Developments at FDA
Steve Gutman, M.D., M.B.A..

DR. TUCKSON: Let's start with Thomas Hamilton and Judith Yost. Steve is going to go first? Do we want Steve to go first?

In that case, we're going to turn to Dr. Gutman. You may recall that Dr. Gutman's last presentation to us was in March when he reported on FDA's Critical Path Initiative and the agencies efforts to facilitate getting cutting-edge medical products to the marketplace. He described FDA guidances on pharmacogenomic tests that were released in February of '06.

Today, Steve will clarify the current regulatory paradigm at FDA related to oversight of genetic tests and tell us about some additional guidances that FDA has issued on this topic.

Steve, please proceed.

DR. GUTMAN: I'm going to describe. I'm not sure "clarify" is the right word. FDA has been involved in the regulation of medical devices in general, and of in vitro diagnostic devices -- that's our co-term for lab tests -- in particular since passage of the Medical Device Amendments of 1976. Those amendments introduce for the first time a variety of general controls for lab tests, including requirements for companies making them to registering their products, to follow good manufacturing practices, and to report adverse events.

As a result of those general controls, for the first time in our history we had a menu of tests on the market. We had mechanisms for showing that companies produce those tests consistently following good manufacturing practices over time, and we had mechanisms for assuring that companies that experienced or identified postmarket adverse events would report those events to FDA and then hopefully collaboratively, if necessary coercively, we would work together to resolve whatever had gone wrong. That entire regulatory framework was based on a risk-based regulatory process.

The 1976 law also introduced for the first time in the U.S., in fact for the first time on this planet, a requirement for premarket review before a new medical device could enter the marketplace. Although that review occurs in very different kinds of administrative packages, there is a common core in our interests. That core is demonstrating that the test is analytically reliable. I would argue that until analytical performance is locked in, you are playing in a sandbox with no sand. For some tests the story might stop there. For hemoglobin we don't generally ask that you demonstrate clinically that hemoglobin is associated with anemia, but for a new genomic marker of unknown significance we might be quite interested in understanding what the clinical meaning of that signal would be. Then for all products we are very interested in labeling and ensuring there are adequate instructions for use, there's a clear intended use, that there's clear performance, and that the limitations -- and I've yet to see a test that doesn't have some either analytical or biological limitations -- are clearly limned.

FDA regulations, as Reed suggested, is not the only path for a new test to come to market. To try and keep Debra happy, I will try and use the term "laboratory-developed test" rather than "in-house" or "home brew" test. These are diagnostic tests created in a single lab for use at that specific lab. They have been called in-house or home brew tests. Use of a laboratory-developed test is, in fact, a very well established practice, that there has historically been a broadening of tests fielded off of this particular practice.

But it's not an entirely trouble-free practice in that there are differences between the regulatory route for the product that visits FDA and for the product that doesn't visit FDA. Some of the differences are that for the product that is developed as a laboratory-developed test, there is no requirement for discrete premarket review, there is no specific separation or segmentation between the research phase and the clinical phase of product use, there is no prohibition against demonstrating clinical validity but there is no explicit requirement for clinical validity, and the outcome of those differences result in some very colorful players. Anyone who hasn't looked at the recent GAO report that was described at the Congressional Committee for Aging might want to go on the 'Net and look at those to see at one extreme some of the very colorful players.

In 1997, the FDA published an analyte-specific reagent rule. It was viewed by us as an incremental change or increase in our regulation of laboratory-developed tests, although it was defined as a down-regulation, since by default analyte-specific reagents -- and we define those to provide an actual comprehensible English definition of them, but I would characterize them as the building blocks or the active ingredients of the laboratory-developed test. We define those as tests that were subject to regulation, and the regulation was a requirement for general controls such as registration and listing, good manufacturing practices, adverse result reporting, but we drew back from requiring general premarket review.

This was not an accident. The analyte-specific reagent rule was deliberately developed to create a safe harbor for laboratory-developed tests to create clarity to allow this practice to go on unimpeded, but to go on with some increased quality because we were trying to care for the building blocks themselves, and also increase transparency in that there were some labeling requirements which said I am a home brew test and FDA doesn't have a lot to do with me. It's crafted a little differently than that, but that's what it's saying.

