

Update from FDA
Allen Rudman, Ph.D.

DR. RUDMAN: Maybe I'll come up there and present.

DR. WINN-DEEN: Do it from wherever you're comfortable. If you're comfortable where you are, you can just say next slide, and they'll do it.

DR. RUDMAN: I'm going to go through these very quickly. This is actually a subset of the slides. We're going to go through them very quickly. Part of this is you'll have the documentation here, so you can go back and review it.

I'll start off with the FDA's mission. It is really to protect and advance public health by helping to speed innovations and make medicines and food more effective, safer, and more affordable. This is really reflected in the critical path initiative.

Next slide. Thank you.

Towards that end, there was a publication, "Innovation, Stagnation: Challenges and Opportunity on the Critical Path," that was issued under Dr. McClellan and Dr. Woodcock. This kind of gave the overarching description of really this initiative.

In addition to that, there was an NCI and FDA joint program to streamline cancer drug development developed by Dr. McClellan and Dr. von Eschenbach, who is now in the FDA. Towards that end, one of the goals was developing markers, biomarkers, for critical development in evaluating new cancer medicines.

This is in November of 2003. A draft guidance came out, genomic data submissions, which created a whole new paradigm for voluntary genomic data submissions. What the FDA had found was really we had not received a whole lot of genomic information from the industry, although we knew what was going on. We had anecdotal information indicating there was a lot of research going on, but we really had no access to it.

The companies were not submitting it as INDs, NDAs, so we knew there was something coming up. The question is how to get that information and work with it, and figure out how to deal with it for the future.

Towards that end, we created this whole process. It really formed around the interdisciplinary pharmacogenomic research group. The goal here was to get companies to submit to a voluntary or required genomic data submission, track it, meet with the companies, find out what they're doing and why, process it, and then there were three major goals.

One was kind of public feedback. Conferences, workshops with industry, with the public, NIH, and so on. Data knowledge, and leading to guidances and policies. How do you know when to get the information? How do we work with it? What do we do with it? And finally, education, both internal to the FDA because there is not a whole lot of mass there in terms of education, and also external.

This was all under the construct of the Critical Path, really.

The IPRG, I'm going to use that because otherwise we are going to be here more than 20 minutes, was created, and it represents representatives from the entire FDA.

Along with that there is a group called the Pharmacogenomics Working Group, which is actually just located in the Office of Clinical Pharmacology and Biopharmaceutics. They have numerous activities, and I'll just briefly go through them.

One is the actual view of genomic data submissions, of which we have a large number now. I'll go into that a little bit later. Required submissions, consults, policy development, which Dr. Gutman just mentioned about the drug/device combination concept paper, education, both internal and external, research. There is a CRADA on biomarker validation, clinical trial protocols, how to design them, analysis of labeling, Pgx, pharmacogenomics.

There is a research grant out there, I am the principal investigator for that, looking into putting all this information, there are actually over 50 labels out there containing pharmacogenomic information, but some of it is more useful than others, and we're really trying to put this together as a useable database.

Finally, there is the information technology area. The FDA is developing software. RateTrack is one of them. We are also looking at database development. How do you get to use this? This goes to the question of knowledge management.

This is a slide of the IPRG organization. You'll notice at the top it's really driven by the FDA. Actually, that's the main message here. This is not a CDER initiative or a CDRH. It covers all the centers that are relevant. NCTR, Office of the Commissioner, CDER, CBER, and so on, and then there is a whole organizational chart.

The chair of the IPRG is Dr. Felix Freuhx. It has center delegates at a fairly high level, division office director, that type of thing. Then there is a whole series of activities associated around that.

I'm not going to spend a whole lot of time on this. There is a whole process involved in this, which you could find on a website.

The guidance was actually finalized in March, 2005. We have received 23, 24 today, we received another one yesterday, voluntary genomic data submission requests, and have scheduled to hold 12 already. These include two joint FDA European Medicines Evaluation Agency meetings, briefings, joint meetings. I'll talk about that in a few minutes, including multiple VGDSs and different drugs and follow up submissions on the initial study.

So companies are coming back to us with follow up information, and coming back to us with the different types of submissions, which is actually very helpful and very useful. It really tells us that we're doing something right.

We expected to see a lot of cancer drugs, and we saw that. But as you can see, we have seen a lot of genomic information, a lot of different areas, including different types of cancer, Alzheimer's, hypertension, hyperglycemia, depression, obesity, and rheumatoid arthritis.

We have also seen a lot of discussion on a lot of different areas. I think this is probably not as clear. One is the whole question of biomarker development. But then we get into the questions of genotyping devices, microarray analysis, validation, analysis software, the assumptions under

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them, databases, metabolic pathways, biostatistics, and enrichment design, clinical designs and clinical protocols.

This is a fairly broad, fairly comprehensive discussion, and it covers a lot of areas. It's actually changing the way the FDA looks at how we do things.

A little bit about the harmonization. Most of the large pharma companies are global. This is really becoming more and more important, this joint effort and consistency among both Europe and the United States. Eventually it's going to be Europe. I think there are initial meetings now scheduled for ICH.

On May 17th we had our first joint FDA/EMEA, that's European Medicines Evaluation Agency, meeting. It was by video conference, obviously being the London and Washington area. As you might imagine, there's a lot of preparation involved in this, including the list of questions that we are really being asked about.

So there was a lot of interaction before the meeting, including in-depth scientific evaluation, sponsors questions and information, dialogue between the FDA and EMEA. We obviously operate under different regulatory environments.

