

Webinar on Genetic Testing
Highlighting ASRs and IVDMIAs
November 6 12pm-2pm EST
Q&A from Webinar

Presentation from Janet Woodcock, MD, FDA Deputy Commissioner of Operations

Q by Sharon from attendees: What is the benefit to using the test developer to interpret the results? Does this impede access to the results for immediate use and medical decision-making? What is the overlap between FDA and medical decision-making, the role of the peer-reviewed literature process and clinical practice, what role does that play in terms of interpreting the tests and incorporating them?

A from Dr. Woodcock: Don't know really what the new analytes are (could be specific gene) but we don't know what that gene does or we may know what it does, but not its quantitative or distinct role. What we will be operating on, until we get into a greater state of enlightenment, is empirically derived correlations (derived from correlating the test results to findings in the clinical world). The first group that does that will be whoever develops the test. That is how you develop the test: you take the test, do clinical correlations, you refine the test to improve its predictive value and its parameters, and then you configure it in some way. Then the FDA will look at the data and details. You could say, "Maybe other people could as well?" Yes. If developers are willing to publish all the data results then some researchers would have the capacity to evaluate that. But that means the test has to remain stable in its configuration and manufacture during that comparison otherwise the comparisons might be meaningless. Of course, say you have a multiplex test that predicts some results and it's a gene expression test, that generates many research projects in and of itself. What are the genes involved? Which ones are most important? Which ones are predictive? What role do they play in pathogenesis? Why are they predictive? And so forth and so on. At some day in the future we may get to a point where the entire research community knows everything about those genes and then anybody will be able to test for their expression and then all of a sudden this doesn't become a black-box correlation, it becomes an algorithm that everybody has understood and they have been able to validate it with other tests for those genes and find that yes, indeed those genes do contribute. We end up with common medical practice and laboratory practice and we are in a different state for that set of genes. We agree that that could occur in the future, but that isn't the present that we are dealing with. That has occurred for other analytes over time so we are in that state for other types of analytes. So, we think for the current approach, it's very important that a single third party, the FDA (an independent body), look at how these tests are developed, how their predictions are validated, and their performance and also look at the manufacturers at the same time.

Q by Sharon from attendees: Could you give an example of a laboratory-developed test, an ASR, and an IVDMIA, and could you make them all real-world examples of things currently on the market so they could get the distinction between these things.

A from Dr. Woodcock: ASR would be a reagent, maybe a primer, that you could use in a laboratory and you would construct some test for genes around that primer. You could buy that from another manufacturer, but in your own lab you would develop and configure the tests; you would simply use the primer that has been manufactured as the essential reagent in your test. You would develop in your laboratory all the different configurations of the test and the quality insurance and quality control and you would take responsibility for that within your laboratory. That would be different if someone sent you a bunch of components and they say put those all together and you will have the tests. How does that differ from an IVDMIA? An IVDMIA would usually look at multiple analytes, that's why it's called multiplex. In other words there are multiple factors that go into the assay and then they aren't simply reported out (an example would be in the form of a numerical score) they are combined because their combined predictive value is what is being looked at to predict some clinical outcome. Whoever you are who is making this IVDMIA you have figured out that these analytes are predictive by correlating them with some clinical data sets. That is what we call empirical. In other words, you say I found this correlation of these genes with some condition, if we combine them in some way. That is usually proprietary and held proprietary by the manufacturer of those processes and could be offered for sale, telling doctors you could run this test on your patient and it could predict X or if you get a score of Y it's bad or a lower score is better. The doctor would have no idea. Unlike the serum sodium where if he doesn't know what it is they could look it up in a medical textbook and there would be a long dissertation on what that means.

A from Courtney: Basically, the doctor may be able to look up what the test developer says what it means, but they ultimately have to get it from the test-developer. The number doesn't mean anything independently: it is linked to the test itself.

Q from Kathy Hudson: If in the peer-reviewed literature, there is a description of how the scores were derived, would that change the equation in terms of whether or not it is an IVDMIA?

A from Dr. Woodcock: No, we don't think so, because in general the test's performance, the test analytes themselves, are not something just out there where other people can perform this test. The test and its configuration are also proprietary ordinarily.

Q by Sharon from attendees: How is the processing of clinical information in an IVDMIA different from what clinicians do with multiple pieces of clinical data in clinical decision-making every day?

