HHS Efforts and Future Directions in Pharmacogenomics
Felix Frueh, Ph.D.

DR. WINN-DEEN: We're going to have the three HHS group talks, and then we'll have a sort of open Q&A to all of you at the end.

Next on our list is Felix Frueh, who we met informally earlier today. We called him up to answer some questions on FDA. He's going to talk to us about the specific efforts within FDA to develop guidance documents in this area.

We apologize in advance for putting you on the spot for all things related to FDA and CDER, but you're the chosen victim, I guess, or the sacrificial lamb.

DR. FRUEH: Well, I would like to thank the committee for giving me the opportunity to present an update on FDA's guidances as they relate to pharmacogenomics.

It was funny. I was three days ago presenting at a targeted therapeutics summit, and the person that introduced me had a graphic of sort of all the stakeholders who have an interest in pharmacogenomics shown in a circle. At the bottom, with the writing upside-down, were the regulators. Then I saw Dick today showing a slide again where the FDA was all the way at the bottom. I was quite surprised, actually, that Eric then show the slide where the regulators were on the top. So I think we're making progress.

I'd like to give you a little bit of an update on what's going on. The role of the regulators. Pharmacogenomics was identified in the critical path initiative at the FDA as one of the key opportunities on the critical path to new medical products. What we need to realize is that this is really a play of two partners. It's the drug developers, and it's the device companies or the creators of devices that need to work together. So pharmacogenomics combines drugs, drug therapy, with diagnostics, and the regulation of both need to adequately reflect this thinking.

I think FDA made it very clear over the past couple of years that we take pharmacogenomics seriously, and we have put forward a series of guidances that illustrate the current thinking that we have in the field, and I would like to go into this. This wasn't meant to be read. This was just to illustrate that we have a website up that deals with genomics at the FDA at which you'll find all the information, the guidances and additional background information that we currently have. The talk is going to be split into basically three sections. I'll talk on the pharmacogenomic data submission guidance that was mentioned earlier. We'll talk about two device guidances. Then I would like to combine these two aspects into drug test co-development guidance, or a concept paper as it is now, that was also addressed earlier today.

Earlier in March of this year, after about an 18-month gestation period, guidance for pharmacogenomic data submissions was published, and we've gotten since a very good response from industry to it. We continue to receive comments to the guidance which are very useful.

Why is this guidance important? The guidance does a couple of things. It illustrates the FDA approach to review of genomic information, so it should facilitate review decisions. It's a guide to drug development. It empowers the FDA to make drug development more efficient, and we provide several news ways for how to interact with the FDA. It's a means for fostering targeted therapy. It's also a new communication tool. It's an encouragement to share information on a voluntary basis for the first time with the FDA, and we have again gotten very good feedback on that, and I will go into that in a minute.

It's also an outreach to stakeholders that have expressed great interest and support in this guidance. So it really was a guidance that wasn't just showing up somewhere on an FDA website, but it actually has made headlines also in the lay press. So it was a very powerful tool for us to start communication with stakeholders that otherwise wouldn't have gotten involved in that dialogue.

The guidance introduces a classification of genomic biomarkers, as mentioned before. It clarifies what type of genomic data needs to be submitted. It introduces a new voluntary submission pathway, and it encourages industry to use it. So it's not a guidance on just a voluntary part, but it really shows how genomic information can be conveyed to the FDA and, if one desires to do so, on a voluntary basis for a certain type of data.

It introduces a new agency-wide review group, the Interdisciplinary Pharmacogenomics Review Group, and it clarifies how the FDA deals with the data.

The guidance does not provide information on how to validate genomic biomarkers. It does also not provide information on how to use genomic biomarkers. We limited the guidance with intention to genomics at this point, although if you read the guidance and you replace the word "pharmacogenomics" with "proteomics" or "metabolomics," I think many of the concepts, if not all, would still apply.

I mentioned that the guidance addresses not just voluntary data but also requires data submissions, which is the main focus of it. Most importantly for industry is that it does not create new processes for the review of data submissions. So it uses the existing framework that we have and puts the genomic data in that existing framework.

The voluntary data submission pathway is a submission pathway for what we call exploratory data, regardless of whether or not that is part of an existing or an active investigational new drug application or a new drug application. It's intended to build expertise and the foundation for developing scientifically sound regulatory policies. So we want to lure them with these submissions.

It creates a forum for scientific discussions with the FDA outside of the regular review process. The data that we discuss in that voluntary forum is not being used for regulatory decisions. So it's really an interaction between the scientists at the FDA and the scientists at the industry or at the company without the regulatory overhead that usually persists in FDA-sponsored interactions.

