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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

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

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

7 MS. HARRIS: Thank you, Dr. Howell.

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

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

20 And then everybody at the table should have received a
21 thumb drive this morning. That thumb drive contains supplement

1 materials to the briefing book. So did everybody get that? The materials
2 on the thumb drive is the same that's on the Web. So does anybody need
3 a thumb drive? All right. Thank you.

4 DR. HOWELL: Thank you very much.

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

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

16 Jerry?

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

19 (Laughter.)

20 DR. VOCKLEY: First of all, for those of you who expressed
21 concern about having gotten stuck in blizzards on the way out last time, I'll

1 have you know we did not get stuck in blizzards, but a nice little, slightly
2 different plague.

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

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

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

20 You have, I believe, in your books the summary that the IOM
21 makes available publicly on this. I had the good fortune of getting a copy

1 of the full 442 pages to review for this session. So more evidence to be
2 careful what you ask for, you might get it.

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

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

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

19 They recommended creative strategies for sharing research
20 resources and infrastructures to make good and efficient use of scarce
21 funding, expertise, data, biological specimens and participation in

1 research by people with rare diseases or with rare diseases, appropriate
2 use and further development of trial design and analytical methods
3 tailored to special challenges of conducting research on small populations,
4 reasonable rewards and incentives for private sector innovation, adequate
5 organizations and resources, including staff with expertise on rare disease
6 research and product development for the public agencies involves and
7 then mechanisms for weighing priorities for rare disease research and
8 product development.

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

18 And then, at the same time, though, as this convergence of
19 things, I was discussing with some of our newborn screening labs some
20 issues that seemed a little bit confusing relative to use of outside kits,
21 commercially-available kits for newborn screening tests, in particular,

1 SCIDs. And so, one of the things that, relative to some of these issues,
2 that the IOM report highlighted was that in relation to the FDA, that they
3 identified that there were insufficient resources for timely meetings and
4 guidance for sponsors, that there was inconsistency in reviews of
5 applications for orphan drug approvals across the divisions and
6 inadequate resources for from products, grants, programs. So this is from
7 the IOM report.

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

16 The recommendations that came out of the IOM were that
17 there should be an assessment of staff reviews of applications for the
18 approval of orphan drugs, that there needed to be a review on how that
19 was being done and how that information was being communicated, that
20 they should evaluate the extent to which studies submitted in support of
21 orphan drugs are consistent with advances in the science of small clinical

1 trials to ensure that NIH funded product development studies involving
2 rare diseases are designed to fulfill requirements for FDA approval, so
3 some interagency communication there, that the FDA should expand its
4 critical path initiative to define criteria for evaluation of surrogate endpoints
5 for use in trials of products for rare conditions.

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

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

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

1 regulations not to talk about specific applications because of confidentiality
2 issues.

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

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

20 Regarding emergency supplies, it's important to note that
21 many of the medications that are used for treatment in IEMs are really

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

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

18 Some of the issues that came up regarding new device
19 approval -- first of all, keep in mind that diagnostic kits are defined as
20 devices, something that is probably not generally appreciated among, at
21 least, physicians in the field. So questions that arose -- what are the

1 regulations for use of existing kits for new purposes, the single lab
2 reagents or tests require approval, and what's that process for approval.
3 We'll hear some comments on that.

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

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

1 little bit more generally available.

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

4 (Laughter.)

5 DR. VOCKLEY: Thanks for coming.

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

7 Okay?

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

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

20 Could I have the next slide? Okay. So why should we
21 partner? This is really what I think is helpful, is why should we, at the FDA

1 and the Office of Orphan Products and the review divisions, be such an
2 important partner to this committee, which does such important work?
3 Inborn errors metabolism, which are a focus of this group, are also one of
4 the focuses of orphan products. Although they actually make up only
5 about 5 percent of all orphan products, they are incredibly important. And
6 we are fully expecting other new therapies to be coming very, very soon,
7 frankly.

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

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

21 Next slide? Okay, so let me bring you back, to start off, to

1 1982, when some of the people here probably weren't born and some of
2 us remember it quite well. Rare diseases basically were very, very
3 problematic. The economic systems that were set up was such that in
4 order for a drug company to make money, you do an investment of a lot of
5 development money and then you sell your pills. And if there aren't many
6 people to sell your pills to, then it just doesn't work. That algebra didn't
7 work, and, frankly, the data supported that from 1973 to 1982. There were
8 only 10 new drugs that are approved for rare diseases.

