Roundtable Discussion
Facilitator: Dr. Leonard

DR. McCABE: Thank you very much. If you could join us at the table.

Before I turn the floor over to Dr. Leonard, I would ask that we try and maintain the questions around the issues of regulation and labeling. Advertising is something we'll take up this afternoon and we'll have an opportunity to discuss that at that time. So for now, if we could focus on regulation and labeling.

Dr. Leonard.

DR. LEONARD: Thank you. This is Debra Leonard. I will take the chair's prerogative and ask the first question, and then if others want to ask, I know Emily has already asked me to ask a question.

This is directed, I think, for Steve or David. The data template that you referred to that you're now using grew out of the SACGT process with a direction to FDA to provide oversight for laboratory-developed genetic tests. You're now using this, I think, for IVD submissions and review. Is it your intent in the future to move ahead with the laboratory-developed test mandate of providing oversight?

DR. GUTMAN: What you see is what you get, actually. The template has no broader design. We loved the idea, we subsumed it into our review program, and we think it fits our review program nicely, so we're grateful. The plan right now is for the agency to look at the ASR rules. So the plan is for us to look at manufacturers and look at reagents, and there are broader schemes on the table but there are other parties involved. There's CLIA. There's still the possibility that professional groups may weigh in. So I'd like to suggest, at least right now in the incremental picture of things, we are looking at a revisit to the ASR rule.

DR. LEONARD: And does that involve the IVAT guidelines/documents that are out there? I mean, is the IVAT related to the revisiting of the ASR regulations?

DR. McCABE: Could you explain what IVAT is, please?

DR. GUTMAN: Yes. The manufacturing community has put a model on the table in which they're suggesting that our premarket review be based only on analytical performance and that the clinical issues that we often struggle with and the clinical signals either be addressed through truthful labeling, which is that they're not clearly known, or that that responsibility be assigned to laboratories.

The IVAT is actually under legal review, and it's hard to say that there's no relationship at all, but it actually isn't directly being plugged into the thought processes about the ASR rules. It could be, I suppose, but it's being treated as sort of a separate entity.

DR. LEONARD: Thank you.

Emily?

DR. WINN-DEEN: I wanted to ask Dr. Lesko a question about what you feel -- you mentioned

in one of your slides that before you required testing in a product labeling, that that testing had to be available. Certainly for 2D6, for example, there are commercial, CLIA-certified laboratories offering that testing. Does that mean that the agency doesn't feel that that meets their definition of "commercially available" and we're waiting for actual IVD products to be available? What is the thinking of the agency about tying the requirement or even strong recommendation for a test in conjunction with prescription of a drug?

DR. LESKO: To continue with the 2D6 test -- can you hear me? My mike isn't working, but I'm speaking into it. I think our preference would be to have these tests approved by the agency, including 2D6 and some of these polymorphic enzyme tests. I think the problem in terms of availability when you move from laboratory to laboratory is the alleles or polymorphisms that are being tested for. There are some laboratories, for example, that do offer a 2D6 test for identifying certain alleles, but it may be limited to, let's say, a *3, 4, and 5. On the other hand, if we had a new drug in development, we'd be much more interested in about seven or eight of those alleles, which would be the *3, 4, 5, 10, 16, and 17, because these are the alleles that predominate in the ethnic populations of Caucasians, Asians, African Americans, and Hispanics or Latinos.

So I think it's an issue of coverage. When we say available, it needs to be available so that the results are generalizable or extrapolatable to the population that's going to get the drug, and it doesn't help to have a test available that's only targeted to a specific group and excludes others, because the absence of a test then becomes the assumption that this individual would be the most predominant allele, which would be extensive metabolizers.

DR. WINN-DEEN: So could you handle that by just making specific recommendations that a test covering the following A, B, C, D, E alleles is recommended and allow the community to decide if that's an IVD or "home brew" from a CLIA-approved laboratory? Or are you still really thinking that the only way that we're going to really see this happen is through the IVD manufacturers stepping up to the plate and starting to take IVD kits into the agency?

