

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On October 23, 2023, FDA announced the availability of a revised draft guidance titled “Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products.” The draft guidance supersedes the agency’s 2014 draft guidance, “Distributing Scientific and Medical Publications on Unapproved New Uses,” and it provides more direction for industry on how information regarding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The draft guidance coins a new acronym, SIUU, for scientific information on unapproved uses of an approved/cleared medical product, and provides recommendations for how to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The revised draft guidance is organized in a question and answer format and addresses: (1) what firms should consider when determining whether a source publication is appropriate to be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stakeholders looking to understand what is new and/or different about these recommendations relative to the 2014 draft guidance, we note that the agency continues to recommend providing disclosures about how the information in these communications compares with the FDA-approved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 However, the revised draft guidance provides more insight into what studies or analyses are “scientifically sound” and provide “clinically relevant information,” such that they could be the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

[Recent FDA Initiatives to Support Development of Individualized Cell and Gene Therapies and Rare Disease Therapies](#)



Last month, FDA issued a [Request for Information](#) (RFI) in the Federal Register seeking information and comments from interested stakeholders regarding “critical scientific challenges and opportunities to advance the development of individualized cellular and gene therapies (CGTs).” Individualized CGTs are therapies “developed for a single patient (or a very small number of patients) based on designing or engineering a product that specifically targets the mechanism underlying a patient’s (or small number of patients’) illness.”

FDA’s request focuses on three core areas:

1. Manufacturing: Manufacturing and product quality challenges and opportunities for individualized CGTs in light of, for example, small batch sizes, tailoring of batches to individual patients, and need for rapid testing and release.

On this topic, FDA asks:

- i. *Given the challenges to develop consistent manufacturing strategies for CGTs designed for a very small number of patients or an individual patient, how can manufacturers leverage their prior experience manufacturing one CGT to support subsequent development and approval of another related, but distinct CGT (potential areas for leveraging may include manufacturing process validation, control strategy, assay validation, and drug product stability studies)?*
- ii. *When the batch size of a CGT is very small, what are some challenges and solutions regarding the volume of product (or number of vials) needed for batch release testing, stability testing, retention of reserve samples, and comparability studies?*
- iii. *What are some challenges and solutions for individualized CGTs that need to be tested and released rapidly, either because the product has a very short shelf life or because the patient’s clinical status may be rapidly declining and treatment is urgently needed?*
- iv. *For many individualized CGT products, each batch is tailored to an individual patient (e.g., autologous CAR-T cells, tumor neoantigen vaccines, certain genome editing products). For such products, what are some challenges and solutions for assuring that each batch has adequate potency to achieve the intended therapeutic effect?*
- v. *What are some challenges and solutions for individualized genome editing products that aim to treat monogenic diseases for which the target gene has different mutations in different patients?*

2. Nonclinical development: The use of nonclinical data to support individualized CGTs, considering the lack of relevant animal models in many instances, the uniqueness or limited applicability of individualized CGTs, and the potential of using prior knowledge from other CGTs—for example, where gene therapy vector products use the same vector backbone.

On this topic, FDA asks:

- i. *What nonclinical studies could be leveraged in support of a related product using similar technologies? What nonclinical studies are important to conduct with each final clinical product?*
- ii. *What nonclinical development approaches could be considered when there are no relevant animal models or animal models are unable to replicate each individual disease/condition?*
- iii. *For patient-specific products where evaluating each individual product is infeasible or impractical, what is the role for nonclinical studies conducted with representative product(s)?*
- iv. *What are the opportunities and challenges with using computational approaches to support nonclinical development?*

3. Clinical Development: Clinical development of individualized CGTs, considering for example the infeasibility (for ethical or other reasons) of conducting randomized controlled studies, novel endpoints, and limitations in statistical analyses.

