical trials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As a starting point, this draft guidance defines several key terms, including the types of trials that can be conducted under a master protocol: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 Here, we highlight some key design and analysis considerations addressed in the draft guidance: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.

* * * *

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.

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.

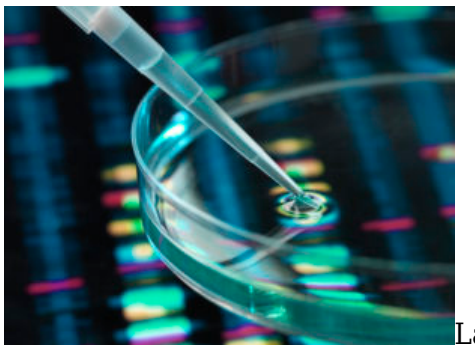
Another clear theme in the revised draft guidance is the need to separate SIUU communications from promotional communications. FDA explains that the use of "persuasive marketing techniques"

(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.

Is it Biosimilar or Interchangeable? It Won't Be Easy to Tell Under FDA's Latest Draft Labeling Guidance



Last week, **FDA released** a draft guidance, "**Labeling for Biosimilar and Interchangeable Biosimilar Products**" that—when finalized—will revise and

replace its July 2018 final guidance, "**Labeling for Biosimilar Products**." FDA noted that this 2023 Draft Guidance reflects recommendations based on the "valuable experience about labeling considerations" that FDA has gained through its approval of 42 biosimilar products, including four interchangeable biosimilar products.

Notably, the 2023 Draft Guidance provides further recommendations regarding when to use a biosimilar or interchangeable biosimilar product name, and when to use the reference product name in labeling:

- The biosimilar or interchangeable biosimilar product's proprietary name[1] (or if the product does not have a proprietary name, its proper name[2]) should be used when –
  - Information in the labeling is *specific to the biosimilar (or interchangeable biosimilar) product*, including such references to the product in the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections, and/or
  - For "directive statements and recommendations for preventing, monitoring, managing, or mitigating risk," including such references to the product in the BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS sections.

- When referring to the *drug substance* in the labeling, the biosimilar or interchangeable biosimilar product's proper name should be used.

- When information *specific to the reference product* is described in the biosimilar or interchangeable biosimilar product's labeling (for example, data from clinical trials of the reference product in the ADVERSE REACTIONS and CLINICAL STUDIES sections), the reference product's proper name should be used.

- In sections of the labeling containing *information that applies to both the biosimilar (or interchangeable biosimilar) product and the reference product*—such as BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS—the labeling should use the core name of the reference product followed by the word "products."[3]

FDA acknowledges that the application of these recommendations is highly context-dependent and may not always be clear, but recommends that biosimilar and interchangeable biosimilar product sponsors evaluate all statements in product labeling carefully to determine the most appropriate product identification approach in each instance.

Another noteworthy aspect of the 2023 Draft Guidance is the Agency's recommendation regarding the biosimilarity statement and footnote in the HIGHLIGHTS section of a biosimilar or interchangeable biosimilar product's labeling.[4] Previously, FDA recommended a biosimilarity statement for a biosimilar product and an interchangeability statement for an interchangeable biosimilar product. The 2023 Draft Guidance now recommends a statement and footnote in the HIGHLIGHTS section that the product is biosimilar to the reference product, *regardless of* whether the product is a biosimilar or an interchangeable biosimilar to the reference product. In the **Federal Register notice** announcing the 2023 Draft Guidance, FDA acknowledges that this marks an "evolution in our thinking" and explains that "a labeling statement noting that certain products within a 351(k) [Biologics License Application] have been approved as interchangeable, and explaining the interchangeability standard, is not likely to be useful to prescribers, who can prescribe both biosimilar and interchangeable biosimilar products in place of the reference product with equal confidence that they are as safe and effective as their reference products." FDA further

states that “information about interchangeability is more appropriately located in the Purple Book rather than labeling.”

