24th Meeting of The Secretary's
Advisory Committee on
Heritable Disorders in Newborns and Children

May 5, 2011

Audio file: Begin “Day 1 1300 – 1400.mp3” at 00:00:54

Renaissance Washington, D.C.

Dupont Circle Hotel
(Whereupon, the meeting was reconvened at 1:05 p.m.)

DR. HOWELL: Before we get into this afternoon’s session, we had the housekeeping comments this morning from Alaina. And she was out in the corridor and missed giving you that information. And so, she's going to currently do the housekeeping thing to also discuss the room that we'll be in tomorrow.

MS. HARRIS: Thank you, Dr. Howell.

The most important thing for the committee members is we are going to have -- we've got our 6:30 dinner reservations tonight. If you would like to join -- this is for committee members and organizational reps. I'm going to send around a sign-up list. Please take a look at that. We're going to meet in the lobby at 6:15 and walk over to the restaurant at 6:30. So we'll just start here and pass that down.

The subcommittee meetings today are from two to five. The Follow-up and Treatment is meeting in this room. The Education and Training is across the hall. And then Laboratory Standards is on the first, the lobby level in the Mount Vernon Room. If any of the presenters have changed your presentations after submitting them, please save the revised copy of the presentation to your laptop.

And then everybody at the table should have received a thumb drive this morning. That thumb drive contains supplement
materials to the briefing book. So did everybody get that? The materials on the thumb drive is the same that's on the Web. So does anybody need a thumb drive? All right. Thank you.

DR. HOWELL: Thank you very much.

A couple things is that we discussed the annual report this morning and voted on that. That's listed tomorrow on the agenda. And we'll take that off tomorrow's agenda because I think that we've taken care of that.

We're now going to hear -- Jerry Vockley is going to have a group this afternoon to look at a session on FDA's policies and procedures relevant to individuals with rare, heritable disorders. And we will hear directly from our friends at FDA, Tim Cote and -- Captain Valerie Jensen and Kellie Kelm, who will present expanded access to investigational drugs, critical drug shortages for necessary medications and provide us an overview of device regulations.

Jerry?

DR. VOCKLEY: Thanks, Rod. I think this qualifies as in the category of, "and now, for something completely different."

(Laughter.)

DR. VOCKLEY: First of all, for those of you who expressed concern about having gotten stuck in blizzards on the way out last time, I'll
have you know we did not get stuck in blizzards, but a nice little, slightly
different plague.

This session started out of some conversations with a couple
of investigators who expressed to me some difficulties that they had in,
sort of, navigating the FDA waters regarding INDs that they had tried to
get in place for some projects that they wanted to do. And it quickly
became clear to me that the problem was really a bit larger than that.

And that is that it appeared that most of us in the rare
disease community really had very little idea of what went on in the FDA
and how to approach it and that there may have been some similar
disconnect at the level of the FDA talking to the rare disease community.
So I thought that it seemed like a good thing if we could bring this together
and perhaps make the connections a little bit tighter.

And so, to do that, I went back to this report that you see on
the screen, the Institute of Medicine report on rare diseases and orphan
products, accelerating research and development, because there really is
a lot of very interesting material in there as it relates to investigational
drugs and FDA interaction with the rare disease community and, as the
name implies, research and development on those conditions.

You have, I believe, in your books the summary that the IOM
makes available publicly on this. I had the good fortune of getting a copy
of the full 442 pages to review for this session. So more evidence to be
careful what you ask for, you might get it.

However, boiling this down to the topic at hand, there were a
number of comments embedded in the IOM report that were focused
specifically on accelerating research. And I thought that that looked like
the place to start a discussion like this. So I've got them summarized on
here, and I think you have these in your briefing book as well, if they're too
hard to see.

And let me just take a second to go through them. So the
bullets are that the IOM recommended active involvement and
collaboration by a wide range of public and private interests, including
government agencies, commercial companies, academic institutions,
investigators, advocacy groups. That's all, you know, motherhood and
patriotism.

But then we get into some more difficult issues: timely
application of advances in science and technology that can make rare
disease research and product development faster, easier and less
expensive and pushing those sorts of things forward.

They recommended creative strategies for sharing research
resources and infrastructures to make good and efficient use of scarce
funding, expertise, data, biological specimens and participation in
research by people with rare diseases or with rare diseases, appropriate use and further development of trial design and analytical methods tailored to special challenges of conducting research on small populations, reasonable rewards and incentives for private sector innovation, adequate organizations and resources, including staff with expertise on rare disease research and product development for the public agencies involves and then mechanisms for weighing priorities for rare disease research and product development.

So in thinking about some of these issues as they related to INDs, one of the things that happened was on the metabeld, the list server that most of the inborn errors people around the country and the world participate in. It suddenly became quite a large issue. But there was a shortage of L.D. arginine because of a shut-down in the sole source company that was providing it in the U.S. And so, Carol Greene, among others, was involved in trying to figure out, you know, what's involved in trying to get emergency access to an alternative approach for that, or a source for that.

And then, at the same time, though, as this convergence of things, I was discussing with some of our newborn screening labs some issues that seemed a little bit confusing relative to use of outside kits, commercially-available kits for newborn screening tests, in particular,
SCIDs. And so, one of the things that, relative to some of these issues, the IOM report highlighted was that in relation to the FDA, that they identified that there were insufficient resources for timely meetings and guidance for sponsors, that there was inconsistency in reviews of applications for orphan drug approvals across the divisions and inadequate resources for from products, grants, programs. So this is from the IOM report.

From the sponsor side, so, those of us who are coming in and saying, "I need this IND," or, "I need this product," there were a longer list. There was a longer list of issues identified, including delayed toxicology studies, inadequate characterization of chemical compounds, lack of natural history studies, poor use of early phase studies to design our phase III trials, inadequate trial design and lack of advanced communication with FDA about the adequacy of the clinical trial plans. And that last one is particularly, I think, important.

The recommendations that came out of the IOM were that there should be an assessment of staff reviews of applications for the approval of orphan drugs, that there needed to be a review on how that was being done and how that information was being communicated, that they should evaluate the extent to which studies submitted in support of orphan drugs are consistent with advances in the science of small clinical
trials to ensure that NIH funded product development studies involving rare diseases are designed to fulfill requirements for FDA approval, so some interagency communication there, that the FDA should expand its critical path initiative to define criteria for evaluation of surrogate endpoints for use in trials of products for rare conditions.

The FDA and the NIH should collaborate on an assessment of unmet device needs and priorities relevant to rare diseases and that the FDA should take steps to reduce the burdens on potential sponsors of humanitarian use devices. So relative to some of those conversations that were going on all at about the same time that triggered this session, three issues seemed to really be consistent across a lot of discussions.

