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The Cross-Labeling Conundrum

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FACING THE CROSS-LABELING CONUNDRUM

With Mark Kramer

>> David Filmore

Companies that think they're developing a device might unwittingly find themselves facing a drug submission mandate they are unable to pursue. Greenleaf Health consultant and former FDA combination products chief Mark Kramer talks about how to avoid or at least prepare for the cross-labeling challenge and why more clarity is needed from FDA and Congress on the issue.

The Question: Is Your Device ... Not Just a Device?

Let's say your company is developing a new twist on a catheter or an updated iontophoresis device. Your route to showing substantial equivalence to a predicate seems passable and you're feeling optimistic.

But as you engage with FDA, the regulatory path takes a dramatic swerve. In the agency's view, it turns out, the product is not a routine 510(k) device, but a device constituent part of a "cross-labeled combination product." That means the drug center, not CDRH, will likely be assigned to lead the review and your company may be expected to submit a drug application that it may be operationally or legally unable to pursue.

Mark Kramer, an executive VP at Greenleaf Health and the founding director of FDA's Office of Combination Products, says this issue crops up more than many companies realize. He's seen it with catheters, injectors, nebulizers, infusion pumps, and any other variety of drug delivery device.

"It happens a fair amount," Kramer said in an interview. "I'm going to say at least 10% or more of my work involves situations where this either is a real issue or can be. The company will explain what they have in mind for a particular product. And right away my mind will just go to, 'Sounds like a cross-labeling issue to me.'"

To be sure, it's possible for a company to develop a delivery device that is viewed simply as a device. There are plenty of unfilled syringes and other generic products out there that fit the bill. The key deciding factors on a product's regulatory fate are whether it is intended to be used only with an "individually specified" drug in a manner in which the device and drug are both required for the intended use, and, in particular, whether or not the drug would be used in a manner consistent with its approved labeling.

If FDA deems that the label of an approved drug needs to be updated to reflect, for instance, a new intended use, route of delivery, or dosage introduced by the device, or, more generally, if there is no drug approved to be delivered in the manner performed by the device, that's when it becomes a combination product. And in these cases, FDA's device review often plays second fiddle to vetting of the revised drug labeling. Even though the company may have no intention of making or marketing a drug and may not be working with the manufacturer of the drug, pursuing approval of the product would likely require the firm to submit a drug application.

At this point, Kramer says, the device firm may have no feasible path forward. It is not able to submit a supplemental new drug application to another company's product, and FDA can't compel a drug firm to work with a device company to support a cross-labeling submission.

This is an area riddled with regulatory ambiguities about exactly how and when the cross-labeling threshold is met, the consultant warns (more on that later). Still, a manufacturer benefits from understanding the risks of devices referencing drugs early in the development process so it has a chance to avoid or at least prepare for the regulatory barriers. In practice, Kramer says, many companies are taken by surprise. "If they find out that what they thought was a device is now going to be regulated as a drug ... it's like a whole different game than what they originally had planned for."

Early Awareness Is Key

In Kramer's view, any company developing a device that delivers, activates, or is intended to be used in conjunction with a drug or biologic in some manner should be thinking about and researching this issue. "I would first encourage companies that are in this space to at least explore the potential regulatory ramifications very early and then start thinking about ways that they could potentially be handled," he says.

One key step to try to avoid getting stuck in the cross-labeling morass, he notes, is to "cast a wide net in researching approved drugs that might be suitable candidates for your device since it's important that you can identify at least one approved drug for such use."

Ultimately, a firm may need to consider adjusting the design and labeling of its device to find a feasible short-term regulatory path. "There may be steps you can take to either mitigate the issue somewhat ... or perhaps avoid it completely with the right kind of thinking," Kramer says.

Designing Around the Problem

Tweaking the design details of its device is one of the primary tools a manufacturer has at its disposal if it wants to steer clear of the combination product zone.

"A company may have its eye on an ultimate 'prized indication' that raises a cross-labeling concern but be able to avoid it at least initially by making the design suitable not only for that 'prized' indication but also for a more general use for which one or more currently available drugs are already approved," Kramer suggests.

A hypothetical example might be a prospective device that incorporates a specially curved tip ideal for locally delivering a drug to an anatomical target that doesn't conform to FDA labeling for the drug.

