ARTICLE 07

CAN OFF-LABEL USE TRIGGER A NEW FILING? FDA STILL NOT SURE

By Tricia Kaufman

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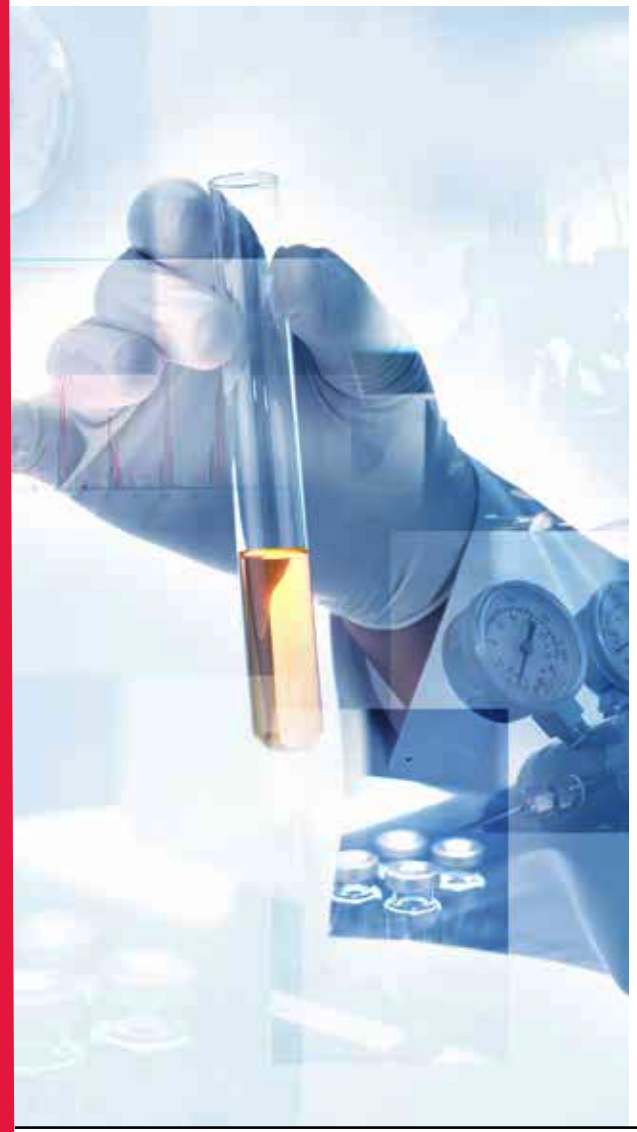
Can Off-Label Use Trigger a New Filing? FDA Still Isn't Sure



On January 12, 2018, U.S. Food & Drug Administration **Commissioner Scott Gottlieb announced** FDA's intention to once again postpone its final rule amending the **drug** and **device** intended use regulations, this time indefinitely. These regulations define the types of evidence FDA will use to determine a product's intended use, which influences whether FDA will see a manufacturer as marketing an unauthorized, and therefore misbranded, product.

Clarification of the regulations is warranted because the current version of the regulations, if read literally, could be interpreted as requiring a manufacturer to file a submission for new uses to which the medical community puts its authorized drug or device once it becomes aware of such use.

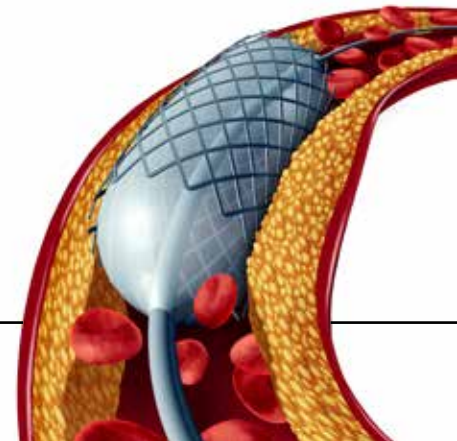
Though seemingly inequitable, this position is not wholly unparalleled. For instance, in products liability law a manufacturer is responsible for providing warnings for reasonably foreseeable uses of its products, even if it did not intend such use. However, the addition of simple warnings are a far cry from the significant cost required for an additional approval or clearance, dollars that could be used for new product R&D.

