Labs juggle string of LDT unknowns

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Karen Titus

July 2024—Like a long-awaited second act, the FDA's final rule regulating laboratory-developed tests as medical devices took the stage this spring. As with any FDA performance, this one opened to mixed reviews.

The spring curtain-raising followed the earlier proposed rule from last October, which drew some 6,500 responses during the public comment period. If that was an out-of-town tryout, no one quite knew what to expect from the rewrite, or if there would even be one.

As it turns out, there were indeed changes, but they didn't necessarily bring clarity. As Jane Pine Wood, counsel for McDonald Hopkins, puts it, the final rule "certainly raised a whole lot more questions than it answered."

The rule calls for a four-year, five-stage phaseout policy with the FDA enacting greater oversight of in vitro diagnostic products that are offered as LDTs.

Stage one, beginning on May 6, 2025, calls for labs to comply with medical device reporting requirements, correction and removal reporting requirements, and quality system requirements regarding complaint files. Additional stages include registration and listing requirements, labeling requirements, and investigational use requirements. By Nov. 6, 2027, labs are expected to comply with premarket review requirements for high-risk IVDs offered as LDTs. And by May 6, 2028, labs are expected to comply with premarket review requirements for moderate- and low-risk tests.

Woven throughout the policy is the consistent phrase "exercise enforcement discretion"—director's notes of sorts.

"Everything we're dealing with right now is an exercise in enforcement discretion," Pine Wood says. The final rule reiterates that point numerous times throughout the agreement, she says, with the FDA making clear that it reserves the discretion to change its mind, as circumstances and the agency's understanding changes. The agency also notes in multiple places it plans to issue further guidance.

"This gives the FDA lots of time to pivot, modify, refine," says Pine Wood. "I think we'll be talking about this for the next four years."

In short, the final rule is more Ring cycle than song recital.

Or, as Diana Cardona, MD, MBA, of Duke University Medical Center, says, "It's not over yet."

The FDA announced it had finalized its rulemaking on April 29; the publication date was May 6.

For laboratories, the days leading up to the rule's release were busy, and not just with worried speculating. Knowing that the agency planned to flex its oversight muscles, some rallied to validate

LDTs before the rule went into effect.

Dr. Cardona, associate professor of pathology and associate director of Duke Health clinical laboratories, remembers it with a laugh: “As soon as the early release dropped, we immediately messaged our director: ‘If you have something near completion, you need to complete the validation now. Review and get the documents signed this week.’ Everyone wanted to make sure we had our i’s dotted, our t’s crossed.”

Jane Pine Wood of McDonald Hopkins suggests a few steps laboratories can take in the next year—requiring time, not money, she says—in response to the FDA’s final rule on laboratory-developed tests. [Photo by Webb Chappell]

Whether those efforts will pay off is anyone’s guess. In these early months since the final rule dropped, nearly everything with the final rule has been everyone’s guess, as it turns out. The fallout goes well beyond any last-minute dash. Like Englishmen of yore fussing over royal succession, the plot is a tangle.

For Dr. Cardona, the first look at the final rule brought not a sense of relief exactly but at least a chance to exhale.

Initially, she says, she and her colleagues had “a mild sense of, *Thank God*.” Sounding like the lucky survivor of a natural disaster, she adds, “It gave everybody a moment to take a breath and at least be grateful it wasn’t as bad as we all thought it was going to be.”

Clearly, the proposed rule last fall had set labs on edge. Dr. Cardona jests that the FDA could even be credited with a bit of reverse psychology: By setting up a doomsday scenario last fall, even the slightest improvements would make labs happy. “I wonder if they did that on purpose,” she says.

Adds Pine Wood: “The transition from last October’s proposed rule to the final rule appears to be a good strategic move by the FDA. And I’m speaking as someone who is not happy with the rule.”

As they pored over the massive document, lab leaders may have felt like they were trying to speed-read *Moby-Dick* in their early efforts to assess what the final rule will mean for their own laboratories as well as the field at large. Not surprisingly, reactions continue to evolve.

Says Dr. Cardona, "Now that we've had a little more time to think about it and dive into the final rule, we at Duke have reached a point where although we feel grateful for some of the concessions—though 'grateful' is probably not the right word—there are still things that need additional clarification."