I suppose if there's anything startling, if you go back to the preamble to the ASR rule, it codifies the fact that in spite of the ASR rule, that FDA did have, in fact it always has had, although in some cases it's been rather silent, perhaps notably silent, it's always had the belief that laboratory-developed tests are in fact within the definition of medical devices, and that laboratories creating those tests are in fact within the definition of sponsors or manufacturers, and all of these are subject to FDA jurisdiction under the 1976 act.

The ASR rule was a very well-named rule. I know and love and was in fact one of many authors who tried to get it right, but it had some surprising and disturbing unintended consequences, and that was that as a follow-up to that rule there was either inadvertent or perhaps in some cases deliberate abuse of the rule in that what people began to do is to take essentially what were either kits or large pieces of kits and call them ASRs. So I say a kit in ASR clothing. To make decisions about test optimization that were intended to fall within the purview of the laboratory, companies began to do that, and to make implicit claims. So again, either inadvertently or deliberately, the ASR rule to a certain extent went right over a cliff.

The guidance in 2006 was intended to do nothing more and nothing less than to clarify where you fall over the cliff. It may or may not have perfectly and brilliantly clarified it, and we are anxious to get input, but we are very intent on not having people take kits, call them ASRs, and market them outside the construct of U.S. laws. So we are very interested in getting that right. So the intent of this document was to better clarify the definition of an ASR, the limitations on marketing of ASRs. From our perspective there is nothing new in substance, spirit or meaning. There may be something new in examples for this document.

This document is not intended -- and this is either good or bad news -- it is not intended to eliminate legitimate home brew testing. It's not a frontal attack on home brew testing, although it might be an interesting dialogue in terms of what FDA might construe as legitimate home brew testing. The labs, in fact, have the same responsibility in this document that they did when the rule was published, that they have to step to the plate and say I designed, I developed, I made, I validate, I stand behind this test. So that's the nidus, that's the intent, that's the spirit of the ASR Q&A guidances, and comments on those guidances close in the first week of December. We are exploring the possibility of at least a one-month extension.

It is very important to note that the ASR rule does, in fact, provide a Class I exempt status to the building blocks of home brew assays, but it didn't go any further than that. It didn't either help or hurt. It didn't provide benefit or provide harm to the laboratory test itself. The ASR rule by itself did not exempt laboratory-developed tests. FDA's action not to regulate laboratory tests remains grounded in the same history, in the same thread as a matter of enforcement discretion, not as a matter of legal exemption. I think there may be some folks outside the agency or within the agency confused by that.

So laboratory-developed tests can't use the ASR exemption. They can appeal or apply benefit from FDA's historic use of enforcement discretion. But, in fact, if you see anything, and the next guidance highlights it, it's that FDA is appreciating changes in laboratory-developed tests that makes the gap for at least some products more disturbing than it has been in the past. The lack of premarket review, the lack of a research to clinical threshold, the lack of parity, as a matter of fairness to various sub-constituencies in industry, the lack of discreet evaluation, and the lack of clinical validation for some assays, particularly novel and cutting-edge and high-risk assays in this wonderful world of 2006, are of interest, and FDA is honestly trying to reassess and do soul-searching in this area.

That, I guess, is startling to various constituencies in part because there has been a period of silence by the agency. All the things that Reed said I did in fact probably say at a previous SACGHS meeting. It's startling because it's an expression of authority, although I would argue that the document was hardly the most dramatic expression of authority. If you want the most dramatic expression of authority, you should go to the GAO minutes on the Congressional hearing on the aging where some nut started to express his authority.

The good news and the bad news is that this is actually not new stuff. This is old stuff. There's nothing new under the sun. That's what I try to tell my daughter at least, and she tries to tell me what is new and what I don't understand. Also, I must tell you that I've stolen this line from a conversation with Dr. Mansfield during our unofficial FDA catch-up break, which is that this is very much like a Dickens novel. You've seen the first chapter, and you haven't seen the last chapter, but assuming that FDA or assuming that I am working with Charles, the last chapter hasn't been written. So I do assure you that there's plenty of time for people to put great ideas on the table about what FDA should do, and there's still time to put on the table about what FDA shouldn't do. It would be better if the ideas put on the table addressed what FDA is worried about. To speak to any groups in any sector that are actually addressing those issues, that's good news for FDA.

