Morgan Lewis

REPORT

# 2023 DRUGS AND BIOLOGICS YEAR IN REVIEW

## Will FDA's 2023 Evolution Usher in Swift Resolutions for 2024?

www.morganlewis.com

© 2024 Morgan Lewis | Morgan, Lewis & Bockius LLP, a Pennsylvania limited liability partnership

# 2023 DRUGS AND BIOLOGICS YEAR IN REVIEW: WILL FDA'S 2023 EVOLUTION USHER IN SWIFT RESOLUTIONS FOR 2024?

## TABLE OF CONTENTS

# 2023 DRUGS AND BIOLOGICS YEAR IN REVIEW: WILL FDA'S 2023 EVOLUTION USHER IN SWIFT RESOLUTIONS FOR 2024?

The US Food and Drug Administration (FDA) was busy in 2023 with significant, and even bullish, developments occurring across several areas, from drug and biologic development and manufacturing to labeling, advertising, and promotion guidance.

The overall theme of 2023 at FDA was finding innovative ways to address existing regulatory obligations, especially in light of new and novel technologies, taking into account lessons learned from COVID-19–era roadblocks and innovations.

Through its policy developments, FDA makes clear that it is open and willing to work with the life sciences industry to address the evolving drug development environment—whether that is achieved by creating efficiencies within the drug development and clinical trials space, implementing new technologies for manufacturing, finding new ways to manage risk, or permitting companies to communicate accurate and truthful information about their products.

While exactly how these new approaches will be implemented by FDA and adopted by industry, and what their impact will be, is yet to be seen, we expect to see a continuation of this pattern in 2024. Accordingly, companies should not shy away from engaging with FDA regarding their new or novel products or ways of meeting the applicable regulatory requirements as FDA is carving out space for increasing regulatory flexibility so long as the overarching regulatory requirements are met.

In this year-end report we provide summaries of 44 FDA guidances and rulemakings issued in 2023 on premarket development, clinical trials, review standards, manufacturing, supply chain, promotion, and labeling considerations. Additionally, we provide insights on what some of these trends and rulemakings may mean for the year ahead as their influence carries forward into 2024 and beyond.

# FDA DRUG AND BIOLOGIC DEVELOPMENT GUIDANCE

2023 was a year of enunciating development program regulatory flexibilities and potential efficiencies, aimed at bringing therapeutics to patients on a faster timeline. Over the last 12 months, FDA issued more than 25 guidance documents related to premarket development programs. Through this guidance, certain key themes and FDA's likely direction for 2024 begin to materialize.

FDA is updating its approach to clinical trials to coincide with new tools, technologies, and methodologies that are currently being used within the industry. This was reflected in FDA's guidance to implement the International Council for Harmonisation's (ICH's) third revision guidelines on good clinical practice, which contain updates for, among other areas, the use of computerized systems as well as various FDA guidance documents discussing new ways to conduct and design clinical trials such as the agency's draft guidance on decentralized studies and guidance on digital technologies used in clinical trials. In many ways, FDA is playing catch-up, working to bring its regulatory structure and stated expectations in line with the current state of technology and practice.

Concurrently, with the growing use of novel technologies and methodologies, FDA is focused on finding ways to ensure that subject rights continue to be protected and that the agency has assurances that the data upon which it relies when making approval decisions reflects the actual results of studies. FDA discusses in multiple pieces of guidance the importance of data integrity, a pillar which has always been an area of significant FDA concern but which is taking on even more importance with the introduction of remote functionalities, and is an area of increasing agency focus. Sponsors of clinical trials are advised to ensure that their procedures and processes for guaranteeing the integrity of study data are robust and being followed and that they truly understand the attributes of their vendors' technologies and tools.

FDA also appeared to be listening to the complaints of many in the industry and patient groups that, due to regulatory requirements, it is taking too long to bring innovative and potentially life-saving products to market. The time it takes to develop and option product market approval not only creates a significant delay for patients but also significantly drives up the cost of product development.

With guidances on areas such as decentralized clinical trials, real world evidence/data, and satisfying FDA's substantial evidence approval requirement with a single pivotal trial, FDA is demonstrating its willingness to work with the industry to streamline the clinical trial process, potentially bringing products to market sooner. In other guidance, such as the guidance on development programs for rare diseases, FDA emphasizes its ability and willingness to exercise regulatory flexibility. Only time will tell whether FDA's newfound flexibility will result in faster approvals.

This may be welcome news for sponsors as it demonstrates that the agency may be more receptive to new ways of conducting clinical trials. That said, sponsors looking to use innovative tools, methods, and vendors in clinical trials should consider discussing these with FDA and demonstrating how such tools and techniques will also provide adequate subject and data integrity protections and generate data upon which the agency can rely.

FDA is increasingly looking for ways to ensure that trials are accurately measuring efficacy in a way that is meaningful to patients and providers. In multiple guidance documents, FDA discusses ways, and its expectation, for sponsors to measure information that is clinically meaningful, whether this be through patient-reported outcomes or primary endpoints. Not only must sponsors show that study results are statistically significant, but they must also be clinically significant.

At the same time, FDA is also looking to sponsors to ensure that study results are meaningful for all patients who will be taking the commercial product and has provided recommendations on collecting

representative study data. Looking forward, sponsors will need to ensure that studies demonstrate that products are safe and efficacious for all patients in a way that will make a difference for them.

What is important to remember is that with all new opportunities comes new challenges, a reality which FDA acknowledges and attempts to remedy via multiple offers to meet and consult with sponsors. Sponsors should take advantage of the opportunity to sit down with FDA and confer on the various nuances of their particular drug development programs and consider FDA's recommendations, especially if using some of the more novel study designs and tools discussed in the below guidances.

We provide below a summary of some of the more significant pieces of guidance promulgated by FDA over the last year in the areas of clinical and premarket development. Given the significant amount of guidance provided by the agency in 2023 on its shifting requirements and expectations, all those involved in the drug and biologic development spaces, including sponsors, investigators, academic medical centers, institutional review boards (IRBs), and other persons and entities providing product development services, should acquaint themselves with the below guidance, considering how they apply to particular programs.

# GOOD CLINICAL PRACTICES/CLINICAL TRIAL CONDUCT

## Good Clinical Practices

One of the more significant FDA updates of 2023 for clinical trials was FDA's issuance of updated draft guidance to implement the ICH's third revision guidelines on good clinical practice (GCP) (ICH E6(R3)), on which we previously wrote. The goal of the draft guidance was to modernize the design and conduct of clinical trials, enabling clinical trials to be more agile while maintaining data integrity and participant protections. ICH E6(R3) was modified to allow for the integration of technological and methodological innovations into clinical trials.

FDA notes that the E6(R3) draft guidelines emphasize the use of risk-based and proportionate approaches to data collection, monitoring, and quality management throughout the clinical trial lifecycle. The guidelines encourage a focus on data and processes that benefit participant safety and data integrity. Overall, the draft guidance updates the approach to the use of computerized systems and has a significant emphasis on data governance and informed consent.

The updated draft guidelines are designed to apply to a wide variety of clinical trials, including those with innovative design elements that can make trials more efficient, such as decentralized clinical trials (DCTs). The modernized GCPs also encourage the use of appropriate digital health technologies (DHTs) to enable agile data collection and patient recruitment.

## Informed Consent

FDA issued in August 2023 final guidance on informed consent, a topic we covered on *As Prescribed*. Some notable elements of the guidance include recommendations regarding obtaining patients' informed consent for tissue sample collection during planned surgical procedures; disclosures regarding payment for injury-related medical care; descriptions of risks, benefits, and comparisons of alternative treatment options; and disclosures regarding insurance implications of clinical research. The guidance further includes a substantial discussion on alternative methods for obtaining informed consent, including remote and electronic consent procedures, reflecting on lessons learned during the COVID-19 pandemic, and considerations regarding financial relationships and conflicts of interest that may impact the consent process.

Finally, and of particular interest to sponsors, FDA provides specific recommendations for informed consent in multicenter clinical trials, stating that if a local IRB requires substantive modifications to an informed consent form, FDA expects that those revisions be shared with all other investigators and their IRBs, potentially complicating the informed consent process when dealing with many sites across global jurisdictions.

Notably, this is not the last of the changes to FDA's informed consent process, as the agency is in the process of harmonizing its regulations with the updates made to the Common Rule in 2018. There is also a proposed rule that would permit IRBs to waive or alter informed consent elements or requirements. Until the proposed rule is finalized, FDA has stated that it does not intend to object if an IRB approves a consent process that waives or alters some or all of the informed consent requirements.