On this topic, FDA asks:

- i. *What are challenges and strategies/opportunities with interpreting efficacy data from individual patients (including expanded access) and small groups of patients? What opportunities are there in leveraging prior and/or collective experiences?*
- ii. *What strategies can be utilized to accumulate and interpret safety data in personalized/individualized CGTs?*
- iii. *For genetic disorders with clear genotype-phenotype associations for disease manifestations or severity, what opportunities are there for tailoring treatments and study design to specific genotypes/phenotypes?*

FDA also requested input on several additional significant questions:

- i. *What additional major scientific challenges to advance the development of individualized CGTs should be considered?*
- ii. *What existing best practices or scientific approaches should be leveraged to address any of these challenges? Are there specific opportunities for collaborations to advance the development of individualized CGTs?*
- iii. *Are there specific areas where flexibility in regulatory approaches would improve the feasibility of developing and commercializing individualized CGTs?*

Comments are due on November 20, 2023.

At the end of last month, FDA also [announced](#) a pilot program “to help further accelerate development of rare disease therapies.” The program, titled Support for clinical Trials Advancing

Rare disease Therapeutics (“START”), will include selected sponsors with an active IND for products meeting certain eligibility requirements. Products regulated by CBER are eligible for the program only if they are a gene or cell therapy treatment for a rare disease or condition that is “likely to lead to significant disability or death within the first decade of life.” Products regulated by CDER are eligible only if they are “intended to treat rare neurodegenerative conditions, including those of rare genetic metabolic type.” Participants selected for the pilot program will “be able to obtain frequent advice and regular ad-hoc communication with FDA staff to address product-specific development issues, including, but not limited to, clinical study design, choice of control group and fine-tuning the choice of patient population.”

FDA will accept applications to the START program beginning January 2, 2024 and until March 1, 2024.

[Mark Your Calendars: This Halloween, Don't Miss FDA's LDT Webinar](#)



The U.S. Food and Drug Administration (FDA) has announced an upcoming [webinar](#) on its [proposed rule](#) on the regulation of laboratory developed tests (LDTs).

The webinar is scheduled for **October 31, 2023 from 1:00 - 2:00 PM ET** and will include an overview of the proposed rule, a description of the proposed phaseout of FDA's general enforcement discretion approach to LDTs, and a question and answer session. Stakeholders must submit questions by **October 23, 2023** to be considered for the discussion.

For our detailed analysis of the 83-page proposed rule, please see our two-part Insight series: [Part I: Underpinnings of FDA's Proposed Rule](#) and [Part II: FDA's Proposed Phaseout Policy - Key Considerations & Open Questions](#).

If you have questions on the proposed rule or its potential impact, contact the authors or a member of the [Goodwin Life Sciences Regulatory & Compliance](#) team.

[FDA's Proposed Rule for Oversight of](#)

Laboratory Developed Tests: Part II: FDA's Proposed Phaseout Policy - Key Considerations & Open Questions



After an over decade-long discourse amongst interested stakeholders, on October 3, 2023, FDA unveiled its [proposed rule and policy](#) to increase oversight over LDTs.

If finalized as proposed, FDA would implement a new “phaseout policy” that would, across five stages and within four years, apply the same regulatory requirements applicable to in vitro diagnostics (IVDs) on the majority of clinical laboratories offering tests as LDTs. Once implemented, tests offered as LDTs that do not meet the applicable regulatory requirements, including premarket review and the quality system regulation, may be expected to come off the market.

In our [first post](#) in this Insight series, we recapped the underpinnings of the proposed rule and policy, including the significant discussions contained in the proposed rule on (1) the rationale for the agency’s proposed phaseout policy and (2) FDA’s legal authority for issuing the rule.

In this Insight, we provide our full analysis of FDA’s proposed five-stage phaseout policy and the open questions that remain. Read the full Insight [here](#).

Federal Court Strikes Down Copay Accumulator Programs



Summary:

On September 29, 2023, the U.S. District Court for the District of Columbia [vacated](#) a Trump-era rule from 2021 that allowed insurers to exclude drug manufacturer co-pay support coupons and

assistance from a patient's annual cost-sharing caps. This practice, commonly referred to as a copay accumulator program, is typically used by insurance companies and pharmacy benefit managers to control drug spending, especially for high-cost specialty drugs, like those required by HIV patients.

Under typical prescription drug insurance programs, patients are obligated to pay a deductible and cost-sharing (i.e. a copay) throughout the plan year, up to an out-of-pocket spend cap. Once the patient hits that spend cap, the insurance company is responsible for the patient's prescription drug costs.