We are very fortunate, the sponsor provided excellent presentation. It was really a good discussion on a lot of different issues, including registries.

One of the novel things about this is we are issuing joint minutes on these voluntary genomic submissions. Just as important, maybe more important, is that the FDA and EMEA evaluated with only minor differences the submissions. Nobody had done this, so we really weren't sure what we were going to hit on this, but it turns out, at least in this case, we were fairly consistent.

We both had to adjust our usual format. EMEA actually, apparently this was one of the first times they had issued written comments to the company. Very positive response, and clearly it is the first step towards harmonizing.

I should add there are three more meetings scheduled, being scheduled. One of them definitely in December, and then two more next year, in 2006. So this is a fairly positive development.

Another area is what do we do with all of this information? Part of it is obviously we issue guidances and concept papers. This is the list, I'm not going to go through this. You'll find these on the genomic webpage. If you go to that, there's a lot more information. I'll give you that information, where to locate that later on.

This is not just the FDA, really this is about building a process with the industry, academia, and NIH. There have been a number of different workshops, public workshops I should say. It started off in 2002 with Workshop #1. That's what they named it. Creative. What am I going to say?

Then there was a draft guidance on genomic data submissions. This has been followed by a whole slew of other workshops, including the FDA/DIA Pharmacogenomics Workshop #2. This is where we really discussed the draft genomic data submission guidance. I actually got a lot of input. This is all done with PhRMA, BIO, the Pharmacogenetics Working Group, which is a collaborative organization, and others.

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In 2004, there was a meeting on the co-development on drugs, biologics, and devices, and AdvaMed was a cosponsor, along with the MDMA. It was a docket to get comments, and we received quite a number of them. Actually, this fed into the concept paper, and ultimately into the guidance.

This year there was a third workshop in a series optimizing the benefit risk of drug development therapy. As you see, coming along more and more, this has been coming from the research side into the regulatory side. Again, it was with PhRMA, BIO, the Pharmacogenomics Working Group, and a lot of others.

Finally, just this October 6th and 7th, we had another workshop on the application and validation of genomic biomarkers for use in drug development and regulatory submissions.

I'm going to talk about this. Why don't I just go to this. If you liked the handout from DIA, these are some of the topics on keynote addresses. I'm not going to go through this, except to say it was well attended, over 200 people, people like Dr. Woodcock and others, talking about really where this is going. Ultimately pharmacogenomics kind of is part of the whole biomarker question, which probably proteomics is next in the line, imaging, and so on and so forth.

But how do you do this? How do you actually get to the stage where you can actually implement this? What do you actually need to do to validate these? So if you look at the topics that we've covered, safety biomarkers, efficacy biomarkers, I'm sure that more and more we're getting toxicogenomics submissions into the VGDS process. That's the one that you received yesterday. So more and more we're receiving large amounts of toxicogenomic data.

Update on the HL-7s, the definitions. As it turns out, that's going to be very important. Even the use of the word "validation" is apparently somewhat controversial.

Electronic Submission Working Group. Standards for developing safety and efficacy biomarkers, validation of these, introduction of how do you actually introduce these into the drug development process? What are the regulatory implications of it? Developing and validating genomic biomarkers, databases and so on. You can read it.

This is kind of like an overview. I like this slide, it puts it into a context rather than just listing all of these, about where we are and how we are doing. The big arrow is really you can use it in a number of different documents.

It goes from basic research to FDA approval, and all the different steps in between. There are a number of different versions of this. But if you look in the bottom, these arrows, actually it turns out this is really what we're talking about.

When you start doing the analytical validation, what does it consist of? How do you do it? What are the criteria? The preclinical feasibility, the clinical validation, and also the clinical utility? The fact that you have a test doesn't necessarily mean it's going to be useful for actually public health reasons.

At this meeting, actually Chris Webster from PhRMA, who works for Millennium, presented this slide. I thank him for this. He announced that PhRMA is going to propose a consortia on biomarkers. You can read it for yourself. The goal here is to expedite biomarker development. They are expecting, hoping actually, that the FDA and NIH will participate, as well as a lot of other organizations.

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We are looking forward to this. We actually don't know a whole lot more than what you see there, but obviously this is an important outcome of the workshop.

Finally, concluding remarks. One is I think the VGDS and pharmacogenomics programs at the FDA have been quite successful. FDA has been a regulatory lead in numerous areas, including guidance development, analysis of pharmacogenomic data, international collaboration, and obviously the workshops.

The VGDS submissions have provided FDA with really a wealth of significant genomic data and information and numerous therapeutic, scientific, and technical areas which would otherwise be unavailable. So in that sense, the guidance really was successful.

The pharmacogenomic research needs to be seen in the context of biomarker development and validation, as well as disease management to expedite the approval of new drugs and indications.

It is not just about finding the drug, it is actually getting it to the public. It has to go through the FDA really to do that, and the need to provide the FDA and industry can readily analyze which expedites review. This is about not just finding the biomarker, not just increasing public health, but how quickly we can do this. How quickly we can get these drugs to the market.

I would like to add FDA does not develop drugs or pharmacogenomic tests, but it can encourage them to be developed. Finally, I would encourage this committee could help as a group by recommending the formation of a task force to develop national standards for pharmacogenomic assays. Thank you.

DR. WINN-DEEN: So I want to thank both of you very much for your --

DR. RUDMAN: And finally, there was a website.