We received the first submission in March of '04. We have about a dozen submissions received since. Several more have been announced. So I would say the program is well underway and it's been successfully started. We have an evaluation of pretty complex raw data, such as microarray data, that we are engaging in, and the dialogue along with that evaluation has been critical to understand and learn what they're doing.

I think the success is illustrated also by the fact that the two companies that submitted the first two voluntary submissions are actually coming back -- one of them already has come back, the other one has announced -- with a follow-up submission. They've been doing some work in the meantime and they want to get our input again.

It's also been an outreach already into other geographic areas. We've had the first meeting with the European regulatory agency in May of this year, and the Europeans as well as Japan have published pharmacogenomic guidances. The interest definitely is growing.

CDRH has issued a guidance on the instrumentation for clinical multiplex test systems. We're moving now to the device arena, which is a device -- and the definition here is coming from the guidance -- a device that is intended to measure and sort multiple signals generated by an assay from a clinical sample. It's used to the specific assay to measure multiple similar analytes that establish a single indicated diagnosis. So it's really targeted at what we've been hearing a lot about, the microarray field, and for giving a specific example, the AmpliChip.

Now, these technologies are a two-component system. So the second CDRH guidance talks about the actual device and not just the reader, and this specific guidance goes into detailing and providing information on such devices that are intended for use in testing DNA to identify the presence or absence of a human genotypic marker. The device itself then is used in an aid in determining the treatment choice and individualizing treatment dose for therapeutics.

We've seen that before. The point I want to make here is that this really for the first time has set a new paradigm in how FDA is looking at such devices, because these are multiplex devices, these are highly complex devices, and we no longer have the option to just look at every single data point itself but we need to look at it in a combination, and with the complexity comes a new challenge on how to review these devices.

For the three bullet points, we've heard a lot about them this morning, so I don't need to go into the detail of that.

Now, if you want to put it all together, we need a strategy to combine devices and drug development process, and in April of this year we published a drug/test co-development concept paper. The comment period for it is still open, and we're planning on issuing a draft guidance on this later this year.

What this concept paper does is really put into perspective a couple of things. If we're talking about biomarkers, we have in the basic research arena the identification of the target, the target validation, and then we move that biomarker along the drug development pathway all the way to what is hopefully an approval. The critical aspects are that early in the process we consider the label based on the marker status, and we visit that often during the development pathway so that we have a label that reflects what we actually see in clinical trials. So that clearly becomes a strategic issue for the company developing tests and drugs simultaneously, and we touched a little bit on this earlier this morning.

What is critical in this process is that this is an interaction between the device area, CDRH, and the drug development area, CDER or CBER. This again puts in perspective what is going on during the drug development process and provides tools and information to exchange opportunities between sponsors and the FDA, and if we're talking about the strategy for how to do these things, I think it's critical to overlay these so that we have a smooth process for how to develop drug/test combinations.

The voluntary submission process is a process that can be used throughout the entire drug development pipeline to discuss novel and exploratory findings that perhaps at some point might actually help in the area here to identify novel biomarkers and characterize them.

The benefits of this approach are, I think, obvious to us. We can use it for patient stratification. So that's an efficacy as well as a safety issue. We can use it for enrichment purposes in clinical trials. The labeling becomes a critical component of it, and it can be crucial for a company to bring the product to the market. I think the example of Herceptin really illustrates that only in the presence of a targeted therapy, the product could be approved. It has the potential to save drugs from being withdrawn from the market, and it can also potentially rescue candidate drugs that otherwise would be stopped in the drug development process.

Strategy, competitive advantages, timing, cost, availability of alternative therapies, the platform choice, and the complexity of the platform itself are all critical issues that need to be addressed during the process. Ultimately, whatever is coming to the market needs to be clinically useful. Otherwise, why develop it in the first place? Often that's actually the bottleneck. So showing the clinical usefulness for the drug/test device at the end is critical.

In summary, the FDA encourages the use of pharmacogenomics and provides a series of tools, such as the guidance documents, meeting opportunities to support the translation of pharmacogenomics into clinical practice. The combination of drug therapy and the use of devices is critical, and we are developing our guidances with this in mind. Pharmacogenomic data submission guidance, the one that was issued in March of this year, has been well received and is currently being successfully implemented, and regulatory agencies around the world are interested in pharmacogenomics, and I think it's fair to say that the U.S. FDA is really leading the way on how to do this.

I would like to thank my colleagues in CDER, CBER, CDRH, and in particular Drs. Janet Woodcock, Robert Temple, Larry Lesko, and Steve Gutman, all of whom have been really visionary and critical in making all this happen. This is the address for the website where you can find all these documents in writing. At the end, I put up a couple of questions for the committee for perhaps the discussion that we have at the end of this series of talks.

Thank you very much.

(Applause.)

DR. WINN-DEEN: Thank you.