One is a, sort of, need for everybody to better understand the issues related to compassionate use protocols, the idea that we have to have some alternative emergency supplies available for single-source medications that are used to treat rare diseases and that there was, at least in our group, a complete lack of knowledge in the process for approval of new technologies for diagnosing rare diseases.

Relative to the compassionate use issue, I think the safest thing to say is that confusion abounds in the scientific community. Now, I was asked by the FDA not to include specific examples because they felt that it would really put them at a disadvantage. They are bound by their
regulations not to talk about specific applications because of confidentiality issues.

But I will say that a lot of the discomfort with the interactions between the FDA and investigators that arose as I was doing a little bit of discussing with the research community, inborn errors community, really, kind of, all came down to the issue of the understanding that the risk/benefit ratio in rare disease is inherently different than in other disorders and other more common disorders and that if we applied all of the regulations to their most strict level, that we would be regulating our patients, literally, to their death.

Frequent questions that came up from specifically in how to interact and how best to pursue these kinds of studies was what are the advantages and disadvantages to the use of a compassionate use protocol versus something a little bit more formal. Does this differ from what is called emergency approval? What constitutes appropriate toxicity data? And when a company has agreed to supply a compound for a study, what else might interfere with approval? So in a very broad sense, the questions that plague anybody thinking about using an investigational -- or a drug in an investigational drug application.

Regarding emergency supplies, it's important to note that many of the medications that are used for treatment in IEMs are really
single-source. I mean, this is part of the Orphan Products Act. They're developed with patent protection. And so, if something happens to that source, as has occurred a number of times now in the last two to three years, what do we do? Well, sometimes there are foreign sources available. Sometimes there are non-medicinal-grade sources available. And it's also important to keep in mind that these are not necessarily complicated biomolecules. So these are not all necessarily recombinant enzymes or DNA vectors or something like that. It may be as simple as a compound that can be purchased off the shelf from a chemical supply company.

We certainly can't anticipate emergency needs for every rare disease treatment out there. So it would be to our benefit to have a well-publicized policy that everybody can easily refer to. And then when the need arises, I think there is, again, in the community a general lack of understanding of what the process is to get approval for alternative-source medications. It's there. It's out there. But what's that process? We need a little bit more of communication in regards to this.

Some of the issues that came up regarding new device approval -- first of all, keep in mind that diagnostic kits are defined as devices, something that is probably not generally appreciated among, at least, physicians in the field. So questions that arose -- what are the
regulations for use of existing kits for new purposes, the single lab
reagents or tests require approval, and what's that process for approval.
We'll hear some comments on that.

Ultimately, the challenges, I think, that surfaced to the top
and face those of us in rare diseases is this communication where it's
really important that investigators know how -- and practitioners know how
to approach the FDA regarding these and that uniform recognition at the
level of the FDA, that they are, in fact, allowed to use their discretion when
applying regulations to rare diseases is an important point to bring out of
this discussion, that we need to be able to consider the risk/benefit ratio
when the inevitable outcome is poor. When you know a child is going to
die in six months without an experimental medication, how do the
regulations allow relaxing some of the long-term toxicity studies, for
example?

And in and amongst all of this, how do we protect
investigators and patients alike, without making treatment impossible?
And so, we're going to hear from several members of the FDA. Rod
introduced them beforehand. At least one of them is the director of a
division or a group that I didn't even know existed. So again, it points to
the lack of knowledge out there. And hopefully, we can resolve some of
that with this session and maybe figure out how to make that knowledge a
little bit more generally available.

So I don't have my list in front of me. I forget who's first. But come on up, and I'll get to my seat and introduce you.

(Laughter.)

DR. VOCKLEY: Thanks for coming.

DR. COTE: Thank you so much. If I can have my slides.

Okay?

Hi, my name is Tim Cote. And it has been, over the last four years, my distinct pleasure to be the director at the FDA's Office of Orphan Products. I call myself the immediate past director because right now we are in the process of having a transition. For those who care, I'll be moving on at the end of this month to be the Chief Medical Officer of NORD, the National Organization for Rare Disorders, half-time. And my other half-time gig will be being a full professor of regulatory practice at the Keck Graduate Institute in Claremont, California.

So that should be a big change. And hopefully, that'll make for a fairly reflective talk here. I guess my charge is to convince you all that the hyperbole of regulating people to their death is untrue and, frankly, unhelpful, I would say.

Could I have the next slide? Okay. So why should we partner? This is really what I think is helpful, is why should we, at the FDA
and the Office of Orphan Products and the review divisions, be such an
important partner to this committee, which does such important work?

Inborn errors metabolism, which are a focus of this group, are also one of
the focuses of orphan products. Although they actually make up only
about 5 percent of all orphan products, they are incredibly important. And
we are fully expecting other new therapies to be coming very, very soon,
frankly.

Gene therapies are incredibly exciting -- small molecules,
stem cells. I mean, the list goes on and on about new things that are
coming down the pike. And newborn screening, as you all know, is
traditionally contingent, not only on a decent test, but you've also got to
have a decent therapy to offer in order for a screening program to be
moving forward.

Next slide? Okay. So I'm going to tell you a little bit about
orphan products. It is the growingest sector of the pharmaceutical
industry at this time. I'm going to give you a little bit of introduction to my
office, what is the Office of Orphan Products and its development. I'm
going to give you a little bit of the basics of the Orphan Drug Act, which
was passed in 1983 and why should all of this stuff matter to this
committee.

Next slide? Okay, so let me bring you back, to start off, to
1982, when some of the people here probably weren't born and some of us remember it quite well. Rare diseases basically were very, very problematic. The economic systems that were set up was such that in order for a drug company to make money, you do an investment of a lot of development money and then you sell your pills. And if there aren't many people to sell your pills to, then it just doesn't work. That algebra didn't work, and, frankly, the data supported that from 1973 to 1982. There were only 10 new drugs that are approved for rare diseases.

As many know here, there are about 7,000 rare diseases. Twenty-five million people have those rare diseases. And congressmen and senators are besieged virtually every week. Somebody comes knocking on their door with a tragic story of a rare disease asking for help with research and drug development.

Move into this picture, Abbey Myer, a housewife from Danbury, Connecticut, who had a couple of kids with rare diseases and who took it upon herself, recognized that, while rare diseases are individually infrequent, they're collectively common. And if she could just get all these people together, they could form a grassroots political movement. She had a special friend by the name of Henry Waxman, an obscure congressman from California at the time, who said that they're like orphans, that they require special care.
A movement was formed, a committee started. It's a uniquely American story. It's democracy in action. And it happened.

