HOW THE FDA'S RULE ON LABORATORY-DEVELOPED TESTS COULD IMPACT THE *IN VITRO* DIAGNOSTICS INDUSTRY

A 360DX/ZEPTOMETRIX VIRTUAL ROUNDTABLE

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The US Food and Drug Administration's (FDA) recently issued final rule on laboratory-developed tests, or LDTs, marks a major change in the clinical testing landscape, as it formally brings these tests under the agency's oversight. Much discussion of the FDA rule has focused on the challenges and disruptions it could bring to clinical labs, but the rule and its requirements are likely to affect in vitro diagnostic (IVD) companies as well, potentially altering their relationships with their lab customers and creating new competitive dynamics.

This report summarizes a 360Dx Virtual Roundtable discussion, sponsored by ZeptoMetrix, in which experts discussed the FDA's LDT rule, the challenges it presents to clinical laboratories, and how IVD vendors can help clinical labs navigate these challenges. The panel comprised Jonathan Genzen, chief medical officer and senior director of governmental affairs at ARUP Laboratories; Donna Hochberg, partner and managing director at Health Advances; and Zach Rothstein, executive director at AdvaMedDx. The panel was moderated by Adam Bonislawski, editor at 360Dx.

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SPEAKERS:
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Zach Rothstein, JD
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Manufacturer and Lab Relationships

Genzen began the discussion by mentioning potential shifts in the relationships between clinical labs and their IVD suppliers that may result from the new FDA rule. He said he expects the costs of compliance to increase for clinical labs as the FDA rule phases in over the next four years. When combined with cuts to reimbursement stemming from the Protecting Access to Medicare Act (PAMA), these increasing costs may be difficult for some labs to manage. "Because of that, I would expect a pretty large degree of consolidation, at least for LDT testing, across the country," he said, noting that IVD manufacturers may end up with fewer customers who order higher volumes of tests.

Clinical labs that continue developing their own tests will likely need assistance in understanding and complying with the new regulatory requirements, said Hochberg. She commented that this will necessitate a closer relationship between labs and their vendors to identify and address these needs as the rule takes effect. As a leader in a policy organization, Rothstein said he looks forward to this increased collaboration between clinical labs and IVD suppliers, but that IVD vendors and clinical labs alike would benefit from modernized FDA rules that are more efficient and tailored to the diagnostics industry. "While the LDT community might lean more on the IVD vendors as it relates to regulatory compliance or just know-how in terms of working with the FDA on certain issues, I think we also do have a shared objective long-term in making this a better process for everyone," he said.

According to Genzen, adverse events reporting is one key area where clinical labs may need additional assistance from IVD manufacturers and the FDA. "Labs need to learn how to do this in the way that the FDA expects that to be done," he said. In particular, he cited a demand for information on how the industry currently reports, how to structure reporting with medical affairs, and what kinds of complaints should escalate to reportable events.

Rothstein confirmed that IVD companies still aren't certain of the answers to these questions. "This has been a pretty different rollout, in my perspective, of an FDA rule," he said. "I just hope long term that FDA will become more comfortable or more willing to provide the more specific advice that various entities need as they come into compliance with the rule."

IVD companies also are proceeding cautiously with the advice they plan to give, particularly for situations where clinical labs ask for guidance for using RUO products in IVD applications or for applying a test in non-diagnostic settings or in other applications that the vendor never intended. Rothstein said he expects some updates to contracts between clinical labs and their suppliers to split the FDA regulatory legal liability between clinical labs and test providers more than they do now.

Other important needs require clarification from the FDA, the panel said, such as what qualifies as automation and what constitutes an LDT. "What regulations apply to open-channel reagents that are FDA cleared and approved, but the package insert doesn't list a specific instrument; it just says a chemistry analyzer?" Genzen asked. "Nobody knows really if that's an LDT or not."

Sample Types

Hochberg said she hopes for transparency surrounding FDA review of the validation of new sample types analyzed on existing IVD kits. New tests are granted initial approval only for use with certain sample types, but clinical labs have well-established guidelines for using tests with different bodily fluids, and previously, clinical labs could validate the tests on their own and use them locally. With the new rule, either the manufacturer or the clinical lab would need to gain approval for use with new sample types.

Clinical labs will need to know what modifications to tests need FDA clearance, particularly for research-use-only (RUO) products, and who will lead the process of obtaining that clearance, Hochberg said. If the vendor will lead, should they look to other vendors to see if the FDA process has already been completed for their sample type? "That's not an easy thing," she said. "It's going to be really challenging because the IVD vendors themselves don't know yet what they're going to do."

According to Genzen, those locally developed tests often bring in negligible revenue, so labs may not have the personnel or budget to submit for approval. They may need to

request data from the IVD vendor to support their applications. If they do submit, the FDA may receive thousands of requests for approval of these local validations. "That is much more administratively burdensome for the FDA on something that I would say has very negligible additional benefit, versus just a validation being done locally under CLIA," he said.

