FOOD AND DRUG ADMINISTRATION

TOWN HALL MEETING

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MEHARRY MEDICAL COLLEGE

NASHVILLE, TENNESSEE

DR. MAUPIN: I'm Dr. John Maupin, president of Meharry Medical College, and for those of you who I haven't had the occasion to meet, hello.

AUDIENCE: Hello.

DR. MAUPIN: For those of you that have been here throughout the day and have not had a chance to see our campus, I hope you will. I just went outside, and I have a few people here that have great powers and we decided to hold off the rain, so you may take a tour as long as the sun holds up for those few minutes.

But all kidding aside, I think what I have heard and have just come back in and have had an opportunity -- have not had a chance to participate today, but I have heard from everybody how excited they are about the program, presentations, and the discussion, and most importantly and most appropriately, how excited and pleased they were to hear from Dr. Joycelyn Elders, who we had the opportunity -- and I want to give -- ask everybody to give her another round of applause.

(Applause.)

DR. MAUPIN: The topic is one in which is serious. The topic is one in which many have some concerns. The topic is one in which I want to share for

just one moment because, in this spot, in 1972, there was a big discussion. It was a gathering of the Congressional Black Caucus meeting on the status of health in the African-American community. It was a discussion about the Tuskegee studies and all that went on during that time frame. It was a discussion about health disparity. Unfortunately, that meeting that day, the issue that was before us then is the same issue that is before this country.

Health disparities, not just health disparities with one ethnic group, but health disparities across many ethnic groups. Health disparities based on not just ethnicity but also continue to be based on where you live and what your economic status is. So this issue -- this country's issue of equal quality health care, this issue of equal quality access to care, this issue of how do we go about making a change in the illnesses and conditions that continue to destroy families and the lives of individuals, clearly, the research that we do in our institutions and across this country, the research that will happen in communities, the population-based research on why we do things, the behavioral questions that need to be answered, the clinical trials that will occur all need to be conducted with the highest level of

ethics, the highest level of moral, moral standards.

And so it's important this evening that we come together as a community, because no matter what Meharry or Vanderbilt across town or Emory University in Atlanta, Georgia, do, what we do in research and how it relates to the community is really the end result. And I know that our friends here from the FDA are pleased to have this opportunity to hear from you so that the Tuskegees don't happen again and that we can answer those questions that are on your mind.

So while you've had a lot of lectures and a lot of questions and a lot of discussions and, from what I hear about those, there are a lot of laughs, too. I just heard one coming in I just talked to. All they said was, all I could hear about was the one hair on the bald man. Since I'm getting thinner, I'm worried about my one hair.

But to start this Town Hall Meeting this evening, I have the pleasure of introducing Gary Dykstra, the chairperson for the Town Hall Meeting and also the Southeastern Regional Director for the FDA.

(Applause.)

MR. DYKSTRA: Okay. Thank you, Dr. Maupin. I have also been rolling that thought around in my head about the one hair, Dr. Elders. I

want to thank her, too, for helping us this evening set the stage for what is to follow for the next couple of hours as we talk about this very important topic of research, research ethics, and all of the checks and balances that we have in that system.

I encourage all of you to take a look at the little brochure that was handed to you when you came in here and look at the one page that talks about the FDA mission and the FDA role in this whole area of bioresearch and the parties that play a role in that check and balance system. FDA is only one of those parties. We are here this evening to talk about that whole system and to talk about some of the issues that Dr. Elders brought up, some of the issues of disparity, some of the issues of what perhaps FDA can do to close those disparities in our health care system and our health care research, and anything else that we can adhere this evening concerning these important topics.

I want to remind everybody that this is a Town Hall Meeting. It's intended to occur in that kind of format. We have some distinguished speakers here who are going to give you some information about what's going on in FDA, how we approach this issue from the government side. That's so that you have, and we all have, kind of a common understanding of where we're

coming from in the government arena, and you can formulate your own opinions about that.

And once we've presented that information, then, in the spirit of a Town Hall Meeting, we'll have a back-and-forth discussion. We would like to keep the questions and the comments and the concerns pretty much in that -- those areas that we've been focusing on really all this week with the meetings that are going on. This is just one more piece of those meetings. However, you know, if you have some general questions about FDA, some things you don't understand about us, we'll be happy to try to address those. And if we don't have the people here to address it, we'll take that question back and try to get the answers for you.

But I encourage everybody. Everybody here has equal time. If you have questions, if you have concerns about what you hear or other things that are on your mind concerning bioresearch, ethics, and other things related to those topics, please let us know what those are.

If you're a little bit shy about coming to the microphone or speaking up, we have some paper. You probably also have pieces of paper. Write your question down and we'll collect it, bring it up here, and see if we can address it anonymously, so you don't have to

stand up and necessarily identify yourself.

I want to move along now in this program and introduce you to our first speaker. Our first speaker is also going to help me set the stage a little bit for the topics that we want to discuss this evening. She is Linda Skladany. Linda is actually brand new to the Food and Drug Administration, but she has a very stellar resume and past, and I'm just now getting to know her a little bit better. And she has some fascinating tales to tell about some of her many jobs that she's held in past administrations and outside of government.

In June of this year she was appointed as Senior Associate Commissioner for External Relations by President Bush. And in this position she oversees the Executive Secretary, Public Affairs, Consumer Affairs, Omsbudsman, Special Health Issues and Advisory Committee Oversight and Management Staff in the Food and Drug Administration. Now, that's a mouthful, folks. I can tell you that is a mighty big job.

Prior to returning to public service, she served as Vice President for Congressional Relations at the public relations firm of Parry, Romani, DeConcini, and Symms -- you may recognize those last two names -- since 1995. She is a graduate of William and Mary.

She's got her masters at Wake Forest and her juris doctor at the University of Richmond in Virginia.

Her background in government service and public policy includes work in health and safety, education, transportation, as well as environmental issues and regulatory reform. Mrs. Skladany began her distinguished government service in 1981 as a Special Assistant to the Secretary of Education. She's also served in a variety of important positions under several different administrations. With that introduction, Linda?

(Applause.)

MS. SKLADANY: Thank you, Gary, for that nice introduction. And all my life I wanted to be a specialist and know more about one subject than anyone else in the world. Because of evil deeds of childhood and youth, I've been condemned to the greer of a generalist. But I must say that I'm really as excited about my new portfolio as any position I've ever been honored to have.

I want to say, though, confession is good for the soul. I can't think of many more humbling experiences than to be invited to speak following Dr. Elders. She is such an excellent speaker. But it is an honor to do so.

As Gary made clear, I really am a relatively newcomer to our agency and, as such, I find being here attending the Meharry conference and visiting the Vanderbilt University Medical Center with Linda Lane today and Meharry Medical Center with Dr. Ray and Dr. Grandison and President Maupin, has been such an impressive learning experience, and I'm already beginning to recruit med students for you all.

I'm particularly glad of tonight's opportunity to participate in the process that plays such a central role in the success of FDA's mission by providing us with insights that are essential for the agency's planning and sense of direction. The laws passed by congress, our professional ethics, and our personal convictions tell us the public health goals that FDA really must reach. How to achieve those goals is something we learn in close consultations, such as one we're about to conduct tonight with your community.

96 years ago the United States Congress decided that assuring the safety of food and drugs for American consumers was an essential obligation of the federal government. The congressional will was expressed in the Food and Drug Act of 1906 which launched the Food and Drug Administration. All organizations thrive or perish with causes for which

they were created, and FDA's cause, the protection of public health, has gained recognition and significance with each of the passing decades.

Today our agency is responsible for the safety or safety and effectiveness of over a trillion dollars worth of food, drugs, medical devices that are essential for human health and well-being. That's 25 percent of every consumer dollar. Rather awesome role there.

Our purview also includes animal drugs and feed, equipment that emits radiation, and cosmetics. This is a huge agenda that gives many, many groups a stake in FDA's policies and actions. What the history of FDA shows and what I'm here tonight to emphasize is that none of these stakeholder groups has a more compelling impact on what our agency does than American consumers, you, your families, your friends.

