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On October 23, 2023, FDA announced the availability of a revised draft guidance titled "Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products." The draft guidance supersedes the agency's 2014 draft guidance, "Distributing Scientific and Medical Publications on Unapproved New Uses," and it provides more direction for industry on how information regarding unapproved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The draft guidance coins a new acronym, SIUU, for scientific information on unapproved uses of an approved/cleared medical product, and provides recommendations for how to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The revised draft guidance is organized in a question and answer format and addresses: (1) what firms should consider when determining whether a source publication is appropriate to be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stakeholders looking to understand what is new and/or different about these recommendations relative to the 2014 draft guidance, we note that the agency continues to recommend providing disclosures about how the information in these communications compares with the FDA-approved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 However, the revised draft guidance provides more insight into what studies or analyses are "scientifically sound" and provide "clinically relevant information," such that they could be the basis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.

Clinical Trial Diversity Plans and Rare Diseases

 Clinical trial diversity is not a new concept–the U.S. Food and Drug Administration (FDA) issued a **draft guidance** providing specific recommendations to industry on how to improve diversity in clinical trials in April 2022 which we blogged about **here**–but the passage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

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

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

During FDA's Rare Disease Day 2023, agency officials noted that the FDA has long encouraged diversity, including through guidances issued prior to the April 2022 draft guidance, but the passage of FDORA marks the first time that addressing diversity with a prospective plan is a *requirement* in the development process. With that in mind, speakers pointed out that developing a candidate in a rare indication is all the more reason to develop a strategy to enroll as many eligible patients as possible.

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

- Engage advocacy groups and community health groups (early and often), as these groups

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

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

PhRMA Issues Updates to Longstanding Code, Addresses OIG's Speaker Program Guidance

PhRMA, the pharmaceutical manufacturer trade association, **announced on Fri. August 6** that it has revised its **longstanding Code on Interactions with Health Care Professionals**. The revisions, which relate to the Code's treatment of speaker programs, track concerns in a **Special Fraud Alert** released late last year by the US Department of Health and Human Services Office of Inspector General. This alert criticized the drug and medical device industry practice of engaging healthcare providers to deliver educational content to potential customers or users of products through so-called "speaker programs." The OIG found in its report that speakers were selected based on past or anticipated business; that attendees of these programs were offered remuneration in the form of lavish meals and alcohol; that programs were often held in high-end locations, often without an agenda, and often without any educational content delivered at all. The OIG also noted its findings that attendees of speaker programs regularly attend the same

program more than once, calling into question their educational value. The alert expressly notes OIG's "skepticism" about such programs.

PhRMA appears to be the first of the major medical products trade associations to update its code of ethics based on the OIG's November 2020 alert. The PhRMA Code revisions from August 6 appear to address the criticisms raised by OIG. PhRMA expands its section 7 discussion of Speaker Programs, emphasizing the importance of speaker programs as a real and legitimate avenue of educating customers and product users about the benefits, risks, and science of particular products. Among the revisions:

- The PhRMA Code reiterates that incidental meals of modest value may still be offered to attendees but that they should be subordinate in focus to the educational presentation. The revisions also make it clear that companies should not pay for or provide alcohol at a speaker program, one of the OIG's chief complaints in the November 2020 alert.
- The revisions make clear that the purpose of any speaker program must be to present substantive educational information designed to help address a bona fide educational need among attendees, and that only those with a bona fide educational need should be invited. The revisions also highlight that repeat attendance at a program on the same or substantially same topic is generally not appropriate unless there is a bona fide educational need for the additional information.
- PhRMA emphasizes that the venue should be conducive to informational communication – no extravagant venues, luxury resorts, high-end restaurants, or entertainment/sporting venues.
- Further, the PhRMA Code also spotlights the fact that speakers should be engaged following the guidelines for engaging consultants as described in the PhRMA Code – including selection based on expertise and professional qualifications rather than past or anticipated business.

Revisions to the new PhRMA Code become effective January 1, 2022. This gives companies just a few months to evaluate their compliance policies and to update messaging to their employees regarding the appropriate set-up and operation of speaker programs, if any revisions to current practices are required.

If you have questions about this update, please contact Matt Wetzel (**mwetzel@goodwinlaw.com**, (202) 346-4208).

