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Modification of In Vitro Diagnostic Devices: Leveling the Playing Field.
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Guest: Dr. Jenna Rychert is a medical director at ARUP Laboratories in Salt Lake City, Utah, and an Adjunct Assistant Professor of Pathology at the University of Utah School of Medicine.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children’s Hospital. I am Bob Barrett.

The US Food and Drug Administration regulates medical devices, including in vitro diagnostics to assure their safety and effectiveness. While most FDA cleared or approved diagnostics are used according to the manufacturer’s labeling and instructions, there are clinical and technical situations where a modification may be deemed necessary or advantageous.

The Clinical Laboratory Improvement Amendments of 1988, or CLIA ‘88, allows laboratories to modify FDA-approved tests, as long as they establish, as opposed to verify, the performance, characteristics of the modified test. Furthermore, such modification recategorizes the test as high complexity, which requires a laboratory to meet the personnel, proficiency testing, and quality requirements of high complexity testing.

An Opinion piece titled, “Modification of In Vitro Diagnostic Devices: Leveling the Playing Field” appears in the June 2020 issue of *Clinical Chemistry*. The lead author of that article is Dr. Jenna Rychert. She is a medical director at ARUP Laboratories in Salt Lake City, Utah, and an Adjunct Assistant Professor of Pathology at the University of Utah School of Medicine, and Dr. Rychert is our guest in his podcast.

Doctor, why do clinical laboratories modify tests that were already approved by the FDA?

Dr. Jenna Rychert: To be fair, most labs use tests just as they come. So, they use them according to the manufacturer’s instructions. That’s the normal thing. But there are some cases where it might be necessary, or for the laboratory it might be advantageous, to change them.

So, for example, a test can become outdated. So, a test that was cleared by the FDA 30 years ago, we may not have the same equipment that was used back then. There’s a

certain kind of testing where we use a microscope and the microscopes that we have these days are much better than they used to be, and that would be considered a modification, even though it's a better thing.

There's workflow and logistics kinds of reasons for changing a test. For example, in the reference lab setting, where we have people sending samples to us, and that takes some time, the manufacturer may not have left us enough room for the stability of the samples. So, the sample might take two days to get here and the manufacturer only made sure that two days was a safe enough time to wait before testing. So, we'll have to do some additional work to make sure that a sample lasts longer than that before tests can occur. So, that would be another reason

Finally, there's, sometimes additional clinical needs. So, for example, a test might become available on a serum or a plasma sample and then, as the test is kind of used out in a hospital or clinic setting, it may become apparent that it's helpful for other sample types, so, other body fluids and things like that and so, that might be another reason why a lab would choose to offer a test that is slightly different than what the manufacturer intended.

Bob Barrett: Well, what happens when a manufacturer wants to modify their own test that was already FDA-cleared and how does this differ than what happens when a lab modifies the test?

Dr. Jenna Rychert: So, this is kind of the crux of the issue here. When a manufacturer wants to modify their own test, the FDA provides pretty good guidance to them. They recommend that the manufacturer first perform a risk assessment, and if during that assessment the manufacturer realizes that it's a major change or a significant change, like changing the intended use, for example, then they just would know that they need to submit a new application to the FDA.

Also, modifications that would affect safety, those would also be considered major or significant, and those things, that's pretty easy. If the manufacturer is not sure based on their risk assessment, that's okay because they have to confirm that the performance characteristics of the test haven't changed once they make the modification. So, they're going to check regardless, and they will have to document that and all that sort of thing. So, they're relying on their, what are called, quality system regulations, to make sure that even those minor and non-significant changes are dealt with appropriately, and the FDA considers that the least burdensome approach.

The dilemma for the laboratory becomes that our guidance from CMS is that, we need to treat any modification as if it's

a laboratory-developed test and so, we have to reestablish the performance characteristics, and that's a fairly large burden, especially if the change is really minor or nonsignificant.

Bob Barrett: What are the manufacturing quality system regulations, and how do they differ from the laboratory quality system requirements?

Dr. Jenna Rychert: So, the quality system regulations for manufacturers essentially outline the requirements that they have to follow when they are manufacturing a device. So, these are things like making sure that they have a quality policy, that there's procedures for controlling the design of the device, they use good manufacturing processes, stuff like that, and they document and record everything, and they have a way to handle when a device doesn't conform to the specified requirements.

So, the quality system regulations for manufacturers basically ensure that any in vitro diagnostic that they producing is coming out with good quality. It's also a way to confirm that the device continues to meet the original specifications that they had established. So, every time they make a change, they do a risk-based assessment and they obtain data and all of that is documented and then, that's made available during audits and inspections. So, this is basically a big quality assurance process to make sure that everything is safe and effective and continues to be over time.

The laboratories have a similar quality system requirement, but it's obviously more specific to the laboratory setting. So similarly, they have to have a quality policy. They need to establish procedures to control pre-analytic, analytic, and post-analytic parts of testing. They have to verify or establish the performance specifications of assays, and they also have to identify any times when there's a non-conformance in the testing and then, have a mechanism to correct those non-conformances and prevent them from happening again.

So, as you can tell, there's actually quite a bit of overlap between those two quality systems, the manufacturing ones, and the laboratory ones. In both cases, everyone is relying on a quality system that's developed and enforced by management. In both cases, processes are put in place to make sure that supplies and reagents and instruments meet all the desired requirements. They make sure that personnel are adequately trained and everything is documented.

So, in general there's quite a bit of overlap. The difference is just that the setting, in the manufacturer setting versus the laboratory setting, requires some nuances. So that's what differentiates the two.

Bob Barrett: Well, if a laboratory does modify an FDA-cleared test, how does that laboratory make sure that the test is still safe and effective?

Dr. Jenna Rychert: Right. So, the role of the FDA is to make sure that all of these devices are safe and effective, that's definitely their role. And as I mentioned before in general, labs perform tests just the way the manufacturer intended. But if they do make a modification, what they have to do is re-establish the performance characteristics.

So, essentially, they go back and do all of the validation testing to determine what the sensitivity and specificity of the assay are, understand the accuracy and precision and reportable range. So, these are all things that the manufacturer would have done originally and then, the lab has to do again, if they make a modification.

Bob Barrett: Well, finally doctor, what are some common modifications that high complexity laboratories make to FDA-cleared tests?

Dr. Jenna Rychert: So, there's one kind of big bucket, which is, procedural modifications. So, for example, we might extend the time that's allowed for a specimen to be at a certain temperature before testing occurs. That's what we talked about earlier. They might need to use a slightly different instrument. In molecular testing when you perform PCR, for example, there's lots of thermal cyclers. Those are the instruments that you use for that kind of test that are pretty similar and they may need to do the test on one kind of thermal cycler instead of another. That would just be one example of a slightly different instrumentation.

In the reference setting, one of the things that we do is, we automate a lot of our assays and so, that automation might come from robots that are doing some pre-analytical pipetting step, or it might be that the whole entire assay is automated. Those are some relatively common modifications that you would expect. Also, I would say, adding additional specimen types; that's quite frequent in our laboratory to add on additional specimen types because of a clinical need for example.

Bob Barrett: That was Dr. Jenna Rychert from ARUP Laboratories in Salt Lake City, Utah, and the University of Utah School of Medicine. Her Opinion piece on leveling the playing field when it comes to modification of in vitro diagnostic devices

appears in June 2020 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.