Other notable elements of the 2023 Draft Guidance include recommendations regarding how to describe pediatric use data in a range of scenarios and how to incorporate immunogenicity data. With respect to immunogenicity data, the 2023 Draft Guidance suggests that a contextual paragraph[5] generally be included in the relevant CLINICAL PHARMACOLOGY subsection before describing the available immunogenicity data for the reference product and the biosimilar or interchangeable biosimilar product. The 2023 Draft Guidance also outlines the Agency’s expectations for patient labeling—such as a Medication Guide, Patient Information, or Instructions for Use—for a biosimilar or interchangeable biosimilar product, if the reference product has such patient labeling.

Information on how to submit comments on the 2023 Draft Guidance can be found at **https://www.regulations.gov/docket/FDA-2016-D-0643.**

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[1] The proprietary name of a biosimilar product is a brand name determined by the sponsor. The fictitious example provided in the 2023 Draft Guidance is “NEXSYMEO.”

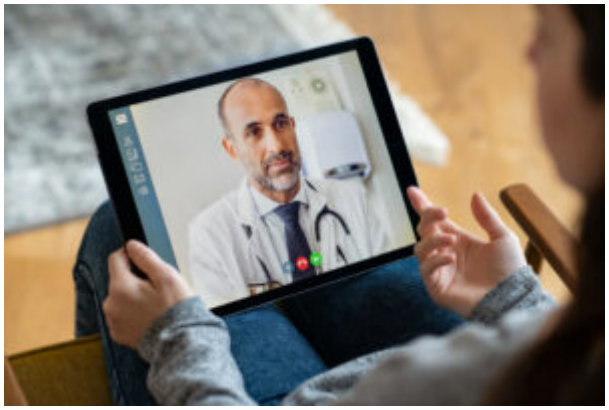
[2] The proper name of a biosimilar product is the nonproprietary name designated by FDA that consists of a biological product’s core name plus a unique four-letter suffix. The fictitious example provided in the 2023 Draft Guidance is “replicamab-cznm.”

[3] The fictitious example provided by FDA in the 2023 Draft Guidance is “replicamab products”.

[4] The fictitious example provided by FDA in the 2023 Draft Guidance is “NEXSYMEO (replicamab-cznm) is biosimilar* to JUNEXANT (replicamab-hjxf)” and the accompanying footnote is “Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of *[BIOSIMILAR OR INTERCHANGEABLE BIOSIMILAR PRODUCT’S PROPRIETARY NAME]* has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration) described in its Full Prescribing Information.”

[5] The Agency’s suggested paragraph is, “The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of [*proper name of reference product*] or of other [*core name*] products.”

The ABCs of DCTs: New FDA Guidance Provides Recommendations for the Conduct of Decentralized Clinical Trials



On May 2, 2023, the U.S. Food and Drug Administration ("FDA") published draft guidance titled "***Decentralized Clinical Trials for Drugs, Biological Products, and Devices***" (the "Draft Guidance"). The Draft Guidance expands on the FDA's **2020 recommendations** issued in response to the COVID-19 pandemic and its **2021 draft guidance** on the use of digital health technologies ("DHTs") in clinical trials, and fulfills the directive under **Section 3606 of the Food and Drug Omnibus Reform Act** to "issue or revise draft guidance [ ] to clarify and advance the use of decentralized clinical studies to support the development of drugs and devices" no later than December 29, 2023.

The Draft Guidance defines a decentralized clinical trial ("DCT") as a clinical trial where some or all of the trial-related activities occur at locations other than traditional trial sites. The FDA clarifies that its regulatory requirements for clinical investigations are the same for DCTs as for traditional clinical trials; however, the Draft Guidance outlines how clinical trial sponsors, investigators, and other stakeholders may meet these requirements in the context of DCTs given the FDA's recognition of the significant potential benefits of DCTs, such as expanding access to clinical trials, increasing trial efficiency, and improving trial participant engagement, recruitment, enrollment, retention, and diversity.

