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FDA Finalizes Guidances for "Consistent Communications" and Payor Communications

A Summary of Final Guidances for Communications That Are Consistent with FDA-Required Labeling and Communications with Payors

On June 12, 2018, the Food and Drug Administration (FDA or Agency) finalized two draft guidance documents that have been closely watched:

(1) *Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers* [hereinafter "*CFL Guidance*"].

The *CFL Guidance* addresses how the Agency will treat information that is "consistent" with, but not contained in, FDA-required labeling (often referred to as "consistent communications" or "CFL communications").

(2) *Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Questions and Answers* [hereinafter "*Communications with Payors Guidance*"].

The *Communications with Payors Guidance* is a three-part guidance that addresses communications with payors, formulary committees, and similar entities (collectively, "payors") about (a) healthcare economic information (HCEI) for approved or cleared drugs and devices, and (b) information about unapproved/uncleared drugs and devices, and unapproved/uncleared uses of approved or cleared products.

The finalization of these guidances, which were first issued in draft form in January 2017, reflects unusually quick activity by FDA to address important questions related to the Agency's off-label policy.

BACKGROUND ON FDA'S POLICIES

Under the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), the FDA regulates drugs and devices, including biologics and combination products (collectively, "medical products"), based on their *intended use*.

Specifically, a product may be regulated as a drug or device if it is intended to diagnose, cure, mitigate, treat, or prevent a disease or condition, or to affect the structure or function of the body.[1] The Agency typically considers "any relevant source of evidence" to establish intended use, such as evidence of how the product is marketed.[2] Medical products that are intended for an unapproved or uncleared new use – colloquially referred to as an "off-label" use – violate the FD&C Act.

FDA's regulatory and enforcement activities for off-label use have triggered First Amendment challenges over the past few decades; however, more recent industry victories in cases such as *United States v. Caronia*[3] and *Amarin Pharma, Inc. v. United States Food and Drug Administration*[4] have escalated longstanding tensions between the Agency's off-label policy and the First Amendment. In June 2014, in the wake of the *Caronia* decision, FDA granted two citizen petitions[5] that asked for better alignment between FDA's off-label policy and the First Amendment by promising additional guidance on the subject.[6] Two years later, FDA hosted a public hearing to obtain input related to its "comprehensive review" of regulations and policies for off-label communications.[7]

In January 2017, FDA issued three related documents: the draft *CFL Guidance*, the draft *Communications with Payors Guidance*, and a "memorandum" defending the Agency's off-label policy under the First Amendment.[8] The draft *CFL Guidance* was intended to broaden the scope of promotional communications by expressly permitting a range of claims that are not within the four corners of FDA-required product labeling, but are consistent with such labeling. The draft *Communications with Payors Guidance* was intended to clarify Section 502(a) of the FD&C Act (as amended by section 114 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and section 3037 of the 21st Century Cures Act (Cures)) for HCEI about drugs and also provide a safe harbor for communications with payors about investigational drugs and devices. The issuance of these documents was contemporaneous with final changes to the Agency's "intended use" regulations, all signaling the Agency's heightened focus on its off-label policy. (Note: The effective date of the "intended use" regulations is delayed indefinitely due to controversy over the revisions).[9]

1. Overview of the *CFL Guidance*

In January 2017, the draft *CFL Guidance* expanded the bounds of manufacturer communications regarding medical products by proposing that communications that are "consistent" with, but not contained in, FDA-required labeling for medical products would not – *alone* – be evidence of a new intended use. The practical significance of the draft guidance was two-fold. First, the draft guidance confirmed that not all manufacturer communications involving information outside the four corners of FDA-required labeling are "off-label." Second, the draft guidance proposed that CFL communications need only be supported by "scientifically appropriate and statistically sound" evidence, a lower substantiation standard than previously required by the Agency.