Protection and promotion of the health of the American public, and that means the very rich diversity of the people of this great nation, is the FDA's paramount job. And when the health of the part of our public lags behind the rest of the nation, as in the case of communities of color, the FDA must seek advice, preferably from members of these communities, on how to close that gap. That's what we're about to do tonight,

by focusing particularly on the participation of African-American patients and health care professionals in clinical trials.

As you will hear from my colleagues, the FDA has taken several steps forward in this area and evidence suggests that they have been effective, but much more needs to be done. Yesterday I told the Meharry conference that the FDA is committed to creating a robust shield of protections sheltering all of our people, regardless of race, immensity, gender, or age from avoidable public health hazards.

Tonight we will engage in a discussion about how to best advance this goal. There are many, many questions to be asked and to be answered. And I will not keep us from getting ahead with our work on our important agenda. Once again, welcome, thank you for coming, thank you for having me, and I'm looking forward to a lively exchange of views and information about challenges ahead of us. Thank you.

(Applause.)

MR. DYKSTRA: Thank you, Linda. I was just thinking and kind of reflecting back upon my experiences in FDA, and it was about 26 years ago when I was just starting out in FDA, that we began to look at this whole issue of bioresearch monitoring and actually

put some staff together to develop regulations, develop guidelines, and begin to really regulate the whole area of bioresearch monitoring.

This was done because we were discovering, much to our dismay, that researchers were not always on the up and up. There were a lot of pressures in research, both in the drug companies as well as in academic institutions, to, as they say, publish or perish. And so they were creating data, in some cases out of thin air. And as we discovered this, we recognized that, within FDA, we needed to create a presence and staffs in our product centers in order to deal with this and to be somewhat of a watch dog.

We also had to develop the expertise out in our field organizations. We had to train our investigators. These were people who were not trained to go in to clinical investigators and pore over all of that data, looking for discrepancies, looking for graphited data and things like that.

We started that 26 years ago. It has matured tremendously since then. We think we do a pretty good job, but the job is immense. There is, as you can imagine -- even though Dr. Elders indicated it's -- it's small in comparison to a lot of other things, there's a lot of research going on in this country.

There are a lot of clinical trials going on in this country. It's a big, big job to try to monitor all of that research and make sure that it's being done correctly and being done in accordance with all of the rules and regulations.

A lot of the researchers think that, as you might expect, there's a bit of over-regulation and it stifles research. There are those kinds of opinions out there. But we try to involve them as much as possible in our process. We try to, as we're doing here tonight, explain what we do and how we do it and why it's so important that we do it. And it's so important to this whole issue of health care and closing the disparities, correcting the disparities.

Our next speaker this evening is someone who is very intimately involved in that whole system of regulation of bioresearch, and he is Dr. David Lepay.

Dr. Lepay has been with FDA for ten years and recently assumed the position of Senior Advisor for Clinical Science and Director of the newly-created Office of Good Clinical Practice in our -- in the office of our commissioner. Prior to that, he was a director of the Division of Scientific Investigations in our Center for Drug Evaluation and Research.

Dr. Lepay has his B.S. from Yale, his

M.D. from Cornell, and he did a residency in Brigham and Womens and also holds a Ph.D. from Rockefeller University. So you can see, he's imminently qualified. He also chairs FDA's Human Protections Steering Committee and serves on a number of working groups and panels in the human protection area.

Dr. Lepay is a frequent spokesperson for FDA on the topics of good clinical practice and the whole area of bioresearch monitoring. So with that introduction, David?

(Applause.)

DR. LEPAY: Thank you so much. I'm going to keep my remarks fairly short this evening because, of course, the goal is to hear the people in the audience, not to hear from those at the podium. I certainly want to thank Dr. Elders, however, for her very eloquent remarks this evening because I think she set the stage for the whole issue of clinical research and its importance, how critical clinical research is to advancing medical science, to advancing public health, and to meeting the health needs of our communities. And we're talking here about the health needs of all Americans. That's what is critical as we move forward in the clinical research.

For FDA, of course, clinical research is

critical to our own mission, our mission of ensuring the safe use of FDA-regulated products that are, themselves, safe and effective. But I think it's also important as we talk about the importance of clinical presearch to certainly talk, as well, about the importance of the research participant.

From FDA's perspective, we understand and we appreciate the role of the research participant. There are impositions imposed on these individuals in taking on the responsibilities to participate in clinical trials. There are certainly inconveniences, the inconveniences of having to come for additional clinical visits, the inconveniences of potential risks and, indeed, the risks themselves. That is clearly an issue that we have to take into account and for which we have to respect clinical research subjects and understand that they deserve protection in this process.

For FDA, part of the process is what we term "good clinical practice". Good clinical practice standards were put in place by the agency back in the 1960s. It's a good system. It's a system of responsibilities. It's a system of shared responsibilities. All of the parties who are involved in clinical research have responsibilities under this system, the investigators and site staff with direct

contact with the subject, the study sponsors and staff who have a responsibility to monitoring the studies, the institutions, the Institutional Review Board, and, of course, government regulators, as well.

As I say, it's a robust system. It works well. But, of course, clinical research continues to evolve and we have to be able to evolve the system accordingly. It's a system, as well, that has been embraced by countries around the world to harmonization efforts. We now receive research at FDA from 72 countries in the world. We've been out to look at the clinical research in over 50 of these countries.

From FDA's perspective, again, we do recognize that we have responsibility in the system. Some of these are direct responsibilities and certainly these are topics that we are -- we look forward to discussing in the course of this meeting, our responsibilities for ensuring the proper manufacturing of products that are going to be used in investigational studies, for ensuring that there's free clinical information to support the introduction of these products into human subjects, to ensure protocols are provided and the protocols are reviewed by FDA, their design, their inclusion and exclusion criteria, and their safety measurements.

The information that's going to investigators is adequate in the form of investigator brochures. Our review divisions look at investigator brochures for those applications that come into the agency. And we follow safety reports, we follow annual reports, and we follow the data that comes from these trials. We've also -- we also have responsibility through our bioresearch monitoring program to inspect, to ensure the quality and integrity of each of the components of this system.

I had mentioned earlier today that FDA has the largest on-site government system for inspection of clinical research. We have the ability to stop studies when they are not appropriate. We have the ability to take administrative or even criminal action where subjects are compromised in clinical research. But it's important, as well, to recognize that FDA itself does not conduct the studies. FDA cannot be present at all times and at all sites and, therefore, we have to work not only directly but also indirectly, ensuring that all parties that are a part of this system understand that research is a privilege and to educate them to the responsibilities that they have in this enterprise. We need to be sure, in fact, parties can and do carry out their responsibilities and that there are channels for

reporting problems in clinical trials and for the follow-up of these problems.

In the nearly 40 years that FDA has regulated clinical research, we've seen a lot of progress, a lot of improvements, we've seen improvements in the quality of clinical research. And we talked earlier today about the fact that 25 years ago, when FDA went out to clinical research sites, we found problems in 1 in 5 studies that we inspected. Now we find problems in 1 in 40 to 1 in 50 in our routine inspections. So quality, overall, has improved, but so, of course, has the amount of clinical research. A good thing, certainly.

We, of course, have made progress in the understanding of JCP responsibilities and, as well, we have improved the representation of populations in clinical research. We recognize, for example, children cannot simply be assumed to be small adults, that there are health problems that involve individual subpopulations, be they ethnic groups, be they cultural groups. So we've made progress in these areas.

But, of course, we have to look for -- look toward the future. And for this, we need increasing dialogue. We need to talk about key issues that affect the treatment of research subjects.

Informed consent, we've heard a lot about that, but it's as much informing as it is informed consent. It's as much as safety and oversight of safety and ensuring, in fact, that risks are properly managed. It's managing conflicts of interest and protecting vulnerable populations. This is where we're going. This is where we need additional dialogue. This is where we need the input from those who are actually involved in patient care who are actually involved in contact with clinical research subjects.