As Pine Wood steered her way through the FDA verbiage—"There's nothing organized about the rule," she says—she tried to refine her focus. She says she skimmed certain areas, such as the FDA's rationale for claiming this oversight. "All that stuff"—though she uses a far earthier noun—"I gloss over. Because anyone working in a lab has the same feeling about some of those comments, which are just overblown," such as language that calls into question patient safety and suggests laboratory testing is dangerous.

Here's how she threads the needle: "Most laboratories do a good job. And the FDA—I don't mean this to be a slam against the FDA—but their regulation of laboratory tests is not going to substantially make testing safer," beyond what CLIA, state licensure, accreditation, and other oversight already provide.

The final rule reasserts a sort of FDA flirtation with primogeniture. Some suggest it sees former CMS territory as its own. The FDA has long held (for 20-some years, says Pine Wood) that it has the right to regulate LDTs as devices. "They haven't backed down one iota from that baseline," she says.

The FDA is also acknowledging that it expects some labs may not survive the added regulatory oversight and that some tests will be pulled off the market, Pine Wood says, though "they're not expecting it to be substantial enough to significantly impact patient care."

A number of well-intentioned patient advocacy groups pushed for the FDA to increase its oversight of lab testing, and the agency's requirements certainly might seem reasonable on the surface, says Pine Wood. "They're keeping the medical device reporting standards, which means if you have an error in your test, you have to report it to the FDA. How do you argue that you shouldn't be subject to that?" she asks. As noted, the final rule also keeps the labeling and registration requirements, which basically require labs to state how their test is used and what the indications for use are, as well as certain quality system requirements. "Again, it's very hard to say you shouldn't be subject to it."

Dr.
Cardona

Dr. Cardona says the vast majority of providers would agree that no one should be lax about situations that have a high risk of harm to patients, such as using a test in isolation to decide about, say, chemotherapy or surgery. (Which, she points out, would rarely happen in clinical practice.) But, she muses, maybe the final rule isn't the appropriate mechanism to address those risks. "Whatever the clinical claim is on that test," there needs to be some safeguards in place, she says. "Now, does that need to be by law, by regulation, or could it be through augmenting the requirement of a validation?"

she asks. “That’s where everyone is going to disagree.”

One way to disagree is by seeking injunctive relief. The gradual phaseout of premarket review for, essentially, new LDTs or substantially modified LDTs—which means most existing LDTs, Pine Wood says—will make it harder to mount a legal challenge.

Though not impossible. On May 29, the American Clinical Laboratory Association and its member company, HealthTrackRx, filed a lawsuit against the FDA in the U.S. District Court for the Eastern District of Texas, challenging the final rule, saying that Congress has never granted the agency authority to regulate laboratories’ professional testing services.

(Regarding this, Pine Wood said in an email to CAP TODAY: “I believe most in the laboratory world are appreciative of ACLA’s and HealthTrackRx’s initiative with respect to the legal challenge. ACLA and its members have been focused on this issue for many, many years, with constant attention to the impediments that FDA regulation could impose upon access to testing [particularly for patients in rural and underserved areas] as well as innovation in laboratory medicine. I know firsthand that ACLA and its legal team have devoted many hours to a thorough analysis of the proposed and final rules, and the legal challenge has been well vetted.”)

As larger legal and philosophical debates unfold, labs are looking to connect the dots from the final rule’s language to their own practices.

Among the more immediate questions Dr. Cardona raises as she navigates wobbly definitions and newly drawn borders are those related to the scope of health care delivery systems. Would the FDA consider creating a percent threshold of testing that would need to be done for patients or providers within the health system for it to still qualify for the enforcement discretion? For example, Duke performs a great deal of testing for patients in the region simply because of a lack of access locally. “Can we still do that?” Dr. Cardona asks. “At this point it seems like we can’t, but it would be nice if we could still provide care to those individuals, as it then becomes an access issue that has nothing to do with quality or safety.

“Some of these things are not yet ironed out or understood, at least from our perspective,” Dr. Cardona continues. She and her colleagues are also weighing the potential impact as they make decisions about future test development.

Another question: What does “unmet need” mean? “They tried to dive into it a little bit with the final rule, but it still needs a lot more definition and clarity,” Dr. Cardona says.