DR. GUTMAN: Well, there is another choice, and I can't speak for CDER, but I know that CBER uses that, and that is when they're looking at a therapeutic trial and there's a home brew-linked diagnostic, because there is concern that they actually have insight into the diagnostic beyond what might be normally seen in the CLIA program, that CBER will frequently ask for information about the test. It's not quite like a CDRH device review, but it's probably a bit more information than might normally be seen.

So I don't know that CDER does or doesn't do that. I would encourage them, if they don't, that they probably should. In-house or home brew or a CLIA test comes with a wide spectrum of expertise, and when it comes from Debra's lab, I'm really, really comfortable, and when it comes from my old lab, I might be a little bit less comfortable. I can't quantitate that because I favor Debra over myself, but I can quantify that by saying, gee, you need to provide us information about the home brew test. It makes sense to support this product as a whole.

DR. LEONARD: I didn't pay him to say that.

(Laughter.)

DR. FEIGAL: There's already been one precedent, though, where a drug was approved that suggested a laboratory test for monitoring that was only available for several years from central labs as home brews, and that was therapeutic drug monitoring for FK506, a tacrolimus test. It took about three years for that test to become commercially available. So we've already sort of

crossed that bridge of having had a drug that was useful and a test which was only available from central labs and approved in that setting.

DR. LEONARD: Right now I have, just so you know and don't keep raising your hand, Reed, Ed, Brad, Barbara, Muin, and Francis and Arden.

Reed?

DR. TUCKSON: I'll try to be short. This is Reed Tuckson. This is in the same area that Emily Winn-Deen was sort of getting at.

Dr. Lesko, you presented a number of cases of drugs that it may make sense to have some more precise specificity of use if we could use a test that would give us that information. Steve mentioned cost-effectiveness as part of the FDA's mandate for this particular Commissioner. Do you see, then, the responsibility of the FDA, given how expensive drugs are today and how everybody is worried about how we're going to handle that, do you see a responsibility of the FDA, then, and can we expect the FDA to provide clear guidance around the use of tests to be able to better monitor/titrate/use expensive pharmaceuticals that will ultimately be a cost/benefit tool? And will you be clear as you all make your recommendations so that those who have to pay for all these things, pay for the drug and pay for the test, will understand that cost/benefit ratio?

DR. LESKO: No. I think it's a good point, but I guess I don't think of that as being part of the mandate that we have when it comes to testing. I think the way I would look at it is that the role of the test is based upon the level of risk management that it might bring to the table, so to speak. I think the decision to put information in a label is dependent on the clinical benefit that can accrue from using that test, or at least making that information available.

DR. TUCKSON: Well, if you've got that database and you're doing all those analyses, who in government, or where would you expect somebody else to reproduce that? If you're not doing that, who ought to? And if some other part of government is going to do that, or are you going to be able to make that stuff transparently available in the literature or in some other way so that everybody else can use it? Otherwise it would be redundant and wasteful, wouldn't it?

DR. LESKO: Yes. I think we have information that can be provided, but the decision on cost/benefit or a cost/benefit analysis would fall more into the area of third-party payers or CMS reimbursement, I would think.

DR. LEONARD: So can you give that to CMS? I think Reed has a very good point.

DR. LESKO: To an extent we can. I guess it would depend on the Freedom of Information extent, what's in the package insert and things like that. I think it would be case by case. I think one can do a decisional analysis type of simulation, if you will, to figure out whether the cost of a test is going to be effective in terms of what happens with adverse events and not having a test available to guide dosing, for example. I mean, some of that has been done and published in the literature already.