The final *CFL Guidance* is very similar to the draft guidance in that it adheres to these principles; however, the final guidance attempts to clarify ambiguity in the draft guidance related to (1) the scope and application of the 3-factor test, (2) the types of communications that could, and could not, be considered CFL communications, and (3) the application of the "scientifically appropriate and statistically sound" evidentiary standard. Although application of the *CFL Guidance* to proposed communications will still require a careful evaluation on a claim-by-claim basis, the clarifications under the final guidance will likely enable industry to apply the guidance more consistently and with greater certainty.

Application of the 3-Factor Test to 510(k)-Cleared and 510(k)-Exempt Devices

The *CFL Guidance* clarifies that the analysis of CFL communications for 510(k)-cleared products should not be governed by the *CFL Guidance's* 3-factor test, but rather by 21 C.F.R. § 807.81(a)(3) and FDA's guidance, *Deciding When to Submit a 510(k) for a Change to an Existing Device* (hereinafter "*510(k) Guidance*").[10] Similarly, when analyzing CFL communications for 510(k)-exempt devices, manufacturers should rely on the existing limitations on the exemptions in the applicable regulations.

FDA's regulation, 21 C.F.R. § 807.81(a)(3), prescribes when manufacturers need to submit a new 510(k) for a change or modification to an existing device, and the *510(k) Guidance* explains how FDA interprets that regulation. The finalization of the *510(k) Guidance* occurred between FDA's issuance of the draft and final *CFL Guidance*,[11] which likely impacted the Agency's recommendations for how CFL communications should be evaluated for 510(k)-cleared products. As a general matter, the principles articulated in each guidance are consistent, in that communications that trigger the need for a new 510(k) are regarded as inconsistent with labeling, and those that do not trigger the need for a new 510(k) are consistent with labeling. If it was unclear how the draft *CFL Guidance* squared with 21 C.F.R. § 807.81(a)(3) and the *510(k) Guidance* for cleared devices, the *CFL Guidance* provides helpful clarity.

Importantly, despite the fact that there is no need to apply the 3-factor test to 510(k)-cleared devices, the *CFL Guidance* affirms that other recommendations in the guidance still apply. Specifically, recommendations in the *CFL Guidance* regarding conveying CFL communications in a manner that is truthful and not misleading are particularly instructive.

New Examples to Demonstrate the 3-Factor Test

The *CFL Guidance* retains the same 3-factor test as the draft version to determine whether communications for products other than 510(k)-cleared or -exempt devices are CFL; however, it provides additional examples regarding how those factors should be applied. As a reminder, the 3 factors to be considered follow:

(1) How the information in the communication compares to the information in FDA-required labeling. With respect to this factor, FDA will consider information to be consistent with FDA-required labeling if: (1) representations or suggestions in the communication relate to the same indication as the one reflected in the product's FDA-required labeling; (2) the patient population represented or suggested in the communication is not outside the approved patient population reflected in FDA-required labeling; (3) the representations/suggestions in the communication do not conflict with the use limitations or directions for handling, preparing, and/or using the product reflected in FDA-required labeling; and (4) the representations/suggestions about the product do not conflict with the recommended dosage or use regimen, route of administration, or strength(s) (if applicable) set forth in FDA-required labeling.

(2) Whether the representations/suggestions in the communication increase the potential for harm to health relative to the information reflected in the FDA-required labeling.

(3) Whether the directions for use in FDA-required labeling enable the product to be safely and effectively used under the conditions represented/suggested in the communication.

One of the main concerns and criticisms with the 3-factor test in the draft guidance was the potential overlap between factors, and whether Factors 2 or 3 were meaningful or even necessary. The *CFL Guidance* expressly acknowledges the potential overlap in the three factors, and provides examples to illustrate communications that would pass Factor 1, but still fail Factors 2 or 3.