## Electronic Systems, Records, and Signatures

In March 2023, FDA published draft guidance on the application of 21 CFR Part 11 to electronic systems, records, and signatures used in clinical trials. The guidance specifically outlines a risk-based approach to system validation; addresses the applicability of Part 11 to technologies that create, modify, maintain, archive, retrieve, or transmit electronic records; and provides recommendations on DHT used for remote data collection. The guidance also discusses the application of Part 11 to real world data and electronic medical records that may not have been collected originally for the purpose of a marketing application as well as data from foreign sites.

As part of inspection preparedness, FDA recommends that sponsors describe electronic systems within the study protocol and create a diagram that depicts the flow of the study data. Sponsors should also maintain documentation and procedures addressing areas such as the setup, maintenance, use, roles and responsibilities, validation, change control, backup, functionality, support, security, and auditing of electronic records, systems, and vendors.

Specifically with respect to vendors, FDA recommends that regulated entities establish service-level agreements with vendors describing how services will meet the applicable regulatory requirements. Supporting documentation will be expected to be available for review by FDA during inspections.

## Clinical Trial Monitoring

For nearly a decade FDA has recommended that sponsors of clinical trials conduct risk assessments to identify critical data and processes needed to protect human subjects and ensure data integrity. To the extent these risks cannot be mitigated, FDA has recommended that sponsors identify, track, and manage the risk through study monitoring and oversight plans, building quality into the design and execution of clinical trials. With its April 2023 guidance on study monitoring, FDA provided additional recommendations for monitoring planning and addressing and communicating monitoring results.

FDA recommends that during study planning sponsors identify study risks and their causes, consequences, and detectability to inform protocol development, monitoring plans, and risk management. This assessment should be documented and periodically reevaluated during the study. When assessing risks, FDA recommends that sponsors not only consider risks posed to a particular trial but also to the sponsor's other development programs. When developing monitoring plans, FDA recommends that sponsors consider a variety of datapoints including site infrastructure and experience, data-recording methods, study stages, and data attributes.

By focusing monitoring activities on the most critical risks, FDA states that sponsors should be able to build efficiency into their trials. If significant issues are detected, they must be evaluated to root cause and appropriate corrective and preventative actions (CAPAs) should be implemented. FDA states that significant issues and CAPAs should be communicated to appropriate parties such as internal sponsor

teams and management, clinical sites, IRBs, data monitoring committees, and potentially regulatory authorities.

# CLINICAL TRIAL DESIGN

## Decentralized Clinical Trials

In May 2023, FDA issued draft guidance on the implementation of decentralized clinical trials (DCTs). DCTs, which increased in popularity during the COVID-19 pandemic, have the potential advantage of diversifying trial participation, enhancing participant convenience, increasing study access, reducing caregiver burden, and facilitating rare disease research. However, DCTs also come with challenges, including working with sites that may not be familiar with clinical trial requirements.

As such, specific decentralization plans and early discussions with FDA, as well as site training, oversight, and upfront risk assessment and management, are crucial. Some areas particularly noted by FDA that should be accounted for when planning DCTs include the impact of data variability and decreased precision on study margins and effect size, the use of DHTs (e.g., suitability, verification, validation), data management measures necessitated by multiple data sources, and specialized monitoring.

Sponsors should additionally give special consideration to measures for reducing data variability and safety monitoring. Any software programs that are used for trial records will also need to be compliant with Part 11 of FDA's regulations. Further, sponsors and investigators will need to account for any local requirements, including licensing and telehealth requirements. Thus, while DCTs may provide significant advantages, these advantages will come with the need for a significant amount of upfront planning.

## Digital Health Technologies

Complementing its guidance on DCTs, FDA published in December 2023 guidance on the use of DHTs for clinical investigation remote data acquisition. The guidance "provides recommendations for ensuring that a DHT is fit-for-purpose (i.e., that the level of validation associated with the DHT is sufficient to support the use, including the interpretability of its data in the clinical investigation), which involves considerations of both the DHT's form (i.e., design) and function(s) (i.e., distinct purpose(s) within an investigation)."

FDA notes that DHTs may be considered medical devices by FDA. If a DHT is a medical device and is not cleared or authorized, the use of the DHT would need to comply with FDA's investigational device exemption regulations. DHTs that are also medical devices are further subject to design controls, "which are basic controls needed to ensure that the device being designed will perform as intended." Design controls will vary based on the DHT and its regulatory status.

When selecting a DHT, FDA recommends that sponsors consider a variety of factors, including the clinical trial population, technical and performance specifications, the datapoint that will be measured, the technology's design and operation, and whether subjects will be able to use their own DHTs (e.g., continuous glucose monitors, smartphones, tablets that a subject may already be using). When submitting a clinical trial using a DHT, sponsors should be sure to describe the DHT, how it will be used, how it is fit for purpose, and the data flow and data management. DHT verification and validation studies/data, which may already exist from the DHT manufacturer, are needed to demonstrate that a DHT is fit for purpose for the remote data collection.

Sponsors should further evaluate the DHT's interoperability and usability, justifying any endpoints that the DHT measures. FDA also recommends that sponsors and IRBs consider both the clinical and privacy risks that may be implicated by DHTs when designing and reviewing studies, including how they should

be described during the informed consent process. Moreover, the data captured using DHTs, including metadata, should be securely transferred and retained as part of the clinical trial record, which retention may be subject to FDA's Part 11 requirements.

Finally, FDA recommends that provisions be made for training, technical assistance, risk management, safety monitoring, data transfer, technology updates and changes, identification of DHT errors and damages/loss, and closeout procedures at both the sponsor and site level.

## Externally Controlled Trials

In February 2023, FDA issued draft guidance on design and conduct considerations for externally controlled trials (ECTs). FDA states that special consideration should be given to a number of areas when designing ECTs to reduce the potential for bias and increase data interpretation. ECT control groups should be prospectively defined in the study protocol and the protocols should clearly describe, among other things, the suitability of the data source, analytic plans, and approaches to minimizing missing data, bias, and confounding factors.

To ensure that control groups are fit for their intended use, sponsors should ensure that the source population is comparable to a treatment arm, with special consideration given to whether baseline measurements (including diagnostic criteria) are the same between the two groups. Care is further required when determining the index date (i.e., day 0) for an external control arm, especially in the case of real world data sources. FDA recommends that treatment outcomes be based on a blinded assessment, which may require readjudication of control data.

When choosing outcome measures, FDA also encourages sponsors to use objective and reliable measurements and states that sponsors should consider the timing of the outcome assessments, variability in the use of assessments, and the applicable diagnostic criteria that is used. Prespecified statistical analysis plans are also critical for ECTs. Individuals making decisions regarding study and statistical designs should generally be blinded to the external control data.

## Substantial Evidence

Since 2019, one of the holy grails of FDA's drug development guidances has been its guidance on the demonstration of substantial evidence of effectiveness, which provided direction on the kinds of efficacy data the agency considers supportive of approval. Within this guidance, FDA discussed that its substantial evidence standard may be met via data from a single adequate and well-controlled clinical trial in conjunction with other confirmatory evidence.

In its draft guidance (and as further discussed here), FDA expands on its prior discussion to provide details for what data it may consider supportive. Under this new guidance, FDA will consider both the quality and the quantity of confirmatory evidence, as well as disease-specific considerations (e.g., unmet needs, size of the patient population), when making approval decisions. The amount of required evidence will vary across development programs and be impacted by the strength of the primary pivotal trial.

When assessing confirmatory evidence quality, a primary FDA focus will be on the data source. Data sources that may serve as confirmatory evidence include clinical investigations in closely related indications; strong mechanistic evidence of a drug's treatment effect; data from adequate and well-controlled studies of products in the same pharmacological class for the same indication; natural history data; reliable and relevant real world data and evidence from well-designed studies; evidence from expanded access programs; and, less frequently, evidence from relevant and meaningful animal models. For sponsors considering supporting product approval with a single trial plus confirmatory evidence, communication with FDA early in the development process is key.

Sponsors should be prepared to provide their rationale for their proposed approach as well as descriptions of the planned clinical trial and confirmatory evidence. Also potentially supportive, though not specifically called out by FDA, would be approvals in other jurisdictions based on similar data.

