Recent Developments in the Government's Evolving Approach to Off-Label Promotion

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The clash between FDA's restrictions on promotional communications relating to unapproved uses of approved medical products and the First Amendment has unfolded over the last decade in a series of guidance documents, civil and criminal judicial decisions, and enforcement actions. In large measure, FDA has not fared well, and court decisions confirming the protection of truthful and non-misleading promotional speech have expanded the avenues for life sciences companies to engage in certain proactive promotional speech regarding unapproved uses of their lawfully marketed products.

Two additional developments landed in October 2023, a draft guidance and a successful prosecution, with each adding to the broader mosaic relating to this issue. In the first, on Oct.13, 2023, the Department of Justice (DOJ) announced that the former chief executive officer (CEO) of medical device company Dolor Technologies Inc. had pled guilty to misdemeanor charges of causing the introduction of misbranded and adulterated devices into interstate commerce, in violation of **21 U.S.C. §§ 331(a)** and 333(a)(1). The case was based on Dolor's failure to seek 510(k) clearance for an indication that the company promoted in its commercial communications. *USA v. Wright*, **Docket No. 2:23-cr-00276** (D. Utah Jul 25, 2023).

Soon after, on Oct. 23, 2023, the US Food and Drug Administration (FDA) published a new **draft guidance** titled "Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products" (SIUU Draft Guidance). The SIUU Draft Guidance expands the types of communications regarding unapproved uses of approved products that medical product companies may disseminate without concern that FDA will view such communications, on their own, to be evidence of an unapproved intended use, while cautioning that there are limits to the types of communications that the agency considers appropriate.

As discussed further below, the *Wright* case reflects DOJ's continuing efforts, perhaps driven by First Amendment concerns, to pursue so-called "off-label promotion" through charges that do not rely solely on manufacturer communications. For its part, the SIUU Draft Guidance appears to reflect FDA's recognition, at last, that medical product companies may, consistent with the First Amendment, proactively disseminate a broader range of truthful and non-misleading information regarding unapproved uses of their approved products. Although these two developments are undoubtedly unrelated, taken together, they reflect the evolution that has occurred—on both the FDA regulatory and DOJ enforcement fronts—over the past decade with respect to so-called "off-label promotion."

Highlights of SIUU Draft Guidance

The SIUU Draft Guidance largely reiterates the principles included in FDA's prior Good Reprints Practices draft guidance with respect to distribution of (1) published scientific and medical journal articles (reprints), and (2) published clinical reference materials. In addition, however, the SIUU Draft Guidance notably adds a new category of firm-generated communications—which as a whole were outside the safe harbor created by the prior Good Reprints Practices guidances—that FDA will not, standing alone, consider to be evidence of a new unapproved intended use: "firm-generated presentations of scientific information from an accompanying published reprint."

The SIUU Draft Guidance also expands the universe of studies within its scope beyond peer-reviewed publications discussing adequate, well-controlled clinical trials—covered in the prior Good Reprints Practices draft guidances—to include "studies or analyses that are scientifically sound and provide clinically relevant information," and states that "[r]eal-world data and associated real-world evidence about medical products" may meet this standard "depending on the characteristics of the data and the nature of the analyses."

As with prior FDA guidance, the SIUU Draft Guidance emphasizes that SIUU communications must "be truthful, non-misleading, factual, and unbiased and provide all information necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the information in the SIUU communication." To this end, the SIUU Draft Guidance contains detailed recommendations regarding information to be included in SIUU communications—including specific recommendations for various types of SIUU communications—to ensure communications meet FDA's expectation in this regard.

Consistent with the prior Good Reprints Practices guidances, the SIUU Draft Guidance admonishes companies not to distribute SIUU communications as part of sales calls or in conjunction with other persuasive marketing techniques; rather, FDA advises that SIUU communications should be shared separately, without a promotional discussion.

Medical Device CEO Plea Agreement

The stipulated facts laid out in the plea agreement in the *Wright* case include that the CEO's former company, Dolor Technologies, registered with FDA and listed its SpenoCath device as a class 1 exempt ear, nose, and throat drug administration device, but in fact promoted the device to treat migraine headaches by administering a nerve block to a bundle of nerves behind the bony structure of the nose. According to the stipulated facts, the device was specifically designed with a curved tip capable of reaching this nerve bundle.

In addition, the company sought guidance from FDA regarding whether the device would require further study to receive 510(k) clearance to administer the intended nerve block. When told a study would be required, however, the company neither conducted a study nor sought FDA clearance or approval. Rather, the company continued to market the device to treat migraines and to provide marketing materials to HCPs relating to this use.

The facts of the *Wright* case bear a strong resemblance to those in *U.S. v. Facteau*, **Docket No. 1:15-cr-10076** (D. Mass. Apr 08, 2015) in which the former CEO and Vice President of Sales of Acclarent were charged with felony and misdemeanor counts of distributing a device that had been cleared as a saline-eluting sinus spacer for use in delivering steroids. As in the *Wright* case, *Facteau* involved evidence that the device was cleared for one use but actually intended and promoted for another, and that the true intended use could be inferred from both promotional statements and from the device's design. Both also included allegations that company had solicited and then ignored guidance from FDA that additional clinical trials would be required to market the device for the intended use.