For example, if there is an FDA-approved test option, that essentially forces all labs to use that one test, she explains. What if the health system could provide something that was equally safe and just as accurate but at half the cost? “We would then have to submit something to the FDA and the burden associated with that process. Why couldn’t this enforcement discretion still apply? That could still be an unmet need, because now we’re expanding access and removing some of the financial burden not only to the health system but ultimately to the patient.”

Pine Wood reports similarly specific questions from clients.

“The ones that are coming up the most are questions about digital pathology,” Pine Wood says. Many labs have built their own digital slide scanning in-house, and they “may be fine.” But more questions

might arise for those who are in the process of doing it, “and putting together bits and pieces, the same way you build your computer system and your LIS—a lot of these are some pieces bought from vendors, and the others are homegrown.”

Pine Wood suggests this also is one area where the FDA might ease up a bit. The interpretation is done by a pathologist; the digital component is the lead-up to a professional medical service. “There is no technical component report issued from the scanning of a digital slide.” Thus the FDA could decline to regulate. “Because the slide itself will still be interpreted by a pathologist, who can always look at the glass slide if need be,” goes her reasoning. It’s a gray area, she says, one closer to the practice of medicine, which, of course, the FDA cannot regulate.

Labs are also asking her about artificial intelligence. “The FDA has said adding AI to a test would most likely flip it into needing to go through premarket review.” But faced with an added regulatory burden, labs may be more hesitant to make such improvements, she worries. “I’m not sure that’s good from a patient care standpoint.”

Another murky area is the enforcement discretion for currently marketed LDTs that are not substantially modified, Pine Wood says, i.e. when the indications for use and the technology are unchanged.

“How far do you go?” she asks. An FDA seminar she attended in mid-May recognized the need for labs to make some modifications to FDA-cleared tests already on the market, to accommodate situations such as reagent shortages or a lab switching out equipment, for example. “That makes sense,” she says. “I was glad to hear that.” But at what point will a lab’s actions be seen as overreach and “fall out of some sort of exercise of enforcement discretion?” she asks. More guidance is needed, and she suspects it’s forthcoming. Otherwise, she fears, labs will cease making regular improvements to their LDTs, worried that normal tweaking will backfire on them.

Any early joy that greeted the final rule’s “unmet need” parameters was soon deflated. “Everyone at first was thinking, *Oh, this is great! We got the academic medical center exception,*” Pine Wood says. For anyone still doing a happy dance, her advice is simple: “Read it—it’s extremely narrow.”

In some cases, this will be clear-cut. For certain LDTs, there truly is no other alternative on the market. But other situations are more nebulous, and a physician may have to make the call as to whether the test falls into the category of unmet need. “You’re asking an individual to take on a pretty heavy burden there,” Pine Wood says.

The exception applies only to testing for patients of the health system and if ordered by a staff member. It’s unclear, at least for now, what that will mean for academic medical centers with large outreach programs.

Pine Wood also takes issue with the FDA’s assertion that simply because an LDT is less expensive than an approved test, it does not fit the “unmet need” criteria—that cost is not a factor, in other words.

“But cost is *always* a factor in health care,” she says. “To me, that’s a very naïve” approach. It’s possible that this will be another area where the FDA will offer more guidance, she says. “Again, this was enforcement discretion, so they can change the rules as they go, on the fly,” she says with a laugh. “They may back down a bit.

“My assumption,” Pine Wood continues, “is that the FDA will probably wait until we start to see the rubber hit the road,” with some tests being pulled off the market (or threatened with being pulled) and possible adverse patient care. Given the phaseout, she says, this wouldn’t happen until the fourth stage. “Which means the FDA certainly has a couple years to be talking, listening, solidifying its position,” Pine Wood says.

The agency will also be busy “figuring out how many people they can hire to do all this work,” she continues. “Some of their modifications may just have to deal with the realities of what the agency has bitten off.”

The New York Clinical Laboratory Evaluation Program exemption has saved the FDA much time and effort, Pine Wood says. “They basically punted to New York and said, You guys can take it over. *You guys need to hire more people? Fine. It’s not our problem.*”

That might well be a lesson the FDA learned during the height of COVID-19, she hypothesizes. “When I look at what the final rule did, and how it was structured, I think they probably do have a better appreciation” for FDA staff shortages and other pandemic-related issues that roiled the agency. “Even if they might not admit it on paper.”