Whether this guidance will change how FDA employs the permitted regulatory flexibility to approve a product based on a single pivotal study is not currently clear. FDA is likely to give close scrutiny to applications that rely on a single pivotal study similarly to other regulators, such as the European Agency for the Evaluation of Medicinal Products (EMA) (in its 2001 Points to Consider on Applications with 1. Meta-Analyses; 2. One Pivotal Study, the EMA states "[i]n cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling.").

Certain products may be better candidates for reliance on a single pivotal study, such as products for serious or life threatening diseases with unmet medical needs, which would be consistent with both FDA's and the EMA's past practice.

## Real World Data and Real World Evidence Use

The potential of real world data (RWD) and real world evidence (RWE) has been a topic of much discussion and is becoming more widely accepted as more sponsors begin to use RWE to support determinations of product safety and efficacy. With this growing use of RWE, FDA provided guidance in August 2023 to sponsors on considerations regarding the use of such data to support regulatory decision-making.

As a general matter, FDA's clinical trial regulations are applicable to RWD when used as part of interventional clinical trials. Non-interventional studies (i.e., observational studies assessing use of a marketed drug during routine medical practice) are not subject to FDA's clinical trial regulations. However, because these studies will include certain protocol-specified activities, sponsors still must ensure that human subject protections are in place (e.g., informed consent, IRB approval).

Such studies may also raise data privacy questions, for which FDA recommends that sponsors consult data privacy experts. Of particular concern to FDA is ensuring that any use of RWD sources is unbiased and the selection of data sources is not made with an eye toward achieving a specific study outcome. To these ends, FDA emphasizes transparency with respect to study design, population selection, analyses, and data. By example, because sponsors will need to analyze data sources for the purpose of study design and feasibility assessments, FDA states that it is crucial that study protocols describe the evaluated data sources and justification for selecting or excluding relevant sources.

Sponsors will also need to describe how the final selected data source and design of the study serves the ultimate research question and demonstrate that the data sources and study design were not selected to achieve a particular outcome. Sponsors should also ensure that they will be able to provide the patient-level RWD to FDA upon request and during inspections, which may require that contractual terms be instituted with the owner of the data set.

Sponsors must further undertake monitoring and safety reporting, even in the case of RWD. Monitoring should begin at the point of data extraction from the RWD source and focus on protecting human subjects and maintaining data integrity. With respect to safety reporting, sponsors are required to report adverse events in accordance with the postmarket study requirements. Finally, as with many new or novel approaches to data collection, FDA recommends that sponsors engage with the agency early.

## RWD Registries

FDA again took up the question of RWD in December 2023, issuing guidance on RWD registry assessments. Of particular FDA focus is ensuring that the use of registries comport with human subject

protections (i.e., that the use is IRB-reviewed and patients have provided their consent to the particular use of the registry) and that any particular registry is relevant and reliable for the proposed use. This will require diligence by sponsors and collaboration with the owners of any preexisting datasets.

If one registry does not address all the elements that a sponsor may need, sponsors can consider linking multiple data sources. When linking multiple data sources, sponsors must consider whether there will be any impact on the registry's integrity and should establish a plan for addressing the adequacy and accuracy of subject level linking. Jurisdictional legal requirements also must be considered, and sponsors should take steps to ensure that data sources are interoperable and appropriately integrated. Documentation on the validation of the data transfer from external data sources into a registry should be available to FDA.

Sponsors should further ensure that any software updates and additional data sources do not impact the integrity, interoperability, and security of registry data. Importantly, when submitting registry data to FDA from sources that are owned by third parties, FDA advises that sponsors "should work closely with the other organization to ensure that appropriate methods for data entry, coding, cleaning, and transformation are in place for each linked data source."

FDA additionally recommends that sponsors confer with FDA prior to using RWD registries, particularly regarding

> (1) the ability to accurately define and evaluate the target population based on the planned inclusion and exclusion criteria; (2) which data elements will come from the registry (versus other data sources) and their adequacy, as well as the frequency and timing of data collection; (3) the planned approach for linking the registry to another registry or other data system, when linking is anticipated; (4) the planned methods to ascertain and validate outcomes, including diagnostic requirements and the level of validation or adjudication of outcomes; and (5) the planned methods to validate the diagnosis of the disease being studied.

Sponsors should also submit their protocols and statistical analysis plans to FDA for review before study conduct. "All essential elements of the design, analysis, and conduct of a study using registry data should be predefined, and for each study element (e.g., eligibility criteria, exposures, outcomes, covariates), the protocol should describe how that element will be ascertained from the selected data source or sources." Finally, sponsors should ensure that they will be able to provide FDA with patient-level data and metadata for inspection, which may require collaboration with any third-party data owners.

## Clinical Trial Representation

As part of the agency's larger effort to increase clinical trial diversity, FDA released draft guidance in July 2023 on postmarket strategies for gathering data on underrepresented populations. In FDA's words, "clinical trials should include patient populations that are historically underrepresented in clinical research (e.g., populations based on race, ethnicity, sex, or age)[.] However, if, despite the sponsor's best efforts, these populations are not adequately represented in premarket clinical trials, it may be appropriate to collect such data in the post[-]marketing setting."

If, upon FDA review of a marketing application, data is not sufficiently representative of the potential patient population, FDA can require sponsors to conduct postmarket studies as a condition of marketing approval via a postmarket requirement or commitment. Confirmatory trials that are required as part of an accelerated approval should also be representative of the US patient population.

Within the guidance, FDA discusses various design considerations for different kinds of studies, including single-arm trials, randomized trials, RWD sources, and pooled studies. FDA states that sponsors should

discuss their approach for developing information on underrepresented populations with the agency early in product development and recommends submission of a diversity plan.

FDA and sponsors should work together to "determine appropriate benchmarks for an inclusive and representative data package that is specific to each development plan. If[,] during the course of the clinical development program, the strategies implemented to recruit and retain a representative population appear unlikely to accomplish the intended objective despite best efforts, the sponsor and FDA should discuss next steps. If it is determined that additional information should be collected in the post[-]marketing period, such data can provide clinically useful information and can potentially be added to drug labeling, when appropriate."

## Patient-Focused Drug Development

FDA issued its fourth draft guidance in April 2023 regarding patient-focused drug development, which addresses endpoint design, conduct, and analysis of clinical outcome assessments (COAs). As a rule of thumb, COA endpoints should be designed to reflect a meaningful aspect of patient health and support inference of a treatment effect. Context matters when selecting COAs, as FDA makes a point of stating that the use of a particular COA endpoint in a trial for a different product may not provide sufficient support for the use in a different trial.

Sponsors will be expected to provide FDA with evidence to justify the meaningfulness of any observed benefit observed in COA endpoints and particularly how the measure demonstrates a product impact on how a patient feels or functions.

As such, it is not only important to demonstrate statistically significant results, but also to demonstrate that a result corresponds with an effect that a patient would consider significant to their daily lives. How readily this may be done and how much evidence is required will depend on the measure's interpretability and how closely the COA measure reflects a patient's health experience.

FDA further recommends that sponsors using COAs give consideration to specific study design issues that may arise in a variety of areas including masking, practice effects, the use of computerized adaptive testing, and how the use of an assistive device may impact COA measures.

## Master Protocols

In December 2023, FDA issued draft guidance on the use of master protocols for drug development. A master protocol is "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."

Master protocols can help sponsors create a number of efficiencies within the clinical trial process by maximizing information that is gathered within a single trial such as via the use of a shared control arm and other shared protocol elements, shared infrastructure, and shared oversight groups. However, master protocols require a significant amount of upfront planning. For example, special consideration should be given to randomization in order to optimize the power of the study as well as with respect to the choice of control group.

Additionally, when obtaining subject informed consent, sponsors should ensure that they are accounting for all arms of the study into which a subject could be randomized. A sponsor's approach to blinding when using master protocols should also be an area of special consideration, with double-blinding being the optimal approach to avoid bias. Blinding may become more complex as the number of drugs within a master protocol and different treatment regimens increase.

For sponsors considering adaptive designs, FDA further recommends that interim analyses be conducted based on pooled data across study arms, rather than based on individual treatment arms, to avoid dissemination of information regarding comparative product efficacy. Pooled analyses, however, may provide less accurate sample size estimates. With respect to safety assessments, the data from master protocols can be used as part of the overall safety database, but additional safety data would likely be required.

The type of master protocol and drug-specific factors will impact the specific approach that sponsors should take for safety data collection. While one advantage of master protocols is that they enable sponsors to use single review organizations (e.g., IRBs, data monitoring committees), special care is needed to avoid inadvertent dissemination of study information from one arm, as such dissemination could result in inferences regarding the other study arms, which could impact the study's integrity.