DR. GUTMAN: This is really a big problem, and there actually have been some seminal efforts to try and make better connections between NIH, FDA and CMS on an informal basis or a semi-formal basis. Some of the working groups have connected in imaging and cancer diagnostics. There was recently an AHRQ-sponsored or an AHRQ/CMS co-sponsored activity to try and figure it out better. So it's on people's radar screen, but you're dealing with different agencies,

different cultures, and different regulatory missions. So it's harder than it seems, but it's not being ignored. It may not be going as fast as you would like, but it's not being ignored.

DR. LESKO: Just to add to that, I think many of us have been up to, for example, CMS, and they've provided educational programs that would lay out what we do know about, say, pharmacogenetic testing and clinical outcomes. The other side of that is, at least with some of the older pharmacogenetic tests, the literature, the published literature, the publicly available literature is quite extensive and can, I think, be used to make a case for or against testing in terms of cost effectiveness.

DR. TUCKSON: Well, there are so many people in line. I think it would be helpful if you could teach us more about whether or not this is a promising area. Do you believe -- and don't answer because we don't have time -- is there any future in this kind of being able to actually more precisely dial in a test for a drug? At the end of the day, is that actually going to have any impact, do you believe, on the cost of drugs in this country that the American people have to pay? If this has any promise, we sure need to understand something about it so we'll know whether we should spend any more time on it.

DR. LEONARD: Thank you.

Ed McCabe?

DR. McCABE: Actually, my question was already answered. It had to do with the home brews. But I notice that somebody from the audience wants to make a comment. I would just point out that we, by tradition, hold those until the very end, and if there's not time when we get through with the people around the table here, then I would ask that you submit your comment during the public comment period. Thank you.

DR. LEONARD: Next I have Brad.

MR. MARGUS: I'm Brad Margus, and I wear several hats, but right now I'm speaking as a consumer rep. I'm questioning the connection between the actual content of the test and how it affects whether there's a gap or not, so let me give you a scenario.

If there's a team of researchers doing a genetic association study and they found a clear connection, a genotype/phenotype correlation between a couple of markers and an important disease or a trait, and then they wanted to provide this test for people but they're not selling a diagnostic test or a kit or anything, this morning from what I heard about CLIA it sounds like as long as they get CLIA approved for being able to reproducibly do that test with qualified people and all that, it can be a CLIA-approved lab.

Then when it comes to the FDA, my question is how much does it matter if -- does it fall through a gap there where it's not really going to need your approval to be provided to people? And I assume that if someone would assign them the reagents to do that test, it sounded like it could get caught. But if it's just that the lab could make or order some primaries to do the genotyping, it doesn't sound like that in itself would get caught.

And then to go one step further, let's just say that that test had been reproduced in other labs, and we all feel good about the science but what it predicts is intelligence for athleticism or tendency toward criminal behavior. Where does it get caught in the FDA, or doesn't it?

DR. FEIGAL: The reproducibility of the test and the ability of the test to measure what it says it's measuring in terms of the genetic information it's looking after is the kind of thing that CLIA would provide, oversight over how the laboratory performed that, and Judy Yost mentioned this morning some of the proficiency testing that's done when the same test is offered by multiple labs.

Some genetic information speaks for itself. If you have the sickle cell gene, we know exactly what that means. If somebody wanted to offer a sickle cell test, they wouldn't need new clinical studies. The literature tells us exactly what it means. They would just have to show us they could accurately measure the genes.

The challenge is the information that is more speculative, and in fact for a CLIA test, there doesn't have to be any clinical evidence. You mentioned that they had clinical evidence that the test meant something, but there are tests that have never been shown to have any clinical correlation, there's no literature, there's no research, and people are offered the test saying that the results speak for themselves, it's up to you to interpret the test. Dr. Collins I think showed some of those results before.