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

14 Move into this picture, Abbey Myer, a housewife from
15 Danbury, Connecticut, who had a couple of kids with rare diseases and
16 who took it upon herself, recognized that, while rare diseases are
17 individually infrequent, they're collectively common. And if she could just
18 get all these people together, they could form a grassroots political
19 movement. She had a special friend by the name of Henry Waxman, an
20 obscure congressman from California at the time, who said that they're
21 like orphans, that they require special care.

1 A movement was formed, a committee started. It's a
2 uniquely American story. It's democracy in action. And it happened.

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

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

18 But you should note that the approval process for orphan
19 drugs is just the same as the approval process for any other drug. The
20 process is that they have to prove safety and efficacy. Now, what safety
21 and efficacy mean have been flexibly interpreted, based upon the

1 conditions of the clinical trial themselves. And Dr. Anne Pariser will speak
2 a little bit more about this when she comes up.

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

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

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

1 considerable time after that.

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

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

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

20 The Office of Orphan Products is an advocate for this
21 process. We want to see more products developed for people with rare

1 diseases. So we're actually pushing the process forward through this. I
2 didn't mention our grants program. We have the largest grants program at
3 FDA. It's about \$16 million, exclusively for clinical trials for rare diseases.
4 We can talk about that later.

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

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

17 Next slide? Okay, so in summary, I believe that FDA needs
18 to be engaged with this committee much more than it has historically, not
19 only on diagnostics, on which we are extremely well-represented in Kellie
20 Kelm, but also on these therapies. And as my parting shot as I'm leaving
21 the door of FDA, I would put forward that there really ought to be some

1 systematic consideration of newborn screening upon the emergence or
2 perhaps the licensure of a new therapy for newborns and children. I don't
3 know how that process works right now.

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

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

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

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

17 Thank you.

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

20 I'm going to be talking about the expanded access process.
21 It's expanded access to investigational drugs. And I'm first going to just

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

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

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

19 And because most of these are for single patients given on
20 an open-label basis, they are really not likely to describe effectiveness.
21 And they are not likely to support a later marketing application. So they

1 really are not intended to support any kind of an approval.

2 Because of this, FDA's main concern is with the safety. And
3 the requirement says that any potential benefit to a patient has to justify
4 the potential risks and that these potential risks should not be
5 unreasonable. So unreasonable is really the operative word here. And
6 that, of course, is subject to some interpretation.

7 FDA does maintain, thought, that the best access to any
8 drug for patients is an approved product, meaning a product that is
9 approved under a marketing application and is available for prescription by
10 physicians. This next best choice would be for patients to be enrolled in
11 well-designed clinical trials that are designed to demonstrate efficacy and
12 safety. And this expanded access process is then available for patients
13 who are unable to access either those mechanisms. But there's also a
14 requirement here that the expanded access use will not interfere with
15 either the initiation, conduct or completion of those clinical trials that are
16 intended to demonstrate effectiveness and safety that could then support
17 a marketing application.

18 So in general, there are four types of expanded access. And
19 these are usually single-patient applications, but not always. And they are
20 considered individually one at a time on a case-by-case basis. There's
21 four general types: emergency, single-patient, intermediate size and

1 treatment protocols. And just very briefly, an emergency use IND -- this is
2 when you don't have time to go through the usual IND process. Usually,
3 what happens is the treating physician or the physician intending to give
4 the product to the patient calls the FDA. The medical officer is then called
5 over, gets on the phone with the physician. And this usually happens very
6 quickly, sometimes within an hour, but usually within 24 hours.

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

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

18 And then the treatment protocol is a little bit different. This is
19 for drugs that have either completed or late in pivotal trials to support a
20 marketing application, or the sponsor is compiling the data. And while
21 that's going on, it's usually desirable to let patients continue to have

1 access to the drug in those situations. But in that situation, you do have a
2 lot more information to work with.

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

12 There needs to be a proposed treatment plan, usually in the
13 form of a protocol. But also very importantly, how are you going to
14 monitor this person? Can you treat them as an outpatient? Is it more
15 appropriate they be in the hospital? What lab tests should you be getting?
16 A statement of the investigator's qualifications -- usually they're C.V. -- and
17 some information on the product. So if this is a marketed product already
18 -- perhaps it's proved for something else -- then all you'd really need would
19 be the label or a certificate of authorization from the sponsor or the
20 manufacturer, if this is something that's already in development, for
21 example, or available from another country.