New Examples of CFL Communications

As in the draft guidance, the final *CFL Guidance* includes several categories of communications that could be CFL. These include certain communications about comparisons, adverse reactions, onset of action, long-term safety or efficacy, patient subgroups, product effects, convenience, and mechanism of action. The final guidance provides updated explanations and examples for communications about comparisons, product effects, and convenience. In addition, the *CFL Guidance* adds a new category for communications about tolerability of a product when it is used concomitantly in a co-morbid condition. This new category is particularly interesting in light of longstanding concerns that communications about concomitant use could create a new intended use for a product when it is not specifically approved or cleared for use with another product. Companies choosing to develop claims in this category, as well as

many others, should carefully scrutinize the communication under the 3-factor test as well as *CFL Guidance* recommendations, including appropriate substantiation and contextual information, to ensure that it is truthful and not misleading.

Importantly, the final guidance also adds two new examples of information that would not be considered to be CFL communications.

SASS Substantiation: Amount and Type of Evidence Depends on the Claim

The *CFL Guidance* retains the new evidentiary standard for CFL communications: "scientifically appropriate and statistically sound" (SASS). FDA expressly acknowledges that the lack of evidence sufficient to satisfy an approval or clearance standard will not alone render a communication false or misleading; however, the "amount and type of evidence" necessary to support a CFL communication will depend on the topic of the communication and the specific representations made in the communication. "To be considered truthful and non-misleading, firms' product communications should not overstate the findings of or the conclusions that can be drawn from such studies or analyses, or fail to disclose their material limitations." The *CFL Guidance* provides several examples of how different data might be evaluated in support of a CFL communication. The net effect is that each proposed communication must be evaluated on a case-by-case basis, considering the adequacy of evidentiary support and accuracy in how the information is characterized and contextualized, including any necessary disclosures.

2. Overview of the *Communications with Payors Guidance*

The draft *Communications with Payors Guidance* clarified how FDA interprets the HCEI provision of the FD&C Act, as amended by Cures. This provision permits the dissemination of HCEI about drugs to "a payor, formulary committee or other similar entity" if the HCEI "relates to an approved indication" and "is based on competent and reliable scientific evidence" (CARSE). The draft guidance also created a new safe harbor permitting pharmaceutical and medical device manufacturers to disseminate certain information about investigational products to payors prior to approval or clearance. In the final guidance, FDA significantly expands the scope of both of these categories of payor communications. First, FDA permits industry to communicate HCEI to payors about medical devices as well as drugs. Second, the final guidance significantly expands the "safe harbor" on pre-approval communications with payors to include not only communications about investigational products, but also communications about unapproved or uncleared uses of approved or cleared products (i.e., off-label uses). FDA's final guidance also addresses several open questions and ambiguities in the draft guidance related to both types of payor communications.

a. HCEI Promotional Communications

Permissible HCEI Communications Include HCEI for Medical Devices

One of the most significant changes in the *Communications with Payors Guidance* is FDA's expansion of permissible HCEI communications with payors to include HCEI for medical devices. Although the statutory HCEI provision is expressly limited to drugs, the final guidance states that HCEI communications with payors about approved or cleared medical devices (that meet the recommendations in the final guidance) will not be considered false or misleading or evidence of a new intended use. The clear direction by FDA on the effective extension of the HCEI to devices is a welcome revision and addresses a longstanding area of uncertainty for medical device manufacturers.

Additional Noteworthy Changes to FDA's Recommendations for HCEI Communications

- **HCEI for HCPs who are also formulary committee members.** Like the draft guidance, the final guidance provides examples of appropriate audiences to receive HCEI and emphasizes that the target audience must be a health care decision-maker making population-based decisions on drug selection, reimbursement, formulary placement,

coverage, etc. FDA emphasizes that the guidance does not apply to communications of HCEI to other audiences, such as consumers or healthcare providers making individual prescribing decisions. One noteworthy addition to the final guidance is language addressing the applicability of the HCEI provisions to individuals with dual roles of formulary committee members and individual prescribers. Industry has often asked how to comply with the guidance when presenting HCEI to individuals who wear "two hats" within an organization. The final guidance does not go as far as providing guidelines on how to structure HCEI communication plans for individuals in dual roles; however, it makes clear that individuals serving multiple roles can be an appropriate audience for HCEI communications when they are "carrying out their professional responsibilities for selection of drugs for coverage or reimbursement for a payor, formulary committee, or other similar entity."

