Plans for Augmenting CLIA to Specifically Address Genetic Testing Laboratory Issues and Concerns

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So now Dr. Joe Boone is going to update us on the agency's plans for augmenting CLIA to address genetic testing issues. I know you've been involved in this for the duration of discussions about genetic testing, so we appreciate you making this presentation, Dr. Boone.

DR. BOONE: Well, thanks very much. It's a pleasure to be here this morning. I want to tell you a little bit about where we are and also try to answer the question why is it taking so long? That's one of the questions we constantly get asked, and I think as I go through this presentation you'll be able to see why things do take time, perhaps more time than most people would like to think.

This issue is complicated, and we're not the only ones that are trying to address it. I just recently returned from the Office of Economic Cooperation and Development. The European Union was considering some of the same issues that we've been debating for some time. They were very anxious to move ahead with the oversight of genetic testing laboratories. Part of this was driven by a recent survey that they conducted which showed that 63 percent of the laboratories throughout the world were receiving specimens from other countries. So specimens are crossing international boundaries, and they don't all have the same standards for laboratory practice. So that was of concern.

Judy has already talked about this three agency group that has the oversight responsibility for CLIA and what each of the agencies' roles are. I am reminded that one of my colleagues, when they found that this was the path that the U.S. government was planning on taking, told me that a troika didn't work in Russia and it won't work here.(Laughter.)

DR. BOONE: However, we've been really trying, and I think we've been successful in many ways. We do have different focal points, but we are really trying to make these three agencies work together in an effective manner.

You're not the only advisory group to the Secretary. We have one ourselves, the Clinical Laboratory Improvement Advisory Committee, called CLIAC, and the members are appointed by the Secretary. There are 20 voting members, there's one industry liaison, and there are three ex officio members. The CDC provides support to that committee, and much like Sarah Carr, sometimes people think of it as being a CDC committee, but it's really not. It is a committee for the Secretary and we report directly to the Secretary for our activities.

Let me kind of go through quickly the standards development process so that you can understand what the process looks like. I think it's important to understand that this is a very open process, and therefore it turns out to be fairly time-consuming because we're trying to get input from as broad a spectrum of individuals as possible, and organizations.

The first thing we look at is what the federal laws that we have to do, and then we look at the voluntary standards and guidance that's available, state requirements, accreditation standards that might be available, what the industry has to say, what the public has to say, and what our advisory committees have to say. Then we develop a proposed set of regulatory standards.

In this particular instance with the genetics, we actually went through another process and we developed a notice of intent which described what we obtained from our advisory committee, what they thought some of the practices should be, and based on those recommendations we circulated a notice of intent and we got comments on that. So we had an additional input to consider in the overall oversight process.

The next step is a notice of proposed rulemaking, which we're not yet at. We're close to it, and that's a proposed set of regulations which again will solicit comments. We'll collect the information, we'll do an impact analysis, and then we'll develop a final rule. Those will then be the CLIA standards that will be in force.

As Judy pointed out, the current requirements do apply to genetic testing laboratories, as do all the general requirements for non-waived testing. There is especially a clinical side to genetics that is already recognized which has specific QC requirements and qualifications for the personnel. In addition, the quality systems rule that was published in January incorporated some language that our advisory committee had been telling us we needed to have for genetics testing, but we realized that it needed to be applied across the board to all other kinds of testing as well. So we incorporated that language into the systems rule, but there were some specific requirements that we did add in that applied to genetic testing.

For example, molecular amplification procedures. We talked about the facilities that need to be available for that and the confidentiality that Judy mentioned earlier. However, there are still some areas where there's nonspecificity that we feel like needs to be addressed in the final rule.

Mike Watson, I think in 1992, told us that we needed to be including genetics in our proposed rule. We didn't do that, and that's maybe part of the reason we're not there yet. But we did have the NIH/DOD task force report which indicated that CLIA needed to be augmented. We've had recommendations from CLIAC. We formed a workgroup, and that group met four times to try to develop a set of requirements. We shared those with the former group, the Secretary's Advisory Committee on Genetic Testing. We supported those recommendations. Then we published those recommendations in the notice of intent, and quite frankly they weren't all widely accepted.

There was some concern about some of the recommendations that were being made. Some people thought they were too stringent, some people thought they weren't stringent enough. So we're having to address those comments, and we had CLIAC actually review the comments and make some suggestions to revise their recommendations. As I pointed out, the quality systems rule has incorporated a few of the changes that were recommended in this process.

So what are some of the issues? Well, the definition is one of the key issues. How do you regulate something unless you know what the definition is? One of the challenges is to try to define what genetics testing is, what the scope of it is in terms of regulatory oversight. Perhaps it doesn't matter as much since CLIA applies to whatever is out there, and so the definition may not be quite as important as some are trying to make it be.

Clinical validity was a concern. It's been a concern of this committee about when is a test ready for use, and the answer to that is still an issue. Who should be authorized to actually be able to order a test, what the informed consent process should be, and whether the laboratory should be part of that informed consent process. Confidentiality results we've already talked about. Whether there should be genetic counseling required for certain genetic tests. Then there are a number of pre-analytical/post-analytical kinds of issues, as well as analytical issues that we felt

like needed to be addressed.