Next slide. Okay. So the new deal of the Orphan Drug Act is this: First, you get a drug designated as an orphan drug by showing to me or to my successor two things: one, that it's promising. And I didn't say effective. I said promising. And promising means that you have some reason to believe that it's going to be effective for treating -- some reason to believe that it might be effective in treating the rare disease and condition. And that could be animal model data. It could be some very sketchy early clinical data -- and that disease or condition is for treating fewer than 200,000 people in the United States, that that's the limit that was set, somewhat arbitrary, but it was set there.

Then you have to still go forward and do the clinical trials to get marketing approval. And if you do this, then you've received some special incentives. The first one and the most important one being market exclusivity. That's really the one that's driven this whole system forward. You also get some tax credits and some fee exemptions.

But you should note that the approval process for orphan drugs is just the same as the approval process for any other drug. The process is that they have to prove safety and efficacy. Now, what safety and efficacy mean have been flexibly interpreted, based upon the
conditions of the clinical trial themselves. And Dr. Anne Pariser will speak a little bit more about this when she comes up.

But the fact is people with rare diseases deserve drugs that work. And FDA approval needs to mean that the drugs work. And they're safe, recognizing, as was mentioned by the previous speaker, that the risk/benefit ratio is different in these particular circumstances. And I believe that there will be examples provided to you shortly that show that the agency's been extremely flexible in the interpretation of a multitude of these products.

Next slide. Okay, so the Orphan Drug Act has been a major, huge success. There have been 366 approved drugs, I mean, fully marketed drugs out of this. About 2,400 designated products have gone on to be orphan drugs. And, as I mentioned, this is an emerging sector that is really growing. About a third of all FDA-approved new molecular entities, NMEs, were orphans in 2010. So more and more orphan products are starting to dominate the pharmaceutical sector.

Next slide. Here is a graphic representation of what's been going on. You can see that approvals are verballying along, and designations are pretty much taking off. Now, there is an important latency period. As I mentioned, orphan designation is a very early stage evidentiary criteria. Whereas a drug approval, full drug approval, takes
considerable time after that.

Next slide. Now, I wanted to compare and contrast because I know that the FDA has a bit of an opacity problem. And to try to -- was that well-characterized? Opacity, yeah. So I wanted to try to characterize the difference between my office, the Office of Orphan Products Development, and the review divisions, which Dr. Pariser will represent.

In order to secure orphan status designation, you have to show promise. And we can designate something as having orphan status. But in order to receive marketing approval from the review division, you’ve got to show safety and efficacy. Frankly, that is the law. So it’s not just FDA’s decision. That’s what the law says you have to do. And if we want things to be different, you are the people who could change the law, not the people inside the FDA.

If you get orphan status designation, you get bragging rights. And you will see many pharmaceutical companies who proclaim from the hilltops of their Web sites that they indeed have bragging rights. And sometimes the venture capital falls down from the heavens. If you receive a positive decision from the review division, you can secure marketing rights.

The Office of Orphan Products is an advocate for this process. We want to see more products developed for people with rare
diseases. So we’re actually pushing the process forward through this. I
didn’t mention our grants program. We have the largest grants program at
FDA. It’s about $16 million, exclusively for clinical trials for rare diseases.
We can talk about that later.

Whereas the review division’s job is being the monks. If
we’re the cheerleaders, they’re the monks. It’s more dispassionate. It’s a
consideration of public health. Is it good for the people, basically, the
people with the disease?

We do attend the guests at the IND meetings and the end of
phase II meetings and so on and so forth. But they are actually the review
division’s meetings. And we’re the ones who actually evaluate what the
prevalence of a particular disease is and come out with the official figures
for that. Whereas that’s fairly irrelevant to the review division, except in as
much as it impinges upon how clinical trials are structured. And we do
share shortage issues. Val Jensen will mention a little bit about that from
CDER.

Next slide? Okay, so in summary, I believe that FDA needs
to be engaged with this committee much more than it has historically, not
only on diagnostics, on which we are extremely well-represented in Kellie
Kelm, but also on these therapies. And as my parting shot as I’m leaving
the door of FDA, I would put forward that there really ought to be some
systematic consideration of newborn screening upon the emergence or
perhaps the licensure of a new therapy for newborns and children. I don't
know how that process works right now.

But I know that it's not tied to a formal systematic, "Oh, when
the FDA has approved this, then this happens at this committee." I don't
think that happens right now. I think it's more sporadic and inspired than
actually part of a regular program. And I think we need that. So I would
say that a closer partnership is well overdue.

And with that, next slide? I'll take any questions. Thank you.

DR. VOCKLEY: Actually, Tim, I think because of a limited
amount of time here, what I'd like to do is get everybody through and then
ask you all to remain available for questions afterwards. Great. Thank
you.

Next up is going to be Anne Pariser, who is the Associate
Director for Rare Diseases and the FDA's Center for Drug Evaluation and
Research.

Thank you.

DR. PARISER: Hi. Thank you. And thank you to the
committee for inviting us to speak today.

I'm going to be talking about the expanded access process.

It's expanded access to investigational drugs. And I'm first going to just
outline some of the regulatory considerations and speak a little bit on the ethics of conducting research in human subjects, from which the law comes. And then I'll give you a few examples of CDER's recent history and a few examples of some expanded access INDs and then just tell you very briefly how to interact with FDA.

I'm going to be speaking specifically from the Center for Drugs' perspective and the Office of New Drugs, which is, as Tim mentioned, that's where the review divisions live. So expanded access, which is more commonly referred to as compassionate use. The intention of this is to provide improved access to investigational drugs to patients who have serious or immediately life-threatening conditions. And this includes many of the rare diseases, most of which are serious.

Patients also have to have a condition for which there is no alternate or satisfactory treatment that is otherwise available to them. The purpose is to enable these patients to have access to the products outside of a clinical trial. Usually, these are products that are either still in development or are not being development. Or sometimes it can be a drug that is approved in, for example, Europe and not available here.

And because most of these are for single patients given on an open-label basis, they are really not likely to describe effectiveness. And they are not likely to support a later marketing application. So they
really are not intended to support any kind of an approval. Because of this, FDA's main concern is with the safety. And the requirement says that any potential benefit to a patient has to justify the potential risks and that these potential risks should not be unreasonable. So unreasonable is really the operative word here. And that, of course, is subject to some interpretation. FDA does maintain, thought, that the best access to any drug for patients is an approved product, meaning a product that is approved under a marketing application and is available for prescription by physicians. This next best choice would be for patients to be enrolled in well-designed clinical trials that are designed to demonstrate efficacy and safety. And this expanded access process is then available for patients who are unable to access either those mechanisms. But there's also a requirement here that the expanded access use will not interfere with either the initiation, conduct or completion of those clinical trials that are intended to demonstrate effectiveness and safety that could then support a marketing application.