The multivariate guidance is a specific example of a guidance that is fueled by FDA's concern that perhaps it wasn't such a great idea not to regulate all laboratory-developed devices, and that perhaps the blanket application of enforcement discretion is not a particularly brilliant public health move for all laboratory-developed devices. The IVDMIAs I think have been -- this document has been overread, because while it's clearly a signal, it is a much narrower signal than

I think the laboratory community or the community in general has appreciated. When we were thinking about the IVDMIAs that we were worried about and interested in, we were thinking about one dozen or two dozen products that might be percolating toward or on the market, and maybe this would be an incredible growth area in five or ten years. We weren't looking at dozens, hundreds or thousands of submissions. That never crossed our minds when we crafted this document.

But we were really worried about a growing category of tests that seemed to us not to fit Judy Yost's mold, not to be the kind of thing an average inspector, whether working for CAP and COLA or CMS would be able to actually assess and understand. Tests had produced novelty with new safety and effectiveness concerns and tests that we thought were very poor fits for enforcement discretion.

So we thought of this. We still think of this. Maybe we didn't communicate it right, or maybe we did communicate it right and it was misread, or maybe we didn't write it right. I don't know. We were looking at a narrow niche of devices, and those devices were devices that had the use of software-driven and software-derived, and I'm talking about complex software, algorithms or formulas, that those algorithms or formulas would take information and create a patient-specific score or index, and that a nominally trained pathologist or oncologist or cardiologist or neurologist would look at that index and say what the hell does that mean and wouldn't know what that meant unless he or she contacted the sponsor and essentially had someone color it in for them in order to explain what the hell it meant, and wouldn't in fact be able to second-guess it if their life depended on it. So that's what we really intended.

What we clearly did not intend was that all algorithms would fall in this category. We never imagined that. We didn't intend to go after all software. I do think there should be a bit more regulation of FDA in the area of software, but a lot of the software, laboratory information systems in general outside of blood banking, in fact only require software quality systems. They don't require premarket review at all. We're not interested in regulating things for the sake of regulation. The device, just because it's multivariate, doesn't automatically mean it's an IVDMIA. Of course, if in doubt, someone needs to chat with FDA. In fact, if we've accomplished nothing else, we've caught the attention of companies in this area and have begun triaging and making decisions about tests that actually don't deserve this designation and tests that, in fact, truly do.

I would argue that the novelty in this profile was intended to be different than for other laboratory-developed devices, and if folks think we haven't got that right, you can tell us in the first week of December, and we are working on an extension of a month. It's not a great analogy, but the analogy that I was thinking of was one where you have a cabinet with a combination lock, and you hand the cabinet and the combination lock to either the laboratorian or the oncologist, cardiologist, neurologist, infectious disease doc, whoever is going to use it, and if their life depended on it, they couldn't unlock the cabinet without the combination from whoever made the cabinet. So it was a very unique circumstance where a physician wouldn't be able to interpret that information by himself or by herself.

Whatever the scope, whether this turns out to be a few or moderate or I've underestimated it and it's many, we're not interested in regulating to death low-risk devices. So this was also risk-based, with low-risk products probably headed for exemption, moderate-risk products headed for 510(k)s and streamlined administrative review, and for scary devices that might make determinations about getting life-saving treatment or not getting life-saving treatment, those might deserve to be Class III products.

What does FDA regulation get you? Wherever we go and whatever tangled web we weave and whatever direction we go, it gets you independent assessment of data and labeling, it gets you a review that's informed by evaluation standards, yet grounded in the 1997 Modernization Act, which told us to be most focused on regulatory threshold and least burdensome, and if it's focused, good science is good science. So we're quibbling over administrative niceties here. I would argue that if the test is being used now, it's a question of the annoyance of regulation, of having to put it in the package and send it to me. If you don't have good science, then shame on you, and you ought to think about would I use the test in my mother, would I use the test in my husband or wife. And if the answer is yes, you're not going to have trouble with the FDA.