There's a gray zone where there's some preliminary results that suggest there's an association and there isn't much confirmation. When that kind of test is brought to us, that's a very difficult situation. There was recently a meeting sponsored by Duke looking for risk factors to predict cardiovascular risk, and they had sample sizes of 2,000 high-risk pairs with 2,000 controls in a typical study. It included groups like Framingham, groups from all around the world. All of them found markers of predictive cardiovascular risk, but none of them found the same markers. All of the markers that each group found were highly statistically significant. It had five zeros in front of the 1, the P value. So they weren't occurring by chance and they were marking the individuals in that sample, but they weren't reproducible, and that's one of the difficult situations for us.

The venture capitalists estimate that there's about a million genetic tests done a year in the United States now, and it will increase to 200 million over the next five years. Currently there are less than a dozen tests that are FDA approved. So right now you're looking at a CLIA-supervised world.

DR. LEONARD: We'll move on to Barbara.

MS. HARRISON: I'm Barbara Harrison. I had a question for Dr. Lesko. We've talked a little bit about the importance of including people from different populations other than Caucasian, particularly in these genotyping studies, and I think it's particularly important given the admixture that's happened in the African American population at several loci. We just have many more alleles than would be found in a population of just Caucasians or just Asians, just because again our admixture is so much higher.

So I was just wondering if there's expectations for these companies when they do these tests. You mentioned that most of the studies involved 95 percent Caucasians. Are there any expectations, is there any way to stop companies from just basing it on a population like that? Is there any regulation on that?

DR. LESKO: I think the answer is yes. There's an interesting report, and you can look at it on the FDA webpage if you put in "ethnicity" as a search term, and it's a study that was conducted over 1995 to 1999 that looked at clinical trial enrollment as it was broken down by race and

ethnicity, and it shows the distribution of different populations in the different phases of drug development. At that time, the distribution of different groups in early clinical development paralleled the percentage in the population in general. So if we're talking about Phase I and early Phase II studies, there was good representation.

Things broke down when you went into the Phase III trials to demonstrate clinical efficacy and get the bulk of your safety data, and that's where the limited enrollment occurred. That was 1995 to 1999. Since then, things have improved. The agency has near final a guidance to the industry on the enrollment of racial and ethnic groups, and it's also on the webpage in draft form. The guidance is intended to encourage this type of diversity in the enrollment in clinical trials consistent with the target population, the disease state, and so on. I think the impact, the hopeful impact of that is that things will change in the clinical Phase III efficacy/safety trials to mirror what already has occurred in the earlier studies. But that guidance will be finalized fairly soon, I believe. That's available for public review on that same website under "Guidances."

DR. LEONARD: Does that mean that a drug could not be approved because they didn't have the breadth of ethnic diversity in their clinical trials information that they're submitting to you?

DR. LESKO: I think the answer is no. It could still be approved. It's going to have perhaps a different label than it might have otherwise, but I don't believe the agency could not approve something based on the enrollment of different patients in a clinical trial. I don't think there's a regulatory mandate to do that. The way we encourage companies to do that sort of thing is through guidances, and a guidance is non-binding, non-enforceable, but a company is obligated to address the issue of why didn't you do something that might be recommended in the guidance.

DR. LEONARD: A follow-up from Ed.

DR. McCABE: So in follow-up -- this is Ed McCabe -- there might be labeling like "a drug has not been tested in children," there might be labeling to specify what populations it has been tested in and that there's limited knowledge beyond that ethnicity. Is that what you're telling us?

DR. LESKO: Yes. That's kind of routinely put in the labels now in terms of what not only is known or what was studied but what also is not known or what wasn't studied, and there is a proposal now, a new physicians labeling that creates specific sections for that type of information under "Special Populations" and other places, depending upon how important that information is to know.

DR. LEONARD: Next comment from Muin.

DR. KHOURY: This is Muin Khoury, CDC. Just want to come back to what Reed Tuckson was talking about a couple of hours ago now, about the issues around pharmacogenomics and cost-effectiveness analyses. This is really where the rubber meets the road. At the end of the day, there's going to be an expansion of many, many, many tests that are going to be used in conjunction with either treatments or prevention, like the TPMT with acute leukemia, et cetera, et cetera.