Under an accumulator program, on the other hand, an insurance company does not count a manufacturer's copay support (for example, a copay card that a patient presents at a pharmacy to cover the cost of the copay) towards a patient's annual deductible or out-of-pocket maximum. By excluding manufacturer copay support and coupons from patients' cost-sharing cap, this means that, even after a manufacturer's copay support is exhausted for the year, patients remain on the hook for all cost sharing obligations up to the insurance plan's out of pocket maximums. Many states have implemented laws to ban copay accumulator programs, asserting that such programs actually increase the financial burden on patients, especially with respect to specialty or more expensive drugs. As of June 2023, 19 states have implemented copay accumulator program bans.

[**HIV and Hepatitis Policy Institute et al v. HHS**](#) was brought by patient advocacy groups including the HIV and Hepatitis Policy Institute and the Diabetes Patient Advocacy Coalition, among others, who challenged a May 2020 rule from HHS, the "Notice of Benefit and Payment Parameters for 2021" (85 Fed. Reg. 29164, 29230-35, 29261 (May 14, 2020)) (the "2021 NBPP") that permitted insurers to impose accumulator policies. Plaintiffs opposed the accumulator program, asserting that manufacturer copay support should count *towards* calculating patients' cost sharing obligations and should not be excluded from such calculations.

In ruling in favor of the plaintiffs on their motion for summary judgment, the U.S. District Court set aside the 2021 NBPP, largely supporting plaintiffs' challenges that the 2021 NBPP rule's language is internally contradictory, that it runs counter to the statutory definition of "cost sharing" found in the Affordable Care Act, and that it runs counter to the agencies' pre-existing regulatory definition of "cost sharing." HHS had previously defined "cost sharing" in a 2012 regulation as "any expenditure required by or on behalf of an enrollee with respect to essential health benefits," which by its terms includes "deductibles, coinsurance, copayments, or similar charges, but excludes premiums, balance billing amounts for non-network providers, and spending for non-covered services." See 45 C.F.R. 155.20. In other words, the regulation treats cost sharing as an "expenditure" by or on behalf of a plan enrollee. According to plaintiffs, and as affirmed by the court, this includes manufacturer copay assistance support.

The court disagreed with the government's technical arguments regarding the language of the 2021 NBPP (i.e. that manufacturer copay support is actually a "reduction" in the amount the patient owes towards cost sharing or a reduction in the "actual economic impact" on the drug manufacturer and not an "expenditure"), concluding that the 2012 regulation was likely intended to define "cost sharing" as costs that are (1) required of an insurance plan enrollee and (2) paid by or on behalf of that enrollee - including manufacturer copay coupons and assistance.

It is unclear if the ruling will be appealed; however, as a result of the District Court's ruling, the government will use an earlier 2020 version of the rule which allowed insurers to exclude from cost-sharing caps only copay support coupons for branded drugs that have available generic equivalents; if there is no generic equivalent, under the 2020 version of the rule, manufacturer copay support must be counted toward cost sharing.

Conclusions: The U.S. District Court ruling is a significant development for drug manufacturers who offer copay support as a means of providing relief to patients with respect to cost-sharing requirements under their insurance coverage as opposed to offering significant rebates, discounts, or other contracting strategies. However, manufacturers of branded drugs with a generic equivalent will still need to consider how copay accumulator programs could affect access in those states that have not yet banned the practice. Notably, in the wake of this ruling, patient advocacy organizations have indicated that they will continue to advocate for a comprehensive state and federal level ban on copay accumulator programs (e.g. [Immune Deficiency Foundation](#)).

Goodwin will continue to monitor any further developments in this case and the impact of copay accumulator programs on the market.

[FDA's Proposed Rule for Oversight of Laboratory Developed Tests: Part I: Underpinnings of FDA's Proposed Rule](#)



On October 3, 2023, the U.S. Food and Drug Administration (FDA) published its widely anticipated [proposed rule](#) on the regulation of laboratory developed tests (LDTs). The proposed rule and policy are the latest in an over decade-long discourse amongst interested stakeholders – laboratories, IVD manufacturers, regulatory agencies, Congress, providers, and patients – as FDA has sought to enhance oversight over LDTs.