I don't think that anyone here in the audience will argue that there are not difficult unresolved realities relating to economic and social inequalities, and it's very critical that dialogue continue on these issues and it's critical that all of the parties that are involved in clinical research be attentive to these inequalities. But again, it is through such efforts as properly designed and properly conducted clinical research that we have enormous potential to benefit both the individuals and society, and if we're all attentive to these issues, perhaps we will be successful in reducing these inequities. Thank you very much.

(Applause.)

MR. DYKSTRA: Thank you, David. How many

people here have recently seen something in the newspaper about FDA either taking a drug off the market or finding some problems in a clinical study?

AUDIENCE: (Raising of hands.)

MR. DYKSTRA: Okay. I think it's fair to say that hardly a week goes by that you don't read something in the newspaper about FDA, and in a lot of cases it has to do with our monitoring of these drug studies that are numerous, a lot of them going on around the country and around the world.

How many people here think that Martha Stewart blames us for her problems?

(Laughter.)

MR. DYKSTRA: No, forget -- forget that, forget that.

Our next speaker is Brenda Evelyn. Brenda is a Public Health Specialist who has been with FDA since 1998 when she started in the Office of Compliance in the Center of Biologics, Evaluation, and Research. She also worked in the Center for Devices and Radiological Health and has been in our Office of Special Health Issues for the past four years. She comes to us with a B.S. from the University of the District of Columbia. Brenda?

(Applause.)

MS. EVELYN: Thank you. Good evening, everyone. Good evening?

AUDIENCE: Good evening.

MS. EVELYN: I know it's been a long day, but I would like to thank everybody for having me here, and we've really had a wonderful time since we've been here and the tours, and I'd like to thank everybody at Meharry for sponsoring this conference.

I'd like to tell you a little bit about what our office does because I think it's not well-known, but we are putting forth some gallant efforts. I work in an office actually under Linda Skladany, the Office of Special Health Issues. And what we are is basically a patient advocacy office. And we do many things in that office. And one of the things that we primarily do is try to help patients get access to investigational products.

We work with patients who have life-threatening diseases, such as HIV, cancers, or chronic diseases such as diabetes or hypertension. And often, some of these people have tried every conventional therapy and nothing seems to work, so they approach us to ask us how can they gain access to an investigational therapy. So we work with them to either direct them to a clinical trial or we may work with a

sponsor and people internally to direct them to maybe if they could get a product off protocol. So that's one of the really big things that we do.

Another thing that we do is we try to get patients and advocates into our regulatory process in our advisory committees. Often -- and we really put forth a big effort to try to recruit communities of color, physicians, particularly, but also just patients. They don't have to have any fancy degrees or anything like that, but we do look for people who have had experience with a particular disease, who, when we have opportunity to bring a product before an advisory committee, that they can express their particular experience. And we've found that to be a very valuable thing at the agency.

Also, we try to make sure that all of our communities and advocacy organizations have information about policy documents. It could be a proposed rule or it might be a guidance document that we need some feedback on. And that gives them an opportunity to voice their concerns. We also participate in a lot of workshops just like this one. We host meetings and conferences, basically on the subject of clinical trials. And some of these, we specifically have targeted to communities of color. One of them in 1996,

we held at Howard University. We had a huge turnout, much larger than we ever expected to have, and we talked about this whole thing of mistrust in communities of color surrounding clinical trials. And then we also repeated that same conference down at the University of Miami.

We participate in annual meetings of the National Medical Association, the National Black Nurses, the National Hispanic Medical Association, places like that so that we can sort of let people know that we are there to help them.

Another function that we do is data gathering. And as its title implies, tomorrow I will be giving you some more detailed information about some of the little projects that we've done looking at clinical trial enrollment. We first started looking at this in 1997 when, actually, the NMA came to us and said, you know, do you know really who's in your trials, you are approving these products, but do you know really the racial make-up of the people in the trials?

And so we started looking at to what extent our people of color and different racial and ethnic groups are involved in the trials. The first attempt we made, we didn't really attempt to quantify it so much as we look at a yes or no answer, are they

there, are they not there. But then we went back a couple years later and we look at some trials of products approved between 1995 and 1999, and we really tried to start to quantify some of those numbers.

And we also looked at the labeling of the products to see if, in fact, sponsors were saying anything about any analyses being done with respect to racial and ethnic groups and were there any specific instructions that were different from the majority population. And most recently, we just completed a review of 12 selected new molecular entities that had been approved between 1998 and 2001, looking at -- they were HIV products, products to treat HIV, diabetes, and hypertension. And we tried to determine the enrollment in those trials.

And briefly, I'll just say this, without giving you my whole presentation for tomorrow, is that it basically appears that African-Americans are enrolling in trials at approximately the same rate or even a little higher than their representation in the population. But when you go to compare it to disease prevalence, it's not the same. So we don't know what the answer is to that, but I'll share more about that with you tomorrow.

Also, in 2000, we did a series of focus

groups out in Los Angeles County, and we selected that county because of their really diverse population, and we asked questions about what do you really know about a clinical trial and are you interested in participating and what kinds of things keep you from participating in a trial and what's the best way to get a message to your community.

And we did two Latino groups, we did two Asian groups, and one African-American group. And we selected one African-American group because we had a pretty good pulse on them but we didn't really have a lot of information about Latino groups and the Asian groups. And a lot of things that you historically hear about investigator insensitivity, you can't understand the consent forms, all of those things came out. But we also got some new information about, well, we don't really know people who have benefited because a lot of times those newly-approved drugs are not on formularies if we have insurance or they cost too much. So it's a lot of things that we discovered there.

So, the last thing that I'll mention about our office is that we do, integrally in our office, do help in policy making. Some of you might be familiar with the 1998 regulation that requires sponsors to report in their annual reports or their new drug

application demographic information by age, gender, and race, and we try to make sure that that got out for comment to our constituent groups.

And, also, we're working on -- I think it's still in draft form -- a guidance document on exactly how do you collect that. You all know that the census that just happened a year or so ago, we have a whole bunch of new categories on how people define themselves. So the way people collect information is just all over the place, and so the agency is working on a guidance document on how should people collect information.

So we're committed to doing a lot of things to try to help people understand. We're not out there recruiting people to get into trials but we are trying to get out there to make sure that people understand what a trial is all about, what's involved, what their rights are, and to try to get them into the FDA so that -- if there are issues to be discussed or that they have concerns about that we can address them.

Also, one of the things that we're working about -- working on with respect to the health disparities issue is trying to include race categories on our -- we call them our med watch forms, they're adverse reaction reporting forms, and that's a debate

we've been having in the agency for a while and exactly what is the best way to capture race information.

So I just want to leave you with the thought that the agency is serious, as you've heard earlier, about listening to all communities and we're making diligent efforts and strides to try to incorporate more people of color and more racial and ethnic group into our decision-making processes. And so we're here to listen and we'll be happy to answer any questions that you might have. Thank you.

(Applause.)

MR. DYKSTRA: Okay. Now it's time for me to come out from behind the podium and attempt to wake you all up. I know it's getting late but I also know that everybody in this audience has opinions, and particularly you young medical students who may be getting involved in this in the not too distant future and may get visited by an FDA investigator when you are conducting clinical investigations.

You are going to get pressured by drug companies, by contract research organizations to work on these studies, to do -- to participate in one fashion or another. I know many of you have questions about that. Now we want to start the dialogue, we want to start the questions, comments, concerns that you may have about

the Food and Drug Administration, and our role in this whole area of bioresearch monitoring, clinical studies, and ethics.

So, who wants to kick it off?

INQUIRER: (Indicating.)

MR. DYKSTRA: Yes.

(Inaudible.)

MR. DYKSTRA: The gracious host comes up here with --

INQUIRER: I work for an IRB and I think we struggle with the regulation that states that you should provide a consent form in a language understandable to the subject. And the Nashville area has a rather large population of Spanish-speaking individuals, and I think we can all acknowledge that as -- if you call any bank or go to any grocery store, they want you to choose the language, and it's between either English or Spanish.