Finally, due to some of the added complexities that come with master protocols, FDA's guidance provides direction to sponsors regarding how to make regulatory submissions to the agency and recommends having a clear communication plan, especially when multiple sponsors' drugs may be involved.

## Rare Disease Studies

FDA also released in December 2023 its guidance outlining considerations for sponsors investigating products intended for rare diseases. While FDA's approval standards for rare disease products are the same as for other diseases, its regulations provide flexibility for how those standards may be met. FDA states that it is "committed to helping sponsors create successful drug development programs" and, in furtherance of this commitment, provides recommendations on a variety of areas impacting rare disease programs.

First, because the natural history of rare diseases is often poorly understood, FDA recommends that sponsors evaluate existing natural history information for the disease, and, if there is not sufficient information to inform development, consider conducting "prospectively designed, protocol-driven natural history studies" in the earliest development planning stages. With respect to nonclinical studies, FDA may exercise flexibility regarding the kind and amount of data required depending on a number of factors, including the severity of the targeted disease and unmet patient needs.

When the target indication is a severely debilitating or life-threating (SDLT) rare disease, FDA intends to exercise the broadest flexibility; as such, it is important for sponsors to confer with FDA to understand FDA's program-specific expectations. Following nonclinical studies, FDA expects clinical pharmacology assessments to inform dose selection and encourages sponsors to identify and evaluate biomarkers that are relevant to the disease process. Biomarkers that are used to support critical decisions during the course of a study will need to be substantiated and the biomarker assay will need to be validated.

During clinical investigations intended to support product safety and efficacy determinations, FDA notes that it is critical to "optimize all aspects of clinical investigation design and standardize the collection and management of data to ensure quality and interpretability," given the limited size of the patient population. In furtherance of this aim, the guidance provides specific recommendations regarding controls, randomization, blinding, endpoint selection, and the use of innovative study designs.

With respect to safety evaluations, FDA further emphasizes available flexibilities and notes that "what is a feasible and sufficient safety assessment is a matter of scientific and regulatory judgment based on the particular challenges posed by each drug and disease, including patients' tolerance and acceptance of risk in the setting of unmet medical need and the benefit offered by the drug." Accordingly, a higher degree of safety uncertainty is common for rare disease development programs "where the prevalence of disease, and consequent limitations of study size, can limit the precision of safety and efficacy characterizations."

With respect to manufacturing development, FDA highlights the importance of ensuring that drug manufacturing development keeps pace with clinical development. FDA recommends that the sponsor assess any planned changes to the drug manufacturing process and keep the agency informed about its drug quality development plans through early-phase meetings to potentially decrease drug developmental or approval delays.

FDA may exercise some flexibility on a case-specific basis regarding the extent of manufacturing information expected at the time of submission and approval of a marketing application after considering factors such as the robustness of the drug quality system and the strength of the sponsor's risk-based quality assessment. Overall, because of the nuances of developing a product for rare diseases, FDA encourages sponsors to engage with the agency and notes that such meetings can result in more efficient drug development.

# FDA REVIEW OF CLINICAL TRIALS

## Benefit/Risk Assessments

When FDA approves a new drug or biologic, the agency's approval decision is based on a weighing of the product's benefits and risks, taking into account any uncertainties that may remain after assessing the relevant data as well as any risk mitigation tools or approaches that can be put in place to shift the risk benefit analysis. In its October 2023 guidance, FDA further articulated how it weighs product benefits and risks.

Per FDA, this assessment is case-specific and necessitates consideration of the condition the product is intended to treat, available therapies, and risk management tools. This assessment is done on a populationwide basis, such that "FDA may conclude that . . . the expected frequency of serious adverse events in the overall intended population would outweigh the demonstrated benefits of the drug, even if some patients might be willing to accept such risks when considering their individual circumstances."

Accordingly, it is critical that sponsors identify a patient population most likely to experience the greatest benefit with the least risks. In such cases, "the product labeling would need to adequately describe the benefits and risks, including the differences in response across the approved subpopulations, as appropriate, thereby facilitating individual benefit-risk treatment decision-making by healthcare providers and patients."

When trying to demonstrate a favorable risk-benefit profile, FDA advises that developers focus on data and quantification of effect. By example, if proposing risk management strategies, developers should be prepared to provide FDA with clinical data on how strategies impact a product's risk profile and evidence regarding the ease of implementation. Developers should also be able to demonstrate the meaningfulness of any particular demonstrated patient benefit (i.e., how will the outcome impact how a patient feels, functions, or survives). In this respect, patient input regarding their symptoms and disease may be especially valuable to "inform and strengthen the rationale for endpoint selection, development of COAs, and the overall benefit-risk assessment."

To these ends, sponsors may want to consider undertaking structured benefit-risk planning during drug development, which would take into account factors such as appropriate patient populations or subpopulations, dose and endpoint selection, study designs that will demonstrate benefit and risk (e.g., through use of an active control and population enrichment strategies), and risk mitigation strategies, all with an eye toward ensuring that data is suited to support the benefit risk assessment and, to the extent possible, fills in uncertainties and data gaps.

Using the benefit-risk assessment, sponsors should consider strategies to prospectively assess subpopulations, whether that be limiting development to specific subpopulations or designing studies to prospectively include appropriately powered subpopulation analyses, which would be more persuasive to FDA than post-hoc assessments. Importantly, sponsors should be prepared to discuss benefit-risk evaluations with FDA throughout the drug development process when obtaining feedback on development programs as well as within the ultimate marketing application.

### Nonclinical Generally Accepted Scientific Knowledge

In its draft guidance of May 2023, FDA discussed circumstances in which it may be willing to rely on generally accepted scientific knowledge (GASK) to satisfy certain nonclinical safety requirements within marketing applications.

FDA states, "[i]n some cases, . . . what is already known, for example, about a drug, the patient's condition, or a relevant biological process (i.e., the biological context in which a drug is expected to act) in a given patient population is sufficient to confidently predict the outcome of a given nonclinical study. If there is GASK relevant to the application, it may be unnecessary for a sponsor to conduct certain nonclinical studies. This may result in streamlined product development that avoids unnecessary animal testing, decreases a drug's development costs, and quickens the drug's time to approval and marketing—and thus[] its availability to patients."

FDA defines GASK as "medical or scientific information that is generally accepted by experts qualified by scientific training and experience in the relevant field, including FDA experts." GASK is typically based on longstanding and widely accepted scientific principles or sufficiently large amounts of scientific studies/information that are applicable beyond the specific context in which that information was developed.

FDA provides two examples of circumstances in which the agency relies on GASK: (1) when a product contains a substance that occurs naturally in the body, and GASK is used with respect to the substance's known effect on biological processes; and (2) where a sponsor has demonstrated a drug's impact on a biological pathway and relies on GASK to conclude that certain nonclinical studies are not necessary.

Importantly, FDA notes that these are not the only circumstances in which GASK may be applicable. FDA states that if a sponsor plans to rely on GASK it should submit its rationale and supporting evidence to the review division as early as possible to obtain agency feedback.

## COMBINATION PRODUCT GUIDANCE

### Human Factors Engineering Principles

In September 2023, FDA provided final guidance, in the form of questions and answers, on the application of human factors engineering (HFE) principles to the development of combination products. HFE is "the application of knowledge about human behavior, abilities, limitations, and other characteristics of the users to the design of products to help ensure safe and effective use of the product." HFE analyses include considerations related to the user population and use environment as well as limitations that may impact the product's use.

The design of a combination product should take into account factors such as the use environment(s), including any limitations (e.g., limited internet/cellular phone service). HFE principles aim to ensure that the user interface enables the safe and effective use of the product. The guidance discusses, among other things, "the definition of a combination product critical task, considerations for combination products due to the use of drug and device constituent parts together, training as part of the user

interface, and human factors (HF) validation data to support the combination product user interface that may be included in a premarket submission."

Development of drug/biologic-device combination products should employ "HFE principles and processes throughout the entire product development process and product lifecycle changes." Notably, as part of HFE, design controls "should include a use-related risk analysis (URRA) of the combination product as a whole, not just" its constituent parts, as there may be use-related risks for the drug, device, or their use together that may influence the user interface design inputs. Notably, FDA is particularly interested in aspects of the combination product and its use that may impact dosing or product administration or that may have a potential to result in harm.