1 For other things like shelf chemicals or nutritional
2 supplements, sometimes that can be a little harder because they aren't
3 always terribly well-described. And this is probably the point of most
4 controversy, I think, as Dr. Vockley brought up earlier, is the
5 pharmacology and toxicology information usually referring to the animal
6 data that needs to support these applications. What's necessary here is
7 there needs to be information that is adequate such that the FDA can
8 conclude that the drug is reasonably safe at the dose and duration
9 proposed for use. So single-patient INDs can be a very big variety. They
10 can be for almost any condition and almost any organ system.

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

18 And if this were a commercial IND, one that is intended to
19 then go through the usual process to get to a marketing application, which
20 expanded access is usually not intended to do, then what's required to get
21 that first in human use is usually two toxicology studies in two different

1 species for 14 to 28 days, safety pharmacology and genetic toxicology.

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

6 Just to give a few frequently asked questions about INDs
7 that also apply to the expanded access, one question that comes up very
8 frequently -- I get this at least once a week, really more often than that --
9 is that the manufacturer has to be willing to supply the drug. We cannot
10 make anybody give a patient a drug. This actually was a court case in
11 2008, Abigail Alliance v. Andrew von Aschenbach, O.C., then FDA
12 Commissioner. And the court ruled that patients do not have right to
13 unproven therapies.

14 Also, all the information, as Dr. Vockley mentioned earlier, in
15 an IND is confidential, in fact, so confidential that FDA can't even
16 acknowledge that we know an IND exists or not. So we can neither
17 confirm nor deny that an investigator has an application. We certainly
18 can't disclose any of the data. And we can only comment on anything
19 that's already in the public domain. So if the drug developers, for
20 example, posted something on their Web site, we can comment on that
21 and only on that.

1 As I mentioned earlier, investigational plans will vary widely,
2 depending on what it is that you're doing, how novel is the drug, who are
3 you intending to treat, is there any previous experience, what is the
4 developmental phase. Independent review by an IRV is always required.
5 And for an initial IND, when it first comes in, the FDA has 30 days to
6 review it. Trial cannot proceed 'til day 320.

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

14 Just a few words on the underpinnings of all of this and why
15 is it we do things the way they do. Well, all of this is written into law in the
16 U.S. Code of Federal Regulations, as Tim mentioned. But the law actually
17 came from shared international ethical principles. These actually have
18 their origin in the Nuremburg code, which was written after the Nuremburg
19 trials after World War II after those horrific experiments in people came to
20 light. But it's the ethical principles that came first, then the law was written
21 down after that.

1 So FDA's objectives flow from that. And we in any phase in
2 any IND application, we will always be concerned with assuring the safety,
3 the well-being and the rights of the subjects in the studies and that the
4 quality of the scientific investigations of this drug are adequate so that you
5 can evaluate the safety and effectiveness for later phase trials. So that is
6 going to be consistent in any protocol that comes in.

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

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

21 And just a final word on this is first, do no harm, is the

1 guiding medical principle. And I'm just going to mention a couple of
2 cases, fairly recently, in about the last 10 years or so where these
3 principles were not entirely followed. And unfortunately, what always
4 seems to happen is that there is a tragedy first, and then the law or the
5 reexamination comes later. And this is why we are always so very careful.

6 But there was an unfortunate Jesse Gelsinger case back in
7 1999 where this young man, who actually was not eligible for the clinical
8 trial, actually died after being administered gene therapy. And what
9 followed the investigation was they revealed problems with the study
10 conduct, that the non-clinical safety testing -- there were signals there that
11 were not given as much weight as they should have been. And there
12 were a lot of problems with consenting patients, what the patients were
13 told and what was reported to regulatory agencies. And this actually led to
14 revision of how, especially investigational review boards are composed
15 and how they look at things.

16 And there was also a very unfortunate case in, I think, 2006.
17 This was in Europe. This did not happen in the United States, thankfully.
18 But TGN 1412, which is an orphan product which was being investigated
19 for malignancies, auto immune disorders and a number of other things, in
20 the very first administration to humans, a single dose, where six subjects
21 were dosed within 10 minutes of each other, they suffered near-fatal side

1 effects: cytokine storm, patients almost died. They had prolonged
2 hospitalizations in the ICU.