So there was a request by an investigator for us to allow a short form consent process for the Spanish-speaking population. And I think the IRB's thoughts on that matter was, well, that's really not unanticipated that you would have that population involved in clinical trials. And then -- so that was somewhat of the decision. But then you go home and lay

in bed at night and you think, wow, you know, what if these children come in that need -- you know, for cancer trials and things and, you know, you've -- you've caused this big dilemma in trying to get translated consent forms. And if you use the short form for that population, what do those people go home with, because it's very complicated therapy and there's a lot of information that is in that consent form. And I know it's not about the document, but it's just like an insurance policy, they can talk to you about it and you understand exactly what they say and go home and all of a sudden it's like, now, what was that again?

And so I think that was our dilemma with allowing a short form, in that there really wasn't anything written for the participants to refer back to in their language. Can you comment on that?

DR. LEPAY: This is clearly an area which is very much at the forefront right now, and we're having a number of discussions about this precise subject between ourselves and the other agencies that are involved in the oversight of -- IRB's oversight of clinical research.

Obviously, this is certainly something an IRB has to look at at its own level. If an IRB itself does not feel comfortable with the information that is

being conveyed in any informed consent, it's incumbent -- regardless of language, it's incumbent upon that IRB to produce something that, in fact, will provide truly informed consent.

So I can't -- you know, I can't come out and say, of course, how an IRB should act in this particular case because you've set the scenario, within yourselves, that you don't feel comfortable with the short form as an IRB. Certainly, what the regulations allow may not, in fact, be the way that you want to implement. The regulations are kind of a floor.

If, indeed, the IRB feels it protects subjects in that particular scenario, they have to embellish beyond that, but it's certainly something very consistent with the way FDA thinks, with the way the other agencies think.

So in answering your question, our view, of course, is very much, informed consent is a process, the form has to be meaningful, the form has to be acceptable to the IRB as a means of conveying information and, ultimately, because the form has a value, as you've mentioned, as something that a subject can later look at, can take home, can think about, can develop questions off of.

So I would, again, defer this very much to

the judgment of the IRB in assuring that the populations for which the IRB is responsible are getting the kind of information that's important to convey about the trial.

MR. DYKSTRA: Okay. One of the things that David mentioned there was the "R" word, "regulations". FDA and a lot of regulatory agencies deal in this area of writing and prescribing regulations that you must comply with. These regulations, as David indicated, are generally minimal requirements; not maximum, they're minimum. And in many cases, they're subject to a certain amount of interpretation, and we allow that so that you can craft things that will serve your purposes and our purposes.

Next question, Pat?

INQUIRER: This is concerning the health disparities that someone had brought up. I was wondering, does the FDA regulate the cost of drugs that the drug pharmaceutical companies put out? And, question two, does that -- well, okay. Are there, like, any financial -- like, does the FDA benefit financially at all from any drugs or food that is produced?

MR. DYKSTRA: Well, let me take a crack at that, and the panelists can chime in on it. First of all, that issue of drug prices and drug cost, that's a very contentious issue in this country. You heard

Dr. Elders talk about it. The answer is, to that first question, is, no, FDA does not regulate the cost of drugs. And we try very hard to stay out of that arena and anything else we want to chime in with. We all, as individuals, have our personal opinions about it. We try not to -- as far as our regulations are concerned, when we write regulations, we have to do something called an Economic Impact Statement, so we try, when we write our regulations, not to add, in any unnecessary way, to the cost of the drugs, so -- and hopefully we don't do that too much, but you recognize that drug companies, in complying with our regulations, have to do things that costs money and they pass that money on -- or that cost on to consumers.

Your second question was, does FDA make any money from the sale of drugs or foods or anything like that. No, we don't -- for the most part, we don't charge any fees. Now, in the drug approval process, now, there is something called the Prescription Drug User Fee Act. That has just been renewed for the third time. It allows the drug companies, and really requires them, to help pay the cost of our review of those drugs. And this allows us to hire qualified people to look at those studies that are coming in on the drugs. It allows us to do the reviews much faster. The whole idea

behind this was to speed up the drug-approval process. But that's the only area right now in FDA, significant area, where we do get user fees from the regulated industry.

Any comments?

(No response.)

MR. DYKSTRA: Next?

INQUIRER: In the spirit of a Town Hall Meeting, I have what is mostly a comment and, perhaps, a question, as well. It's really a continuation of your question, in a way. I think if you look over the 20th century, and I know it's the 21st century now, but I'm looking at the 20th century, most of the progress made in health really has come from public health and from improvements to the environment, environmental conditions.

It occurs to me that the FDA may suffer from being, in a sense, marginal. What I mean by that is that the increments of the improved health that we get from the advances in pharmacology, from the releasing of new drugs which may be very expensive for 17 years, is small compared to the increments of improved health we would get from improved social justice.

I wonder if you could comment on this. It

would almost be asking about an unnatural act, that is to say, to go before Congress and say, at the time of appropriations or authorization, you know, I think the FDA has an important role, in fact, an indispensable role, but in a sense, it's a small role and what would be a big role if we wanted to improve health, would be to follow what Dr. Elders was talking about earlier, i.e., to pursue social justice more directly and not to try to do it, in a sense, what I believe is marginal ways that we've heard discussed tonight.

MR. DYKSTRA: Well, I think, probably all of us in FDA have various opinions on that, that particular issue. One of the things that I've learned in 35 years in FDA is that we do have a pretty proscribed mission that, under our system of government, has been established by Congress, laws have been passed. Those laws are enforced by the Food and Drug Administration.

When we venture too far outside of that, either the Congress or the judicial system, it's usually the judicial system, will yank us back in to our -- our boundaries. And I only, you know, call your attention to the recent efforts on the part of FDA to try to regulate tobacco, recognizing that that's an area that causes a lot of health problems in this country. And we

recognize that.

We tried to stretch our authorities as far as we could stretch them, and the judicial system came back and said, no, you -- you stepped over the boundaries. You've got to come back. Congress has got to change your law before you can -- you can do that. So we tried and we failed. And, you know, you get your hand slapped, you tread lightly from -- from that point on. But we do -- when we see, you know, some injustice or some public health problem that we think we can reach, there have been many instances in FDA where we've tried to reach it. You know, we've looked for mechanisms in the law, we've looked for ways, we've sought advice from the Congress, from the judicial system on how we can reach that particular problem under our authorities. Sometimes we get to it, sometimes we don't.

Other comments, David?

DR. LEPAY: Well, I think I would probably look at this as a cost-to-value issue, because I think that you are raising that issue. From FDA's perspective, our total budget is somewhere on the border of about a billion dollars a year. For that, we are responsible for nearly 25 percent of the U.S. economy, for the safety of foods, for the safety of medical

products, for the safety of medical devices, for ensuring the quality and integrity of the studies that support the scientific approval decisions.

So one has to argue, in fact, this is a smaller budget than most individual drug companies have for their own research and development activities, certainly less than most drug companies spend on advertising. So I think as we look across at value added and as cost is going into the system, I would probably argue this is a very important use of the monies that are put into the system. That's not to say there are not other uses for monies and that there are not other places in which we could look at appropriations, but from my standpoint in arguing perhaps this issue, I think that FDA provides a fairly good cost benefit for what the American public gets out for the amount of money that goes into the process. But that's my opinion.

MR. DYKSTRA: And I would just add to that that our budget, and I often remind people of this, won't even buy an aircraft carrier. And when you consider, as David pointed out, everything you take for granted when you walk into a grocery store or pharmacy, all of that relative safety is because of the things that -- that we do in FDA.

Yes?

INQUIRER: To move it across a little differently, I will express a point. Perhaps remove FDA from the scene and then see the issues that would be involved in the cost of managing those issues. That is what I'm trying to say.

MR. DYKSTRA: Take us out of the equation?

INQUIRER: And then see the issues that will be --

MR. DYKSTRA: Yes, right. See the problems that would --

INQUIRER: Absolutely.

MR. DYKSTRA: -- result.

Yes?

INQUIRER: Who will protect food that is prevental now that it's increasingly impacting people's health? I was wondering what the FDA's position is.

MR. DYKSTRA: Do you want to repeat the question? We didn't catch the first part of it.

INQUIRER: What I mean, is herbal protected?