Sponsors should also pay special attention to products whose use is time-sensitive or time-urgent. Following HF validation testing, sponsors should thoroughly analyze any remaining risks and make appropriate adjustments to minimize those risks as "FDA will evaluate the HF validation study results to determine whether the combination product user interface design has been optimized such that the use-related risks have been sufficiently reduced." HF principles will also play a role in whether FDA permits clinical trials to proceed and, accordingly, sponsors should begin considering them as soon as possible.

# ONCOLOGY-FOCUSED GUIDANCE

## Oncology Accelerated Approval

In March 2023, FDA provided draft guidance recommendations to oncology drug sponsors on trial design considerations for accelerated approval. Per FDA, single-arm trials with response endpoints (and supportive duration of response data) have historically been used to support oncology product accelerated approval. However, there are significant limitations for these trials that can introduce uncertainty with respect to safety and/or efficacy and that may be an impediment to product approval. Accordingly, FDA states that its preference is randomized controlled clinical trials in support of accelerated approval applications in the oncology space.

There are certain circumstances in which single-arm trials may be appropriate such as when there are significant feasibility concerns. FDA recommends careful consideration of whether single-arm trials are appropriate and that sponsors confer with the agency before initiating the study. Potential study options, for which FDA provides specific design considerations within the guidance, include conducting two randomized controlled trials (one for accelerated approval and a separate one to provide confirmatory evidence of efficacy), a single long-term randomized controlled trial that serves as both the basis for accelerated approval and confirmation of efficacy, or, in certain circumstances, a single-arm trial.

## Oncology Dose Optimization

FDA officially updated its draft guidance recommendations on dose optimization in the oncology space in January 2023. Whereas oncology dose finding traditionally had focused on finding the maximum tolerated dose (MTD), because technologies now under investigation in the targeted oncology space may not require the maximum dose to be maximally effective and the MTD may never be reached, FDA found that the MTD paradigm may not be fit for purpose. The agency stated "[d]ose-finding trials that investigate a range of dosage(s) and select the dosages to be further investigated based on clinical data and an understanding of dose- and exposure-response[] represent a more informed approach to identify the optimal dosage(s)."

While nothing new, FDA begins by saying that any doses selected for clinical trials must be adequately supported. Importantly, FDA notes that sponsors pursuing drug development under an expedited program (e.g., breakthrough therapy designation) are not exempt from dose optimization and "should

plan their development programs such that identification of the optimal dosage(s) can occur prior to or concurrently with the establishment of the drug's safety and effectiveness." FDA recommends that dose optimization be accomplished through clinical pharmacokinetic, pharmacodynamic, and pharmacogenomic data, along with trials comparing multiple product doses (ideally a randomized, parallel dose response trial).

## Real-Time Oncology Review

In its November 2023 guidance, FDA provided recommendations for submission of marketing applications under the agency's real-time oncology review (RTOR) program. Under this program, sponsors may make an "earlier submission of top-line results (i.e., efficacy and safety results from clinical studies before the study report is completed) and datasets, after database lock, to support an earlier start to the FDA application review." Per FDA, "[t]he intent of RTOR is to provide FDA reviewers earlier access to data, to identify data quality and potential review issues, and to potentially enable early feedback to the applicant, which can allow for a more streamlined and efficient review process."

To be eligible for RTOR sponsors must have adequate and well-controlled study data that indicates the drug may demonstrate substantial improvement on a clinically relevant endpoint(s) over available therapies, the clinical trial endpoints must be easily interpretable, and no aspect of the submission must be likely to require a longer review time (e.g., a product requiring a risk evaluation and mitigation strategy or an advisory committee).

If sponsors are considering RTOR, once top-line pivotal results are available and the database is locked, an RTOR application may be submitted, which should include the top-line results and a proposed submission timeline (the timeline will subsequently be agreed to with FDA). During the pre–new drug application (NDA)/biologics license application (BLA) meeting, FDA may share preliminary key review questions or issues and critical analyses needed.

Application fees are due upon the submission of the first application component and, notably, the FDA review clock does not start until after the agency has received the full application. Accordingly, while RTOR may allow for earlier identification of application issues, it may not result in earlier product approval.

## Oncology Drug Products Used with In Vitro Diagnostic Tests

In June 2023, FDA issued final guidance regarding its voluntary pilot program on the use of oncology drug products with in vitro diagnostic tests (IVDs). FDA stated that, in most circumstances, companion diagnostic IVDs should be approved or cleared by FDA contemporaneously with the approval of the therapeutic product.

However, there are circumstances in which FDA may approve a therapeutic product without an approved/cleared diagnostic, such as when the product is "intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an in vitro companion diagnostic with marketing authorization."

Accordingly, FDA has approved some oncology drug products that require a companion IVD without the IVD receiving marketing authorization. Under these circumstances, a category of IVDs, referred to as laboratory developed tests (LDTs), are being used as companion diagnostics. Per FDA, the agency "has generally exercised enforcement discretion for LDTs, meaning that, at this time, FDA generally does not exercise its authority to enforce the regulatory requirements for these devices, although it maintains that authority."

Under its voluntary program, "FDA intends to pilot a new approach to provide greater transparency regarding performance characteristics that certain tests for oncology biomarkers should meet. Through this transparency FDA seeks to support better and more consistent performance of certain LDTs used to identify patients for treatment with certain oncology drug products, resulting in better drug selection and improved care for patients with cancer."

Under the pilot, if a therapeutic meets FDA's approval standards, FDA states that it "intends to rely on the same pivotal clinical trial(s) that support approval of the drug product to establish the clinical validity for the clinical trial assays (CTAs) used in those trial(s)." FDA also will recommend minimum analytical performance characteristics that may be used as a reference point for other tests when conducting validation studies. The approved drug label will state that the product is "indicated for patients identified as exhibiting a named biomarker by in vitro diagnostic tests that have FDA's recommended performance characteristics."

Enrollment in the pilot is voluntary, and sponsors wishing to participate must apply to FDA and meet certain criteria. Note that it is unclear how this pilot may be impacted by ongoing efforts to further regulate LDTs by FDA's medical device center.

# PROCESS GUIDANCE

## Formal FDA Meetings

In September 2023, FDA updated its draft guidance on formal Prescription Drug User Fee Act (PDUFA) meetings between FDA and clinical trial sponsors. While the bulk of FDA's former guidance remains the same, FDA did add a new category of meetings (type D meetings) and added guidance on requests for INTERACT meetings.

Type D meetings are intended for discussion of a narrow set of issues at key development program decision points to enable sponsors to receive timely feedback on areas critical to moving a program forward. Typically these meetings should address no more than two issues and associated questions and should not require extensive advice or address highly complex topics/topics that require the feedback of more than three disciplines or divisions.

INTERACT meetings are intended for novel products and development programs that present unique challenges before a sponsor would otherwise have a pre–investigational new drug (IND) meeting, with topics such as IND-enabling toxicity studies, complex manufacturing technologies or processes, development of innovative devices used with a drug or biologic, or the use of new approach methodologies. Sponsors must have selected a specific investigational product or a product-derivation strategy to be eligible for INTERACT meetings.

## 2024 Outlook

On the whole, 2024—and beyond—is shaping up to be an exciting time for clinical trials as FDA is clearing the way for sponsors to explore more novel clinical trial designs that may speed up the time to market. Sponsors looking to avail themselves of these new tools, however, will need to invest increased time and effort in upfront planning and study monitoring to ensure that studies are being appropriately conducted. Sponsors also should be prepared for increased FDA interactions, as both sponsors and FDA work through these new clinical trial constructs.

# DRUG MANUFACTURING

In 2023, FDA demonstrated its intention to evolve with changing times as the agency issued guidance documents on cutting-edge issues in the drug manufacturing space. Certain key ideas reflected through the agency's actions in 2023 included

- the use of emerging technologies to modernize manufacturing capabilities to improve pharmaceutical product quality and manufacturing efficiency and potentially minimize supply chain disruptions such as drug shortages and recalls;
- the importance of monitoring, evaluating, and managing manufacturing-related risks to limit negative implications on patient access and safety; and
- the impact of consensus and collaboration among stakeholders with an interest in pharmaceutical development in promoting innovation.

## Continuous Manufacturing

In March 2023, FDA issued final guidance implementing the ICH-developed guidance describing development, implementation, operation, and lifecycle management of continuous manufacturing (CM). Distinct from batch manufacturing, CM is a method for manufacturing pharmaceutical products that involves the "continuous feeding of input materials into, the transformation of in-process materials within, and the concomitant removal of output materials from a manufacturing process."