So in general, there are four times of expanded access. And these are usually single-patient applications, but not always. And they are considered individually one at a time on a case-by-case basis. There's four general types: emergency, single-patient, intermediate size and
treatment protocols. And just very briefly, an emergency use IND -- this is when you don't have time to go through the usual IND process. Usually, what happens is the treating physician or the physician intending to give the product to the patient calls the FDA. The medical officer is then called over, gets on the phone with the physician. And this usually happens very quickly, sometimes within an hour, but usually within 24 hours.

And then the paperwork follows. The IOB has to be notified within five days. A regular submission, the written submission to FDA then comes within 15 working days. And these are generally limited to one course of treatment. And, again, it's just so that the paperwork can then catch up.

Single-patient INDs are intermediate size. These are for either one patient or small groups of patients with a similar treatment condition and those who do not qualify to participate in a clinical trial for any number of reasons, either the drug isn't available in this country, there is a trial that's ongoing and they don't qualify, or perhaps the drug is not under development.

And then the treatment protocol is a little bit different. This is for drugs that have either completed or late in pivotal trials to support a marketing application, or the sponsor is compiling the data. And while that's going on, it's usually desirable to let patients continue to have
access to the drug in those situations. But in that situation, you do have a lot more information to work with.

So just to say a little bit more about the single-patient, non-emergency ones. This is an abbreviated list of what needs to come in. And it's a limited amount of information. But essentially, it just -- it's a brief clinical history of the patient and the rationale for why you want to use this drug. And then the criteria for selecting appropriate patients for study -- now, that sounds obvious, but I'll give a couple of examples a little bit later where this actually fell down. And when you're doing that risk assessment that the potential benefit has to outweigh a potential risk, it's very important that the patient is selected appropriately.

There needs to be a proposed treatment plan, usually in the form of a protocol. But also very importantly, how are you going to monitor this person? Can you treat them as an outpatient? Is it more appropriate they be in the hospital? What lab tests should you be getting? A statement of the investigator's qualifications -- usually they're C.V. -- and some information on the product. So if this is a marketed product already -- perhaps it's proved for something else -- then all you'd really need would be the label or a certificate of authorization from the sponsor or the manufacturer, if this is something that's already in development, for example, or available from another country.
For other things like shelf chemicals or nutritional
supplements, sometimes that can be a little harder because they aren't
always terribly well-described. And this is probably the point of most
controversy, I think, as Dr. Vockley brought up earlier, is the
pharmacology and toxicology information usually referring to the animal
data that needs to support these applications. What's necessary here is
there needs to be information that is adequate such that the FDA can
conclude that the drug is reasonably safe at the dose and duration
proposed for use. So single-patient INDs can be a very big variety. They
can be for almost any condition and almost any organ system.

They can be for acute single-dose treatment or for chronic
treatment. They can be with products that are already marketed, for which
you have human data, or this can be a first in human study. So what is
required to give that adequate information that you're reasonably safe to
proceed? I mean, there's just no one-size-fits-all of how to summarize
this. But there does have to be data there that does support what you are
proposing to do, what you're proposing to treat the patient with.

And if this were a commercial IND, one that is intended to
then go through the usual process to get to a marketing application, which
expanded access is usually not intended to do, then what's required to get
that first in human use is usually two toxicology studies in two different
species for 14 to 28 days, safety pharmacology and genetic toxicology.

Now, is this always required for a single-patient IND? No, it is not. It's just that the amount of information is going to vary tremendously, depending on who you're going to treat, how long, what the proposed dose, proposed route of administration.

Just to give a few frequently asked questions about INDs that also apply to the expanded access, one question that comes up very frequently -- I get this at least once a week, really more often than that -- is that the manufacturer has to be willing to supply the drug. We cannot make anybody give a patient a drug. This actually was a court case in 2008, Abigail Alliance v. Andrew von Aschenbach, O.C., then FDA Commissioner. And the court ruled that patients do not have right to unproven therapies.

Also, all the information, as Dr. Vockley mentioned earlier, in an IND is confidential, in fact, so confidential that FDA can't even acknowledge that we know an IND exists or not. So we can neither confirm nor deny that an investigator has an application. We certainly can't disclose any of the data. And we can only comment on anything that's already in the public domain. So if the drug developers, for example, posted something on their Web site, we can comment on that and only on that.
As I mentioned earlier, investigational plans will vary widely, depending on what it is that you're doing, how novel is the drug, who are you intending to treat, is there any previous experience, what is the developmental phase. Independent review by an IRV is always required. And for an initial IND, when it first comes in, the FDA has 30 days to review it. Trial cannot proceed 'til day 320.

And a core review team typically would consist of the chemistry team, also sometimes called product or quality team, animal pharmacotoxicology and a medical officer or the clinical reviewer. At times, other people will be called in as well. For example, you need a consultation from a different specialty, clinical pharmacology. Sometimes ethics is consulted. And we can and we do call in these people if we need them.

Just a few words on the underpinnings of all of this and why is it we do things the way they do. Well, all of this is written into law in the U.S. Code of Federal Regulations, as Tim mentioned. But the law actually came from shared international ethical principles. These actually have their origin in the Nuremburg code, which was written after the Nuremburg trials after World War II after those horrific experiments in people came to light. But it's the ethical principles that came first, then the law was written down after that.
So FDA's objectives flow from that. And we in any phase in any IND application, we will always be concerned with assuring the safety, the well-being and the rights of the subjects in the studies and that the quality of the scientific investigations of this drug are adequate so that you can evaluate the safety and effectiveness for later phase trials. So that is going to be consistent in any protocol that comes in.

And just speaking a little bit more broadly, good clinical practice guideline -- that guides, not only the FDA, but all developed nations. Internationally-accepted principles are written down in these good clinical practice guidelines. So they are accepted here, and they are accepted in Europe as well.

And in general, these state -- they say a lot more than this, but just in general, that, "Before you proceed with a protocol, you have to make a thorough evaluation of any scientific information that's available, including clinical and non-clinical. You have to conduct your protocol such that the results are credible and accurate and that before this trial starts and really at every phase along the way of an investigation, you have to constantly be reevaluating that the risks do not outweigh the potential benefit to subjects." And this is as new information comes in, you have to take that into consideration.

And just a final word on this is first, do no harm, is the
guiding medical principle. And I’m just going to mention a couple of cases, fairly recently, in about the last 10 years or so where these principles were not entirely followed. And unfortunately, what always seems to happen is that there is a tragedy first, and then the law or the reexamination comes later. And this is why we are always so very careful.