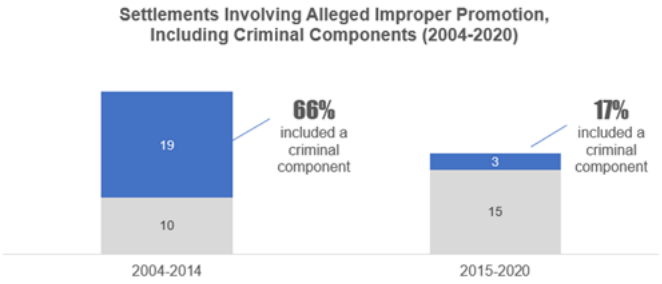
After the *Facteau* defendants were convicted of 10 misdemeanor misbranding and adulteration counts, they challenged their convictions on First Amendment grounds, arguing that the convictions had relied on evidence of truthful, non-misleading speech. The district court denied the defendants' motion, holding that while speech alone cannot be prosecuted, the government can use speech as evidence of intended use in connection with a non-speech crime.

Current Status of Off-Label Regulation & Enforcement

As industry observers may recall, throughout the 2000s and into the early 2010s, DOJ regularly pursued criminal off-label misbranding cases based on evidence of how sales representatives promoted medical products to HCPs. The tide began to turn in the early 2010s, however, starting with the 2011 Second Circuit ruling in *U.S. v. Caronia*, **703 F.3d 149** (2d Cir. 2012).

The court in *Caronia* held that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the [Food, Drug, and Cosmetic Act (FDCA)] for speech promoting the lawful, off-label use of an FDA-approved drug." This principle was amplified three years later when the court in *Amarin Pharma Inc. v. FDA*, **119 F. Supp. 3d 196** (S.D.N.Y. 2015) explained that although the "First Amendment does not protect false and misleading commercial speech," when the "speech at issue consists of truthful and non-misleading speech promoting the off-label use of an FDA-approved drug, such speech *cannot* be the act upon which an action for misbranding is based."

In the years since, DOJ has continued to pursue certain cases involving unapproved uses of approved medical products, never publicly acknowledging that *Caronia* and *Amarin* have had any impact on its enforcement approach. A review of the data, however, suggests otherwise.



As this chart reflects, while DOJ continues to regularly resolve matters involving alleged improper promotion, the percentage of those cases that involved a criminal component has dropped precipitously since 2014. Instead, DOJ has largely pursued promotion-based cases through civil False Claims Act resolutions, premised either on allegedly false or misleading promotion or on allegedly causing the submission of medically unnecessary claims for unapproved uses.

Where DOJ has pursued criminal charges, as in *Facteau* and now *Wright*, a driving aggravating factor often seems to be present. Specifically, DOJ's enforcement appears to be driven in part by companies flouting FDA's regulatory scheme, as shown through evidence that a company or its executives sought guidance from FDA regarding regulatory requirements and thereafter failed to heed that guidance. Consistent with the district court's ruling on the *Facteau* motion for judgment of acquittal, DOJ now typically relies on promotional materials as evidence of an unapproved intended use while charging a non-speech crime—such as distribution of a medical device without the requisite pre-market approval or clearance.

For its part, FDA continues to assert that promotional activity may be evidence of an intended use. The 2021 Final Rule regarding the intended use regulations states that "intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising, and any other relevant source," including knowledge of actual use by customers, internal documents, and—as in both *Facteau* and *Wright*—a product's design or composition.

At the same time, over the past decade-plus, FDA has invested considerable effort in publishing guidance documents that elucidate its thinking regarding specific practices that companies may rightfully feel are within the bounds of constitutionally protected truthful, non-misleading speech. These include the unsolicited request guidance from 2011, the various social media guidances in 2014, and the payor communication and consistent with labeling guidances from 2018.

The SIUU Draft Guidance is the latest addition to this string, and appears to reflect FDA's recognition that it is consistent with the First Amendment to communicate truthful, non-misleading firm-generated content about well-designed trials involving unapproved uses of approved products and that, indeed, many companies already may be engaging in such communications. At the same time, the SIUU Draft Guidance does not concede that HCPs have unfettered rights to receive—or companies have unfettered rights to disseminate—truthful, non-misleading materials; to the contrary, it appears clear that FDA may continue to view at least some

arguably truthful and non-misleading speech—such as purely promotional speech or speech regarding less scientifically sound studies—as evidence of misconduct.

The SIUU Draft Guidance therefore may provide medical product companies with welcome comfort that some affirmative communications regarding unapproved uses will not be considered evidence of a new intended use, but it also leaves open a number of questions that companies will have to grapple with as they proceed. These include, among others:

- How to interpret the new "scientifically sound and provid[ing] clinically relevant information" standard, including the vague guidance that, for human and animal drugs "other well-designed and well-conducted trials" may meet this standard, and the circular guidance that studies are "clinically relevant" when they "provide information that is pertinent to HCPs making clinical practice decisions for the care of an individual patient."

- Whether it is consistent with the First Amendment to disseminate communications regarding additional analyses that do not meet this standard, such as retrospective case studies or unpublished data on file, and if so, what considerations should apply to such communications.

- How the Draft SIUU Guidance squares with FDA's 2011 **Draft Guidance regarding Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices**, and whether that guidance's preference for distribution of off-label information by medical affairs—rather than commercial—personnel is relevant to SIUU communications.

- How to address format and other challenges posed by varying communication platforms, including social media, particularly given FDA's recommendation that SIUU communications be made through "dedicated vehicles, channels, and venues . . . that are separate from the vehicles, channels, and venues used for promotional considerations about approved uses of medical products."