- **Examples of HCEI that are and are not "related" to an approved indication.** The HCEI statutory provision, as amended by Cures, requires that HCEI be "related" to an approved indication. The draft guidance provided much needed clarification on the meaning of the term "related," including a definition and numerous examples. The final guidance largely maintains the original language of the draft guidance, including the examples of HCEI "related" to an approved indication. On page 10 of the final guidance, FDA provides new examples of HCEI that are not considered to relate to an approved indication.
- **New examples of relevant third party standards for establishing CARSE.** The draft guidance clarified the "competent and reliable scientific evidence" (CARSE) standard for HCEI ,which is defined by FDA as "generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results." The final guidance maintains this language and adds two new examples of authoritative bodies with standard and good research practices that can be considered in establishing CARSE (the International Society for Pharmacoepidemiology (ISPE) and the Agency for Healthcare Research and Quality (AHRQ)).
- **Scope of contextual information required to accompany HCEI.** The draft guidance provided a list of contextual information that should accompany HCEI, including information on study design, methodology, generalizability, limitations, and sensitivity analyses. One complaint was that the scope of required contextual information was burdensome. In addition, the cited contextual information was not necessarily applicable for all types of HCEI. FDA addresses this issue in the final guidance, stating that the contextual and background information "are examples" and some "may not be applicable to particular HCEI presentations." FDA adds that "the disclosure of the pertinent information can be concise, so long as all material information . . . is provided." Throughout the discussion on contextual information, FDA also removed language such as "comprehensive" listing and "full" disclosure, suggesting that it is not requiring accompanying contextual and background information to be exhaustive. Other important clarifications regarding inclusion of contextual and background information include the following:
  - Contextual information should be presented "in conjunction with" the HCEI. Alternately, the HCEI presentation can include a prominent reference to where the contextual information exists within the presentation.
  - FDA acknowledges that some authoritative bodies have recommended formats for communicating information to payors that include recommendations for disclosing the types of contextual and background information listed in FDA's final guidance. FDA suggests that those formats may be sufficient as long as material information is provided prominently. FDA states that its recommendations in the final guidance "are not meant to suggest that firms should make duplicative disclosures."
  - FDA has softened its recommendations for disclosure of assumptions. The draft guidance onerously recommended that "all evidence to support assumptions should be provided." The final guidance makes clear that "a list of references" is adequate and that full copies need only be provided to payors upon request.

- **Material categories of information must always accompany any presentation of HCEI.** In the draft guidance, FDA had identified additional material information relevant to providing a balanced and complete presentation (e.g., conspicuous and prominent statement describing material differences, FDA-approved labeling, risk information, disclosure of omitted studies or data sources, financial / affiliation biases). FDA maintains this list in the final guidance, but suggests that this information must always accompany an HCEI presentation, stating that "FDA believes the categories of information . . . are generally material to any presentation of HCEI." FDA also expands on what it means for information to be disclosed in a "conspicuous and prominent" manner, including considerations of font size and style, contrast between text and background and white space between and around the text.

b. "Safe Harbor" for Pre-Approval/Off-Label Communications with Payors

"Safe Harbor" for Pre-Approval Communications with Payors Expanded to Include Communications about Unapproved or Uncleared Uses of Approved or Cleared Products

The final guidance greatly expands the "safe harbor" on pre-approval communications with payors to include communications about unapproved or uncleared uses of approved or cleared products, as well as communications about investigational products (i.e., products without any clearance or approval). FDA acknowledges in the final guidance that it sought to achieve a balance of competing interests in permitting pre-approval communications with payors. FDA weighed payors' need for broad enough information to make informed coverage and reimbursement decisions with the need to maintain appropriate incentives for firms to continue to conduct robust clinical trials for new indications and uses. FDA asserts that the information permitted under the final guidance strikes this balance. FDA also acknowledges that payors are a sophisticated audience with the expertise, resources, and motivation to carefully scrutinize information provided by firms. As such, the Agency believes that the risk that payors will be misled is relatively low.