Could such real-world constraints, for all the players, eventually bring about more discussions and less diktat?

At Duke, Dr. Cardona and colleagues wasted no time in reaching out to congressional offices. “Is there still an opportunity to consider legislation that would take some of the good things we see, improve on them, and allow for additional security and stability in the laboratory field?” she asks.

Pine Wood eyes the four-year phaseout with guarded optimism. “That’s a lot of time for lobbying with the VALID Act” or other approaches, she says. “And also discussions with the agency. The agency doesn’t want to fight a lawsuit.” Even if the VALID Act isn’t resurrected, she says—and opinions on the helpfulness of this vary—it might make sense to talk with legislators about more carve-outs. “In my mind, we have about two years before the first more substantial requirement,” she says, “which is a lot of time for activities to go on in the back room.”

Two years becomes briefer when it’s a deadline for laboratories in the throes of puzzling out the here and now. “My God,” says Pine Wood. “They still have to run a lab, on a shoestring and short of staff.”

You’ll get no argument from Dr. Cardona. “All we’ve done is added more burden, more cost, at a time when we’re getting paid less but being asked to do more. Especially in laboratory medicine. We can’t ignore the fact that the clinical lab fee schedule and the physician fee schedule are the only two Medicare programs not tied to inflation. So more requirements, more burden on a system that’s already stressed.”

“We don’t have the expertise now,” she adds. “So either somebody needs to become the FDA regulatory expert in the lab”—which will pull them away from their work—“or we need to hire somebody. So regardless, we’re probably going to have to hire more people to help us manage this overall.” She and colleagues are talking about whether the lab will need to create a technical validation position, someone who can map out the risks, validation levels, and paperwork for the entire health system. “But since we have all those question marks,” Dr. Cardona continues, “to be honest, we’re not sure what’s going to

happen next," in terms of the lawsuit, possible legislation, and evolving regulation. "There's still a sense of being in limbo."

Pine Wood refrains from telling labs to pour money into final rule-related activities, but she does offer a few steps she says are worth taking in the next year.

One is putting together a team—"recognizing no labs have extra staff sitting around"—that can take stock of current offerings. This is not so much a Swedish death cleaning of the lab's LDTs, but rather an LDT census. "Make sure you know what you're running. Not every lab necessarily has a list of all its LDTs, or thought about it," to the point of knowing, for example, if an FDA-approved test it's running has been modified to where it would now be considered an LDT.

After taking the tally, "Make your best guess whether they're class II or class III," she advises. The FDA has indicated that for existing FDA-cleared tests, it plans to move many that are currently class III to class II, Pine Wood says. Again, she expects more guidance to emerge. "But I'm going to guess that most LDTs today, based on what I've heard the FDA say, are going to be class II."

For such devices, she says, labs will need to figure out, as best they can, what exemption(s) might apply.

Pre-1976 tests, including some immunohistochemistry tests and flow cytometry, that require specialized technologists and use no automated procedures, "are in the clear," she says. "Continue to do those."

Tests that have gone through the New York CLEP might also be in the clear, but it depends on the lab's location, Pine Wood cautions. "[It] is going to apply to the lab that has the New York license for that test."

And for LDTs run in an academic medical center in an integrated health system, multiple exemptions might apply. "You need to line up which enforcement discretion exemption you fall in," Pine Wood says. In some cases, it could be three: an academic medical center with New York CLEP and a currently marketed LDT.

Once this has been sorted—"Again, for all this you're spending time, not money"—labs will need to determine, for each affected test, when timeline requirements will need to be met and best-guess cost requirements.

The third step would be to determine whether each test falls in the black or the red. Explains Pine Wood: "You have to make that financial decision. You can continue to do the LDT now; there's no reason to phase it out," and even if a lab decides to do so, it can wait until 2027. "You could do it sooner. But where do you stand with the test? Is it worth doing? Is it going to cost too much money? Do you have the personnel?"

Pine Wood pauses, barely, for a breath, then continues: "If you've got two LDTs and they break even, and they're something you can buy from someone else at a competitive price, you might say, *You know what? I don't need to offer this anymore. I'll just send it out to a reference lab.* Or maybe there's an FDA-approved test."