Some of FDA's key recommendations include:

- An important initial determination is whether it is appropriate for a particular trial to be conducted as a fully decentralized or hybrid DCT. Whereas a fully decentralized trial may be appropriate for an investigational product ("IP") that is simple to administer, has a well-characterized safety profile, and does not require complex medical assessments, a hybrid approach may be more appropriate where the trial involves more complex medical assessments or supervision and monitoring of IP administration. The FDA recommends that questions related to the feasibility, design, implementation, or analysis of a DCT should be discussed early with the relevant FDA review division.
- Given that trial-related activities for a DCT may involve a network of locations where clinical trial personnel, local health care providers ("HCPs"), and trial-related services (e.g., labs) may be provided, for inspectional purposes the investigator should select a physical location, to be listed on Form FDA 1572 – Statement of Investigator or in the investigational device exemption ("IDE") application, where trial participant records will be stored and where trial personnel may be interviewed.
- Both sponsor and investigator should evaluate whether certain trial-related activities may be delegated to DCT personnel located near participants' homes. Such activities should not require detailed knowledge of the protocol or IP. Trial-related activities that are unique to the trial or require detailed knowledge of the trial protocol or the IP should be performed by qualified trial personnel who have been appropriately trained.
- Obtaining informed consent remotely may be appropriate for a DCT as long as the process is

adequate and appropriate. Oversight by institutional review boards ("IRBs") should ensure that electronic informed consent at remote locations meets applicable requirements, and the FDA recommends the use of a central IRB in DCTs to provide for more streamlined review of the informed consent documents as well the protocol and other trial-related documents.

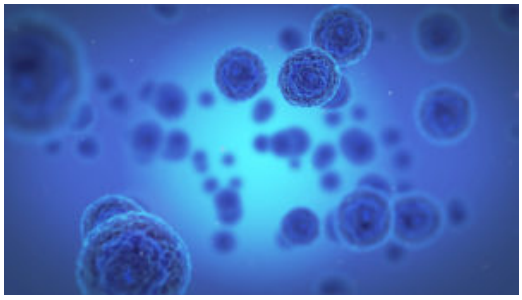
- As with any trial, sponsors must ensure proper monitoring of DCTs based on the sponsor's risk assessment. Sponsors should also implement a safety monitoring plan that accounts for the decentralized nature of the clinical trial, including by prespecifying whether safety data will be collected via telehealth or in-person visits and whether DHTs will be used to collect certain safety information. The Draft Guidance underscores the importance of providing sufficient instruction and contact information to the trial participant should an adverse event occur and allowing the participant to arrange an unscheduled visit (either remotely or in-person), as appropriate. The FDA also recently finalized its **Q&A guidance on risk-based monitoring of clinical investigations**, which we blogged about **here**.
- FDA notes that the "variability and precision" of data obtained from a DCT may differ from data obtained in a traditional site-based clinical trial. For example, remote assessments may vary from on-site assessments, particularly if trial participants are performing their own assessments at home. Similarly, assessments performed by local HCPs may be less precise and consistent than assessments conducted by on-site trial personnel. FDA states that while such variability may not affect the validity of a finding of superiority, it could compromise a finding of non-inferiority relative to an active control drug that has been evaluated in a traditional site-based trial. FDA therefore recommends that sponsors consult with the relevant review division if planning a DCT with a non-inferiority design.
- For telehealth visits during a DCT, investigators should confirm a participant's identity during each visit and complete the relevant case report forms and other documentation for each visit. Additionally, the sponsor and investigator are responsible for ensuring that remote clinical trial visits comply with relevant state telehealth laws and as applicable, the telehealth laws of countries outside the U.S.
- Given multiple sources of data collection in a DCT, the sponsor should develop a data management plan that includes the data origin and data flow from all sources to the sponsor; methods for acquiring remote data from trial participants and personnel; and a list of vendors for data collection, handling, and management.

The Draft Guidance demonstrates the FDA's support of more widespread use of DCTs. At the same time, the Agency acknowledges that DCTs can be challenging to implement successfully, including because DCTs require coordination of trial activities with numerous parties in multiple locations that are not traditional trial sites. The Draft Guidance also notes that if significant safety risks emerge due to remote administration or use of an IP, or if other circumstances arise that warrant in-person visits, the sponsor should discontinue remote administration or use of the IP, inform the FDA, IRB, and investigators, and determine whether the trial should be amended or continue.