As I was listening to Dr. Lesko give the presentation on the few cytochrome-based available genetic tests, what came to my mind was the wonderful analysis which was a framework that was done by David Veenstra from the University of Washington a couple of years ago on the cost-effectiveness of pharmacogenomics, and he used specifically TPMT as an example. I don't want to take too much time here, but it's a complex set of factors that come into play.

One of them is the frequency of the allele itself, or the trait. If it's rare, like 0.3 percent of the population, as he showed, it may not be cost-effective to test the whole population, especially if you have a phenotypic test or a measurement that can follow or track the levels of the drug in the body to assess the body burden of the disease. So the value added of a genetic test, whether in the context of pharmacogenomics or prevention or screening a whole population, is much more complex than the analytic validity of the test, which could be wonderful, the clinical validity of the test, which could be wonderful because there is genotype/phenotype correlation, but the clinical utility is a complex scheme of factors that involve economics.

For that to happen, it's going to require working hand in hand with the regulatory paradigm and the practice of medicine and the professional organizations coming together and reviewing the evidence for or against different uses of technologies. It's sort of an objective way, using technology assessments. There are processes that already exist within the government, like the U.S. Preventive Services Task Force that's housed at AHRQ, and the Community Preventive Services Task Force that's housed at CDC, and a whole variety of other existing mechanisms that can complement the regulatory paradigm to come to bear on the actual utility of genetic information and practice.

DR. LEONARD: As a follow-up to Muin, I was a little disturbed to look at the table for 2C19 genotype for voriconazole and find that there is no dose reduction recommended because the test was not broadly available. It would help physicians to know that if they could get the genotype, what to do in response to that, and I would encourage that when these things are done, that even if the test is not available, that there be some recommendation that if it were available, this would be an appropriate response, because that's the only way that physicians are going to be able to move forward, and many times laboratories will not develop tests unless physicians will use them, and this would drive that motivation and more appropriate use of drugs.

DR. LESKO: To clarify the situation on that example, I had mentioned on one of the slides that there was no testing in Phase III of that development program, so there was no evidence to point towards a risk factor of a genotype predisposing somebody to an adverse event. There was no evidence pointing in that direction, so there was no way to label the product. What we did know is that genotype does increase exposure to the drug. What wasn't known was whether the increase in risk associated with the higher exposure warranted a stronger language statement in the label.

So I think that was a case of basically what we knew about the drug was put in the label in terms of descriptive clinical pharmacology, but there was no evidence upon which to recommend a test or any other measure other than somebody reading that information, putting two and two together and figuring that maybe a test might be beneficial in figuring out, for example, why a patient might have an adverse event when it wasn't expected.

DR. LEONARD: Thank you.

Francis Collins?

DR. COLLINS: Francis Collins from NIH. I actually have two questions. One is a more specific, practical one, and another is more of a broader policy issue.

The practical one really follows up a bit on the question that Brad Margus asked. Having had the good fortune to interact with my fine FDA colleagues over many years, I still find I get lost in the

arcana sometimes. So I wonder if you could help me here in terms of what was proposed now as far as the use of ASR oversights in terms of how that would play out.

So I am a laboratory that is CLIA certified, I have a good track record of doing good analytical validity, and I have decided that I would like to market to physicians an in-house home brew test on the gene CETP, a gene involved in cholesterol metabolism which has some very interesting data associated with it in the published literature. In one way, it seems to be that variants in this gene play a role in risk of heart disease. In another way, variants in this gene seem to play a role in predicting response to statin drugs, whether you're going to have a beneficial effect on progression or non-progression of coronary artery disease. Of course, last week this publication indicated that a variant in CEPT is associated with exceptional longevity. So a lot of things sort of focusing in on this gene.