But there was an unfortunate Jesse Gelsinger case back in 1999 where this young man, who actually was not eligible for the clinical trial, actually died after being administered gene therapy. And what followed the investigation was they revealed problems with the study conduct, that the non-clinical safety testing -- there were signals there that were not given as much weight as they should have been. And there were a lot of problems with consenting patients, what the patients were told and what was reported to regulatory agencies. And this actually led to revision of how, especially investigational review boards are composed and how they look at things.

And there was also a very unfortunate case in, I think, 2006. This was in Europe. This did not happen in the United States, thankfully. But TGN 1412, which is an orphan product which was being investigated for malignancies, auto immune disorders and a number of other things, in the very first administration to humans, a single dose, where six subjects were dosed within 10 minutes of each other, they suffered near-fatal side
effects: cytokine storm, patients almost died. They had prolonged
hospitalizations in the ICU.

And the European Commission that subsequently took a
look at this, again, they revised their protocols, especially for biologic
products. But one thing that they saw, again, was inadequate non-clinical
evaluations and evaluations of safe storing doses in human subjects.

So just some common concerns, then, coming out of this,
that when we're looking at these protocols and we're concerned about
safety, there are concerns for not wanting to allow investigational
protocols to go forward -- are almost always safety-related. And the two
most common -- these are called clinical hold criteria, which means that
the protocol would not be allowed to proceed -- is either that subjects --
there is evidence to believe that subjects would be exposed to
unreasonable and significant risk of illness or injury or that there isn't
enough information available that you could conclude that subjects would
be put at risk. And almost always, this means there's a lack of
characterization, either in the product or in the non-clinical data.

And for later phase, these safety concerns still arise, but also
that sometimes the investigations are deficient to meet objectives. But
that really isn't a consideration for an expanded access protocol.

So if something is assessed as not safe to proceed -- and
just some clarifying terminology here. INDs are not approved. They are essentially allowed to go forward. So if we're talking about approved, what we're talking about is a marketing application approval where something you can prescribe. INDs just are allowed to move forward, or they're put on hold. So if you don't hear at day 30, that's one of the few times that no news is good news from the FDA. But if you do hear from us, it usually means that there's a problem.

So what normally would happen, then, if something is being assessed as not safe to proceed, then the review team will call the investigator. And we can only communicate with the investigator. We cannot communicate with anybody else. Well, we communicate with the IND holder. So either the drug company or the investigator, but whoever is the IND holder, that's the only person we can communicate with.

You'll get a call from a review team. And if possible, they will try to negotiate changes and try to allow this to move forward. If we're unable to resolve the issue, then the protocol will go on hold. And that means at day 30, it cannot go forward. Subjects will not be given the drug. And then what follows within 30 days is a letter. And it will list what the hold issues are and what you need to resolve them.

Or in some cases, it's put on what's called a partial hold, where there are limits to what you can do. For example, you cannot
exceed a certain dose, or you can only give one dose, or some other limitation. Hold letter will include a listing of the deficiencies. This is very specific. It will tell you exactly what needs to be addressed. And then it will tell you exactly what you need to do to get yourself off hold.

Now, it's a minority of protocols that go on hold. And the ones that do go on hold most of them come off hold if you address the deficiencies. And when you come back, it's called what's called a complete response.

So this is just some summary statistics of recent regulatory history in just the Center for Drugs in calendar year 2010. And this is just expanded access. And the top -- could I have the pointer? Okay, the numbers up here, these are emergency INDs. This is for a new IND. You can actually have an expanded access protocol to either a new IND or an existing one where you just submit a protocol to an existing open IND.

And I hope you can appreciate here that the overwhelming majority of expanded access protocols are allowed to proceed. In calendar year 2010, there were -- sorry -- there were 12 out of 446 emergency INDs that were denied. Everything else was allowed to proceed. And then there was 100 percent of the single-patient INDs were allowed to proceed, as were intermediate size and treatment INDs. So again, going back to the purpose of expanded access, it's to allow access
to investigational drugs for patients with serious and life-threatening
disorders. We do believe that FDA does consider the condition of the
patient and does show flexibility in these situations.

And just to show you that this was not a fluke, this was not
one year, here's the emergency INDs going back three years. And it's a
very consistent percentage.

So I'm just going to give you a hypothetical hold example.

This is not one specific example, but it is consistent with things that we've
seen. At times, over-the-counter drugs, nutritional supplements or food
additives are proposed for investigational use. Many of these are
described as GRAS, meaning generally regarded as safe. But GRAS is
determined based on exposure. And usually, what's being proposed is
that these be given at a much higher dose than the GRAS level, 100 times
sometimes, and maybe by a different route of administration.

If this is an additive and it could be used for topical use, for
example, investigative may be proposing giving it intravenously. So you
would expect a much higher exposure. So in the example I'm giving here,
there would have been no animal toxicology submitted with the protocol
and a search of the literature, so as severe toxicity at a dose that would be
lower than what they were proposing in the protocol.

So in a situation like this, FDA would very likely request
additional non-clinical testing because it does not appear reasonable to let
this go forward. And it does not appear that the proposed benefit
outweighs the proposed risk.

Just a quote back from the 16th century, it just said, "All
substances are poison, and it really does depend on the dose." And often
the dose and the exposure that is determining what would be safe and
what is not. And just to use an example of salt, which is a very obvious
example, the RDA is about 90 milligrams per kilograms in adults, which for
your proverbial 70 kilogram men would be about a teaspoon a day.

I think we could all agree, even if we should cut down on our
salt, that nobody's going to drop dead in front of you if they take that. But
to give a hundred-fold dose increase of this would actually exceed the
lethal dose in mice by quite a bit. And that would be about one big
container of salt. And not only would it probably kill you, but this would be
an agonizing, really horrible, painful death.

(Laughter.)

DR. PARISER: So just my final slide here is that we had
mentioned earlier about -- Dr. Vockley had mentioned earlier how critical it
is to have interaction with the FDA and discussion protocols. But if you
find out that things end up on hold or you're not sure, you can avail
yourself of meetings. And we actually encourage the use. And I put in
here the guidance on how to request those meetings. So I'll stop here.

DR. VOCKLEY: Thank you, Anne.

We are running significantly behind, so we're just going to move on to our next talk. And hopefully, we can get caught up.

And so, we'll be hearing from Captain Valerie Jensen, who is the Associate Director for the Drug Shortage Program at the FDA and the Center for Drug Evaluation and Research.

Thank you very much.

CAPTAIN JENSEN: Thank you. Good afternoon, everyone.

Okay, thanks.