Interested stakeholders may submit comments on the Draft Guidance by August 1, 2023 to Docket **FDA-2022-D-2870**.

Contact the authors or another Goodwin FDA team member with any questions or if you would like to submit comments to the FDA on the Draft Guidance.

The Long (Un)Winding Road Part 2: FDA's Final Transition Guidances for COVID-19 Devices



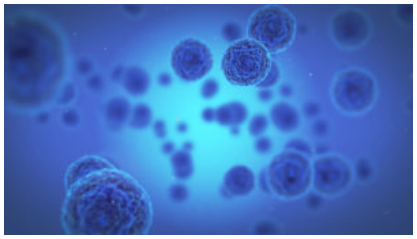
On March 24, 2023, the FDA's Center for Devices and Radiological Health announced the issuance of two much anticipated final guidances that describe the Agency's transition plans for medical devices that fall within certain COVID-19 enforcement policies or that were issued emergency use authorizations ("EUA"s):

- **Transition Plan for Medical Devices That Fall Within Enforcement Policies Issued During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency** (the "Enforcement Policies Final Guidance")
- **Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) Related to Coronavirus Disease 2019 (COVID-19)** (the "EUA Transition Final Guidance")

The guidances follow the announcement in early 2023 that the Biden Administration plans to wind-down a number of pandemic-related programs and to allow the COVID-19 public health emergency ("PHE") declaration, which has been in effect since January 2020, to expire on May 11, 2023.

We summarize some of the key takeaways from FDA's finalized transition plans. Read the client alert **here**.

The Long (Un)Winding Road: FDA Maps Out How the End of the Public Health Emergency Will Impact its COVID-19 Policies



Since the beginning of the COVID-19 pandemic, the United States Food and Drug Administration ("FDA") has issued more than eighty (80) guidance documents describing flexibilities that would be

available to manufacturers of medical devices, drugs and biological products, and foods during the public health emergency. Several of these guidance documents have been modified, updated, or withdrawn as circumstances have changed, and on March 13, 2023, the FDA issued a **notice** in the Federal Register that outlines how it intends to unwind a large swath of COVID-19-related guidance documents that are still in effect. FDA sorted seventy-two (72) COVID-19-related guidances into several categories, based on how long and in what form they will continue to be in effect after the expiration of the public health emergency declaration, which is expected on May 11, 2023.

Read the client alert **here**.

On Remote Control: FDA Issues Draft Guidance to Facilitate Use of Digital Health Technologies for Remote Data Acquisition in Clinical Trials

 During the COVID-19 pandemic, decentralized clinical trials and remote patient monitoring and data acquisition became a necessity, accelerating the use of digital health technologies in clinical trials. Acknowledging that technological advances "have revolutionized the ability to remotely obtain and analyze clinically relevant information from individuals" and that "DHTs [ ] are playing a growing role in health care and offer important opportunities in clinical research," the FDA issued during the last week of December 2021 a draft guidance, ***Digital Health Technologies for Remote Data Acquisition in Clinical Investigations***, which provides recommendations for sponsors, investigators and other stakeholders to facilitate the use of DHTs for remote data acquisition in clinical trials, including clinical trials that will be submitted to the FDA in a marketing application for a medical product.

The draft guidance defines a digital health technology (DHT) as a system that uses computing platforms (such as a mobile phone, tablet, or smart watch), connectivity, software, and/or sensors for healthcare and related uses. Some DHTs may meet the definition of "device" under the Federal Food, Drug and Cosmetic Act, but the draft guidance specifically does not address the circumstances under which a DHT would meet the statutory definition of a device and notes that DHTs used in clinical investigations generally are exempt from premarket clearance or approval requirements, as long as the clinical investigation is compliant with 21 CFR Part 812.

The draft guidance explains that sponsors must foremost ensure that a DHT is "**fit-for-purpose**" for its proposed use in a specific clinical investigation. In essence, the level of verification and

validation associated with the DHT must be sufficient to support its use and interpretability in the clinical investigation. This may require sponsors to work with the developer or manufacturer of the DHT, patients, caregivers, and other technical and clinical experts to assure that the DHT is suitable for its intended purpose in the clinical investigation. The draft guidance advises sponsors to select a DHT that corresponds to the clinical outcome to be assessed, and that considers the clinical trial population and the design/operating characteristics of the DHT that may affect trial participants' use of the DHT.