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

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

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

21 So if something is assessed as not safe to proceed -- and

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

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

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

20 Or in some cases, it's put on what's called a partial hold,
21 where there are limits to what you can do. For example, you cannot

1 exceed a certain dose, or you can only give one dose, or some other
2 limitation. Hold letter will include a listing of the deficiencies. This is very
3 specific. It will tell you exactly what needs to be addressed. And then it
4 will tell you exactly what you need to do to get yourself off hold.

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

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

15 And I hope you can appreciate here that the overwhelming
16 majority of expanded access protocols are allowed to proceed. In
17 calendar year 2010, there were -- sorry -- there were 12 out of 446
18 emergency INDs that were denied. Everything else was allowed to
19 proceed. And then there was 100 percent of the single-patient INDs were
20 allowed to proceed, as were intermediate size and treatment INDs. So
21 again, going back to the purpose of expanded access, it's to allow access

1 to investigational drugs for patients with serious and life-threatening
2 disorders. We do believe that FDA does consider the condition of the
3 patient and does show flexibility in these situations.

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

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

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

21 So in a situation like this, FDA would very likely request

1 additional non-clinical testing because it does not appear reasonable to let
2 this go forward. And it does not appear that the proposed benefit
3 outweighs the proposed risk.

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

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

16 (Laughter.)

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

1 here the guidance on how to request those meetings. So I'll stop here.

2 DR. VOCKLEY: Thank you, Anne.

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

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

8 Thank you very much.

9 CAPTAIN JENSEN: Thank you. Good afternoon, everyone.

10 Okay, thanks.

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

21 And then bulk drug or API shortage -- that would refer to the

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

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

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

17 And when we looked at the reasons for those sterile
18 injectables, what caused those, we knew that there were some large firms,
19 two very large firms, that had quality issues that were affecting a large
20 number of products. And that's captured here. Fifty-four percent of all of
21 our shortages included quality issues. And some of those issues were a

1 particulate in the product, contamination of microbial and other types of
2 contamination, impurities and some stability changes. Those are some
3 examples.

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

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

20 And 2 percent were due to component problems such as a
21 syringe issue or a vial issue. So the problems that we see with these

1 older sterile injectables in general, we see that there is not enough
2 capacity at the sites that are making these problems. When one firm has
3 a problem, there really is not the capacity for all the remaining firms, even
4 if there's two remaining firms. It's really tough for those two remaining
5 firms to suddenly ramp up production.

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

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

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

20 So what is our process? We have a MaPP, a manual of
21 policies and procedures process. And our first step is to verify that a

1 shortage exists. And we use IMS data, which is market share data. And
2 so, we can see who has the largest percentage of the market and who's
3 making the product and talk with those manufacturers, find out what the
4 problem is. And we get a medical necessity determination for the product.
5 And I'll talk about that in a little bit.

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

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

16 And so, for the quality problems, we're working with the firm
17 to address those issues. And sometimes that takes time, especially if it's
18 a very severe issue such as sterility or particulate. We're dealing with
19 some particulate issues right now, unfortunately, with another
20 manufacturer. And so, those issues are very high-risk for patients. And
21 they take some time to resolve.

1 There are very low-risk problems that occur as well such as
2 the previously mentioned packaging issues or labeling issues. Those we
3 can usually resolve really quickly within a day or so. So once we hear
4 about the problem, we need to hear about it, and then we can help the
5 firm address it.

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

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

20 Another thing that does happen -- and sometimes the firm
21 will have inventory that's not yet expired or it might be close to expiry or

1 it's already expired. And if they can give us data to support an increased
2 expiry, we'll review that quickly as well.

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

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

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

21 So our key issues, really -- we'd like notification from firms

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

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

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

18 And then, the ways that we see to prevent shortages are
19 really that firms have to have a commitment to quality, producing safe
20 products. And that does require investment of resources. And then, of
21 course, redundancy of manufacturing supplies and having an additional

1 inventory -- that's another way to help address shortages, prevent
2 shortages.

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

8 Thank you, everyone.

9 DR. VOCKLEY: All right, thanks.

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

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

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

17 DR. KELM: Devices is always the ugly stepchild.

18 (Laughter.)

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

21 (Laughter.)

1 DR. KELM: No one wants to hear about the laws. But
2 actually, the interesting thing is medical devices really -- you know, the law
3 for devices was specified in '76. And at that time, this is when it started
4 classifying devices that were out there and set a new bar for devices,
5 going forward, requiring all the medical devices to be manufactured under
6 good manufacturing practices, that companies had to register and list with
7 the FDA, report adverse events. And then we started our risk-based
8 regulation by intended use, definition of an IVD. And this includes tests
9 that are running in clinical laboratories, but also other settings: point of
10 care or point of service, over-the-counter. We regulate all these as well.