So our deal is to promote public health by getting good products out quickly. Our deal is to protect public health by keeping bad products off the market. We don't actually have the strongest laws in the world. Ours aren't quite as strong as in drugs, and very frequently we take very blemished tests and we label them. We do believe in transparency. If you want to see what our regulatory process is like, go to Google and type in not OVID but the reverse, OIVD, and we make all of our regulatory decisions a matter of public record. So if you want to know what we did with cystic fibrosis, with UGT1A1, with the Roche Amplichip, with the latest PSA test, all you need to do is go on our website. Everything we do, if we ask too few questions, if we ask too many questions, it's all a matter of public record and you are always free, everyone is free, and in fact lots of people aren't shy about telling us what we're doing well and what we're doing poorly in the way of premarket review.

We do like to think that our mantra is good science and that if our science is good, if our science is focused, you can get rid of us. You can get us out of the picture, but you can't get rid of the damn pesky questions we're wanting to put on the table. Thank you.

DR. TUCKSON: Thank you, Steve. Before you go, I notice that our colleagues from CMS are here, and we're going to turn to them in a second. Let me just ask you one thing, and then we'll open this whole thing up for discussion.

I guess I just want you to be as simple and straightforward as possible.

DR. GUTMAN: That's hard for me.

(Laughter.)

DR. TUCKSON: No, it isn't. You're the best person to ask this question. If we're sitting here as a committee trying to make sure that we are being attentive to our responsibility for thinking about issues that protect the public in this regard, and we're trying to figure out whether there is a gap that we should be attentive to, you and FDA, you get paid. That's what you do is protect the public in this regard. So this is all you guys do all day long.

DR. GUTMAN: We dream about this stuff.

(Laughter.)

DR. TUCKSON: You dream about this. So the question becomes, when you boil down your presentation about good science and good public health and yadda, yadda, yadda, at the end of the day do you consider from your perspective, does FDA consider there to be a gap or not that anybody should be worried about? Is the sum of your report saying all is well, return to your homes?

(Laughter.)

DR. TUCKSON: Or are you saying something different?

DR. GUTMAN: Yes. The problem as I see it is that there is a partial gap because the sector we don't regulate and the sector that Judy does regulate is very heterogeneous. So there are entities that do it very, very well, and there are people in that community that I would turn to if I had a question that I didn't know the answer to. There are people sitting at this table that if I had a hard submission I would be wanting to call them for advice. So when it's good, it's very, very good, and when it's mediocre, it's kind of mediocre, and when it's bad, it's really awful. So there is not a uniform gap. There is unequivocally in my mind a gap. There are a variety of ways to address that gap. FDA isn't the only way. I think FDA is not a bad way.

DR. TUCKSON: Steve, people are not smart about this like you are, and we're getting ready to have the CMS walk right up here. Would you please, with your expertise, define the gap? What is this gap from your point of view?

DR. GUTMAN: From my point of view there are three things. As good as CLIA, as good as CAP, as good as COLA, as good as JCAHO are, they can't go in in a credible way in one or two or even three days and actually figure out what's going on in the data. Judy has been too generous with me in terms of sharing validation packages and information from multiple endpoints, and I've seen a lot of bad data manipulated in odd ways from people who do it because they don't know, from people who do it in spite of the fact that they do know. So, one, there is a gap.

There is some value to independent data assessment and labeling. I think there's value added to that. The second is that this is a very competitive universe. I understand that both labs and companies are not like me. They're not against public health, but their bottom line is their stockholders. With labs, it's their hospital administrators. There are economic pressures that make their decisionmaking process different than ours, but I would say that there are differences in decisionmaking, and in the laboratory community there is a capacity that does not exist in the IVD community, which is after the first publication you can spring to life as a non-research test. All you need is that first publication.

Then the third gap is that I do think, and you can ask Judy or you can ask her boss, I do think there are differences in the law itself, in the reg itself, in the ability to go after clinical validation. I believe that we have that as a core principle, and I believe CLIA has that as a basic limitation.