Sponsors should also be prepared to describe how they will analyze data collected from DHTs in their statistical analysis plan, including prespecifying "**intercurrent events**" (defined as events that occur after treatment initiation that result in missing or erroneous data associated with the clinical outcome of interest) that may be related to the DHT and/or the general purpose computing platform, and how these events will be accounted for in the analysis. To maintain data integrity, FDA recommends that the output of the DHT and associated metadata be transmitted to a **durable electronic data repository** that is protected from alterations and maintained until the end of the record retention period. FDA generally will consider data in such a repository to constitute the source data and should be made available for inspection and to reconstruct and evaluate the clinical investigation.

FDA further notes that "unique privacy risks" may arise when DHTs are used in a clinical trial. Sponsors are advised to evaluate the risk of potential disclosures of personally identifiable information through breaches of the DHT, the general computing platform on which the DHT runs, and/or the durable electronic repository, assure appropriate security safeguards are in place, and consider including such information in the informed consent documents for the clinical trial.

The draft guidance recommends that sponsors:

- train trial participants and trial personnel on the use of DHTs and develop a plan to provide technical assistance to trial participants and study personnel;
- develop a risk management plan to address potential problems with the DHT (e.g., interference between mobile applications, or loss, damage and replacement);
- develop a safety monitoring plan that addresses how abnormal measurements related to participants' safety measured by DHTs will be reviewed and managed; and
- develop a contingency plan for any changes to the DHT (e.g., discontinuation of a specific model, operating system updates)

The draft guidance includes appendices with specific examples of how different types of DHTs could be incorporated into a clinical investigation. Given the particular circumstances of each DHT and clinical investigation, the draft guidance encourages sponsors to engage early with the appropriate FDA Center responsible for the medical product under development to discuss the proposed use of DHT(s) in a clinical investigation and, for DHTs or DHT-collected endpoints that require qualification, engage with an appropriate FDA qualification program, such as the **Medical Device Development Tool Qualification Program**.

Comments on the draft guidance are due March 23, 2022.

Reality Check: FDA Draft Guidance Outlines Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drugs and Biological Products

Last week the FDA issued another draft guidance in its series of recent guidance documents setting forth the agency's views regarding the generation and use of Real-World Data (RWD) and Real-World Evidence (RWE) for prescription drugs and biological products. (see our **recent post** on FDA's draft guidance relating to registries).

This latest draft guidance, **Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products**, clarifies the agency's expectations for sponsors submitting new drug applications (NDAs) or biologics license applications (BLAs) with studies using Real-World Data (RWD) to support the safety or effectiveness of drugs or biological products, when such studies are not subject to FDA's investigational new drug (IND) application requirements under **21 CFR Part 312**. The draft guidance focuses on non-interventional (*a.k.a.* observational) studies, in which patients receive a drug during routine medical practice, according to a medical provider's clinical judgment and based on patient characteristics, rather than via assignment to a study arm and according to a clinical trial protocol.

Key considerations outlined in the guidance:

- *Sponsors designing a non-interventional study to support a marketing application should engage early with the relevant FDA review division* (e.g., through a Type C meeting) and be prepared to submit draft protocols and SAPs for FDA feedback *before* conducting the study analyses.

- *To assure the FDA that the results of a non-interventional study were not skewed to favor a particular conclusion,* sponsors should provide evidence that the non-interventional study protocol and statistical analysis plan were finalized *prior* to reviewing outcome data and *before* performing prespecified analyses. Sponsors should provide a justification for selecting relevant data sources and generate audit trails in their datasets. FDA also recommends that sponsors post their non-interventional study protocols on a publicly available website, such as **ClinicalTrials.gov**.

