FDA Draft Guidance for Industry and FDA Staff on Pharmacogenomics Tests and Genetic Tests for Heritable Markers
Steve Gutman, M.D., M.B.A.

Dr. WINN-DEEN: I'm going to turn the podium over now to Steve Gutman, who's going to go through and give us a short update on the FDA draft guidance for industry, which you also have at the very back of tab 6. Sorry. I should also say Steve's slides are in your table folder, if you want to take notes on that.

DR. GUTMAN: Good afternoon.

As Emily indicated, the Critical Path Initiative remains a very important work product at FDA, and that initiative is aimed at the notion that FDA should, in a proactive way, work to remove obstacles from the critical path to bring new cutting-edge medical products to the marketplace.

In the original white paper that Dr. Woodcock actually sponsored about two years ago, biomarkers figured prominently and, in fact, were explicitly mentioned several times. It's not your father's Oldsmobile anymore. Biomarkers were for the purpose of diagnosis, but in fact, there was what isn't a completely revolutionary but a somewhat revolutionary construct that biomarkers might actually be very important in the development in the early life cycle of selecting drugs for development.

In fact, recently that critical path has been reconfirmed. There's been a lot of publicity from the agency about a collaborative partnership with a nonprofit group in Tucson called the Critical Path Institute, and there has, in fact, recently been the publication of an opportunities list which, if you'll look at it, would demonstrate that we are either very broad, very catholic in our thinking, or perhaps a bit delusional --

(Laughter.)

DR. GUTMAN: -- because it's very extensive and there's something there for everyone. I urge you to search for those.

My work group, OIVD, the Office of In Vitro Diagnostics, is frankly a small cog in a very large wheel, but we do have a real passion for this work and that passion's most recent outpouring is in the presence of the guidance document, which you all have and which is also available on the Internet.

That draft guidance was published in February of this year. There is a 90-day formal comment period, so we're about halfway through the comment period. In fact, if you look at the guidance, it will explicitly tell you where to comment, and we are, fact, very anxious to get comments, very anxious get either general or specific comments to ensure that that document is all that it can and should be.

To recap the history, FDA first issued a broad document on multiplex testing in February of '03 and did, in fact, get very lively comments on that document. Perhaps the most recurrent theme or leitmotif in those comments was that that document may have been too ambitious and may have been overreaching and that we might do well to break that into two pieces to try and maintain some immediate focus and then to go for the more garden variety test -- I hesitate to use the term because there's nothing at all garden variety about this testing -- and then to worry about very

complex permutations of tests and complex proteomics and perhaps microarrays, and particularly expression microarrays a little bit further down the line. We have taken that advice.

If you look at this guidance, there are several things that might strike you. One is it is a draft guidance that has been reissued as a draft guidance because we do think there has been so much substantial change. There has been a narrowing in the focus. We haven't forgotten the expression array part. We did what we could do and now we have to start moving on towards the even harder stuff.

We're from the government, but we're willing to take help if there's anyone in the other public or private sectors who would either like to write a first draft, write an outline, or provide any support, intellectual or written.

The purpose of this draft guidance is explicitly noted in the up-front introduction, that we're trying to help shorten development and review time lines by creating a road map for sponsors and creating a certainty in the kinds of data expectations that we're likely to put on the table when we see a new product. We obviously are very anxious to facilitate rapid transfer of new technology from the research bench to the clinical lab, and we are actually anxious to do what we can do, not as a primary educational but certainly as an agency that's interested in risk communication and safety communication, to encourage the informed use of pharmacogenomic and genetic diagnostic devices.

The guidance is directed at our usual clientele, manufacturers, particularly the diagnostic companies that know and love us and that are traditional submitters, traditional sponsors of new diagnostic devices, and of course, the FDA review staff. That's explicitly noted up front in the title. But, in fact, it probably has a broader audience than usual because there is a lot of development and a lot of interest among venture caps. There's a lot of development and there's a lot of interest among pharma companies. And these will tend to have less knowledge base about what a diagnostic is, what a diagnostic regulatory pathway might be. So this is actually also geared towards rather nontraditional sponsors. And last and perhaps not in the least bit least, this is directed at academics, at government researchers, at entities that might be funding translational research, so that they might have some target for how they might spend their time and spend their money.

Among the key elements, first and foremost, is intended use. Any of you who've heard me talk about our regulatory process over the years of the life of this committee will know how important and how passionate intended use is for us. It is, in fact, the basis for our entire risk calculation. It drives everything about the review process. Intended use will determine the kinds of risks we would attribute to a device. The intended use will determine the regulatory threshold, we would expect, needed to bring a device to market, and the intended use will, frankly, dictate the kinds of data that we would expect to see.

So we've clearly posited the importance of intended use and the options. We frequently suggest that people be relatively non-ambitious and look for focused and clear intended uses. We've indicated the need for explaining to us the clinical purpose and the target population for the new product.

And then we've acknowledged -- we've not solved -- the challenge of addressing the issues of rare events, the issue of low prevalence of some disease processes, and defining performance for predictive tests if the entity that's being predicted, if the outcome that's being predicted, in fact, is

occurring far in the future, how challenging that will be to sponsors and how challenging that will be to us.

The document goes on to describe device design and to explain the kinds of questions we will likely be asking about the device design. This is not rocket science, but it's also not for amateurs. We are looking for information that will describe what the device does. We are looking for information on samples, for information on methods, and for information on controls.