The guidance addresses scientific considerations that impact the development of a CM process, including

- a process for evaluating performance and product quality;
- knowledge of process dynamics, including the impact of transient events;
- understanding material characterization, variability, and control;
- considering equipment design and system integration;
- understanding process monitoring and control;
- tracking for traceability and diversion of nonconforming product; and
- use of process models.

In addition, the guidance addresses various approaches to changing CM production output and how continuous process verification can be achieved through the use of process analytical technology (PAT) tools and process models to allow real time data collection. FDA provides regulatory considerations for the CM process dossier per existing ICH guidance including a description of manufacturing process and process controls, input material attributes, process monitoring and control, drug stability, and process validation in order to ensure product quality throughout production.

The guidance also provides examples of how to implement CM of drug substances and drug products for chemical entities and therapeutic proteins, including additional regulatory considerations that can impact process dynamics.

## Quality Risk Management

FDA released final guidance in May 2023 implementing ICH-developed guidance that discusses principles and tools that can be applied to enable more effective risk-based decisions regarding the quality of drug substances and products across the product lifecycle. Two principles of quality risk management are (1) basing the evaluation of the risk on scientific knowledge and considering patient protection and (2)

employing a level of effort, formality, and documentation of the quality risk management commensurate with the level of risk.

Generally, quality risk management should involve initiating a quality risk management process, risk assessment, risk control, risk communication, and risk review. The guidance discusses risk management methodology, risk-based decision-making, and managing subjectivity in the identification of hazards and in how risks are assessed. FDA recommends that individuals knowledgeable about the quality risk management process should take responsibility for coordinating risk management activities and ensure that subjectivity is managed and minimized to facilitate scientifically robust risk-based decision-making.

## Voluntary Consensus Standards

In July 2023, FDA published final guidance on the Center for Drug Evaluation and Research's (CDER's) program to recognize voluntary consensus standards related to pharmaceutical quality with an aim to promote innovation in pharmaceutical development and manufacturing. CDER intends to consider standards developed by voluntary consensus standards bodies that adhere to the elements of (1) openness, (2) balance, (3) due process, (4) appeals process, and (5) consensus in its standard development processes. The guidance further outlines policies and procedures for submission and evaluation of voluntary consensus standards.

In evaluating each request, FDA will determine whether the proposed standard conflicts with any statute or regulation under FDA's authority, whether the proposed standard is within the program's scope and adheres to the five elements discussed above, and whether recognition of the standard would be beneficial enough to justify allocation of FDA resources for standard review for possible recognition. Recognized standards will be listed on FDA's webpage within six months of the evaluation process. The guidance also describes the agency's expectations when a recognized standard is referenced in a marketing application or when a recognized standard is referenced for drug products that are legally marketed without an approved application.

## Manufacturing Changes for Gene Therapy Products

In July 2023, FDA published draft guidance with recommendations for sponsors of IND applications and applicants for BLAs of cell and gene therapy products (CGTs) regarding management and reporting of manufacturing changes and comparability studies to assess the effect of manufacturing changes on product quality. FDA recommends sponsors apply a regular and systematic approach to identify, assess, analyze, and mitigate potential risks to product quality when implementing manufacturing changes.

Further, product stability may be affected by manufacturing changes, including changes made during processing or when shipping or storing the substance or product. As a result, drug product stability should be assessed after introducing a manufacturing change, and sponsors should determine if there is a need to perform stability and/or delivery device compatibility studies to assess the effect of the change on product quality. Finally, additional studies, nonclinical or clinical, may be needed to support manufacturing changes for a licensed product or an investigational product after clinical studies have been initiated.

FDA recommends engaging with the agency if nonclinical comparability studies may be insufficient to ensure that a manufacturing change would not adversely affect product safety. Reminding sponsors that manufacturing changes to an existing IND or BLA must be reported to FDA as an amendment, the guidance also notes that certain changes may sufficiently alter the design or nature of the CGT product such that a new IND submission may be required to implement the change.

The guidance also provides information on how to assess comparability between a pre-change and post-change CGT product, including considerations for designing a comparability study, analyzing

comparability data, and submitting a comparability study report. FDA recommends that sponsors seek advice from the agency when planning significant manufacturing changes and designing study protocols for comparability studies.

## Recommended Acceptable Intake Limits for Nitrosamines

In connection with its broader efforts regarding the identification and assessment of nitrosamine drug substance-related impurities (NDSRIs), FDA issued direct-to-final guidance in August 2023 recommending a framework for predicting the mutagenic and carcinogenic potential of NDSRIs that may be present in drug products and recommended acceptable intake (AI) limits in assessing potential oncologic risk.

In connection with this guidance, FDA posted recommended AI limits for certain NDSRIs based on the predicted carcinogenic potency categorization listed by active pharmaceutical ingredients (APIs) that have the potential to form NDSRIs.

FDA expects drug manufacturers to ascertain the presence of NDSRIs and recommends different implementation timelines depending on the product's regulatory status. FDA recommends manufacturers complete confirmatory testing of drug products and submit required changes in drug applications by August 1, 2025.

For drug products in development and under FDA review, the guidance recommends applicants conduct a risk assessment for NDSRIs and conduct confirmatory testing prior to submission of an original application, or, if already submitted, supplementing the application as quickly as possible. If the original application has already been submitted, the testing may be submitted in an amendment as quickly as possible.

## Use of Alternative Tools to Assess Drug Manufacturing Facilities

In September 2023, FDA published draft guidance providing information on how the agency intends to use alternative tools (e.g., remote regulatory assessments, remote interactive evaluations) to assess drug manufacturing facilities identified in new drug and biologic applications and their compliance with current good manufacturing practices.

Given its experience using these tools during the COVID-19 pandemic, FDA announced that it intends to continue risk-based use of these tools in the context of preapproval inspections (PAIs) or prelicense inspections (PLIs) to enable agency flexibility and timely facility evaluations.

The guidance does not apply to postapproval, surveillance, for-cause, or bioresearch monitoring inspections. FDA intends to evaluate risks on a case-by-case basis when determining whether the use of alternative tools may be appropriate in advance, in lieu, or in support of a PAI or PLI.

FDA may consider the following factors when making a determination of whether to inspect onsite, use one of the tools, or a combination of both: (1) the facility has a drug inspection history and the proposed operations in the application are the same or related to existing operations covered in previous inspections; (2) application-specific risks or applicable facility operations can be adequately assessed through the tools; (3) the product addresses an urgent need such as a pervasive drug shortage; or (4) an inspection is not feasible as a result of travel limitations.

## Remote Interactive Evaluations of Facilities

Related to the use of alternative tools, FDA published draft guidance in October 2023 addressing remote interactive evaluations (RIEs) in detail. As described in a prior blog post, FDA relied on alternative inspectional tools, including RIEs, during the COVID-19 pandemic, and this guidance demonstrates FDA's continued use of the tools to enhance its ability to assess facilities.

The guidance describes how FDA determines whether a RIE is appropriate, how it will request and conduct RIEs, what a RIE virtual planning meeting may look like, and FDA's expectations during and following a RIE.

## Advanced Manufacturing Technologies Designation Program

In December 2023, FDA published draft guidance describing its new Advanced Manufacturing Technologies Program, facilitating the development and review of drugs and biological products manufactured using an advanced manufacturing technology (AMT) that has been designated under this program.

As described in a recent blog post, this program relates to novel manufacturing technologies or established technologies used in a novel way to improve the drug manufacturing process while maintaining equivalent, or providing superior, drug quality. AMT designation promises enhanced interaction with the agency as well as prioritized review of applications incorporating designated AMTs.

## 2024 Outlook

On the manufacturing front, we expect FDA to continue implementation of the many policies announced in 2023 as well as work toward implementation of a program related to platform technologies. Further, CDER's Office of Pharmaceutical Quality (OPQ) has recently announced a planned reorganization slated for 2024, intended to continue its lifecycle approach to product regulation, centralizing OPQ's research function, and reinforcing "stronger connections between assessment, inspection, surveillance, research, policy, and administrative operations."

# ADVERTISING AND PROMOTION

It has been a busy year in the advertising and promotions space at FDA, including for the staff in CDER's Office of Prescription Drug Promotion. Activities included publishing a long-awaited final rule updating FDA's regulations on direct-to-consumer (DTC) advertising as well as finalizing guidance in the same arena.

The year also included FDA's publication of draft guidance regarding dissemination of information on unapproved uses of approved drug products. Finally, while the issuance of Untitled Letters started off relatively slowly, FDA issued four Untitled Letters between June and October of 2023.