MR. DYKSTRA: Herbals, one of our favorite topics. How is that affecting?

INQUIRER: It's increasingly impacting people's health. (Inaudible.) What's the FDA's

position?

MR. DYKSTRA: That's a very complex issue for the Food and Drug Administration. Many of these products have been around for sometimes thousands of years. Many of them have come from the far east. There's lots of both anecdotal as well as maybe even a little bit of clinical evidence that they may be effective and may be safe.

FDA is participating with the National Institutes of Health on a number of studies, a number of issues with regard to the regulation of these kinds of products. I think there is some -- some recognition that they need -- or there's a lot of recognition that they need to be studied, that they need to be looked at more closely, that they ought to be subjected to the same critical review that other drug substances are subjected to, and that they just shouldn't be out there on the shelves in the grocery stores and the pharmacies for people to take sort of willy-nilly.

Again, it's a difficult subject for the agency. I can tell you that from personal experience and a lot of scars over the years, having tried to come up with various ways in which the agency can deal with these substances and assure the public that they're safe and effective. Right now it is pretty much, in a

lot of cases, buyer beware.

And another thing that, all of you are, I'm sure, sensitized to the issue of, when you talk to your doctor about the medications you're taking, that you've got to tell them about the dietary supplements, herbals, and other substances that you may be taking. And that oftentimes is left out and it does cause problems.

Do you have anything on that, David?

DR. LEPAY: This is -- certainly, this is an area we have a lot of conversation about right now. Obviously, having mentioned earlier today that we were in China not all that long ago, it's obviously come up very much in conversation. FDA certainly very much controls the kind of information that can be provided about herbal products as dietary supplements.

If the dietary supplement is going to make a nutrient -- a health claim or a nutrient claim, nutrient content claim, it can still be regulated as a food but there has to be evidence behind that before those claims can be made, including information going to the agency prospectively.

We are certainly very interested in areas for further research. Obviously, many companies come forward wanting to develop dietary supplements, not only

as dietary supplements but with the possible potential for their carrying specific disease claims as drugs. And, indeed, when such products come forward to FDA, with the potential for a drug claim, that is to diagnose, to treat, to mitigate a disease, we approach them very much as we approach drug products. That is, they need to go into clinical testing.

The one major achievement I think over the past several years has been to find mechanisms whereby we can get such products into clinical testing in a way that ensures human subject protection but, as well, recognizes the fact that some of these products are very difficult to characterize chemically. They're not pure compounds as chemical entities within drugs. And so we provided some guidance. We provided guidance out there how to get these products into early-phase testing in very well-controlled, in very limited circumstances so we can begin to get the kind of data that we need to be able to see what the real value of these products is in many of the tauted or at least publicly perceived claims versus what is actually on the label, necessarily. So we're working in that direction. It's a very active area. But it is a very complex area, as you can imagine.

MR. DYKSTRA: There is a brochure out on

the table as you walked in called "My Medicine" that addresses some of these issues, so I encourage you to pick that up. Pat?

INQUIRER: Good evening. Hi. We heard earlier today a little bit about the hesitation that some minority groups might have in participating in certain clinical trials or clinical study. I spent about four and a half years working in Baltimore at Johns Hopkins doing research, and I noticed that we had a lot of problems recruiting minority participants in some of our studies.

What role does the FDA have in evaluating protocols that PIs might present when looking to release a drug or a medical device out into the population, looking at the ethical practices that are existing in these protocols and -- for example, sometimes some PIs might try to target populations of lower socioeconomic stature to sort of, you know, release a paper quicker. How does the FDA evaluate or not evaluate those circumstances?

MR. DYKSTRA: David?

DR. LEPAY: Well, we certainly do look at every protocol that comes into FDA. But, in fact, you're asking a question that is very much one within the realm of the responsibility of the Institutional

Review Board because, in fact, it is the IRB that should be looking at the protocols from the standpoint of whether these, in fact, meet the basic ethical criteria that we talked about in the Belmont report, that is, respect for persons and distribute it justly, that is, that no one group is being adversely disadvantaged to participate in the clinical trial while the benefits are going to another group.

So much of the responsibility that you're talking about is a responsibility of the Institutional Review Board. And, of course, FDA has to be out there working with our federal colleagues to make sure the Institutional Review Boards are acting properly, are, in fact, properly constituted, are operating properly to look into these kind of issues.

But we always do look at protocols from the standpoint of who they're including, who they're excluding, and why. One of FDA's functions in our review divisions is one that if we see a protocol that does not have a scientific basis, that is, it cannot meet the objectives of the protocol in a fashion that provides for the safety of the subjects, we can stop that protocol from proceeding under a process that we call "clinical hold".

So we are looking, as well, at the nature

of the protocol, their inclusion/exclusion criteria, and the assurance that there is safety there. But the primary answer to your question is, we seek input from the Institutional Review Boards and properly constituted and properly operating IRBs to do that.

MR. DYKSTRA: Okay?

INQUIRER: I had a question tying into the lady who mentioned the patient situation that sounded to be Hispanic on a trial. My question is, in that particular case, just from my listening to what you were saying, it sounded as if you were not comfortable that this patient was truly informed about the research activities they were participating in. In that particular instance, would you suggest that that patient perhaps have an interpreter or even a Spanish informed consent developed to ensure that that patient would be adequately informed?

DR. LEPAY: Well, I should clarify. I was answering on behalf of the IRB, which the IRB and the members of the IRB were the ones who felt uncomfortable with the level to which subjects were being informed in that particular circumstance, and I think a great deal of judgment, again, has to go to the IRB in these particular instances.

Certainly, the mechanisms that you've

talked about, either having the inform consent translated and back translated to ensure if, indeed, that is -- there is a significant Hispanic population participating in that trial, the use of translators, all of those are appropriate means. But at the end of the day we need a process in place that ensures that, in fact, we are comfortable, the IRB is comfortable that the subjects are being adequately informed. We don't want to see subjects participating in clinical trials who don't understand that this is research and it does carry with it inconveniences and risks.

MR. DYKSTRA: We have one right here.

INQUIRER: Yes. I want to ask about -- first of all, I want to say that you all have done a great job of talking about the different kinds of under-served populations and recognizing that it's not just racial but it's also gender, age, and some other cultural biases.

I work within the mandated community advocacy structure of the adult AIDS clinical trials group and just got back from a national meeting. And one of the things that we constantly fight, which parallels the previous question, is enrollment of women into our trials. And we've addressed a lot of those questions within the structure of the AACTG and made

incremental process on improving that.

But one thing came out of the last meeting, and I heard very loud and clear frustration with, is that the perception there is, is with these kind of experimental drugs, we automatically exclude women of childbearing age. And that was found by the community to be extremely sexist and very insulting to women.

And I'd liked to know what we have to do and what do we have to go through to recognize that women are capable of using birth control responsibility -- responsibly and participating in these clinical trials?

DR. LEPAY: I'll say that we've had a large number of discussions. I, having come originally from the Division of Anti-viral Drug Products in the early days of that division, to talk about how to, in fact, allow for women's enrollment in the clinical trials and to ensure that they're protected in the trials.

It's important, of course, to recognize, FDA does not design clinical trials. That is, again, a function of the sponsor. It's the sponsor's responsibility to design clinical trials. We are part of the system of looking at that clinical trial, again,

to ensure the trial is meeting certain defined regulatory requirements and is meeting certain ethical requirements as they exist within regulation.

We certainly appreciate that there are circumstances where it's perfectly appropriate for women of childbearing age with proper controls to be included in those trials, and we've talked with many sponsors about these issues and mechanisms by which such inclusion would take place. Clearly, we can't dictate to sponsors how they want to design trials and what they specifically want to look at in that design.

Sponsors certainly have liability concerns, we recognize that, but we certainly are out there trying to bring these issues to the forefront and I think we've made significant strides in that area. I've seen a lot of progress. We're not completely there, but I have seen a lot of progress in these clinical trial designs.