A from Dr. Woodcock: It isn't, it's the "who does it?" The physician integrates multiple pieces of information about a patient under the practices of medicine: that is the physician or other care provider's job. Here we have somebody who is using a medical device to generate a claim, treatment recommendations usually or prognostic information, that's very different from what is done by physicians in the context of individual patients.

Q by Sharon from attendees: A lot of questions (many questions in one group) on what is the length of time the FDA anticipates will be necessary for reviewing the individual IVDMIA products and still lots of requests here for you to actually name one that is on

the market so that people have an idea-it tests for blank and it is what-and just overall questions about FDA's resources for reviewing many tests.

A from Courtney Harper: IVDMIAS like all other medical devices will be regulated by their risk. So if an IVDMIA came in and it was determined that the claim they made put it into Class II then it would be reviewed and the timeline for that would be 90 days up to 180 days. I think we have a lot of mechanisms in place to get these through in a very reasonable manner as long as the submissions are based in science. We are very interested in working with IVDMIA manufacturers to accomplish that.

A from Dr. Woodcock: We actually have a number of manufacturers who have come to us who are initiating trials. For example, some groups are doing perspective trials so we have experience in working with manufacturers on these.

Q by Sharon from attendees: Given that this is a lot of information to digest, and this is coming from several advocates on the list, this is an area we are newly getting up to speed on, can you comment on the short period for public comment and again remind us what that is.

A from Dr. Woodcock: Open to comment until December 6th and we are looking into a 30 day extension. If need be, we may have more educational and public discussion after that point, but they would obviously have to be with the whole public and it depends on how many questions we get and if there's confusion about this. Guidance is guidance from the agency, we would like to get something final out, but if there continues to be confusion we can always amend our guidance and have further workshops or different things on these topics until we achieve good clarity.

Q by Sharon from attendees: Will there be a grace period for tests currently on the market for them to come in for submission.

A from Dr. Woodcock: We can't really comment on things like that directly, but we can say we look forward to working with manufacturers and anyone who feels they have a product that falls under this rubric should contact us soon, immediately if possible.

Q by Sharon from attendees: Could you comment on what you mean by clinical validity in the context of the guidances?

A from Courtney Harper: Clinical validity has a well-established meaning in the diagnostic world and what it means is that it actually predicts something real. Just like diagnostic device regulation, the claims that are made are supported by the data submitted. It doesn't generally go into what we sometimes refer to as clinical utility, which would be long-term outcomes or long-term benefit of the use of the test. It's more along the lines of the data submitted support the claims that are made about the tests.

Q by Sharon from attendees: FDA issued a letter to CombiMatrix determining it was not an IVDMIA. Does FDA expect to do this with other IVDMIA manufacturers if they initiate the process?

A from Dr. Woodcock: We obviously don't want to be in the business of writing hundreds of letters to folks, we would prefer to talk to people and hopefully more clarity will be developed as we move along and people will understand if they are in or out. But we are very happy to talk to people if they want to know about a particular test.

Q from Kathy Hudson: You talked about the safety and effectiveness concerns for IVDMIAS and I'm wondering how those safety and effectiveness concerns are unique to IVDMIAS as opposed to another laboratory-developed test where the information about the test-performance characteristics may not be totally transparent—you mentioned transparency a number of times—and I'm wondering how this class of devices or tests raise higher safety and effectiveness concerns as opposed to other laboratory-developed tests?

A from Dr. Woodcock: Obviously there are concerns about any tests. We feel though under ASR regulations, under manufacturing, under CLIA regulations, for many of these tests that are currently laboratory-developed tests that there are a fair number of safeguards in place, we just feel those safeguards do not reach this category of tests for the reasons I hope we have gone over in some detail, because they do not get into the factors of how they are developed and how their claims were validated.

Presentation from Kathy Hudson, Ph.D., Director of Genetics and Public Policy Center

Q by Sharon from attendees: Is the draft guidance process the appropriate manner to shape and enforce new regulation oversight for genetic testing? What in your opinion would be the best method or process for moving forward?

A from Kathy Hudson: Draft guidances play an important role, but the puzzling part here is what is the big umbrella in how we want to see all genetic tests and their quality overseen? There's a danger in taking one piece at a time and thinking of that in a silo. We need an over-arching strategy of how we are going to deal with these tests. It's inconceivable to think that FDA would be able to review and approve all the genetic tests on the market and the many more coming. I'm wondering if there is some mechanism where by we could encourage information sharing and transparency of information. That as an initial move may help both the innovators in the field and also the patients. We need a big strategy before we start to move into the details.

