Opening Salvo In New FDA Attack On Off-Label Use?

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There aren't too many other blogs that we'd characterize as "essential" to what we do, but the FDA Law Blog is one of them (SCOTUSblog is another). Yesterday's post (emailed this morning) on the FDA Law Blog about a new draft FDA guidance concerning certain investigational in vitro diagnostic devices may seem arcane at first glance, but it describes an FDA regulatory departure with potentially far reaching implications – maybe even a renewed attack upon off-label use on a scope not seen since the nadir of the Kessler commissionership in the mid-1990s.

Here's what's up. The FDA determines what's "on" and "off-label" on the basis of a product's "intended use." An ancient FDA regulation, substantively unchanged since the 1950s, defines "intended use" in terms of "objective intent" of the manufacturer:

> The words intended uses or words of similar import . . . refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, **with the knowledge** of such persons or their representatives, offered **and used for a purpose for which it is neither labeled nor advertised**. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. . . . But **if a manufacturer knows, or has knowledge of facts that would give him notice that a 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.

21 C.F.R. §801.4 ("Meaning of 'Intended Uses'") (emphasis added). There's an essentially identical definition of "intended use" for prescription drugs. See 21 C.F.R. §201.128. Since the FDA's new draft guidance concerns devices (see n.1), we'll discuss it in those terms.

The literal terms of §804.1 could be read to render "adulterated" or "misbranded" any device simply because the manufacturer knew (or even more extreme, should have known ("knowledge of facts that would give him notice")) that the doctor/hospital/etc. to which the device was sold was going to use it off-label. Under the last sentence of §801.4, such knowledge could trigger an "adequate labeling for use" obligation as to the off-label use.

But not having the required "adequate labeling" would make the device "adulterated,"

"misbranded," *etc*. And to complete the regulatory Catch 22 – the manufacturer can't add the required labeling because, by definition, an off-label use hasn't been approved by the FDA as "safe and effective," which is a prerequisite to putting anything on the labeling about any use. That's the import of the first paragraph of regulatory gobbledygook under §III(B)(2) of the draft guidance.

Notwithstanding the literal terms of §801.4 (and §201.128), the FDA has never chosen to enforce them in such a restrictive fashion. Rather, as the FDA Law Blog points out, the FDA has a "well-established practice of determining intended use based on the manufacturer's conduct, rather than how a customer uses a product."

There are a variety of more or less formal FDA statements to that effect over the years (which we'll leave to the FDA Law Blog to collect if they're interested), but one practical aspect of this longstanding agency policy is the emphasis on off-label "promotion." If the FDA were to interpret §801.4 as broadly as it's written, there would be no need to worry about "promotion" – mere knowledge would be enough to trigger enforcement.

And this new draft guidance would do exactly that. Check out the second paragraph of §III(B)(2) – right after the gobbledygook – which changes the well established rules of the game:

> In addition to overt expressions by the manufacturer such as those present in labeling and advertising [that is to say, "promotion"], intended use may be shown by the circumstances surrounding the distribution of the product6 and **the manufacturer's knowledge that its product is offered and used for a purpose for which it is neither labeled nor advertised**. For example, FDA **may consider a manufacturer's knowledge of the purposes for which its customers offer and use its IVD product**, and the manufacturer's provision of technical support for those activities, to be evidence that the IVD product is intended to be used for such purposes. The weight of this evidence will vary with the circumstances.

(Emphasis added). The FDA is basing "objective' manufacturer intent on the actions, not of the manufacturer, but of its customers.

We usually omit footnotes, but we left in the FDA's footnote 6 for a reason. Any guesses as to what that's a reference to? Why §804.1, of course: "6See, e.g., 21 CFR 801.4." What's more, the FDA purports to impose the most extreme knowledge standard – that enforcement could be based upon "[s]ales to clinical laboratories [that is to say, customers] that the manufacturer knows, **or has reason to know**, use the . . . product [off-label] in clinical diagnostic use." Draft guidance §III(B)(2), third and seventh bullet points (emphasis added)

So what's a manufacturer of these devices supposed to do if it merely learns of an off-label

use? The FDA wants to order manufacturers to "halt" sales anytime that they learn that their customers intend to use the product off-label:

> Manufacturers . . . should **not sell** such products to laboratories that they know use the product [off-label] for clinical diagnostic use. If a manufacturer learns that a laboratory to which it sells its RUO-labeled IVD product is using it in clinical diagnosis, it should **halt such** sales. . . Draft guidance §III(b)(3) (emphasis added)

Make no mistake about it, this draft guidance is a major departure from the FDA's longstanding policy of regulating labeling based upon what's actually in the label. Again, we'll defer to the regulatory expertise of the FDA Law bloggers:

> However, FDA's stance that . . . manufacturers must "halt" sales to a customer because its use of [a device] for diagnosis [an off-label use] is a major departure. Moreover, FDA's reliance on customer conduct to define intended use has implications for other products beyond those [in the draft guidance], by determining intended use through customer behavior, not manufacturer's conduct.

Fortunately, as the FDA Law Blog points out, the draft guidance is subject to comments until August 30, 2011. We'd recommend that **any** regulated entity – device, drug, whatever – weigh in if it's in a position simply to know about off-label uses of its products. Under the regulatory interpretation in this draft guidance, mere knowledge, even imputed "should have known" knowledge, would be enough for the FDA to come knocking.

This draft guidance regulating a small group of medical devices could well be the tip of a very long and painful spear, since the FDA could invoke the same definition of "intended use" to demand that **any** manufacturer halt sales to customers known (or allegedly that "should be known") to engage in off-label use.

While the regulations read this way, the FDA hasn't ever enforced them as written. That alone may be enough. Another FDA power grab failed in the face of decades of non-use of purported agency authority in FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120 (2000).

Finally, specifically with respect to devices, we think it's apt to call upon a 1997 amendment to the FDCA:

> **Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient**

relationship. This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of a device that are part of a determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.
21 U.S.C. §397 (emphasis added).

With respect to “devices” (there’s no statutory drug equivalent) query whether this new draft guidance is simply *ultra vires* in light of §397. The effect of this new interpretation of §801.4 would certainly “limit or interfere with” off-label use by making it impossible for doctors to obtain the necessary products. It’s stated in a mere "draft guidance," not in a “regulation” nor is it part of a device approval/clearance. Nor does this unprecedented departure involve “promotion” – only mere knowledge, which would make resort to "promotion" unnecessary. Finally under FDA v. Brown & Williamson, it’s questionable whether there’s even any “existing” FDA authority.