

Pharmacogenomics Session
Q & A and Committee Discussion I
Facilitator: Emily S. Winn-Deen, Ph.D.

DR. WINN-DEEN: -- speedy overview of what's going on at FDA. We obviously should have allocated a little more time for the "update."

I had one question for you, Dr. Rudman. When you did this joint program with EMEA, was that at the request of a particular drug sponsor that you do that? Or was this something where you sort of got together and said we ought to pick a project and see if this would work?

DR. RUDMAN: You're talking about the CRADA? We had an interest in this, and so did the company. We found through one of these interactions that we had a common interest, and that's really how it came about.

DR. WINN-DEEN: Okay.

DR. RUDMAN: They were doing biomarker development, and we were interested in this, so CRADA came out as a natural outcome of that.

DR. WINN-DEEN: Is there a mechanism for companies to do that on a regular basis? Or are you working towards that?

DR. RUDMAN: Well, they can actually submit them. We have a website, we have email addresses, and people call us all the time and ask about these things. So we are very receptive to them.

We do have limited resources. We can't do an infinite number quite clearly, but we are very interested in continuing on with this process.

DR. WINN-DEEN: We have maybe 10 minutes for Q&A. I've got Julio and James, Kevin and Agnes.

DR. LICINIO: Just following on one of the things at the end on the need for national standards for the testing, which I think is crucial, because we discussed a lot both here and in different contexts this issue of what do you do with the test result, the privacy, and this and that.

The issue is what is the best to begin with, which is kind of a very crucial issue. We discussed this informally before the meeting began. Not only is there no kind of national guidelines or licensing board for that, but if such an entity were to exist, where would it belong?

Is it in the purview of the FDA? Of the CDC? Who would be responsible for monitoring for issues like, you know, a standard of quality control, ensuring that it meets that kind of standard?

DR. RUDMAN: That's a very good question, and actually a very complicated one. You are really asking a number of different questions, and I'll try to address them.

One is it is not just about the validation. Actually, that's part of the issue. There are numerous types of validation. Is the test validated in vitro? Are the labs performing it correctly? I mean, this is kind of a CLIA question.

Does it work in humans? Is it clinically validated? And finally, does it have clinical utility? I mean, the fact that the test works doesn't mean the public health would be necessarily improved by it.

So all of these, these are all questions. So you have to kind of parse these out. The first step before you can even get to enforcing these, and there are processes in place such as CLIA, is really to define what you mean. That's what we really need to start doing, get some consistency on this. Then I think we can assign responsibilities accordingly.

DR. GUTMAN: Let me just augment that response, because at least for the diagnostic industry, there really is a premier standards crafting group, that's the CLSI, the Clinical Laboratory Standards Institute. So if you were able to subsume drug issues, the most logical place to turn to for standards in this country at least is CLSI.

CLSI is also the Executive Secretariat for the international standards group working in the area of labs, ISO CT212. So you technically have capacity to kill two levels of standards with one stone in turning to CLSI. Again, they are focused largely on the diagnostic issues, and so there is no reason they couldn't be a little more inclusive. They wouldn't start creating pharmacology standards.

DR. EVANS: I'm naive as to what the purview of the FDA is and all of its manifestations. I was wondering if you have anything to do with guidance of how results are reported.

The reason I ask is that I contacted Roche, and I asked for a sample of a report from the Amplichip, and it was really completely incomprehensible. I'm a geneticist, and I do pharmacogenomics.

So I worry greatly about the access to this information in an understandable way to clinicians, and I'm really glad that you brought up twice the issue of a difference between clinical validity and clinical utility. It goes beyond public health into the individual as well.

Unless we have understandable types of reports, then the utility and validity can really get blurred. I was just wondering if the FDA has any role in that.

DR. GUTMAN: The FDA in general does not regulate the reporting system itself. We will sometimes be concerned enough about some aspects of the way information would be reported out that we'll try and push the limits on it, but we don't have direct authority.

Unfortunately there's no one from the CLIA program -- do you know, Muin? Does Judy Yost have the capacity to tell a lab? I mean, there's the expectation, CLIA clearly has both pre and some post-analytical requirements. I actually don't know, but we can certainly take that back and find out what their authority over that is. I assume they have some, but I don't know how strong it is.

DR. KHOURY: I'm not sure how much they have authority, but I can tell you one thing. CDC, the CLIA group that works with the CMS program, has looked at genetic test reporting in general and the variations around that. Not necessarily in pharmacogenomics, but in other areas. There is quite a bit of variation in genetic test reports. That was a project that just got finished.

I think the SACGT, I guess our parent group here, kind of took on these issues for I guess a couple of years. They tried very hard to sort of develop an overarching package for the oversight

of genetic testing and the transition from research to practice. They came up with very thoughtful comments about the need for three or four processes.

One as an FDA-driven process, which I think FDA has kind of taken over the last couple of years and struggled through. The second is a CLIA-driven process, which includes the development of genetic testing subspecialties.