Rothstein added that the FDA process for IVD approvals is not simple for manufacturers either. "What might seem like a simple update to your product could take both a lot of time and money to get the FDA to sign off on," he said. AdvaMedDx is currently preparing a new legislative agenda that includes regulatory reform to reduce some of the burdens of bringing tests to market.

Sample types also influence where manufacturers direct their development budgets. "Is there enough upside in terms of either test volume or revenue to warrant that investment, particularly when you already have a pipeline of assays that you're taking through your R&D programs?" Hochberg asked. She pointed out that data on what sample types clinical labs accept are not readily available, so keeping closer communication with customers than in the past will be essential for estimating costs and opportunity costs.

Budget isn't the only consideration, however, Hochberg added, as adding a sample type can delay clinical trials and delay the time to market for essential diagnostics. "This is a really difficult decision-making process for IVD manufacturers," she said.

Implementation Uncertainty

To further complicate matters, Rothstein pointed out that there remains considerable uncertainty around FDA regulation of LDTs that will continue for years. "We have litigation filed at a district court in Texas. Whoever loses, whether it's the government or the LDT community, they're likely to appeal. And that would take us to the Fifth Circuit, and then that could potentially be appealed as well to the Supreme Court," he said.

These challenges to the rule open possibilities that the timelines might be paused or altered, making it difficult for vendors and labs to proceed confidently. The new US presidential administration, which will include a new FDA commissioner and Health and Human Services secretary, also adds to the long-term uncertainty. "A lot of labs are being cautious about making very large decisions until they get a little bit more clarity there, because you don't want to set off on the wrong trajectory," Genzen added.

Genzen said he sees two approaches for moving forward in this environment: test providers can either attempt to include every specimen type in their FDA submissions, or they can limit the marketing messages but permit flexibility for clinicians to use the tests as they see fit. With either approach, diagnostics providers need to be conscious of the information included in the label. How tests are described in marketing materials is increasingly considered labeling, which increases potential FDA regulatory risks, he said. "That's a new thought process for laboratorians who are always excited and proud of their assays and want to talk about how great they are and how much better they are than a competing assay," he added. In her advisory capacity, Hochberg has already received a few requests from companies for advice on how to handle these questions, particularly for RUO portfolios, although she commented that progress towards implementing the rule has been slow.

Even when considering the lawsuit, Rothstein emphasized the importance of preparing for the first deadlines coming on May 6, 2025. "You do not want to be the poster child of FDA's enforcement arm once the rule starts to be in effect, if we get there," he said.

Audience Q&A

The discussion was followed by a Q&A session with the audience. This transcript has been lightly edited for clarity and length.

Adam Bonislawski:
How might these uncertainties affect payor coverage?

Jonathan Genzen:
You probably saw me laughing as soon as you mentioned payors. This is absolutely going to have an impact. And I would not default to the idea that just because LDTs become FDA cleared and approved, there is now a greater chance

of reimbursement. Right? That's just not the way that the reimbursement world works. There's not all of a sudden going to be a lot more money flowing into the lab industry. But certainly, payors may decide not to reimburse certain tests depending on the mechanisms outlined in the final rule for test clearance and approval. I could certainly see a world where perhaps payors may say, if you have not gone through that pathway, we're just not going to reimburse you. So, the payor side of this is going to be really important, and I think it's too early to see how it's actually going to shake out.

Donna Hochberg:
I would agree with that. I think it is too early to see where it's going to come out. I think coverage is definitely a piece of the puzzle, but the coding situation could also be affected, right? I don't have a specific example in mind, but particularly if you're adjusting something that's under a PLA code, are you then no longer able to even bill for it because there's just no code? Or do you have to submit under a miscellaneous code that requires a lot more paperwork? I think it's possible that adjustments or LDTs may end up in a situation where there isn't an appropriate code, particularly if they have a specific label claim or name for their test that's different than what the coverage policies actually apply to and what the codes actually cover. So, I think there's a lot of uncertainty here, and frankly in my mind, it's not getting enough attention in terms of preparing, right? We're all focused on the regulatory aspects, but we could go through all this hassle to get through the regulatory and then not get paid for what we're doing. So, it's really critical, and we need to elevate its importance in our preparation.

Adam Bonislawski:
What are your thoughts on the "unmet needs" provision of the rule, under which the FDA will exercise enforcement discretion for labs using LDTs in settings where there is no FDA-authorized test that would meet certain patients' needs.

Jonathan Genzen:
There's conflicting things happening there. Right? Like I said earlier, the final rule is going to force industry consolidation. I believe that's true. The unmet needs provision is restricted to testing within your healthcare entity for only patients within that entity. And so, it makes the unmet needs provision unusable in the reference labs where testing is being consolidated. So, I think the unmet needs provision was an olive branch to say that the final rule is addressing something, but with so many restrictions to it, it may not actually work in the settings that are doing a lot of unmet needs testing.

Zach Rothstein:
I think olive branch is a great way to phrase what that provision was in the final rule. I think it was a mechanism for FDA to at least give on some elements of what they received in the public comments, but it does feel like that's an area that that would be ripe for additional discussion and for the community to better figure out a provision that's more adequate for those types of tests.