Let's just quickly go over some of the comments that we received on the big three, I think, in terms of controversial issues related to rulemaking in this area. One is the definition. I just mentioned that. About 50 percent felt like that the definition was too broad. The definition really encompassed both the heritable kinds of conditions as well as the non-heritable kinds of conditions, and there was strong sentiment among some of the comments that we should not include both of those in the definition of genetic testing. So the determination of what is a genetic test is a little bit problematic.

Some people thought we ought to base that definition on the intended use of the test. That didn't seem to always work, and as the FDA knows, sometimes things don't get used for their intended purpose. Subspecialties' definition of what should be included, and a number of other areas about whether they should be addressed or not in this overall definition.

In terms of clinical validity, again we had about 50/50, and what do you do with a 50/50 comment? They disagreed with the notice of intent proposal which was developed by the CLIAC committee and was fairly prescriptive in what they thought ought to be done by the laboratory to document clinical validity. There were, as I said, different positions that were sustained. Some people thought it was impractical and out of the laboratory's purview to develop clinical validity for their test. Others really felt like strongly that it should be required, but only required for certain types of tests.

There were concerns about how would it be monitored, what would be the criteria, where would data come from, how many samples would you have to test in order to document clinical validity for the test that you were offering. No easy answers in this area.

Informed consent. About 60 percent felt that laboratories should not be required to ensure documentation of informed consent. The recommendation to CLIAC was basically that there ought to be a checkbox on the requisition form that would indicate whether informed consent had been obtained -- fairly simple, fairly innocuous to the laboratory. But the questions, of course, are, well, what happens if the box is not checked? How do you verify it? Do you have to verify it before you perform the test? Lots of questions, more questions than answers in this area. Most felt that the oversight should be deferred to the states, not a federal responsibility, but the laboratory should be required to establish policies and procedures, and there was controversy, as I said, on the extent of the responsibility of the laboratory.

So we're left with the same major issues that we need to consider in our final rule -- our proposed rule, I should say. This is a proposed rulemaking -- what the definition should be and what subspecialties should be recognized, how do we deal with informed consent, test validation, proficiency testing, specific requirements for each of the subspecialties, how do we deal with the retention and use of specimens, what should we require.

At the same time that OECD meeting was going on, there was a meeting in Paris by UNESCO in which they were talking about a human rights declaration, and one of the provisions in that human rights declaration was that once a patient received the results, the laboratory or care provider was required to destroy the background information. They had to destroy the specimen, they had to destroy any data that was behind that result. Of course, that violates a lot of our state laws and other requirements that we have in the U.S., so we were quite concerned about that.

But everybody is taking off from this on different pathways, so it's really a little bit difficult to

kind of steer the ship, if you will, in the right direction.

In terms of CLIA itself, we really do follow some basic principles in terms of how we develop a rule. We want to make sure that we ensure quality in all the phases of testing, not just the analytical part of testing. So we're really concerned about the pre- and post-analytical issues. We want to provide flexibility to those so they can accommodate the different testing environments. Judy talked about the wide spectrum of places that genetic testing might be done, and we have to make sure that we are encompassing that whole range of activities.

We have to ensure that there are appropriate personnel to do the test and that it is available, that there's access to the test. We don't want to inhibit that process and the development of new technologies.

So what will the NPRN look like? It will contain a preamble which will explain and clarify what the proposed requirements are. We will address all of the comments that we received in the notice of intent and provide responses. We will describe the sources of information that we had in our rulemaking process, and we will provide everyone with a regulatory impact analysis about where the data came from, what are the cost/benefits for this proposed rule. That's all standard. Then we'll have the proposed requirements.

We just completed the regulatory impact analysis for this proposed rule, and in so doing we did try to identify all sources of information that we had. In some instances we're working with inadequate data. No one really knows what the test volume of genetic tests is in this country. We wish we had that number, that magic number, but we don't have it, so we had to estimate how much genetic testing there was in the country.

We also are concerned about the availability of people who have the specialty training in genetics. Are there enough genetic counselors? Your committee has talked about that as well. Do we have the right kinds of personnel to implement the requirements? We had to project this over a five-year period and what the costs and benefits were going to be, and this will all be in the proposed rule.

So where are we in the development? I described a notice of intent that we sent out. We've got the revised recommendations from CLIAC. We've looked at all the different inputs, and at this point we've got something that we're transferring to CMS for them to begin putting the final touches on the rule. So we are making progress. She's got it on their regulatory schedule, I believe, so we can report progress for this. I hope I've given you some indication of why it's taken so much time to develop this, because it's not where you have black and white answers. You have to really take into account a broad spectrum of use.

We have to clear this through the Department, which means that we have to get concurrence from all the other agencies. CMS, CDC, FDA, the HHS sister agencies all have to concur with this proposed rule. Then we also have to get it through the Office of Management and Budget, which takes a very close look at the rulemaking process, decides whether or not there's a benefit here that outweighs its cost. Congress can even weigh in on this if they think this is a significant rule. I don't know that they would on this; they don't do so very often. Then finally we get to the Office of Federal Regulations.

This Judy didn't say, I don't think, but this isn't the only thing in CLIA that we've got to work on. We've got a number of other areas that require our attention that haven't been addressed since the final rule in 1992 when you go back to them and update them. So we're getting hit by a number

of groups that say these are really out of date, you need to change them. So these are some of the areas that are big areas for us to try to address for the future. With that, I think I will close. Thank you.

DR. McCABE: Thank you very much, Dr. Boone. If you could join us at the table here also.