These have different arms. The third is sort of more voluntary, what we call a public health related effort for developing the kind of data that is needed from a non-regulatory process. This is something the CDC and others have worked on for the last few years, that kind of led to the EGAPP initiative that you heard about yesterday.

So we are all moving in some direction, but I think there are just too many gaps right now in that process. I think pharmacogenomics is uncovering some of these gaps, and this committee could sort of take it on again.

DR. WINN-DEEN: So Kevin passed his turn, and Agnes is going to be the last question before the break.

MS. MASNY: Thank you. This is a good segue, I think maybe some of what Muin just said would cover some of the issues that I wanted to just bring up regarding the education.

Really thank you very much, because it was exciting to hear all the numerous initiatives of the FDA in moving forward in this area of pharmacogenomics. But yesterday we did hear from some of the speakers regarding our concerns about launching large population studies suggesting that one of the major barriers was the lack of genetic literacy from the public in agencies such as the FDA, as well as in the health professional community itself.

So I just wanted to say that I think that some of your responses show the definite movement in that area sort of lessens some of my own concerns about that. But at our last meeting, we also had some updates on pharmacogenomics, and one of the presenters talked about the use of TPMT testing for children who would be treated with 6-mercaptopurine, and also brought up that there was a lack of the use of that testing because the clinicians, even with the labeling and things like that, were not sure of how to use it, or maybe had other concerns about liability.

I know in your slide, Dr. Rudman, you had education initiatives, both external and internal. If you'd comment a little bit more both on what education initiatives are going on within the FDA and possibly for the community, health care provider community to make use of some of these tests, that would then come out.

DR. RUDMAN: This is a very good point. Internally, actually we've started a whole series, I think there are three or four of them now, of internal FDA seminars and training sessions. We have also brought into the process as part of this whole process, not only is there formal training in the FDA in terms of teaching people about genomics, about different types of software and so on and so forth, these types of formal training programs, but we're also bringing reviewers and their division directors and management basically into these meetings more and more to try and get them to understand the issues and actually get their feedback on some of these issues.

So internally, we have internal websites, we have training programs, we have presented I don't know how many times already to different divisions in different areas to try to do this. I'm sure CDRH has similar type of programs in addition to this.

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Externally, a lot of our effort has been through really two mechanisms currently, because of resource limitations, actually. One of them is workshops. We do a whole slew of workshops. We try and invite people to participate. You saw the list up there. But a large part of it is also through our website, which I have the website address up there, to try and get people to really understand these issues.

Some of these are fairly eclectic and difficult to understand frankly for the layman. In terms of going outside, we have had preliminary discussions with some people, universities, about moving forward on this. We have also talked to the American Association of Clinical Science about setting up programs.

We don't actually have the resources to go physician to physician obviously to do that, but we do recognize a need, and we are trying to move forward on those issues.

DR. WINN-DEEN: Can I just ask a follow up to that?

DR. RUDMAN: Sure.

DR. WINN-DEEN: Do you think clear direction in drug labeling and package inserts would be helpful to physicians? I mean, I think right now when you just say by the way, this is metabolized by this enzyme, that really doesn't provide the physician with any real guidance, to be frank.

DR. RUDMAN: Well, actually, you have brought up a very good point. It is a difficult issue in some ways, and in some ways it's very simple.

We start off at the beginning, and that is actually what this grant is really about, in order to actually categorize this. When I tell people there are about 60 or more labels out there with genomic information, a lot of people are actually surprised at this.

Most of it is the CYP P450s. Some of it is more informative, and we're finding that the labels that are recent are more informative than previous ones. Some of these are fairly -- it's not always clear.

For instance, it's a TPMT issue that has been brought before an FDA advisory committee. Actually, that's part of how the outcome was generated. In terms of how physicians see this and how the FDA sees this, there are different proposals out there.

So a lot of this is bringing these before these advisory committees to get their input.

DR. GUTMAN: Well, it's a glass half full and the glass half empty. You have to realize I'm a clinical pathologist, not a geneticist. If I were to survey what is going on in lab tests, or if you looked at the recent activity that CDC has initiated with the Institute for Quality and Laboratory Medicine, the average physician doesn't know how to order a prothrombin time, so I can't imagine the average physician would actually know how to order a genetics test.

The issue of ignorance in laboratory medicine, the appropriate use of laboratory tests, transcends the genetics issue. It is a core issue. If you look at medical school curriculums and clinical pathology, it is frightening, horrifying, disgraceful.

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If you as a group, I just don't think you can underestimate -- I doubt the average practicing physician at a fine academic medical center would have understood my hurried explanation of predictive values, because they wouldn't know a predictive value if it bit them in the nose.

So this is an area that is replete with opportunities for improvement. Genomics or genetic testing would be a great way to start. I certainly hope that if you made recommendations to fix this problem, you wouldn't stop there.

DR. WINN-DEEN: Okay. I think that's probably a good place to pause for our break.

(Laughter.)

DR. WINN-DEEN: You know, if people feel the need to talk further with Steven and Allen, they are there. Before they escape out the door, we can probably get a few more questions answered.

We're going to take a 10-minute break and be back at 10 to 11:00.

(Recess.)