I can set up my highly validated method to determine whether there's a T or a C in a particular nucleotide position, and I think there are three indications here that might make this a useful test in certain clinical applications, and I would like to put this out there and expect that physicians will figure out the appropriate way to use it or not.

What is FDA's interest, if any, in my doing that if I have gone through the CLIA approval part? What does your oversight of ASRs have to do with whether or not this test is going to easily find its way into the hands of a physician for application?

DR. FEIGAL: So you're making your own ASRs? You're making your own reagents?

DR. COLLINS: Yes.

DR. FEIGAL: We currently say you are supervised by CLIA, so you can advertise anything you want, you can claim anything you want. The FTC may have issues with you, but from FDA's standpoint --

DR. COLLINS: I'm not marketing to consumers. I'm just marketing --

DR. FEIGAL: Physician advertising also has to be -- that's this afternoon. But essentially that's CLIA supervised under the current scheme. The gray zone is whether or not any reagent manufacturer is under FDA jurisdiction or whether that reagent -- it has to be someone who sells reagents to others.

The area that we decided to focus on when we felt there were already a number of products was the -- if you looked at a test that was developed with that ASR, irrespective of whether it was an ASR or a kit, that you'd say this is not an exempt product, this is a product that has issues that require review. Originally, we actually specified that ASRs could be Class I, Class II, or Class III products. So part of where we are starting from is to take a look at the ASR manufacturing and ask what's the most appropriate way to do risk classifications within ASR.

The original rule said the default would be that they'd be exempt and gave some examples when they would be II's and III's. But for the in-house test where everything is developed in-house, currently that's just between you and CLIA.

DR. COLLINS: So let me then ask my second question. I gather from your response that this is sort of this regulatory gap that you referred to in one of your presentation slides.

DR. FEIGAL: Yes.

DR. COLLINS: Obviously, there has been an ongoing debate, it seems, about whether or not FDA has the legal authority to take a larger role in terms of their oversight of in-house testing of home brews. Earlier conclusions four or five years ago seemed to indicate that yes, the law would in fact cover that kind of authority if FDA chose to exercise it. More recently we understood there was a review of that going on, and I don't think there was ever a clear answer provided as to whether FDA currently feels they have that authority or not, not getting into whether FDA wants to use it right now, but does the FDA actually have that authority.

Is there anything new to say about the status of that legal review?

DR. FEIGAL: No. It's an issue that hasn't been settled, and unfortunately some of these issues don't get settled until you take a stand and then go to court.

DR. LEONARD: Arden?

DR. BEMENT: Arden Bement, Department of Commerce. In the near future, the EU will require mark for IVDs, and this is a practice that may also carry over in the future to other regional economic blocks in the world. This brings a new international dimension to mutual recognition arrangements, harmonization of regulatory pathways, and perhaps labeling in order to minimize barriers to trade.

My question is how is the FDA anticipating or preparing for these new challenges, and what do you see that needs to be done in addressing these international dimensions?

DR. GUTMAN: I can start. I have a narrow picture, and I know David has been involved in global harmonization on a much broader base. But in the area of IVDs, there actually is a standards group, ISO 212, that is trying in a proactive way, racing as quickly as they can to keep up with the changes. Some of the things that they've done are crafted IVD-specific standards that could be used across continents, and probably the most important single standard, and it's one that's now right in the heart of the development process, is an international standard for labeling. If that international standard for labeling is in fact concluded with a reasonable outcome, which I actually believe it will be, then the FDA can recognize that standard and then can have its review process parallel the requirements for whoever else would recognize that standard.

There are, at least in terms of the regulation of IVDs, some interesting differences. In Europe they have the IVD Directive, and it is actually in some ways -- it's administratively a little looser than our regulation, although scientifically it's quite a different process and in some ways a stronger process. Instead of being founded on the notion that you'll find a product equivalent to a product which is equivalent to a product which might have been marketed in 1944, what they require is that you actually find that the product can be properly made in relationship to a higher-order reference material or method. So they actually require a standards-based approach.