FDA Answers New Questions on Foreign Trial Sites Operating Under INDs

On May 19, 2021, the U.S. Food and Drug Administration (FDA) released an **updated guidance** in draft form on how to complete the Statement of Investigator form

(Form FDA 1572). The guidance addresses frequently asked questions from sponsors, clinical investigators, and institutional review boards (IRBs), and it provides new information on waivers of the Form FDA 1572 signature requirement, which is particularly relevant for sponsors of clinical trials that include sites located outside the U.S.

Form 1572 is an agreement signed by an investigator to provide certain information to the sponsor and comply with FDA regulations on conducting a clinical investigation of an investigational drug or biologic, and under 21 CFR Part 312, an investigator must sign this agreement before participating in a trial. FDA's **previous guidance** on the Form 1572 requirements and process, issued in 2010, touches briefly on the responsibilities of investigators conducting foreign studies under an investigational new drug application (IND) in the U.S., but it does not go into detail on how sponsors should proceed when an ex-U.S. investigator cannot or will not sign the 1572 (e.g., because the commitments for investigators on the Form 1572 extend beyond or conflict with what local law requires).

Under the updated guidance, FDA provides detailed steps for sponsors to request a waiver of the Form 1572 signature requirement for foreign investigators. A Form 1572 waiver allows a trial at a foreign site to take place under an IND even when the investigator cannot or will not sign the Form 1572, as noted above. When requesting a waiver, the sponsor should propose an alternative course of action to adequately satisfy the purpose of a signed Form 1572, and the sponsor must request and receive a 1572 waiver for an investigator before the study is initiated at the investigator's site. Importantly, the guidance provides examples of sponsor and investigator commitment statements that would satisfy FDA's guidelines for granting a waiver, and FDA recommends using these templates to enable FDA's efficient review of a waiver request.

Overall, the guidance provides greater clarity on when a Form 1572 waiver would be needed and how a sponsor can obtain one. Sponsors planning to conduct a clinical study at a foreign site under an IND should review the updated guidance and, if a waiver is needed, factor in time for submission and FDA review of a waiver request before initiating the trial at a foreign site. Additionally, sponsors should ensure that clinical trial agreements with foreign sites contemplate Form 1572 completion and signatures and/or waivers when necessary.

Are Pre-Approval and Pre-Licensure Inspections Limiting Approvals During COVID-19?

In this post, we discuss FDA's conduct of inspections of manufacturing facilities for new drugs and biologics during the COVID-19 pandemic. These

inspections, known as pre-approval and pre-licensure inspections (PAIs/PLIs, respectively), are performed to give FDA assurance that a manufacturing site named in a new drug or biologics license application is capable of manufacturing the product according to current good manufacturing practices (cGMPs) and producing the product at commercial scale.

In **July**, FDA resumed limited domestic on-site inspections after temporarily postponing all domestic and foreign routine surveillance facility inspections in March. Since **June**, FDA had conducted only mission-critical domestic inspections. Currently, domestic on-site inspections are pre-announced and are prioritized on a newly developed rating scale that uses real-time data on the number of COVID-19 cases in a local area to qualitatively determine when and where it is safest to conduct inspections. Foreign PAIs/PLIs continue to be temporarily postponed unless deemed mission-critical. FDA may deem an inspection mission-critical based on a variety of factors including, but not limited to, whether the product has received breakthrough therapy or regenerative medicine advanced therapy designation.

In response to COVID-19, FDA has used, on a limited basis, various tools to conduct alternative inspections. These tools include the use of FDA's authority under Section 704(a)(4) of the FD&C Act, which enables the Agency to request records directly from facilities "in advance of or in lieu of" drug inspections. In addition, FDA has indicated that it may also look to records of recent inspections and information shared by foreign regulatory partners through mutual recognition agreements. And while the concept of virtual inspections has been floated, it remains to be seen if video-based or other virtual inspection strategies can be used to fulfill PAI/PLI requirements and how long such proposals may take to implement.

Worryingly, FDA explains in its **August 2020 guidance** that should the Agency determine that a PAI/PLI is necessary, and such an inspection cannot be completed during the review cycle due to restrictions on travel or other COVID-19-related risks, FDA generally intends to issue a Complete Response letter or may defer action. The guidance, along with a number of concerns raised quietly by sponsors regarding delayed inspections leading or potentially leading to Complete Response letters, paints a potentially ominous picture for drug and biologic approvals and the advancement of the public health over the coming months. Sponsors submitting marketing applications in the near-term would be wise to proactively prepare for discussion of alternative inspection approaches during the review of their applications.