To the relief of many, **the 2015 proposed rule** planned to delete the last sentence of the "intended use" regulations, which reads:

> *"But if a manufacturer knows, or has knowledge of facts that would give him notice that a drug [or device] introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put."*

However, instead of deleting the last sentence as was proposed, **the 2017 final rule,** which has not yet gone into effect, amended the last sentence to read:

> *"And if the totality of the evidence establishes that a manufacturer objectively intends that a drug [or device] introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than ones for which it is approved[, cleared, granted marketing authorization, or is exempt from premarket notification requirements] (if any), he is required, in accordance with section 502(f) of the FD&C Act, or, as applicable, duly promulgated regulations exempting the drug [or device] from the requirements of section 502(f)(1), to provide for the drug [or device] adequate labeling that accords with such other intended uses."*



This change in plans was purportedly in response to confusion about whether FDA would consider a manufacturer's knowledge of off-label use at all in determining a product's intended use or whether knowledge of off-label use was completely taken off the table. According to FDA, the deletion in the 2015 proposed rule was intended merely to clarify the one point that, absent extraordinary circumstances, FDA would not find that a manufacturer intended a new use for its legally marketed product based solely on its knowledge that the product was being prescribed or used by doctors for that use.

In other words, the deletion was never intended to remove knowledge of such use from the evidence that could tip the balance in favor of finding a new intended use, and FDA cited myriad cases to support its authority to do so. FDA wants to use this evidence to "pursue firms that attempt to evade FDA medical product regulation by avoiding express claims about their products." To some, however, it seemed like FDA took back with one hand what it had granted under the proposed rule with the other.

In reality, the reaction to the final rule may be less about FDA's interpretation of whether off-label use by healthcare professionals is a legitimate factor in evaluating intended use and more about an opportunity for industry to demand clarity regarding the factors FDA will consider in such an evaluation, especially in light of FDA's concurrent reexamination of its position regarding a manufacturer's dissemination of truthful and non-misleading statements relating to unauthorized uses.

Though FDA asserted that the First Amendment issue is wholly separate from the limited issue addressed by the final rule, the two are inextricably intertwined, inasmuch as the dissemination of truthful, scientific evidence naturally would lead to an increase in off-label use by the medical community.

In fact, the same regulations address how a manufacturer's speech is used in determining intended use: "intent is determined by [responsible party's] expression …by…oral or written statements by such persons or their representatives", and, despite its dismissal of the relevance of the First Amendment issue to the final rule, FDA spent significant time in the preamble defending its limited interpretation of First Amendment case law.

The Concern Over Safety (or, FDA's Balancing Act)

FDA's reluctance to give up any one type of evidence in its evaluation of intended use is not surprising given its responsibility to protect the public health and the adverse events that result from off-label uses that are unsupported by good science.

Yet by clinging to power, FDA threatens to stifle truthful communication between industry and providers, which could work to the detriment of patients. It also leads, in today's information age, to the bizarre result that everyone else except the entity with, perhaps, the most current, comprehensive and accurate information can freely discuss the science supporting off-label uses.

As shown in guidance relating to the distribution of reprints and product communications consistent with labeling, FDA appears to recognize this juxtaposition and has been taking small steps towards allowing the greater free flow of information while trying to balance patient safety, though to many, it is not moving fast enough.

What's Ahead and How to Respond

Last week's statement from Dr. Gottlieb indicates that FDA will reconsider its approach to the intended use regulations and attempt to provide clear rules to industry. It will be interesting to see whether FDA will take this time to develop a comprehensive scheme regarding intended use that also addresses the constitutional issues.

In the meantime, manufacturers at least have FDA's clarification that off-label use alone will not lead FDA to find a new intended use, but would be wise to tread carefully in all of their communications, both internal and external, to avoid allegations of misbranding.

The FDA is taking comments on the proposed indefinite delay until February 5, 2018.

If you have any questions regarding this topic or the process for filing comments, feel free to reach out to Tricia Kaufman or Sheva Sanders.

Supply Chain Series Contributors

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