"You want the design of the device to be more generalizable in a way, so that it couldn't only be used for that one unique indication," Kramer explains. "So maybe you could look at having a variety of different shapes and then present that family of shapes as the product or have one design that perhaps avoids that tip somehow."

Often this approach requires the firm to make some compromises for the sake of regulatory expediency. The company can start by gaining authorization for a more general use/design via a device submission pathway. Then, with a version of the product already on the market, it may be in a better position to seek approval for more specialized indications.

In addition to device design, manufacturers should also of course consider the proposed product labeling to ensure it doesn't unnecessarily reference unapproved drug indications. But the labeling needs to be a credible representation of the device's capabilities or FDA will challenge it.

"It can't be in words only," Kramer stresses. "If hypothetically the device had a unique tip or shape that was designed for use in a specific part of the body, you can't just say that it's intended more generally. The design must also be suitable for the purported, more general use."

Don't Go to FDA Too Early

Experts commonly advise companies developing new devices to get early input from FDA directly, via the pre-submissions process or otherwise, to be better prepared for what the agency will expect. In this case, however, Kramer cautions against seeking input from FDA prematurely. "I find that companies might sometimes go to FDA too early, before they have thought these issues through, and then they kind of get on a track that it might be difficult to get off of," he notes.

If a company is working through design considerations and ends up moving toward more generalizable labeling for the device, it could find itself being challenged if it previously asked FDA about the more specialized, "prized" indication, as Kramer describes it.

"Once you've put it out there—maybe without realizing the regulatory ramifications—that your device is really intended for [use] X, it kind of gets hard to take that back," he says. "Careful thought and strategy into the way you're positioning your product to FDA—thought about the design, thought about how you're describing the intended use—is important."

Companies need to consider whether they even want to raise any specific questions with FDA about the prospect of cross-labeling. "Do they want to first put this idea in an FDA reviewer's mind or wait to see if it arises and then further explore options with FDA?" Kramer poses.

In cases when it's an obvious call, FDA's device center is apt to tell the company right from the start that a device raises a cross-labeling issue and direct it to the Office of Combination Products to designate the proper lead review center. But if there are some ambiguities, as there

often can be, FDA will more likely wait to consider the issue until it has been able to review the data and context more thoroughly as part of the pre-submissions or submission review process, Kramer suggests. This means that a company may not have clarity on whether cross-labeling will be required until sometimes relatively late in the review process.

Embracing Your Inner Combo Product

But a device firm can't always avoid seeking an indication that qualifies as cross-labeling. If the point of a development effort is to advance therapy beyond the status quo, it might necessarily involve pushing drugs to different use cases not reflected in current labeling. If this is the case, a company has a few options.

When possible, an ideal strategy is to partner with the manufacturer of an approved drug that would be referenced. If the device firm can convince the drug maker to get behind the updated delivery mechanism and submit a companion drug application, that could lead to a more straightforward FDA process. "Many companies do that, and it's the preferred approach," Kramer says. "It just may not always be possible."

There are an array of reasons why a drug firm may not be interested. The company could have concerns about known or unknown risks cropping up from a new use of its product, or it could even sense commercial risks if the device is intended to deliver the drug in a manner that, for instance, is more targeted and thus requires lower amounts of medicine per treatment.

If the drug firm won't come on board, the other option, particularly in cases of off-patent, generic drugs, is for the device manufacturer to actually produce the drug and submit it (likely in the form of a 505(b)(2) application) in parallel to a device submission or to submit the device as part of the drug submission. That seems like a high bar for a company that doesn't have any experience with pharmaceutical manufacturing or submissions, but Kramer points out that the firm could work with a generic drug supplier to handle the actual production.

For certain devices that go beyond passive drug delivery to feature some sort of active treatment mechanism independent of the drug, there is a potential third option. For these types of cases, Kramer suggests, it's possible the most efficient regulatory route might be to develop a more traditional combination product where the device is physically combined or co-packaged with the drug. If the company can make the case that the device is responsible for the combination product's primary mode of action (the regulatory basis by which a combination product is assigned to an FDA product center), it could pursue a device submission (510(k), De Novo, or PMA) rather than drug application.