Q from Sharon by attendees: Why has no one mentioned intellectual properties issues so far in this discussion?

A from Kathy Hudson: It relates in part to the transparency, to the extent to which a sequence or a test or algorithm has intellectual property protection, that means that the information is in the public domain. In some ways the intellectual property system was created to encourage transparency, but at the same time it can restrict access. So the number of labs that can perform a specific test, and the ability to innovate on that test, could be limited by existing intellectual property protections and the licensing arrangements.

Q by Sharon from attendees: Can you explain the differences between draft guidance versus rulemaking and what is the process to make a new regulation?

A from Kathy Hudson: The tradition in this country is that before we put new rules in place, the government puts out an idea, a proposal, a draft and actively solicits the public input. Then there is a requirement that the agency consider that public input before moving forward with a final regulation. I think in the FDA's context, the difference from a rule or regulation is first put out there a Notice of Proposed Rule Making (NPRM) and you end up with regulation. What the actual difference is, I will defer to the FDA.

A from Dr. Woodcock: Rule making is about a five-year process whereby we are issuing basically law (binding framework) that is based on statutory authority that we have. We have gone through that in this area of devices, there is statutory authority and there are rules and regulations in place. Guidance explains FDA's thinking on a certain area and is in a different realm. What we are trying to do is explain existing regulatory framework as it applies to newly emerging products. As I said earlier, our approach based in statutes is that all these diagnostics are medical devices, they are applying enforcement discretion to some of them. What we are trying to do is give people guidance on where enforcement discretion will and won't be applied.

Presentation from Mara Aspinall, President of Genetics at Genzyme

Q from Sharon by attendees: Do you see the FDA guidances as positive or negative with regard to incentivizing innovation? Will FDA standardization of IVDMIAs make it clear for doctors and patients what should be used in the clinic? Could you address that while innovation is very important, we also have to think about that not all products are created equal, whether lab-developed or industry-developed and how do you suggest that regulators balance the need for continued innovation and the need for quality products?

A from Mara Aspinall: Too early to tell. We have heard Dr. Woodcock talk specifically about their objectives, which I very much appreciate, and FDA has been clear from the beginning that they do not want to stifle innovation in doing that. I think every aspect of the industry and the market and the broadest point of view has said that. I think you can point to various examples in several different industries where regulation has led to contraction and regulation in other health care industries has led to a broadening of its appeal. So the answer, legitimately from me right now, is that it's too early to tell. I think what is critical in this referral to extra time is we as an industry need to get our comments into the FDA and as they have been opened, suggestions about how to do it. And how, if there was a system that potentially changed, how to take that to ensure innovation from an individual company or academic lab point of view. I think it is critical that as we do that, we think about how we balance it. We need to be looking at how it impacts patients, which doesn't necessarily mean volumes of patients because many of the tests out there, as we all know, make a tremendous impact to a small number of patients. I think we need to ensure that our tests are really meeting the criteria of really making an impact on the clinical decision-making as we go forward. I know the industry has talked about that as our goal, and if we do that, we need to ensure that those continue to be the key value elements of what we provide.

Q from Sharon by attendees: What are your ideas about how reimbursement can be increased for genetic tests?

A from Mara Aspinall: I do believe that it ultimately needs to increase, but I like to think about it as not pushing for it to go up but having a rational system that rewards value and not just activity. The challenge that we all have now, in every aspect of the industry, is that the current system is based on activity, the number of any particular process. That to me is something that discourages innovation. I use, for example, a certain test which many labs use, which uses X number of probes. If you find a way to do it with fewer probes rather than more probes in the simplest way, the reimbursement goes down. It very well may be faster, higher quality, and you need to come up with fewer probes. You need to put money, resources, into coming up with a better way to do that. If you were to do that, your reimbursement would go down. We need to create a system that is based on value rather than just doing things. Today, the more you do, which may or may not mean it takes longer, the more you are reimbursement for. There is a logic to that that came at a very difficult time in this industry's past, but I think we are beyond that. Before we just say we need more money, and I think for the most part we do, I think we need to come up with a rational system that rewards innovators and patients, because we are coming up with vast diagnostics which truly make an impact so it's changing the system from activity-based, not even cost-based today, but to a value-based system that really looks at rewards in the system and repairs.