So I'll talk today about our shortage trends that we're seeing, especially over the last year, the process that we use to address shortages, our role in addressing shortages as well as some key issues that we face. So this is a list of the reasons for shortages that we've always seen. As you're probably aware, manufacturing difficulties can occur any time in the process from early on in the process with the raw material to the end result, labeling and packaging issues. And then, discontinuations are another major reason for shortages, limited capacity - so that just means there's not enough production lines at the companies that are making these products, not enough raw material as well.

And then bulk drug or API shortage -- that would refer to the
raw material and an issue with the raw materials such as an impurity or some type of contamination -- changes in clinical practice, newer things come along. There might be an increase in demand, other products fall off in favor. And then, emergency situations can, of course, increase demand. And then, local issues are another reason that we see. And these would be mainly contractual issues at pharmacies.

So unfortunately, over the last six years, we’ve seen a rise in shortages. And 2010 has been our -- that was our worst year ever for shortages. And particularly disturbing is that we saw a large percentage, larger than past years, of sterile injectable drugs going into shortage.

So 178 shortages occurred in 2010. And that's compared with 157 in all of 2009. And then, as I mentioned, 74 percent of 2010 shortages involved sterile injectables. And these were critical drugs, as you're well-aware. Arginine was one of them -- oncology drugs, succinylcholine, naloxone, furosemide, emergency syringes on crash carts.

And when we looked at the reasons for those sterile injectables, what caused those, we knew that there were some large firms, two very large firms, that had quality issues that were affecting a large number of products. And that's captured here. Fifty-four percent of all of our shortages included quality issues. And some of those issues were a
particulate in the product, contamination of microbial and other types of 
contamination, impurities and some stability changes. Those are some 
examples.

And twenty-one percent were due to just delays and capacity 
issues, so firms just having delays in the manufacturing, changing over 
what they're producing, maybe changing a different -- changing to one 
drug and then putting another drug, kind of, on the back burner for a while. 
That was another reason.

The discontinuations has always been a reason that 
concerns us, especially for these older sterile injectable drugs. And we 
did see 11 percent due to discontinuations. Five percent were due to API 
issues, so some quality issue with the raw material. Four percent were 
due to increase in demand from another shortage. So the ametinide 
 injection went into shortage because of the lasix injection shortage. We 
also had 3 percent due to a loss of a manufacturing site. So a site 
suddenly decided to stop manufacturing, and that sometimes happens, 
especially with contract manufacturers, where some of these products are 
made by a contract manufacturer. And that's a business relationship that 
sometimes just suddenly gets severed.

And 2 percent were due to component problems such as a 
yringe issue or a vial issue. So the problems that we see with these
older sterile injectables in general, we see that there is not enough
capacity at the sites that are making these problems. When one firm has
a problem, there really is not the capacity for all the remaining firms, even
if there's two remaining firms. It's really tough for those two remaining
firms to suddenly ramp up production.

We do, over time, over the last, especially, five years, we've
seen fewer firms making these older sterile injectables. We're down to -- it
would be great if, you know, three firms were making some of these. But
a lot of them are sole-source now.

As you know with sterile injectables, it's a very complex
process. It takes 21 to 30 days from start to finish to make an injectable
product. And that's compared with only a couple days for an oral product.

And then, in general, these older sterile injectables are just
not economically attractive. We continue to hear from firms when they do
discontinue these products. We ask them why, and we ask them to
consider continuing because we really want more and more firms in this
market. And they do tell us these are business decisions, and they are
just not attractive products. So unfortunately, when one firm has a
problem, a shortage almost always occurs.

So what is our process? We have a MaPP, a manual of
policies and procedures process. And our first step is to verify that a
shortage exists. And we use IMS data, which is market share data. And so, we can see who has the largest percentage of the market and who’s making the product and talk with those manufacturers, find out what the problem is. And we get a medical necessity determination for the product. And I'll talk about that in a little bit.

We look at a long-term and short-term plan for the product. And then, of course, we also try to get information on our Web. And we have to get information from the companies to provide on our Web site.

So this is the medical necessity definition. And so, a product is considered medically necessary if it's used to treat or prevent a serious disease and there is no alternate that's available in adequate supply. And the steps that we're taking -- so when we find out something is in shortage, if it's medically necessary, it's getting prioritized. It doesn't mean if it's not medically necessary we're not working on it. It's just it's going to be a priority if it's a medically necessary drug.

And so, for the quality problems, we're working with the firm to address those issues. And sometimes that takes time, especially if it's a very severe issue such as sterility or particulate. We're dealing with some particulate issues right now, unfortunately, with another manufacturer. And so, those issues are very high-risk for patients. And they take some time to resolve.
There are very low-risk problems that occur as well such as the previously mentioned packaging issues or labeling issues. Those we can usually resolve really quickly within a day or so. So once we hear about the problem, we need to hear about it, and then we can help the firm address it.

And when we do address it, we’re using regulatory discretion. So, for example, for a particulate problem, one thing that we’ve done is allow the product to go out, even though it has a risk of particulate, with a health care professional letter advising the use of a filter. And it’s not an ideal situation, but it’s a way to get a medically necessary drug back onto the market while the firm addresses the issue that’s causing the particulate.

So if one firm’s having this quality problem, manufacturing problem, if we’re lucky enough to have another firm making the product, we’re encouraging them to ramp up. And, as I mentioned, a lot of times, they have capacity issues. So we’re telling them anything that they need to help, we’ll help with. So if they need a new manufacturing line approved, we’ll quickly expedite that. If they need a new raw materials source, we expedite that as well.

Another thing that does happen -- and sometimes the firm will have inventory that’s not yet expired or it might be close to expiry or
it's already expired. And if they can give us data to support an increased
expiry, we'll review that quickly as well.

And then, in rare cases, we've used temporary import. And I
shouldn't say -- it's not so rare anymore, actually. We're actually importing
six drugs right now. And so, when we do import a drug to address a
shortage, we're evaluating that overseas product to make sure that it
meets FDA standards, make sure it doesn't present any risk for U.S.
patients. And we're allowing the firm that is willing and able to import to
bring that into the country to address a shortage. These are three
eamples here: propofol, foscarnet and ethiodol. And, as I mentioned,
currently there are others that we're currently importing.

And arginine -- unfortunately, we have not found a firm that
has supply that's able to import now. That's something that it's very
frustrating when we don't have a firm that's able to supply the U.S. in this
manner.

So what we can't do -- we can't force the manufacturer to
make a product. And this is our one regulation, really, for shortages, is
that firms have to tell us if they're going to discontinue a product only if
they're the sole manufacturer and only if it's a medically necessary drug.
And there's no penalty if they don't tell us. So that's the regulation.

So our key issues, really -- we'd like notification from firms
for all shortage issues, not just even discontinuations. We'd always like to know if a firm's considering discontinuation. But we'd also like notification about shortage issues. So if a firm is experiencing any problem, any supply problem -- maybe they're having issues getting raw material or having an issue at the plant. They don't have to tell us that. And we would like to know that because that allows us to, not only help them with their issue, but also encourage the others to ramp up, if there are others and give them time to do that.