In this Insight, we recap the underpinnings of the proposed rule and policy, including the two lengthy discussions contained in the proposed rule on (1) the rationale for the agency's proposed phaseout policy and (2) FDA's legal authority for issuing the rule. Stay tuned next week for our additional analysis of the details of FDA's proposed five-stage "phaseout" policy and the open questions that remain.

Contact the authors or a member of the Goodwin [Life Sciences Regulatory & Compliance](#) team for any questions. Read the full Insight [here](#).

[A Look Ahead in Life Sciences: What We Are Tracking in Q4 2023 and Beyond](#)



As the life sciences, medtech, and diagnostic industries continue to expand and grow increasingly complex, so do the legal, regulatory, and compliance landscape. To help companies and investors navigate the many evolving and emerging laws and regulations across pharmaceuticals, biologics, medical devices, diagnostics, and laboratory testing, our Life Sciences Regulatory & Compliance team has provided an overview of key developments. We update and publish a quarterly tracker detailing these developments. You can read about the Q4 2023 updates [here](#).

[FDA Proposes Phased Approach to Regulating Laboratory Developed Tests](#)



On September 29, 2023, the U.S. Food and Drug Administration (FDA) posted and scheduled for publication its long-awaited **[proposed rule](#)** concerning FDA regulation of laboratory developed tests (LDTs). If enacted, the proposed rule would amend the Agency's regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act; and this includes when the manufacturer of the IVD is a laboratory.

Upon finalization of the rule, FDA proposes to phase out its general "enforcement discretion" approach for LDTs so that tests manufactured by a laboratory would generally fall under the same enforcement approach as other IVDs.

Comments to the proposed rule are due 60 days after the date of publication of the proposed rule in

the Federal Register. We will provide our full analysis of the proposed rule in the coming days. Contact the authors or a member of the Goodwin [Life Sciences Regulatory & Compliance](#) team for any questions.

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



Last week, [FDA released](#) a draft guidance, “[Labeling for Biosimilar and Interchangeable Biosimilar Products](#)” that—when finalized—will revise and replace its July 2018 final guidance, “[Labeling for Biosimilar Products](#).” FDA noted that this 2023 Draft Guidance reflects recommendations based on the “valuable experience about labeling considerations” that FDA has gained through its approval of 42 biosimilar products, including four interchangeable biosimilar products.

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

- The biosimilar or interchangeable biosimilar product’s proprietary name^[1] (or if the product does not have a proprietary name, its proper name^[2]) should be used when –
 - Information in the labeling is *specific to the biosimilar (or interchangeable biosimilar) product*, including such references to the product in the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections, and/or
 - For “directive statements and recommendations for preventing, monitoring, managing, or mitigating risk,” including such references to the product in the BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS sections.
- When referring to the *drug substance* in the labeling, the biosimilar or interchangeable biosimilar product’s proper name should be used.
- When information *specific to the reference product* is described in the biosimilar or interchangeable biosimilar product’s labeling (for example, data from clinical trials of the reference product in the ADVERSE REACTIONS and CLINICAL STUDIES sections), the

reference product's proper name should be used.

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

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

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

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

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

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

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

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

[4] The fictitious example provided by FDA in the 2023 Draft Guidance is “NEXSYMEO (replicamab-cznm) is biosimilar* to JUNEXANT (replicamab-hjxf)” and the accompanying footnote is “Biosimilar means that the biological product is approved based on data

demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of *[BIOSIMILAR OR INTERCHANGEABLE BIOSIMILAR PRODUCT'S PROPRIETARY NAME]* has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration) described in its Full Prescribing Information."

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

Modernizing the FDA's 510(k) Program for Medical Devices: Selection of Predicate Devices and Use of Clinical Data in 510(k) Submissions



On September 6, 2023, the US Food and Drug Administration (FDA) released a trio of draft guidances in its efforts to "strengthen and modernize" the 510(k) Program and provide for more "predictability, consistency, and transparency" for the 510(k) premarket review process. In this post, we discuss the two new draft guidances with broad applicability to the 510(k) Program:

- [**"Best Practices for Selecting a Predicate Device to Support a Premarket Notification \[510\(k\)\] Submission"**](#)
- [**"Recommendations for the Use of Clinical Data in Premarket Notification \[510\(k\)\] Submissions"**](#)

The two draft guidances address a number of fundamental issues of concern with the 510(k) process.

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