Additional Noteworthy Changes to FDA's Recommendations for Pre-Approval/Off-Label Communications

- **Scope of information that may be disseminated pre-approval to payors.** Like the draft guidance, the final guidance lists the types of information that may be disseminated pre-approval to payors. Examples cited include: information about the indication sought, anticipated timeline for approval/clearance, pricing information, patient support programs, and the like. The final guidance includes three notable changes to the original list. First, it adds patient utilization projections (e.g., epidemiological data projection on incidence and prevalence) to the list. Second, it further clarifies information that may be appropriate to provide when discussing study information with payors. Like the draft guidance, the final guidance emphasizes that results of studies must be presented factually without characterizations or conclusions regarding safety or efficacy. As illustrated by the new examples of appropriate and inappropriate communication of study results, information on studies must be provided in a non-promotional manner without characterizations or conclusions. Third, the final guidance drops "targeting/marketing strategies" as a category of permissible information. The removal of this category is another indication of FDA's intent that only factual, non-promotional information regarding unapproved/uncleared products and uses be communicated to payors.
- **Additional contextual information/disclosures.** Like the draft guidance, the final *Communications with Payors Guidance* recommends that pre-approval information provided to payors be accompanied by a clear statement of the product's regulatory status (e.g., investigational or unapproved/uncleared) and information on the stage of product development. The final guidance also recommends that communications of study results include material aspects of study design and methodology and limitations of the study. Communications about unapproved/uncleared uses of approved or cleared products should also include a prominent statement disclosing the indications for which FDA has approved, cleared or licensed the product and a copy of the most current FDA-required labeling.

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[1] *See* 21 U.S.C. § 321(g) (drugs) and (h) (devices); *see also* 42 U.S.C. § 262(i) (defining a "biological product" as "applicable to the prevention, treatment, or cure of a disease or condition of human beings").
[2] 82 Fed. Reg. 2193, 2206 (Jan. 9, 2017); 21 C.F.R. §§ 201.128 and 801.4.
[3] *United States v. Caronia*, 703 F.3d 149 (2d. Cir. 2012).
[4] *Amarin Pharma, Inc. v. United States Food and Drug Administration*, 119 F. Supp. 3d 196, 224 (S. D. N.Y. 2015).
[5] *See* Citizen Petition submitted from a coalition of pharmaceutical companies (July 5, 2011), Docket No. FDA-2011-P-0512; Citizen Petition of the Medical Information Working Group (September 3, 2013), Docket No. FDA-2013-P-1079.
[6] Letter from Leslie Kux, Associate Commissioner for Policy, FDA, to counsel for the Medical Information Working Group (December 22, 2014), at 8, *accessible at* https://www.regulations.gov/document?D=FDA-2011-P-0512-0009.
[7] 81 Fed. Reg. 60299 (Sept. 1, 2016).
[8] For a summary of these developments, please see our Client Alerts:
- *FDA Takes Action in the Last Days of the Obama Administration to Clarify Some of Its Views on Off-Label Communications* (Jan. 19. 2017);
- *FDA Issues Draft Guidance Addressing Communications with Payors* (Jan. 20, 2017); and
- *FDA Defends Its First Amendment Position in "Memorandum"* (Jan. 26, 2017).

[9] 83 Fed. Reg. 11639 (March 16, 2018).
[10] Guidance for Industry: *Deciding When to Submit a 510(k) for a Change to an Existing Device* (October 2017).
[11] 82 Fed. Reg. 49375 (Oct. 25, 2017).