It's no secret that one of the appeals of LDTs is they're less expensive, Pine Wood says. "But maybe you run your numbers, and now they're pretty close." An LDT could cost more, even under one of the

exemptions, once labs factor in the costs of complying with the medical device reporting, labeling, registration, and quality systems. “Maybe it’s cheaper to go ahead and buy the kit.”

Unsurprisingly, Pine Wood spends considerable time thinking about the decisions laboratories make.

If a lab is contemplating an upgrade to a new platform, for example, the usual decision-making will have to include final rule calculus. “Now you look at it in terms of: *Do I switch? Can I?* What if the same test is run on a different platform, but one is more expensive, or you don’t have sufficient volume? All those decisions, when you’re already with such thin margins on testing, become so much more acute.”

“I don’t think the FDA truly understands all those day-to-day decisions laboratories make,” Pine Wood says. That’s not necessarily the FDA’s fault, she quickly adds. “Pathologists and the laboratory industry are the worst in terms of not tooting their own horn, and not explaining to people what they do, and the safety advances that are being made. And I think that’s created a problem.”

Nor are labs the only ones affected by the final rule, Pine Wood says. “What’s going to happen with reagent vendors, who have for years been developing and selling reagents for research use only? That’s the biggest wink-wink, nod-nod in the world.” An RUO reagent for an LDT “is the baking soda in the cake mix, and now that the cake is baked, it’s no longer RUO.”

However, she points to an FDA warning letter posted to Agena Bioscience in April that clamps down on RUO labels for products allegedly being promoted for clinical diagnostic testing purposes.

The final rule preamble discusses such scenarios, Pine Wood says. She’s curious about how this will play out among vendors. “Some might say, *This is a wonderful opportunity, because everyone’s now going to have to use our FDA-approved kit.* But I think it’s going to put more pressure on some of these vendors to actually go through the premarket review process for their reagents.”

“It will be interesting to see how the vendors and manufacturers look at this,” she adds. “Do they take the opportunity, given their greater resources, to go ahead and really push and get a lot more FDA-approved and -cleared test kits on the market, to make up for what may be a loss of RUO reagent sales?”

And although they’re still two years away, “The labeling and registration requirements mean that sales reps are going to have to play by the same rules as the pharma reps do, which is, you [must] stick to the script,” Pine Wood says. “You can’t go into a doctor’s office and just wing it. Or, if the doctor says, ‘Well, what about your competitor’s test?’ *Oh, yeah, ours does that*—they can’t be doing that.”

Ditto for labs’ marketing materials, Pine Wood says. “They’re going to have to go by the very strict guidelines that pertain to the labeling. You’re going to have to document that you’ve had an internal committee look at that, and make sure that all your marketing materials are sticking to the script of the labeling.”

It’s not an impossible task, but it is more rigorous, she says. “I am advising clients: Start thinking about that now, because you really need to start socializing those ideas with your sales and marketing teams today.”

Does the final rule solve any problems?

A “top 20 offender” list the FDA presented with its proposed rule in the fall failed to truly identify systemic or underlying safety problems with clinical testing, Dr. Cardona says, noting there was even confusion about the role of screening tests. “Unfortunately, I think the FDA is harping on some examples that shouldn’t have been drivers for this regulation,” including at least one test that was being used in a clinical trial, not within a clinical laboratory. “The list is flawed.”

The issue that does need to be addressed is clinical claims, Dr. Cardona says. “But that’s something the FDA rule or VALID haven’t addressed.”

Pine Wood concedes there could be some benefit to the added oversight, such as the mandated medical device reporting. “It’s going to make sure, if there’s some test errors, that it’s actually documented that there’s follow-up with the ordering physicians to let them know. That’s good. Most labs do that already, though.”

But overall, her response is a firm “no.” “Laboratory is already highly regulated, one of the most highly regulated areas of health care,” she says, drawing on her nearly four decades of representing labs.

“Are there errors? Yes,” she continues. “Now, do physicians have errors when they are treating patients or do surgeries? Yes. Do hospitals have errors? Yes. There are always going to be errors that happen. Are there systemic quality deficiencies? I really don’t think so.”

For now, she and others will continue to juggle the unknowns that the final rule has unleashed. As is true of any upending, they could bring both threats and opportunities. “And maybe some hopes,” adds Pine Wood.

Karen Titus is CAP TODAY *contributing editor and co-managing editor.*