11 IVDs are used for many things: diagnosis, screening,
12 surveillance. But we don't look at forensics. We don't look at, you know,
13 when people are trying to look at whether or not they're related to
14 somebody else or environmental screening.

15 So when we're looking at a device, the first thing we look at
16 is what is the intended use of the device and what we are going to look at
17 and what we're going to ask for the company depends on what the
18 intended use is that the company specifies. So we regulate by intended
19 use. And so, Class I is low risk. And usually, these Class I devices don't
20 have to come in to FDA before they go on the market. But they do have to
21 be produced under good manufacturing practices, register and list. They

1 should also record adverse events. All those things are required of
2 manufacturers.

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

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

17 And sometimes, these submissions include clinical, but
18 many times, they don't. And the high risk intended uses require the PMA.
19 This is, a lot of times, includes devices with new intended uses, new
20 technologies, methodologies or something new -- they present new
21 scientific questions. And here, you actually have to submit information

1 describing safety and effectiveness of the device, usually including
2 performance in clinical trials.

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

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

19 So here is an example of an intended use from a newborn
20 screening kit. This is a tandem mass spec. kit to evaluate amino acids,
21 free carnitines in the newborn heel prick blood samples on filter paper.

1 And this is the quantitative analysis of these analytes and their relationship
2 with each other: is intended to provide analytic concentration profiles that
3 may aid in screening newborns from metabolic disorders. That's an
4 example of one.

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

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

18 So if clinical performance is necessary, there is many ways
19 that that can be established. There could be existing clinical data. There
20 could be new clinical data we have to evaluate. A lot of times, there's
21 information in the literature that can be used. And sometimes, there's

1 even current clinical knowledge. It depends on what you're proposing and
2 what's out there.

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

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

21 And a lot of times, you know, manufacturers work with state

1 health laboratories. A lot of times, they have a professional relationship
2 and can work with them to actually get newborn samples to screen.

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

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

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

18 So let me discuss -- I know one of the things that was
19 mentioned about new technologies -- so, as I said, newborn screening, a
20 lot of times, those are a lot of old technologies. But we're getting new --
21 like the, actually, tandem mass spec. underwent de novo petition for

1 classification. So we created a new regulation for that device. And that
2 was clear under 510(k), not a PMA.

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

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

17 We have many guidance documents that are very helpful. I
18 point out the second one down on informed consent for IVD studies using
19 leftover human specimens that are not individually identifiable. That would
20 be used a lot as well as some of these others that you can look up on our
21 Web site.

1 So our office posts summaries of the data that we use to
2 clear a device on our Web site. We've been doing this since mid-2003.
3 So you can go to this Web site and look up a device that has been
4 cleared. And if you go to this link, for example, here is a device that was
5 cleared -- and click on the decision summary. You'll find a long sheet that
6 actually is the summary of the data that the firm submitted to us in order to
7 get clearance and be marketed in the U.S.

8 And so, that's it.

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

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

13 DR. VOCKLEY: Okay.

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

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

18 So go ahead.

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

21 As you know, we're trying to work with Perkin Elmer on a

1 SCID test. And, as you know, the four or five states that are currently
2 screening are using a track assay. They're all pretty similar. It's not FDA
3 approved. There's no kit. Some states are prohibited from doing the
4 screening without a kit.

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

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

20 DR. KELM: So you're right. There is no FDA cleared kit.
21 And we can't compel a manufacturer to come in, as was discussed, for a

1 drug or to give it. So we are interested in having somebody come in. And
2 I can't comment on whether or not a company has come in to discuss with
3 us whether they're interested.

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

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

21 DR. LOREY: So FDA doesn't have a --

1 MALE SPEAKER: Fred, it's a little too specific for this. Can
2 we move on?

3 DR. LOREY: Okay.

4 DR. VOCKLEY: Sorry.

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

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

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

20 (Laughter.)

21 MALE SPEAKER: And I don't know who should put that out,

1 but if one of our FDA colleagues out there has a suggestion, I mean, you'd
2 really be doing yourselves and certainly, us, a service to have something
3 like that.

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

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

8 (Laughter.)

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

11 (Laughter.)

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

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