INQUIRER: My turn? Thank you. I'd like to draw a brief scenario in order to ask a question about it. The NMA, in evaluating prostatic cancer prevention -- I shouldn't blame it all on the NMA -- let's say the Medical Practitioner Establishment of the United States, whatever that means, has decided that prostatic cancer screening is of limited utility that's

connected with a variety of factors, one being that the testing can -- blood testing is possibly a little costly, maybe costs more than $4. Maybe, I guess, someone decided that was expensive. And the other -- another perhaps more significant factor is the potential reactionary types of effects that could mushroom from either inappropriately-managed communication of the news of the results or misinterpretation of the results on one side or the other.

At the same time, probably the -- it's a pretty widely promulgated fact or estimate that the expenditure for alternative remedies that we are currently calling nutritional supplements for such things as the prevention of prostatic cancer, especially in the older male population, are in the millions of dollars.

So the question is, in evaluating the variety of factors that are necessary to be evaluated to determine how to respond to the classification of a nutritional supplement as either a drug or a supplement, are economic impact studies included in that in any kind of way at all?

MR. DYKSTRA: I'll -- I'll take a stab at that first, and then let David talk about it. But generally, no, we don't get into the economic impact of

particular supplements. As I said earlier, the NIH has an office that is engaged in looking at supplements. I don't know if they're currently evaluating any of these that are -- that make claims for prostate cancer or not, but, you know, the list is long and they have to set priorities and they have limited budgets to do this.

And it's -- as we already said, it's a very complex area. It's a very emotional area. It's an area that the Congress is very actively interested in. It's an area that we're -- our role is very -- has been very prescribed by the Congress, what we can do and what we can't do. So it's, I think, something that's going to be around for quite a while in terms of sorting out the issues, deciding how we're going to evaluate these products, who's going to do it, who's going to pay for it, and how it's eventually going to be resolved.

David?

DR. LEPAY: Well, the first issue in the evaluation of investigational products is quite correct, we don't look or take into consideration the financial end of it, the cost benefit end. There are other parts -- other parts of the department that certainly make some assessments but not necessarily product related.

Our mandate under the law is to establish whether a product that comes forward to FDA as a

prescription drug, biologic or device, meets our standards of safety and ethicacy. That's what we're called upon to do by law. Those are really the two major issues that we are required to look at.

Now, when you talk about prostate cancer, you're clearly then -- from the standpoint of an herbal product, you're talking about something that is being developed as a drug. Our expectation would be that this needs to be studied as a drug. And as mentioned, the NIH, as well as independent sources, are looking into mechanisms to put some of these products into clinical trials and to find ways in which we can gather data, not so much about their cost benefit, but whether, in fact, they are even safe effective. So that's -- that's the primary consideration from the standpoint of our agency and what we're called upon to do under the law.

MR. DYKSTRA: Do you have one in the back there?

INQUIRER: How do you explain the long delays in releasing drugs to the market, to delay drugs that have already been released to markets in Europe and other places? And are you concerned of these long delays preventing the consumers in this country from having access to medication that could be useful to them?

DR. LEPAY: I'm going to answer this because I think what you have to understand is, until FDA receives an application for new product marketing, FDA does not act on the product. So, in fact, much of the time that is spent in product development is time that is spent by the sponsor to carry out the pre-clinical studies, the manufacturing, the early phase studies.

From the time the FDA receives an application in for marketing -- and, again, it's the sponsor who determines when that application will appear in FDA. We have no way of pulling that application out from a corporate sponsor and say, we're ready to look at this, we have to get this application. We have very defined time frames that we're prescribed as part of the Prescription Drug User Fee Act that was discussed here.

From the time FDA gets a marketing application for a new drug, for a standard application, we have ten months to review that application from the time it arrives at our door. For an application that deals with a priority submission, for example, a new product for Alzheimer's, a new significant product for HIV, we have six months to review that application.

Many in here may think six months and ten months, even, is a long time for the agency, but, in

fact, one of the -- one of the key elements of FDA review that is very critical is FDA looks at the scientific data, looks to be sure that this data supports the conclusions that are made. Many drug authorities look at summary information. They will accept a statement, if you will, of what the results are and what they show.

Within that six- to ten-month period, in contrast, FDA takes the data that is part of that submission, looks at the analysis, looks at the integrity of the data through inspections and has to complete all of that within a six- to ten-month period.

So from our perspective, again, we can't -- we can't control the time up to when the sponsor submits the application to FDA. And with critical products, we work with sponsors, we work with sponsors so that they avoid unnecessary clinical trials that will take excess time to bring these products to development.

That's one of the key issues that has taken place in FDA over the ten years that I've been with the agency, is that we work very directly with sponsors throughout the course of drug development. Ten years ago, it used to be the sponsor put this application on our door. We never had any previous contact with that product or knew exactly when that --

other than, you know, the investigational new drug end of it, but we never knew when that application was coming. We never had dialogue about the kinds of studies that should individually be conducted to support the final drug approval.

So we've made great progress in there. And as I say, we have it down such that in 95 to 99 percent, depending on the year, 95 to 99 percent of the time we are meeting that six-month or ten-month time frame.

MR. DYKSTRA: I think when you hear those reports of the length of time it's taking us to approve these drugs, as Dr. Lepay said, you have to look behind those numbers to see what it really means and when the drug was actually presented to us and actually how long did we really take to -- to approve the drug.

And as I was mentioning earlier with the advent of the prescription drug user fee, we do have very strict guidelines that we have to follow. The drug companies are paying for it. They're expecting it. They're expecting performance for their money. And you may hear about some outliers, but generally we are doing very good in terms of our drug approval times as compared to five, ten years ago.

We had one right over here.

INQUIRER: In working for a CRO, how can you ensure that ethnic backgrounds are covered when doing clinical trials, because in most times to none, certain sites have already been pre-selected for these certain trials, so how can you ensure that these backgrounds are covered?

DR. LEPAY: I'm not sure I understood the first part of the background. I couldn't hear.

INQUIRER: Working for a CRO and with the trials that are being brought forth, how can you ensure that the sponsor is covering the ethnic backgrounds, how can you make suggestions that these areas are covered?

DR. LEPAY: Well, normally again, and the CRO, of course, you're contracting for specific functions from the sponsor. It is the sponsor's responsibility in designing a clinical trial to ensure that that clinical trial is going to be representative. This is what we're trying to get at as we work with the individual sponsor toward trial designs.

We have to make sure, in fact, that the populations that are covered by that clinical trial are going to represent the populations that are ultimately going to use the product and that we can ascertain through, as product comes to FDA in the form of applications, that analyses are done to look at the

various groups that are part of that clinical trial.

I think from the standpoint of Contract Research Organization, it depends a bit on a function of the CRO. There are some Contract Research Organizations that have contracted to design clinical trial protocols. And in that kind of setting, I would imagine there are mechanisms there whereby the CRO can bring that to attention.

When a CRO is contracted to do study monitoring, of course, that is their contract function. I would hope that there is communication between the CRO and the sponsor on issues that either the sponsor brings to the CRO or the CRO recognizes with regard to the sponsor. But ultimately, it is the sponsor's responsibility. And this is something that we work at when we get these studies in to FDA and, again, we hope that the IRB's are looking at as they are approving trials at their sites. It's not -- it's not a perfect system.

INQUIRER: I would like to return to an answer that you gave in response to the question about the inclusion of women in AIDS clinical trials. And you rightfully indicated that the FDA does not design the protocols, however, you do hold a very big stick, indeed, which is the approval process. And if you make

it clearly known that the inclusion of women or any other demographic group in a study will assist in the timely approval of that study, then you will see these populations included.

DR. LEPAY: There are certainly many ways that we dialogue with sponsors, and this is part of the interaction that goes on. But let me correct one notion here because you used a word that I'm very sensitive about with regard to clinical trial protocols and clinical research, and that's the concept that FDA approves protocols.

We often hear FDA approves protocols. FDA approves informed consents. Actually, our function is to review the protocols.

INQUIRER: Approval of the drug.

DR. LEPAY: Approval of the drug, fine, okay. I'll take that correction, then. But FDA doesn't approve protocols. We have the ability to stop protocols when, indeed, the protocols cannot proceed safely or meet their goals, but we can't -- we don't actually approve the protocol.