Presentation from Mike Watson, Ph.D., Executive Director at the American College of Medical Genetics

Q by Sharon from attendees: What specific improvements or innovations would be slowed down by the FDA selective regulation of lab-developed tests?

A from Mike Watson: Depends on how it is imposed on labs. If manufacturers became reluctant to make ASRs available for particular rare mutations, then labs would be slowed in their access to products and would be developing them internally. They would be limited in ensuring the compatibility of the various ASRs when put together into a package that are commonly used in both clinical investigations and diagnostics. One of the fundamental problems that we face is a lack of organized data collection that allows one to get the answers to both the analytical and clinical validity questions that are underlying the development of these particular guidances. FDA's typical mechanism or phase for surveillance that is used in drug clinical trials is where they accept something at a certain level and then go on to acknowledge that they want to collect data over a period of time to ensure that the decision made was appropriate. There are lots of these variations of the regulatory system itself that give some protection to orphan diseases and to humanitarian devices and to collecting data around rare and not so rare diseases that if better developed, would actually off-set some of the problems that one can foresee from the guidances.

David Mongillo, M.P.H., VP for Policy and Legislative Affairs, American Clinical Laboratory Association

Q from Sharon by attendees: Because a condition is rare does that mean that we should not be concerned about the overall accuracy of the tests? What kind of system would you recommend to ensure that the most vulnerable, those with the rare diseases, get the kinds of tests that they need?

A from Mike Watson: No, we don't want bad tests out there, there is a reason why the devices side of the FDA has a humanitarian device exemption and that is to recognize that one cannot get the kind of statistical power in rare diseases that one can get in common diseases where one can run randomized control trials and other types of validation tests that demonstrate at a quite high level that a test is valid. The reason the humanitarian device exemption is there is to allow for somewhat lower levels of regulation and oversight to be put in place, so as not impede the availability of the rare disease test. However there are still mechanisms available whereby one can assure that those tests are doing what they are expected to do and performing well.

A from David Mongillo: There are current mechanisms in place and of course we want to have all testing to be accurate and safe and we think that a test that is done for rare diseases, that that category, if it is lab-developed, there are plenty of oversight mechanisms to ensure that the test is safe and accurate and does what it is being asked to do

Q from Sharon by attendees: Better information about the clinical utility of genetic tests is clearly needed for regulatory review, for patient decision-making, and for third-party payment. Who will ultimately provide the funding necessary to conduct these desired clinical studies? Will industry be able to finance these studies? If not, what government industries might step in to fill the void?

A from Mike Watson: I don't think clinical utility is something FDA oversees. They do pay attention to validity and if a manufacturer or laboratory is able to demonstrate that they have an analytically and clinically valid assay, then the FDA is much more likely to approve it. Now that doesn't necessarily mean that someone is going to pay for that test to be done. Commonly, that's where the utility question comes in and it is often the payers who are in the business of establishing utility, who will make an ultimate decision as to whether the utility is sufficient for them to cover the test itself. It's who oversees these different pieces of the puzzle that is the issue.

Q from Sharon by attendees: Under the new ASR guidance, will every lab doing a specific test on gene ABC with their own DNA primers have to go through and FDA process as a manufacturer and won't there be a lot of duplicative review going on?

A from Courtney Harper: The ASR guidance document is actually intended for the manufacturers of ASRs, so it's not actually a guidance document that talks about the use of ASRs in laboratories. The guidance outlines the specifications on the marketing of the ASRs by the manufacturers.

Q from Sharon by attendees: What category do genomic micro-arrays for detection of chromosomal gains or losses fall into?

A from Courtney Harper: It depends on the technology used and how the test was developed. Some may not be IVDMIAs if they are basically identifying deletions or insertions in the genome and they do that through standard mechanisms that may not be an IVDMIA. We recommend people come and talk to us if they have questions about their specific tests.

Q from Sharon by attendees: Is the FDA currently working with any international regulatory bodies on harmonized guidances for ASRs and IVDMIAs?

A from Courtney Harper: Certainly this isn't an international issue. ASRs are unique to the United States at the moment, but FDA is always interested in global harmonization, so certainly if the international community is interested, we would be interested in participating in that.