A good FDA review, of course, would be nothing without a preoccupation with the analytical performance of the assay, and so we're likely to ask about the core studies that demonstrate analytical performance, look at issues of accuracy, look at issues of precision, look at issues of specificity, when appropriate, look at issues of levels of detection or measurement, and of course, look at cut-offs.

We are interested in putting on the table in a clear, forthright, and on the front burner the important issues of the mechanisms of software and instrumentation that will drive the methodology at hand.

We are very interested in the clinical performance as well. As you know, for many analytes, for common analytes, for analytes like hemoglobin or like sodium, we actually allow extrapolation from analytical to clinical use with relatively great facility. It would be absurd for us to take a new submission for hemoglobin and ask the sponsor to please demonstrate that it's associated with anemia. That might not be true with the new Steve Gutman gene. We might be very interested in understanding the eccentricities with which it is associated, and we're likely to ask all kinds of nosey questions.

If you look at this document, you will notice that it would be kind to say the clinical section is a bit laconic, that it's terse. It references itself in the STARD initiative, so certainly it uses what I would characterize as the fundamental, most important road map of modern laboratory diagnostic science. So if you don't know the STARD initiative, please look at it on the Internet.

It also defers a bit to the concept paper on co-development of drugs and diagnostics, which has very detailed sections on clinical performance, both the clinical validity and the clinical utility of the test. That guidance document is under revision and I think we'll probably, in some more clear and comprehensive way, chart various options for the clinical characterization. The concept paper is not a bad starting point. If you haven't looked at the concept paper, please do and particularly look at appendix C and D, if you're interested in issues related to clinical performance.

Then last, but again not least, what would a good FDA review be without obsession over labeling and truth-in-labeling, and that labeling includes all of the parts of our Code of Federal Regulations starting with intended use and ending with communicating the appropriate performance parameters.

FDA has a fairly comprehensive program that it brings to the table when it does regulate any medical device, certainly an in vitro diagnostic medical device. It has a comprehensive device authority for ensuring minimum data and labeling thresholds are met prior to marketing of a new diagnostic. It has quality system regs to assure that there's consistency in the manufacture of that product over time, and it has both mandatory and voluntary reporting obligations that it puts on laboratories or on health care users so that if something goes awry, the FDA can hopefully

collaborate with the sponsor to fix whatever what's gone awry. Of course, if the company is not as enthusiastic we are, then we will coerce the company to fix what has gone awry.

This guidance document is now joining an arsenal of other interesting guidance documents, all addressed in many ways towards this same fundamental issue, the issue of co-development. The voluntary genomic data submission -- the primary ownership of that product is in the Center for Drugs, but it is shared by us, and that either pharma or IVD interests, in fact, do have -- I know you're not supposed to use the term, but I'll use it anyway -- a safe harbor in which to explore interesting data very early in the life of a product to play, to inform themselves, to inform FDA, or to create some increased certainty about what regulatory and scientific options might be on the table.

We have a, I think, probably too long, but nonetheless very well-intentioned and very nuanced and very -- I'm highly biased because I was very involved in drafting many sections of this, and I have colleagues who were very involved in drafting many sections of this. But we have a concept paper on the co-development of drugs and diagnostics, which isn't quite on the mark, but has many treasures in it and is an interesting starting place.

We have also snuck in along the way a very nice statistical document for test method evaluation that explains core issues like sensitivity and specificity and tells you what to do when you can't find a gold standard. So it's also a treasure.

In terms of our next steps, we do intend, hopefully with input from the public, to continue to develop and publish guidance documents to clarify regulatory routes, that we continue to promote informal or formal early interactions with sponsors so that we can clearly understand what's coming in the pipeline, we can clearly make sure we have the requisite expertise. We turn to other Federal agencies for requisite help, that we make sure that our panels have the appropriate scientists to provide the scientific grounding we may need for cutting-edge diagnostics. In CDER, they have the voluntary genomic data submissions. In my center, we have what is called a terrible name. It's called the pre-IDE. What that means is a protocol review.

Now, a pre-IDE is about the only work product we still offer that's free, and we ask companies to bring in their protocols, hopefully before they've started their studies. I use the example that the protocol in the pre-IDE process is a little bit like a pop quiz except we give you the questions ahead of time. The companies get to answer the questions ahead of time and submit them so we can tell them whether the answers are right or not. In fact, if the companies don't like particular questions, we can argue about it before rather than after the study has gone on, and we can clarify where we agree and where we disagree and, if nothing else, try to make the pop quiz not at all a pop quiz, but in fact a very well-defined path to market that will allow us to work quickly and allow the company to work quickly and allow us to reach what I believe is our mutual goal, slightly different perspectives, but mutual goal to get good products onto the market quickly.

We continue to look for ways to better communicate our existing regulatory requirements. As you know, as I've said at this group before, we do have a dual mission to promote public health and that's by getting good products out quickly, to protect public health. That's by ensuring that the products are properly labeled and, in fact, if they're bad products, they never make it to market. There is a tension in these dual goals, and we attempt to address that through good science and by maintaining regulatory focus. It would be my view that if we do maintain the right regulatory focus, you can take us off the table, but you can't take the table away. And so the pesky questions we're likely to ask will still be in the room.

Thank you.