So when we looked back at 2010 data, all the issues that we worked on that did not become shortages because of early notification -- we actually had 38 products where the firm did notify us early on. We had a good relationship with the firm, they notified us. And we were able to prevent 38 shortages due to early notification. So we want to continue encouraging firms to do that.

And then, Web site postings -- we know those are extremely helpful. We try to get as much information from the firms as we can through posting. But again, it's up to the firms to provide the info.

And then, the ways that we see to prevent shortages are really that firms have to have a commitment to quality, producing safe products. And that does require investment of resources. And then, of course, redundancy of manufacturing supplies and having an additional
inventory -- that's another way to help address shortages, prevent shortages.

And one thing we really appreciate is notifications from you all. So if you're seeing something on our Web site that doesn't agree with what you're experiencing, or you're experiencing a shortage, let us know. We have a Web site. There's the address. And then report shortages to us at our e-mail address.

Thank you, everyone.

DR. VOCKLEY: All right, thanks.

Sorry, we have a little bit of a scheduling glitch here. This was originally -- we thought this was a 90-minute session. It's 60.

So Kellie Kelm is our next speaker. And being a committee member, I can impose on her to keep it very, very brief. She's just going to give us her summary so that we can try to get back as close to schedule as we can.

So, sorry, Kellie, but thank you for your --

DR. KELM: Devices is always the ugly stepchild.

(Laughter.)

DR. KELM: So let me just skip -- we can skip all of the good stuff.

(Laughter.)
DR. KELM: No one wants to hear about the laws. But actually, the interesting thing is medical devices really -- you know, the law for devices was specified in '76. And at that time, this is when it started classifying devices that were out there and set a new bar for devices, going forward, requiring all the medical devices to be manufactured under good manufacturing practices, that companies had to register and list with the FDA, report adverse events. And then we started our risk-based regulation by intended use, definition of an IVD. And this includes tests that are running in clinical laboratories, but also other settings: point of care or point of service, over-the-counter. We regulate all these as well. IVDs are used for many things: diagnosis, screening, surveillance. But we don't look at forensics. We don't look at, you know, when people are trying to look at whether or not they're related to somebody else or environmental screening.

So when we're looking at a device, the first thing we look at is what is the intended use of the device and what we are going to look at and what we're going to ask for the company depends on what the intended use is that the company specifies. So we regulate by intended use. And so, Class I is low risk. And usually, these Class I devices don't have to come in to FDA before they go on the market. But they do have to be produced under good manufacturing practices, register and list. They
should also record adverse events. All those things are required of manufacturers.

Class II -- most of our devices fall here, moderate risk. And the way the law was set up is that you require a predicate device or a regulation to exist and show that you are linked to a device that's already on the market. And Class III is our high risk or novel intended use devices. And that requires what's called a PMA, or pre-market approval. And so, as I said, how we, sort of, look at your intended use is what is the consequence of a false result.

So if you get it wrong and, you know, talking about a diagnostic versus, for example, you know, whether or not you're -- a test that you should go on a certain chemotherapy or obviously, a pregnancy test is considered a little lower risk than an HIV test. So moderate risk is what we call a pre-market notification, or 510(k). And this is where you show that you're substantially equivalent to devices that are already on the market.

And sometimes, these submissions include clinical, but many times, they don't. And the high risk intended uses require the PMA. This is, a lot of times, includes devices with new intended uses, new technologies, methodologies or something new -- they present new scientific questions. And here, you actually have to submit information
describing safety and effectiveness of the device, usually including performance in clinical trials.

So when I'm looking -- as a reviewer, if I look at 510(k) for an IVD, you need to establish adequate analytical performance. We're looking at accuracy. We're looking at precision, how reliable can you measure the analyte. Clinical performance -- how reliably does the test measure the clinical condition that you specify in your intended use? And IVDs, as opposed to a lot of other devices, actually has a special labeling regulation. And so, we can require more of the intended use directions, warnings, limitations and summary of performance data by the manufacturer.

And so, here's what we usually look at in a submission, as I said. You know, we also look at the instrument. If it's a specific instrument, it's going to be marketed, so the software that's onboard the instrument or any interpretation software, for example, on a P.C. that you hook up to. And then for a PMA, there's more. There's manufacturing. There's design controls, quality system requirements. There's inspection and more paperwork required for the PMA.

So here is an example of an intended use from a newborn screening kit. This is a tandem mass spec. kit to evaluate amino acids, free carnitines in the newborn heel prick blood samples on filter paper.
And this is the quantitative analysis of these analytes and their relationship with each other: is intended to provide analytic concentration profiles that may aid in screening newborns from metabolic disorders. That's an example of one.

So there is more information in tables, but they have to specify the analyte. They have to specify the specimen and lots of other things as well as a clinical indication, in this case, to screen newborns for metabolic disorders.

So I already, sort of, talked about this. We look at reproducibility, so looking over many days and sometimes extra instruments, operators. If you take one sample and repeat the test multiple times, do you get the same result? How do you compare to truth? And this might be a reference method, a clinical endpoint, the predicate device, which is a previously-marketed device. We also ask to look at -- you have to assess the limit of detection for your device, potential interference or cross-reactants and the possibility of cross-contamination or carry-over. That should be provided in the labeling.

So if clinical performance is necessary, there is many ways that that can be established. There could be existing clinical data. There could be new clinical data we have to evaluate. A lot of times, there's information in the literature that can be used. And sometimes, there's
even current clinical knowledge. It depends on what you're proposing and
what's out there.

If someone needs to do a new study or even using a
retrospective study, we love to see the study being done at least at three
sites using, of course, your intended use population. And if it's
retrospective, one of the many problems is making sure the study
reflected, once again, your intended use and what happens if the samples
are stored for over a period of time or the analyte may have degraded
over time -- clearly define inclusion/exclusion criteria. And you need to
make sure the number of people who are actually -- or samples from
affected individuals is statistically appropriate.

So coming from working with manufacturers and not
laboratories as much, these are the challenges that we frequently see
when we're talking to manufacturers as they come in. And I'm sure some
of this reflects even what you may see in the laboratory. But it's difficult
for them to obtain patient samples, especially true positives because we
want to see -- it's very easy to get a lot of negative samples. But we
definitely want to see how -- make sure that the device, in terms of, for
example, newborn screening, can accurately and reliably identify the
patients that should be identified.

And a lot of times, you know, manufacturers work with state
health laboratories. A lot of times, they have a professional relationship and can work with them to actually get newborn samples to screen.