## Final Guidance: Presenting Quantitative Efficacy and Risk Information in DTC Promotional Labeling and Advertisements

FDA finalized its guidance in December 2023 providing recommendations for presenting quantitative efficacy and risk information (i.e., information that numerically addresses the likelihood or magnitude of a drug's efficacy or risks) in DTC promotional labeling and advertisements.

The guidance includes information on (1) providing quantitative efficacy or risk information for a control group, and encourages the inclusion of control group data; (2) presenting probability information in terms of absolute frequencies, percentages, and relative frequencies (which may be more challenging for consumers to understand and require additional context for understanding); (3) formatting recommendations for quantitative efficacy or risk information; and (4) using visual aids to illustrate quantitative efficacy or risk information (which are encouraged, provided that the type of visual aid matches the purpose and objectives of the communication).

## Draft Guidance: Communications From Firms to Healthcare Providers Regarding SIUU of Approved/Cleared Medical Products Questions and Answers

As we wrote in an earlier Lawflash, FDA published much-awaited draft guidance in October 2023 revising its approach to the dissemination of scientific information on unapproved uses (SIUU) of approved or cleared medical products. The draft guidance outlines communications that, if undertaken in accordance with the guidance, would avoid enforcement action by the agency.

Most notably, the draft guidance would expressly permit firm-generated material, provided that it meets the criteria laid out in the draft guidance, which would, among other things, require that any communications regarding SIUU would need to be truthful, nonmisleading, factual, and unbiased and would need to provide healthcare providers (HCPs) all information that may be necessary to understand the "strengths and weaknesses and validity and utility" of the information being conveyed.

Furthermore, the draft guidance would in some ways expand the scope of information on which firms would be able to rely when disseminating information regarding unapproved uses of approved products. For example, unlike the FDA's prior guidance on the dissemination of reprints that required that studies be well-controlled clinical investigations, the draft guidance provides for other kinds of studies so long as they are scientifically sound and clinically relevant.

## Final Rule: DTC Prescription Drug Advertisements: Presentation of the Major Statement in a Clear, Conspicuous, and Neutral Manner in Advertisements in Television and Radio Format

As further discussed in a previous blog post, FDA published a final rule pertaining to the presentation of the major risk statement (i.e., the name of a drug and its conditions of use, including the major side effects and contraindications) in DTC advertising to be made in a clear, conspicuous, and neutral manner.

The final rule establishes five conditions to meet this standard:

- The information is presented in consumer-friendly language using terminology that is readily understandable.
- Audio information is presented in a manner that is at least as understandable as the rest of the advertisement in terms of volume, articulation, and pacing used.
- Television-format advertisements present the major statement concurrently in audio and text, with additional requirements around timing and scope of text information provided.
- Television-format advertisements present the text portions of the information such that they are read easily in terms of size, font style, contrast, and placement of the text.
- The advertisement does not contain elements that are likely to interfere with the comprehension of the major statement, including audio or visual elements, alone or in combination.

The final rule will become effective on May 20, 2024, with a compliance date of November 20, 2024. FDA also published a small entity compliance guide on the rule providing additional guidance on compliance with the rule and agency resources available with respect to compliance.

## 2024 Outlook

As noted above, 2023 saw a late-in-the-year uptick in the issuance of Untitled Letters, leading some to wonder whether this could indicate a trend of greater enforcement from FDA in the advertising and promotion space than we have seen in recent years. However, in the DTC advertising space more generally, the finalization of the guidance on the presentation of quantitative risk and efficacy information could serve as a trigger for greater enforcement in the space.

The compliance deadline for implementation of the final rule recently issued on presentation of the major statement in DTC advertising will also fall within the year, which may provide more information on FDA's implementation and enforcement in the space as well. What's more, especially if/when FDA moves to finalize the draft guidance regarding dissemination of information on unapproved uses of approved drugs, we may begin to see firms utilizing the concepts outlined in the guidance and/or enforcement from FDA, which would likely provide greater clarity in how this new guidance will be received, addressed, and implemented by industry and FDA.

# LABELING

As is typical, FDA policy developments in the labeling space span from nuts-and-bolts practices around how drug information is conveyed in the labels to HCPs and other stakeholders, to policies that are reflected in labeling but, at the heart, relate to broader policy determinations, and 2023 was no exception to this.

Representing the first camp, FDA published revised draft guidance on dosage and administration of drug and biologic labeling and proposed a regulation that would establish a new type of medication guide for drugs used in the outpatient context. In the second, FDA issued draft guidance related to the use of prescription drug use-related software and how that would be reflected in labeling as well as revised draft guidance pertaining to how biosimilar and interchangeable biosimilar products are labeled.

## Draft Guidance: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

FDA issued revised draft guidance regarding the dosage and administration section of human prescription drug and biological product labeling. Withdrawing an earlier 2010 guidance on the same topic, this newly issued draft guidance replaces the previously issued draft. Among other things, the draft guidance notes that information in the dosage and administration section of labeling should be presented in a "clear, concise manner, using active voice and command language whenever possible." In addition, the prescribing information in this section should be pertinent to and presented in a manner understandable to HCPs, which can help reduce medication errors.

## Patient Medication Information Proposed Rule

In May 2023, FDA issued a proposed rule that would require a new type of medication guide in labeling for prescription drug products used, dispensed, or administered on an outpatient basis. Termed "Patient Medication Information," such a medication guide would be a one-page standardized document highlighting essential information for patients, including common side effects, important safety information, and how to use the prescription drug product.

If finalized, the regulation would require Patient Medication Information for all new and approved NDAs, BLAs, and abbreviated new drug applications (ANDAs) that are to be used, dispensed, or administered on an outpatient basis on a proposed five-year phased-implementation schedule.

## Draft Guidance: Regulatory Considerations for Prescription Drug Use-Related Software

With rapid developments in digital health in recent years, FDA issued in September 2023 draft guidance that delineates how the agency intends to regulate the end-user output of prescription drug use-related software (PDURS) through labeling after seeking public comment on a proposed framework in 2018. The draft guidance describes an end-user output as any material that the PDURS presents to the end-user that supplements, explains, or is textually related to the drug product.

The draft guidance also describes types of PDURS that may be appropriate to describe in the prescribing information (PI) of the drug's labeling and regulatory impacts of data regarding a drug product with a PDURS. The draft guidance distinguishes between two general categories of prescription drug labeling—FDA-required labeling and promotional labeling—and describes several functional and evidentiary factors used to delineate these categories.

The draft guidance defines "FDA-required labeling" as labeling that is reviewed and approved by FDA pursuant to a drug or biologics application submitted to FDA (including the PI) and defines "promotional

labeling" as all other labeling, with each category having a different regulatory status and related consequences and implications.

The draft guidance further describes how PDURS that is determined to be essential for the safe and effective use of the drug product or that relies on data transferred directly from the device constituent part of a combination product should be described in the PI as well as when and how sponsors should coordinate with FDA and submit PDURS-related information to FDA.

## Labeling for Biosimilar and Interchangeable Biosimilar Products

In connection with a number of activities aimed at examining the scientific and regulatory distinctions between interchangeable and noninterchangeable biosimilar products, FDA issued a revised draft of its guidance on labeling for biosimilar and interchangeable biosimilar products in September 2023.

Most notably, these revisions reflect a shift in approach, in that FDA now recommends including the same statement of biosimilarity in the highlights section of the PI. Previous recommendations provided for the inclusion of different statements for interchangeable and noninterchangeable biosimilars.

## 2024 Outlook

We expect similar trends in drug and biologic labeling policy in 2024 as we saw in 2023. Namely, we'd expect a mix of developments around general labeling practices as well as new developments that reflect broader policy determinations around other labeling-related areas of FDA interest, with both types bearing attention and consideration.

# DRUG SUPPLY CHAIN SECURITY ACT IMPLEMENTATION AND COMPLIANCE

Implementation of the Drug Supply Chain Security Act (DSCSA) has been a work in progress as FDA has released guidance and policies over the last decade since the act's 2013 enactment. The DSCSA outlined steps for manufacturers, wholesale distributors, dispensers, and repackagers to build an electronic system to identify and trace certain prescription drugs distributed in the US pharmaceutical distribution supply chain by the statutory deadline of November 27, 2023.

In this year alone, FDA issued seven pieces of guidance clarifying the DSCSA requirements and its current thinking on (1) suspect and illegitimate product identification; (2) waivers, exceptions, and exemptions; (3) compliance policies; (4) enhanced security requirements at the package level; (5) wholesale distributor and dispenser verification requirements; (6) adoption of DSCSA standards; and (7) verification systems.