This approach obviously raises an array of potential challenges, but, Kramer says, "I have seen this in more than a handful of situations be an attractive way to pursue approval."

The Imaging Model

Often, though, unless a company has a prearranged business partnership with a drug firm, none of these options are ideal.

"The conundrum of this cross-labeling issue has really been that some devices may have no pathway to get to market absent the cooperation of the drug sponsor," Kramer laments.

FDA first took a stab at fashioning a solution to this conundrum when it organized a public meeting on the topic in 2005, just a few years after FDA formed the Office of Combination Products under Kramer's leadership. More recently, in 2017, FDA made a specific proposal to allow devices that raise cross-labeling issues to pursue the PMA pathway, rather than a drug application, as long as the device maker can independently demonstrate safety and effectiveness of the drug, establish an appropriate postmarket plan, and meet other requirements. FDA ultimately abandoned the plan, facing pushback from the pharmaceutical industry on multiple legal and logistical fronts.

During the same period, however, Congress enacted a pathway for one set of devices that could serve as a model to resolving this issue more broadly over the longer term. The 2017 FDA Reauthorization Act includes a provision responding to a long-held frustration by imaging device manufacturers about their inability to seek authorization through the device center for imaging equipment updates and new applications that don't align with drug labeling of approved contrast agents. The FDARA provision now allows such modifications to proceed via a PMA, 510(k), or De Novo as long as the device company can show the update does not adversely affect the safety and effectiveness of the contrast agent when used with the device.

To be clear, this is far from a free pass for imaging manufacturers. Kramer is aware of at least one De Novo authorization, for a linear accelerator/PET system, that leveraged the FDARA provisions. The special controls established under the De Novo decision not only require makers of these devices to perform clinical testing and analysis, but it also requires sponsors to establish a postmarket plan to monitor for labeling and formulation changes to the contrast agent and how they will impact safety and effectiveness when used with the device.

"You still have to do the work," Kramer affirms, but, the point is, it provides a possible pathway. "I think this is an attractive approach that's now set out in the law. For me, I guess the question is, 'Why can't we do something similar for all the rest of the [non-imaging] products that are in this situation?'"

Closing Message: Clarity Is Needed

A broader legislative solution is unlikely in the near term. But Kramer has some hope that FDA will at least help clarify the current regulatory framework sooner rather than later. FDA Office of Combination Product officials have made public statements suggesting a guidance on cross-labeling is in the works, he says.

It would be helpful simply for FDA to more precisely define some basic terms and concepts included in the regulatory definition of cross-labeled combination products, to support more consistent decision-making by FDA reviewers and more predictability for manufacturers, Kramer notes.

For instance, the regulation says a device that might be subject to cross-labeling rules is intended for use "only with an approved individually specified" drug or biologic. But the consultant says it remains unclear whether that means a device label must reference a specific brand name of a drug or if the cross-labeling requirement applies to a device that references a generic drug name, which could be sold by many companies.

There is also a lot ambiguity about what level of inconsistency is acceptable between a device and drug label and which specific sections of the drug label are subject to the cross-labeling rules. The regulation specifically mentions intended use, dosage, and route of administration, among others, as areas of the drug label where a cross-labeling requirement is triggered if a device requires a change, but the wording suggests that it is not intended to be a comprehensive listing.

For instance, if a drug label details specialized training for providers that employ the medicine, but a device is developed to make the drug simpler to deliver without the training, does the training statement in the drug label need to be revised to allow clearance of the device? That is one example of a gray area offered by Kramer and a co-author in a recent article in the Regulatory Affairs Professionals Society's *Regulatory Focus* publication, in which they call for more regulatory and legal clarity in this area.

"It's a jumble of words that you really have to dissect carefully," Kramer says about the current regulatory language. "In general, there's not a really good appreciation of what the definition of a cross-label product means."

Kramer had hoped an FDA guidance might be published on the topic as early as this year, but it's not clear that timing will be met. For now, the best that companies can do is to appreciate the issue as an important consideration and at least avoid getting blindsided late in the regulatory process.

Companies will "back into this situation unwittingly sometimes because they think, 'Well, I'm not doing anything with the drug. It's simply a device,'" Kramer says. "It could really cause companies to go back to the drawing board."