Now, they don't have a tough regulatory scheme or a lot of experience. It may be a great regulatory scheme but not a lot of experience and oversight of that. So there actually are some differences that are cast in the laws that will make, at least for IVDs, make complete harmonization challenging. But we obviously are quite interested in trying to learn and trying to exploit synergisms between processes.

DR. BEMENT: I think you bring up a very good point, that in some of these regimes the ISO is

going more toward performance-based standards, which used to be the U.S. approach. In some cases we're a little bit behind, and it may be in this area we're somewhat behind as well.

DR. FEIGAL: Well, it's a statutory difference. The U.S. requirements for manufacturing are less rigorous for middle-class products, the Class II products, the 510(k) process, than they are in Europe, or Canada, or Japan, or anyplace else in the world. So currently, for better or worse, we've really evolved into two systems, a U.S. system which is tougher for the highest-risk products than anywhere else in the world, but we've taken a different approach with the middle-risk products where we do not even require that a manufacturer have even begun manufacturing in order to get their market clearance. In Europe, Canada, other parts of the world, you actually have to have certified that your manufacturing is up and running and meets quality standards, and there are strong economic reasons to maintain the two systems.

So I think there will be some things we'll harmonize and some things where industry will work with the two systems.

DR. LESKO: I just can add to the issue that from our center in communicating with the European Union, the EMEA and CPMP, we have agreed on a terminology for samples that might come out of a genomic or genetic study, which has helped the informed consent process a bit by having common language between studies done here and studies done in Europe. That guidance has been put out by the EMEA. It's available on their website. We worked on that more or less together in getting the terminology harmonized, along with industry.

The other connection is more informal. When we talk about workshops like in May of 2002, or there's one coming up in Europe next week, the agency participates in those in Europe, and they participate in the ones being held here domestically. As part of those workshops, we're trying to exchange information on where each of the respective regulatory agencies are, where they're going, and in addition to that just some offline discussions about what's going on. So there's a communication link as things evolved that I think is being established.

The final thing is all of the regulatory agencies around the world are involved in a WHO initiative on a pharmacogenomics working group that consists of perhaps 35 to 40 people representing the three major regions -- Japan, U.S., and Europe -- both industry as well as regulatory agencies, and that's another forum in which to discuss common issues.

DR. BEMENT: Thank you.

DR. LEONARD: I think we'll have Hunt and then Chris, and then we'll wrap it up.

DR. WILLARD: Hunt Willard. I want to make sure I understand the issues of FDA purview. It in part follows up on Francis' question, but I actually had come to it before that.

I certainly understand the issue of the FDA wanting to know whether a test or a device or reagents that underlie that test, whether it's valid and it's clinically meaningful. That makes sense to me. However, to what extent is it the FDA's purview to then ask questions about when that test might be indicated, whether it's available broadly -- that's the part that jogged the question -- and/or whether it's cost effective in terms of it really truly being value added and therefore clinically useful, as opposed to just clinically meaningful?

Maybe I'm more of a believer in the open market approach here, which would, to me, say that all those questions can just be left to the open market. If no one wants to buy a test because it turns

out not to be clinically useful even though it's clinically valid, well, so be it. So to what extent does the FDA think that everything I just described is in the purview either for tests in general, devices in general, or for those within the realm of genetic and genomic tests?

DR. FEIGAL: The phrase "cost-effective" has to be linked to the cost-effective regulation, not cost-effective products. The marketplace will determine whether the products are cost-effective, as you point out. We don't consider the cost of the product, but we do realize that what we require does increase the cost of development of products, and that will eventually have to be paid for by the consumer. So the Commissioner's mandate is that we develop regulatory mechanisms that are as least burdensome and as least costly as possible.

So that's the context there. But we're actually forbidden from considering cost when it comes to a product. If you want to charge a half a million dollars per test, if somebody will pay for it, great.