Despite FDA's one-year extension until November 27, 2024 to begin enforcement of the DSCSA requirements, the recent increase in publication activity demonstrates FDA's continued efforts to ensure a secure pharmaceutical distribution supply chain.

## Suspect and Illegitimate Products

In March 2023, FDA issued final guidance clarifying its interpretation of the definitions of "suspect product" and "illegitimate product" to help manufacturers, repackagers, wholesale distributors, and dispensers identify and handle these products to meet verification requirements under the DSCSA. The guidance clarifies FDA's interpretation of the terms "counterfeit," "diverted," "stolen," "fraudulent transaction," and "unfit for distribution" found within the definitions.

## Waivers, Exceptions, and Exemptions

In August 2023, FDA released final guidance describing the process stakeholders should use to request a waiver, exception, or exemption from certain product tracing, identification, and verification requirements under the DSCSA. The guidance addresses factors FDA intends to consider when evaluating such requests, the renewal process, and the process for FDA-initiated exceptions and exemptions.

## Enforcement Time Extension

FDA also released in August 2023 final guidance granting a one-year extension until November 27, 2024 to trading partners to meet requirements under Section 582(g)(1) of the Federal Food, Drug, and Cosmetic Act, which includes requirements pertaining to the exchange of transaction information in a secure, interoperable, electronic manner; package-level product identifiers; systems and processes for package-level verification; recall and investigation response; and information gathering and tracking of saleable returns.

Despite FDA granting a one-year reprieve period to meet DSCSA requirements, FDA makes clear that the guidance "is not intended to provide, and should not be viewed as providing, a justification for delaying efforts by trading partners to implement the enhanced drug distribution security requirements." Rather, FDA "strongly urges trading partners to continue their efforts to implement necessary measures to satisfy these enhanced drug distribution security requirements."

FDA recognizes the "technical and operational complexities associated with the implementation" of the DSCSA requirements and therefore provides additional time and flexibility to develop appropriate systems and processes.

## Enhanced Security at the Package Level

FDA also released final guidance in August 2023 clarifying enhanced security requirements described in the DSCSA and describing the "system attributes" of the DSCSA to ensure enhanced product tracing at the package level, including the use of verification, aggregation, and inference as necessary. The guidance clarifies the use of the terms "aggregation" and "inference," which are not defined in the statute but are referenced in the context of product verification and are recognized by the FDA guidance as common practices. FDA further recommends the use of physical security features on shipping units.

Additionally, the guidance outlines FDA's expectations in the form of elements that trading partners should consider when developing policies and procedures to implement the DSCSA security requirements. These elements include

- data architecture (i.e., the use of a "distributed" or "semi-distributed" model using the Electronic Product Code Information Services (EPCIS) standard to capture and exchange data);
- adoption of data and system security to protect against falsification and breaches;
- protection of confidential commercial information and trade secrets;
- ability to request and respond to trading partners' requests for information related to verification activities;
- incorporation of the product identifier (e.g., the standardized numerical identifier (i.e., National Drug Code (NDC) and serial number), lot number, expiration date) into the product tracing information;
- reconciliation and confirmation of transaction information;
- handling aggregation errors or other discrepancies;
- ability to receive product tracing information from trading partners involved in transactions related to a specific product as part of an investigation of suspect or illegitimate product or a recall, as applicable; and
- enhanced electronic verification information exchange.

## Wholesale Distributor and Dispenser Verification Requirements

In September 2023, FDA released a revised version of the 2020 Compliance Policies guidance, which required wholesale distributors to verify the product identifier prior to distributing saleable returned product and dispensers to verify the product identifier for suspect or illegitimate product in the dispenser's possession or control. FDA intends to extend enforcement for these requirements for an additional year, on account of stakeholder concerns related to industrywide readiness for implementation of the verification requirements.

Specifically, the guidance provides that the agency does not intend to take action before November 27, 2024 against (1) wholesale distributors that do not verify a product identifier prior to resale or other further distribution of a package or sealed homogenous case of product; (2) wholesale distributors for providing a transaction statement to a subsequent purchaser of product on the basis that such wholesale distributor does not yet have systems and processes in place to comply with the saleable return verification requirements; or (3) dispensers that do not verify the product identifier of suspect product or illegitimate product that is the subject of a notification by FDA or a trading partner.

Despite the one-year extension authorized by FDA, stakeholders must note that this guidance does not affect other required activities. For example, manufacturers are not relieved of their verification

obligations upon receiving a verification request from an authorized dispenser. In addition, dispensers must still quarantine product, conduct investigations, and dispose of illegitimate product.

## DSCSA Standards

FDA also released in September 2023 final guidance identifying standards necessary to adopt a secure, interoperable, electronic data exchange among the pharmaceutical distribution supply chain. The agency recommends that trading partners adopt the EPCIS standard to manage transaction information and transaction statements. The guidance clarifies that only electronic methods of product tracing will be permitted, and verification of product at the package level will be required unless a waiver, exception, or exemption applies.

## Verification Systems

In December 2023, FDA published draft guidance describing the verification systems required under DSCSA, including systems to detect suspect product, the quarantine and investigation of suspect products, and the quarantine and disposition of illegitimate products. The guidance also addresses related notifications to FDA and other trading partners as well as requirements related to responding to requests for verification and processing saleable returns.

## 2024 Outlook

Per FDA, the agency has now published all the required guidance contemplated by DSCSA and, as such, we anticipate that much of 2024 will be focused on establishing necessary systems, processes, and procedures to ensure that entities are on track to meet the revised November 2024 timelines.

## CONCLUSION

We anticipate that in 2024 FDA will continue its trend of working with the industry to find new ways to meet the agency's regulatory requirements, including in the areas of drug and biologic development, promotion, labeling, and manufacturing. It is possible, however, that we will also begin to see increasing FDA enforcement as, among other things, the agency's facility inspections are beginning to reach prepandemic levels. Moreover, with the agency's new policies on communication of product information, FDA may feel more empowered to undertake promotional enforcement, an area that it has not been as active in the last few years.

More specifically, in 2024 we expect rare disease development to continue to be a focus for FDA and will be keeping an eye on how it implements its START (Support for Clinical Trials Advancing Rare Disease Therapeutics) pilot program and whether we will see the "Warp-Speed"-like program for rare disease expand in 2024 or beyond. On a related note, we expect the uptick in applications, activity, and staff and program expansions in the Center for Biologics Evaluation and Research, especially in the areas of cell and gene therapy, to continue through 2024.

We also expect to see continued implementation of the Food and Drug Omnibus Reform Act of 2022 (FDORA), including with respect to the new provisions related to clinical trial diversity, accelerated approval, and platform designations. Finally, the significant reorganizations penned for 2024, including establishing the planned Office of Inspections and Investigations out of the current Office of Regulatory Affairs and a separate reorganization focused on CDER's OPQ, will bear close attention as they move forward.

As always, the Morgan Lewis FDA team will be monitoring all of the changes that are coming in 2024. Stay abreast of all things FDA and life sciences by subscribing to our *As Prescribed* blog, including posts the week of January 8, 2024 from San Francisco as the healthcare industry gathers in the Golden Gate City for the annual J.P. Morgan Healthcare Conference.

Be sure to also tune into our Life Sciences Growth Webinar Series and, later this year, our Asian Life Sciences Webinar Series for hot topics, trends, and key developments in the life sciences industry essential to our clients and contacts operating in Asia. Agendas for both series' upcoming programs will be announced in the coming months.

## CONTACTS

If you have any questions or would like more information on the issues discussed in this report, please contact any of the following:

**Washington, DC**

| | | |
|---|---|---|
| Jacqueline R. Berman | +1.202.739.5057 | jacqueline.berman@morganlewis.com |
| Rebecca L. Dandeker | +1.202.739.5614 | rebecca.dandeker@morganlewis.com |
| Maarika L. Kimbrell | +1.202.739.5348 | maarika.kimbrell@morganlewis.com |
| Kathleen Sanzo | +1.202.739.5209 | kathleen.sanzo@morganlewis.com |


## ABOUT US

Morgan Lewis is recognized for exceptional client service, legal innovation, and commitment to its communities. Our global depth reaches across North America, Asia, Europe, and the Middle East with the collaboration of more than 2,200 lawyers and specialists who provide elite legal services across industry

sectors for multinational corporations to startups around the world. For more information about us, please visit www.morganlewis.com.