INQUIRER: You review it, and after review, you let it go on the final stage. Is this not in any way approval? You have used the word "approval".

DR. LEPAY: No, it's not an approval. We

have specific criteria under the regulations where we can stop a protocol, which is a different process than approving. The law gives us the authority where certain conditions aren't met to stop the protocol.

INQUIRER: You review. After your review, is it allowed to be proceeded?

DR. LEPAY: Well, in fact, once the IND is established, the protocol can proceed from the moment the protocol is filed. From the first protocol, it cannot start until 30 days after the protocol is submitted. And we have the ability at that point to make a judgment whether that first protocol can proceed.

For every subsequent protocol after the first, the sponsor can start that protocol as soon as they're filed. We have the ability, of course, to place that protocol on a clinical hold if there are problems. That's what the law allows us to do.

More often than not, of course, sponsors don't want to take the risk that they're going to start the study and 30 days or 15 days later, whenever FDA gets the protocol and looks at it and it has some problems with it that will stop it. They prefer to have the dialogue more and more upfront. They prefer to wait the 15 or 30 days with each protocol. But there is no requirement for that under the law.

MR. DYKSTRA: Sir?

INQUIRER: But you can stop it, approval, if it's late.

DR. LEPAY: The protocol is acceptable to proceed. I know that sounds like governmentees, but that is exactly what it is.

MR. DYKSTRA: Or a legal nicety, right? Okay. Another question up here on the right?

INQUIRER: Over here. In continuing with the theme of women in clinical trials, I work for an academic institution which happens to be Catholic, so we ran into the barrier of -- because of Catholic church's stance on birth control, our institution had a problem -- specifically, a priest who was sitting on our IRB at the time had a problem with the fact that most protocols required women of childbearing age to be on some type of birth control.

We eventually got around this by having a disclaimer which the university did approve saying that it is the requirement of the sponsor that you be on birth control rather than the university, which kind of, according to the university legal department, kind of got us off the hook.

But my question is, have you seen that -- especially Ms. Evelyn, have you seen that in your

research to be a significant barrier to recruiting females into clinical trials?

MS. EVELYN: Actually -- actually, we have not specifically looked at the issue of women as much as we've looked at the issue of racial and ethnic groups, but I'm not aware of that issue. This is the first time that I've heard that with respect to Catholics. So I don't know if David has heard anything at that before or not.

DR. LEPAY: Well, I've certainly seen such provisions in clinical trial protocols. I've certainly seen -- heard of such discussions between sponsors and institutions where they've wanted to conduct research. I'm not sure that I could say quantitatively how frequently this occurs or provide any kind of numerical basis to make any kind of conclusion. But it is something that review divisions within FDA have had discussions with sponsors or with institutions about.

MR. DYKSTRA: Yes?

INQUIRER: I think we're learning more and more of something that we may already have known, which is that African-Americans have substandard access to health care. And in light of that, I was quite surprised by the outcome of your study, Ms. Evelyn, that African-Americans are represented in proportion to their

representation in the population in research studies, so we have better representation in research than we do in access to health care generally.

And I'm wondering if we could explain that possibly by suspecting that African-Americans may use research as a way to get health care when they don't have access to standard health care and whether the FDA has a role in evaluating that -- that question or -- or resolving the issues if there is a disparity there.

MS. EVELYN: I'm not really sure of the reasons underlying why we found the results that they are represented in proportions equal to their representation in the general population. Certainly, I think access to what they perceive as medical treatment in health care might be something that would cause them to join trials. But I don't really think that that's probably the driving force of it.

And we did really look at products that we had approved in a specific time frame, so I don't know how it relates to the access to care. We really -- we can't measure that in the applications that we get. We can just measure the demographic groups and how many are there. And even that, we can't measure really well. So I'm not quite sure how FDA would ever be able to make the connection between why we see that -- those numbers.

I mean, like 12 up to as high as 20 percent of African-Americans in some of the trials that I've looked at. We can't make the distinction of whether it's related to access to care or not.

MR. DYKSTRA: Next question?

INQUIRER: I'm John Maser, and I head the Veterans Administration's Office of Research Compliance and Assurance, which, if you catch the acronym, it's ORCA. And ORCA is the killer whale and I promised him that I would ask a killer question.

The issue that I have is really related with what we've had to deal with, I think, is allegations that we don't really, across government, have harmonization of all of our regulations. I mean, we're talking here about, you know, the fact that FDA 21 CFR, and yet this other thing called the "common rule" hangs around and we've heard stories about differences.

And I want to focus the question down on childhood and the regulations, vis-a-vis children, and what has gone on now recently with the FDA and the charge that came from the Congress last year. They really spent a little bit more time on this and the way things are coming out in terms of some sense that there's harmonization with respect to what is done with children in an investigative area.

DR. LEPAY: This is very clearly an important area for the agency. I think many here know that it's one of the initiatives of FDA to get better information about the use of FDA-regulated products in children. Children are major users of FDA-regulated products. Much of the research that has been developed over the years is research that's been extrapolated from studies in adults, and we've taken many steps to, again, encourage the development of clinical trials directed towards specific issues of products use in children.

To do this, though, effectively, we realized that we needed to have controls in place very clearly articulated about protections for children in clinical trials. FDA has always stated, or at least has stated as long as we've been regulating clinical trials, the vulnerable pop -- there need to be additional protections for vulnerable populations. We had not explicitly spelled out what those additional protections might be until the last couple of years.

Fortunately, we have a standard available for federally-funded research. There were regulations that existed in -- for federally-funded research that are enforced by the Office of Human Research Protections, for example, and based on both our own recognition of this problem as well as Congress'

recognition of this problem, we moved over the past year and a half, two years, to adopt very explicit language in this area, to adopt in harmonized format with the regulations as they exist from OHRP.

This is a direction we're consistently trying to pursue right now. We certainly believe that there are issues specific to products and product applications that will still require some FDA regulations that are unique to FDA. As I mentioned before, at the end of the day, we have to rely not only on the conduct of the study and the design of the study, but the data from that study.

And that differs quite significantly from other funding authorities. Funding authorities have to be concerned about whether to fund the study and that the study they're funding is going to be ethically conducted. But at the end of the day, the funding authorities don't have to rely on that data. That data goes into scientific publications. We have to rely on that data for public health purposes.

So to try to make what I'm making a very long answer a bit shorter, the bottom line is, we're looking for ways across government, working with the V.A., working with the Office for Human Research Protection, working across a group that's known as the

Human Subject Research Subcommittee, all of the signatories of what is called the common rule. That's 8 -- 17 agencies across government. Some that you wouldn't even think do human research work, such as the Department of Transportation and their use of cadaver studies to study automobile accidents. We're working together to try to harmonize, to the maximum extent possible, our regulations. We don't like to see inconsistencies that may in any way affect the protection of human research subjects, either directly or through misunderstanding. So we're making progress in that direction.

MR. DYKSTRA: I'll just add on to that comment that many of you may not realize how really hard and difficult it is to work across agency lines because of exactly what the commenter said, the difference in our laws and our regulations and our missions, it takes an enormous amount of energy, and I know this from personal experience, to work with other agencies and try to harmonize those -- those requirements. Just trying to understand another agency's viewpoints and their requirements is sometimes very difficult. So you can imagine trying to work with 16 or 17 different agencies on this issue. Just trying to get them in the same room is almost impossible, much less trying to harmonize all

of these requirements. So it's -- it is, indeed, a difficult task. That's why I keep wondering about this whole thing about Department of Homeland Security, whether they'll ever be able to bring it off.

I've got a question, a written question, it's my first written question here, and I love this one because it's starts out with, "I'm getting sleepy". You wonder why I'm standing up here. Something to keep me awake.

"My question is, is there a tool or report that an individual that participates in a clinical study can report negligence in the study or actions that were not mentioned in the consent form?"