- *Sponsors must be able to submit patient-level data from the RWD.* Where a third party owns or controls the RWD, sponsors should have agreements with such parties to ensure that patient-level data and source data to verify the RWD can be provided to the FDA for inspection, as

applicable. Sponsors should have well-documented programming codes and algorithms that would allow the FDA to replicate the study analysis using the same dataset and analytic approach.

- *Non-interventional studies should be monitored*. The FDA advises sponsors to use a risk-based quality management approach, with a focus on preventing or mitigating important and/or likely risks to study quality. If a non-interventional study does not include any activities or procedures involving patients, monitoring can focus on assuring the data integrity of the RWD, from extraction to analysis to reporting of results. When a non-interventional study protocol includes ancillary activities or procedures, sponsors should exercise appropriate oversight of processes critical to human subject protection.

- *Adverse events that a sponsor becomes aware of through a non-interventional study must be submitted in accordance with postmarketing safety reporting regulations*. However, the agency acknowledges that if a sponsor is conducting a non-interventional study that appropriately utilizes only a subset of a larger dataset, the sponsor will not have to search the entirety of the dataset for adverse events.

- *Sponsors should take responsibility for all activities related to the design, conduct and oversight of a non-interventional study that is being submitted for regulatory review*. This includes selecting qualified researchers, ensuring the study is conducted in accordance with the protocol, maintaining and retaining adequate study records, and maintaining an electronic system to manage RWD that complies with **21 CFR Part 11**. Where a sponsor engages third parties to perform certain study-related tasks, the responsibilities of each organization should be documented and made readily available to the FDA upon request.

Comments on the guidance should be submitted to the docket by March 9, 2022.

It's Starting to Register: FDA Draft Guidance Addresses Use of Registries to Support Regulatory Decision-Making for Drugs & Biological Products

Showing no signs of food coma, the FDA issued **draft guidance** on the Monday following the Thanksgiving holiday weekend that outlines considerations for sponsors proposing to design a

registry or use an existing registry to support regulatory decision-making about a drug's effectiveness or safety. This draft guidance represents the Agency's latest response to the mandate in the 21st Century Cures Act to issue guidance on the use of real world evidence in regulatory decision-making, and expands on the **Framework for FDA's Real-World Evidence Program** from December 2018.

The draft guidance, ***Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products***, defines a registry as "an organized system that collects clinical and other data in a standardized format for a population defined by a particular disease, condition, or exposure," and identifies three general categories of registries: disease registries, health service registries, and product registries.

Given the range of registry types, FDA notes that registry data can have varying degrees of suitability for use in a regulatory context depending on several factors, including how the data are intended to be used for regulatory purposes, the patient population enrolled, the data collected, and how registry datasets are created, maintained, curated, and analyzed. FDA advises sponsors to be mindful of both the strengths and limitations of using registries as a source of data to support regulatory decision-making. In general, the draft guidance advises that (i) a registry that captures objective endpoints, such as death or hospitalization, is more likely to be suitable to support regulatory decision-making than a registry that collects subjective endpoints, such as pain; and (ii) a registry that is specifically designed to answer a particular research question is more likely to be useful to support regulatory decision-making than a registry that was designed for a different purpose.

At the same time, the Agency acknowledges that an existing registry can be used to collect data for purposes other than those originally intended, and that leveraging an existing registry's infrastructure to support multiple purposes can be efficient. Therefore, the draft guidance describes factors sponsors can use to assess the **relevance** and **reliability** of a registry's data to determine whether the registry data may be fit-for-use.

When determining **relevance** of registry data, the draft guidance advises sponsors to consider, among other things, whether the data elements captured by the registry are sufficient given the intended use or uses of the registry (e.g., external control arm vs. a tool to enroll participants in an interventional study) and whether the methods involved in patient selection may have impacted the representativeness of the population in the registry.

When assessing the **reliability** of registry data, the draft guidance advises sponsors to assure the registry has appropriate governance measures in place to help ensure the registry can meet its objectives, such as processes and procedures governing the operation of the registry, adequate training of staff, and other recommended practices including:

- Defined processes and procedures for data collection, management and storage;
- A data dictionary and rules for validation of queries and edit checks of registry data;
- Conformance with **21 CFR part 11**, as applicable, including access controls and audit trails; and
- Adherence to applicable human subject protection requirements, including safeguarding the privacy of patient health information.