So we know about special circumstances with the sample of a newborn specimen on a dried blood spot. And so, we know about potential interference from certain drugs and endogenous substances that may happen in this patient population. And so, we usually make sure that that's evaluated in some way, even if it's just spiking a sample, for example.

And obviously, sample collection issues -- and sometimes it can be very difficult, depending on what types of collection or what types of samples we're looking for.

So FDA has cleared many devices. So you notice I say cleared. These are all Class II. These are not PMA. Most newborn screening has been Class II. We have the tandem mass spec. assay for inborn errors of amino acid, free carnitine, acylcarnitine metabolism, TSH and T4, 17a-Hydroxyprogesterone, IRT biotinidase deficiency. And I'm sure there are many more.

So let me discuss -- I know one of the things that was mentioned about new technologies -- so, as I said, newborn screening, a lot of times, those are a lot of old technologies. But we're getting new -- like the, actually, tandem mass spec. underwent de novo petition for
classification. So we created a new regulation for that device. And that was clear under 510(k), not a PMA.

And if you use -- going down to investigational devices, so if you're using an unclear or unapproved device in a significant risk study, then you should come in and actually have an investigational device exemption and come talk to the FDA about that. And one note about that -- a lot of times, IRBs make determination that, in their opinion, it's not significant risk. But in our opinion, the manufacturer must read the FDA regulations and make that determination. It's not based on what the IRB determines. It's the manufacturer's responsibility.

HDE is an application that comes in after a HUD determination is made by Tim's office. We also have emergency use authorizations. This was just recently used for the H1N1 flu assays. And that's for a short period defined by the Secretary of HHS. And then, we also have a compassionate use IDE, which is right now not in use too often, at least in my office.

We have many guidance documents that are very helpful. I point out the second one down on informed consent for IVD studies using leftover human specimens that are not individually identifiable. That would be used a lot as well as some of these others that you can look up on our Web site.
So our office posts summaries of the data that we use to clear a device on our Web site. We've been doing this since mid-2003. So you can go to this Web site and look up a device that has been cleared. And if you go to this link, for example, here is a device that was cleared -- and click on the decision summary. You'll find a long sheet that actually is the summary of the data that the firm submitted to us in order to get clearance and be marketed in the U.S.

And so, that's it.

DR. VOCKLEY: Well, Rod, do we have five minutes for questions? Or do we have to have to go to our sessions?

DR. HOWELL: No, I think, why don't you have a few minutes for a question, and then we'll go for our session.

DR. VOCKLEY: Okay.

DR. HOWELL: If there are questions. They've been quite comprehensive in their review.

DR. VOCKLEY: Fred had come to me in between time and asked for a question or an opportunity for questions.

So go ahead.

DR. LOREY: Yeah, this may be a little much for this time period, so stop me if it is. I think this would be a question for Kellie.

As you know, we're trying to work with Perkin Elmer on a
SCID test. And, as you know, the four or five states that are currently screening are using a track assay. They're all pretty similar. It's not FDA approved. There's no kit. Some states are prohibited from doing the screening without a kit.

So this study would be to look at this new procedure, which is actually very similar to the existing track assay with the exception of not having a separate DNA extraction step. And we would run these side-by-side with our existing track assay. What I'm being told, though, is what FDA is asking of me is virtually impossible. And I guess I don't understand what the reasons are. And that's that, at least on first take, I was told all of the negative kids had to have a flow cytometry screen. And that's a diagnostic test. It's not a screening test. We're looking at the screening test.

It's something probably the IRB would approve. Would the four or five states that have screened now screen over 800,000 kids for SCID, very successfully, no false negatives. I guess my question is why can't that existing test, which we're running now and we'd be running along with the new one, be used as the standard and we would only send positives or maybe even discrepant results for flow cytometry?

DR. KELM: So you're right. There is no FDA cleared kit. And we can't compel a manufacturer to come in, as was discussed, for a
drug or to give it. So we are interested in having somebody come in. And I can't comment on whether or not a company has come in to discuss with us whether they're interested.

But in terms of your study design, I, of course, would encourage you to talk to our office director -- and you may have already -- about that. And if there is a company that's already worked with -- or maybe a partner with you that may have already talked to the FDA, I would encourage you to -- if there are issues with the study that you have questions -- to go to them and ask them some questions, and if they need some clarifying comments from the FDA, to do that. But I can't directly comment on that.

But, I guess, you know, the one issue is these are relatively new assays. And I'm not sure how yours is the same or different. But you obviously need to establish that your device is safe and effective and is measuring, you know, what it says it's going to measure. And there may be a reason why some negatives, you know, need to be measured just to establish so that we understand that what you are saying is negative by the tracked assay is definitely a negative, whether that be by flow or by enough clinical follow-up data or something to actually establish that the negative is definitely negative and that a positive is measuring unaffected.

DR. LOREY: So FDA doesn't have a --
MALE SPEAKER: Fred, it's a little too specific for this. Can we move on?

DR. LOREY: Okay.

DR. VOCKLEY: Sorry.

MALE SPEAKER: It is too specific, but it's actually a good question because it highlights something that you and the whole audience should take away from these three discussions, which is when you hear something from a sponsor, you're hearing half of the story. The other half of the story from the FDA you won't hear, you can't hear. It's not allowed for us to tell it. Okay? So when you hear something from a sponsor, that's one part of the story.

If there were a toxicologic disaster, we couldn't tell you that. Okay? So we're not used to that in science. Right? We're used to hearing the whole story and then evaluating the data. But you're not going to get the whole story. And that is the reason it's a good question. Thank you.

MALE SPEAKER: Yeah. Okay. A summary comment or perhaps a request -- one of the things that seems would be very useful would be essentially an FDA guide for dummies.

(Laughter.)

MALE SPEAKER: And I don't know who should put that out,
but if one of our FDA colleagues out there has a suggestion, I mean, you'd
really be doing yourselves and certainly, us, a service to have something
like that.

And I'm going to call the session to an end. Sorry we didn't
have more time to comment.

DR. HOWELL: Well, it was a very fruitful 80-minute
discussion and so forth.

(Laughter.)

DR. HOWELL: But when you publish this book on the FDA
for dummies, we can obviously ask Fred to be the editor.

(Laughter.)

DR. HOWELL: We will need to go to our sessions. And
perhaps we can run a few minutes late. Let me remind you that in the
morning, we will start at our usual time, which is 8:30 in the morning and
not the leisurely 9:30 of this morning. And thank you very much for a very
good discussion. We'll see you in the morning. And for those who -- let
me point out is that if you're not in the Long-Term Follow-Up Committee,
you need to get out of this room promptly.

(Whereupon, at 2:20 p.m., the meeting adjourned.)