We also don't have any particular opinions about how broadly the test is available. Where breadth comes into the matter is whether or not you're selling reagents or creating them for your own use, and that's where there's this sort of distinction between the in-house test where everything is manufactured in-house versus where you purchase the reagents. We clearly have the authority -- it's in my first slide, in the statute -- to regulate people who sell reagents and those reagents.

The standard for medical products is not let the buyer beware but is that the products have to actually be safe and effective. A product isn't effective if it provides information that is of no known use. So that's where it comes back to having to actually look at indications for use and some evidence for that. Sometimes it's completely evident from what's known from the literature and longstanding experience with the information. Other times we're on the frontier where it's difficult, and that's where the judgment calls are difficult, and that's sometimes where the cost of developing an FDA-approved use, as opposed to just saying this is an analyte that measures the following genes, make of them what you will, which is sort of the analyte proposal, is a different standard. The FDA is a higher standard. It was a standard intended by Congress for medical products.

DR. LEONARD: Chris?

DR. HOOK: Chris Hook. First just a comment and follow-up to Dr. Khoury's comments about approaching the question of the parameters you use for cost effectiveness. Certainly frequency is important, but oftentimes in these analyses it's the severity of perhaps that rare side effect, and when you might have 15 to 20 percent mortality because of neutropenic sepsis and death, I still think that that should weigh very heavily, not just the frequency in the calculation.

My question, perhaps to Dr. Lesko to begin with, you were showing these very good examples of the knowledge that we're learning from the pharmacogenomic data, but at the present time the FDA can only report what it is provided in this regard. Since we're finding more and more, perhaps in some of these instances with antidepressive agents, SSRIs and others, that 10 percent may be significantly and adversely affected depending upon their ability to metabolize the drugs, shouldn't the FDA be requiring pharmacogenomic data in order to even approve a drug at this point?

DR. LESKO: It's an excellent question. Again, requiring and encouraging are two different things.

DR. HOOK: I understand.

DR. LESKO: Requiring anything is hinged on the evidence, and I think we're fairly early in the game with many of the things we're seeing. The evidence has to come from studies that are prospectively designed to answer the questions. I think what we have in many cases is evidence that might be more retrospective analyses, circumstantial, as opposed to something that's prospectively designed to answer the question.

The other thing that we've seen, I think, is the distinction between an at-risk patient and one not at risk. They're not clear distinctions. This is a probability, an odds ratio type of thing, and the distinction between those if they're not necessarily clear becomes difficult to make the case to mandate something like that.

So it's a moving target right now, I think, and we have to see how things play out going forward. But I think it would be difficult to mandate unless we had the evidence appropriately established.

DR. HOOK: To assist you in getting that evidence, then, should we not require that drug studies that are being sponsored by the NIH or the NCI have as requirements for that sponsorship the collection of pharmacogenomic data to help provide you that additional evidence that you need?

DR. LESKO: I think it's an excellent idea.

The other aspect of drug development would be other things besides genetics that may play a role in outcomes, and it would seem the absence of information generally we've dealt with by the appropriate labeling, which is basically what we do know and don't know, for the most part. But what you point out as far as having more information in an appropriately designed study would be great. It may not necessarily come from the drug development process in the future.

DR. McCABE: Well, thank you very much, Dr. Leonard. Thank you to our guests and our ad hoc from the FDA. This has been very informative to me and I'm sure to the rest of the committee.

At this point we will take a one-hour break for lunch. We will begin sharply at 1:30. Just to let you know where you can eat, there are hotel restaurants. The American Grill and Old Dominion Brew Pub are located downstairs in the lobby. Seating has been reserved in the American Grill for members, ex officios and presenters to try and facilitate your getting through the lunch. There's also a food court on the Metro level.

We'll be back sharply at 1:30. Thank you.

(Whereupon, at 12:30 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m.)