The draft guidance specifically recommends that sponsors interested in using a registry to support a regulatory decision should meet with the relevant FDA review division (e.g., through a Type C meeting), *before* conducting a study that will include registry data. Sponsors also should be prepared to submit protocols and statistical analysis plans for FDA feedback prior to conducting a

study that includes data from registries.

Comments on the guidance should be submitted to the docket by February 28, 2022.

Things for Pharma and Biotech Companies to Watch in the Cures 2.0 Proposed Legislation

Last week, Diana DeGette (D-CO) and Fred Upton (R-MI) introduced in the House highly anticipated bill language for "Cures 2.0", a follow-up to the transformational 21st Century Cures Act enacted in 2016. For full text of the bill, click **here**. The 21st Century Cures Act included a variety of measures seeking to accelerate medical product development and bring advancements and innovations to patients more efficiently. Cures 2.0 seeks to improve and expand on those strides, as well as address pressing public health priorities that became apparent through the COVID-19 pandemic.

The Cures 2.0 bill is structured around five main topics:

- Title I—Public Health
- Title II—Patients and Caregivers
- Title III—Food and Drug Administration
- Title IV—Centers for Medicare & Medicaid Services
- Title V—Research

While all of these sections are ripe for further analysis, we selected a few provisions to highlight here that may be of particular interest for the pharmaceutical and biotechnology companies out there. We'll keep tracking these as the bill moves through the legislative process:

Section 204: Patient Experience Data

- Would require sponsors developing a drug under an IND to collect standardized patient experience data during clinical trials and include that patient experience data "and such related data" in an NDA or BLA; and
- Would direct FDA to consider this patient experience data and "related information" in its approval decision for the NDA or BLA.
- These proposals to standardize and require patient experience data collection could be significant, and they underscore lawmakers' continued interest in elevating the relevance of clinical outcomes that are meaningful to patients living with a disease or condition.

Section 302: Grants for Novel Trial Designs and Other Innovations in Drug Development & **Section 310:** Recommendations to Decentralize Clinical Trials

- Section 302 would appropriate $25 million annually, for 3 years, for the FDA to award grants to clinical trials conducted under an IND with protocols incorporating complex adaptive or other novel trial designs and that collect patient experience data. The section further specifies that grant awards should prioritize the incorporation of digital health technologies and real world evidence.
- Section 310 proposes a multi-stakeholder meeting, including industry representatives and patient advocacy groups, to discuss incentives to adopt decentralized clinical trials. The section also would adopt a definition of decentralized trials: "a clinical trial method that includes the use of telemedicine or digital technologies to allow for the remote collection of clinical trial data from subjects, including in the home or office setting."
- These provisions reflect a sustained emphasis on fostering clinical trial innovation, including building on the experience with remote clinical trials during the COVID-19 pandemic.

Section 304: Increasing Use of Real World Evidence (RWE) & **Section 309:** Post-Approval Study Requirements for Accelerated Approval

- Section 304 would call for new guidance on the use of RWE in post-market review of drugs that were designated as a breakthrough therapy or fast track product, or considered for accelerated approval. Section 309 would further specify that the post-approval study requirements to verify and describe the clinical benefit for products granted accelerated approval could be satisfied through RWE, including analyses of data in clinical care repositories or patient registries.
- Section 304 also would establish a permanent Real World Evidence Task Force to coordinate programs and activities within the Department of Health and Human Services related to the collection and use of RWE.
- These and other sections of Cures 2.0 share a common theme of enhancing the use of RWE in regulatory decision-making. Although the inherent variability in RWE likely will continue to present challenges to doing so, the signal is clear that legislators would like to see FDA and HHS continue to move forward in this area.

Last week's introduction of Cures 2.0 and President Biden's announcement that he will nominate Robert Califf for FDA Commissioner contributed to a newsworthy week for those of us who follow the FDA. We look forward to seeing how Cures 2.0 develops and how the Agency's policy priorities unfold in the coming months.