Donna Hochberg:
I think it's important that we do find some way to wrestle with that issue, because I do think this is where the innovation comes from, right? New markers and how they actually get into clinical practice needs some kind of grace period or some kind of mechanism where, as we're learning about them, we can use them. And this provision was trying to do that, but I think didn't take into consideration, as Jon said, the logistics of where testing is actually going to be performed.

Adam Bonislawski:
To what extent does the ability of labs to modify tests play into an IVD firm's business projections for that test? Do IVD manufacturers assume that labs will modify and use their tests beyond the labeled use cases? If so, does this rule impact that assumption and their business projections? And if so, does this rule impact that?

Donna Hochberg:
It's a hard thing for companies to do, right? They have to be careful about predicting off-label use of their tests, right? And that's essentially what these modifications would be. And so, most of the time when I work with companies, they're focused on the intended use that they're developing and the market for that particular intended use, or that particular sample type, or however they've constrained the test that they're developing. So, my opinion is most firms don't rely on that. And they're not building a business case on that. And so, I don't think that pressure on a lab's ability to make these adjustments is going to change the business

calculus for the tests firms are already planning to develop.

Zach Rothstein:
I think it goes back to what we talked about earlier around some of the liability issues and how the two entities, the seller and the buyer, might structure their contracts as they acquire new equipment or put new requirements within the agreement. So, I agree with Donna. It's hard to know as a manufacturer, unless you've specifically asked the customer to report back to you or otherwise provide that information. If they're going through FDA, I guess you could scrape that data, but you could only use public data from FDA, which means that it's gone through and been either cleared or approved. So, I think it's a really difficult question, and we just have to see how it falls into place over the long term.

Adam Bonislawski:
There's been a lot of discussion about how the final rule might stunt innovation in the lab LDT space, but do you think it'll stunt innovation in the IVD space itself?

Zach Rothstein:
No. I don't see a reason why the rule would stunt the IVD space. And the reason I say that is this whole webinar has been premised on how the rule impacts the existing regulated IVD industry, right? But if you take a step back from there, the IVD industry has always been regulated by FDA. And so, outside of some products, the majority of what the IVD industry makes goes through FDA or at least is complying with FDA regs if it's a Class I device. And so, all the innovation that the industry has been able to produce under the current regulatory framework has occurred while being regulated. So the rule doesn't change how FDA regulates the IVD industry, and as a result, I don't see why it would have an impact on innovation within our industry.

Donna Hochberg:
I wouldn't say it's a concern. I guess, I mean, there are two sides to the equation, right? I think the IVD manufacturers themselves have a pipeline, they have a mechanism for sourcing that pipeline and continuing to invest and innovate. But one of those sources of innovation is LDTs from places like an oncology hospital, right? So, you could take the pessimist position that because that hospital is going to have a hard time doing LDTs, there's going to be less content coming from them. Or you could take the optimist position, which is we're already having and seeing deeper collaboration between IVD companies and these academic centers to get that content more quickly into the universe. And so maybe this will jumpstart that. You're having tighter relationships between the IVD manufacturers and the labs so that earlier on in the research stage, you're seeing that content and making decisions to move it into the regulated world more quickly. And you see that happening a lot as well when you think about IVD companies supporting biopharma and their clinical trials. So I think there could actually be an opportunity here to tighten that relationship and strengthen some innovation.

Jonathan Genzen:
The one layer I would add to that is I worry about the pipeline of talent of physicians and scientists who are interested in test development and who build that initial interest locally in their academic medical center setting. If that innovation isn't happening in that setting, you would still need to find a way to get those folks who are interested to find that opportunity outside of that setting. And it's just a shift in talent. It's a shift on where innovation would be occurring. There are probably some downsides to that, but there are also new opportunities associated with that as well.

Adam Bonislawski:
Are there companies either in the IVD space or outside that can be helpful for labs and help consult on some of these questions around FDA submissions and how to handle this?

Jonathan Genzen:
We're starting to get inquiries from outside companies. There are certain groups that are looking for consulting opportunities to help labs navigate this process. I've heard of some organizations who are thinking about perhaps offering adverse event reporting services to handle the logistics of things that could occur as early as stage one. I would say clinical laboratories have very little experience in the FDA submissions themselves. Most of them probably never heard of the eSTAR form and process. So, there are going to be opportunities there to just teach laboratories if the final rule stands to teach laboratorians how to comply with the rule. And there certainly are companies that are starting to identify those opportunities and try to find customers and partners.

Donna Hochberg:
On my side, the IVD companies are starting to come to us to help make those decisions on how to interact with their customers to learn that. I think one other thing that might be interesting here, and this is totally off the cuff here, is, are there big data companies or tech companies that can help collect information broadly to help labs and IVD manufacturers make some of these decisions? Because one of the challenges we do have is we don't know enough about what customers are doing and who's doing what. And maybe there are some big data solutions there to help make some more rational decisions. I haven't seen anything like that yet. ■