DR. LEPAY: Absolutely. This is one of the points we tried to raise earlier today. In fact, every agency has such a system. At FDA, if you go to our website "www.fda.gov", very simple web address, you'll see problems for clinical trials that will take you to our offices. Our Office for Good Clinical Practices' website is prominently displayed. As you open that page, there's a note on how to report complaints in FDA-regulated research. Click on that, you will get a series of contacts numbers. Of course, you can contact any FDA office if such an event occurs, but we hopefully have made it simple to where it is and

where it can be most directly reported.

But when such instances happen, one of the things we need is good information. We need as much information as you can provide. It doesn't help us simply to say, I had a problem, and not remember what the trial was, where the trial was conducted, when the trial was conducted, or with what product. And indeed, occasionally, we do -- as with any complaint source, we do get such complaints. So we're, of course, going to be very interested in trying to get the kind of information we need to be able to appropriately investigate.

MR. DYKSTRA: Next question?

INQUIRER: I have a question directed to the Office of Special Health Ser -- Special Health Issues. My question is along the lines of health disparities. What does your office provide for minority patients that might be seeking to participate in these new or more non-conventional research clinical trials that may aide in their -- you know, improving their health care, because -- I guess, how do you get the information out there to these communities that you exist as an advocacy for them when their positions may not have access to these current clinical trials and things of that nature that might be beneficial to them

in their health care endeavors?

MS. EVELYN: One of the main things that we do is we try to direct patients to -- there's actually a big website "clinicaltrials.gov", which has a listing of all of the government-funded clinical trials for various diseases and, also, we're trying to get more commercials, pharmaceutical ones in there, as well.

Most of the people who call us are actually actively seeking to get the investigational product. So one of the first things we do is direct them to that website or try to actually find the trial for them.

As far as educational efforts go, we do -- we actually work with maybe like support groups or community groups or patient advocacy groups to just tell them what a clinical trial is and just give them basic information about that. And if we can try to find a trial they're looking for in their area, we can usually get that out of that website.

We don't necessarily tell people a clinical trial is the end all to be all or that this is going to cure you or this is going to save your life if you do that. But when people approach us and ask us, we do at least let them know that it's an option. And we have a little brochure -- I didn't bring any with me --

that talks about -- it's called "Why Volunteer", and it has a lot of information about what your rights as a clinical trial participant are, you know, what they are, and how a trial is conducted and those kinds of things.

So we really do more of an educational type of effort than we do try to help people, you know, necessarily try to direct them to a specific investigator or anything like that. We just try to point them into the direction of the trial.

On the other side of that coin, though, we do -- we have done work, especially with the National Medical Association, and David can probably speak to that more, too, with the results that we have been finding throughout clinical trial research with our protocols, looking at the enrollment. And then David has been working with that organization specifically on investigator training, to try to build more education within racial and ethnic communities and physicians, to get them on board and have their expertise built to the point that they can, you know, become investigators.

INQUIRER: It seems to me that one of the key resources for your office is using the internet or using a website in terms of a resource for education. Looking at the issues of the huge digital divide within our community, why would you choose that as a primary

resource as trying to get the word out into the minority communities about clinical trials and availability as an alternative form of health care?

MS. EVELYN: Well, let me clarify, when we get a call into our office, we don't necessarily direct them to the website. We will ask them if they have that resource. If not, we will do the footwork for them. We're basically the foot soldiers out there, and we'll make the calls. We'll, you know, try to get on the internet for them, and we will actually mail them actual copies of protocols that are listed in their area and things like that. So we don't necessarily say, well, look at it on clinicaltrials.gov. And then we also try to just really get active in the community. We do a lot of mailings, we do a lot of visits, and we do a lot of talks about that. So we do multi-faceted things.

INQUIRER: You may have answered this question. I'm sorry. But I just want to know for sure, how does the patient get to even make the phone call to know that you exist as an advocacy for them, because I know that many patients might not even know that they have that in the FDA, in terms of the service available to them, especially in a lot of unrepresented minority communities. But how would we get that information out there, that, you know, this office exists and is there

to assist in an alternative form of health care if conventional ways don't work, you know, as they might hope it would in their situations?

MS. EVELYN: I understand your question and, unfortunately, everything comes down to resources. But we try to utilize our field office people. We have a variety of public affairs specialists around the country. We work with them in similar situations like this, to put on information, informational seminars about what we do. And, actually, we have found our best way of doing -- getting information out there is actually by going into the communities and speaking and having these arms of the district offices that we have around the country to do those.

Now, I will admit, we haven't reached as far as we would like to, and so we're working on that, but we are using what we have at our disposal at the time, you know. And we try to go to big meetings where there are a lot of community people, a lot of physicians, and we have information there. We usually have some type of presentation at some of those meetings so that we can reach the physicians, the nurses, the big patient advocacy groups and try to get the information out like that. And I will admit that it's a slow process.

MR. DYKSTRA: I'll add on to that and say that we always encourage the citizens, consumers, et cetera, to simply call their local FDA office. We have offices -- about 100 offices scattered around the country. We're located in all of the major Metropolitan areas, and our numbers are in the phone book. So if they start there, we generally can get them the answer, and get them to people like Brenda or David or whoever can provide that answer.

INQUIRER: Is it possible -- is it possible that the pharmacists -- we have pharmacists on each corner.

MR. LEPAY: We're talking -- let me just say we're talking about a lot of mechanisms right now, and we've had a very fruitful relationship over the past three years, as Brenda had mentioned, with the National Medical Association. I don't know how many here are aware of their project or their initiative that they've called "Project Impact". That is the initiative to increase minority participation and awareness of clinical trials.

FDA has had a small role in that. Certainly, the significant role should be addressed to Dr. James Powell who heads that initiative for NMA and who has been critically active in seeking support from

FDA and other federal agencies to work with -- with the NMA to increase awareness of these kind of issues, to get information out. NMA has had training sessions across the country, different parts of them at various times, for clinical investigators. And now they're looking at how to approach the community as a whole, how to increase the awareness in the community and what research is and what kind of controls exist and how to, in fact, prevent problems in clinical research.

So I think it's a very important, as I say, fruitful initiative from our perspective in having had that opportunity and one, again, I would encourage people here to increase their own awareness of because I think it has been a very good effort.

MR. DYKSTRA: Other questions? You're getting sleepy. They warned me not to do any karaoke up here. Anything else on your mind about FDA? Anything.

INQUIRER: Yes.

MR. DYKSTRA: Wait for the microphone.

INQUIRER: You had mentioned earlier about some of the recalls that had probably been publicized. I was wondering, is it possible that you can comment on that, like some of the recalls and why there was such a -- it seems like a very thorough type of scrutiny of the drug or the food, why would it have to be recalled after

that?

MR. DYKSTRA: Why would something have to be recalled?

INQUIRER: Yeah, if there's such an elaborate scrutinizing of the product, then what element is overlooked during that scrutiny?

MR. DYKSTRA: Well, as -- as hard as we try or, you know, if I can use an analogy, as hard as an auto maker tries to create the perfect car, it doesn't always happen. And I know David can comment on this, but a lot of times what happens when we arrive at a conclusion to approve a particular drug, it's based on a finite amount of data that has been gathered from a finite number of people.

Now, we -- we try to create -- or the sponsors try to create studies that mimic or duplicate the general population, but oftentimes when they put that drug out to millions of people when they've only tested it in thousands of people, you start to see other effects that were not picked up during the course of the studies. And sometimes these effects can be overcome by labeling, by other things, working with the sponsor to hopefully keep that drug, if it's a very beneficial drug, on the market. If we conclude that you can't overcome those problems, then the drug comes off the

market until something is done to modify the formulation or change something to minimize those effects.

David?

DR. LEPAY: I think that -- I think that's precisely the answer. Remember, in a clinical trial, you may have a thousand patients enrolled, but what if an adverse event -- a serious adverse event only occurs in 1 in every 5,000 or 1 in every 10,000. No matter how you do the trial, you're statistically -- there's a statistical probability you may not pick up these events until the drug is actually available to a larger group, a larger population.

This is why it's so important that we have in place pharmacal vigilance techniques that pick up and bring in information. Sponsors are required to continue reporting adverse events to the agency after products are approved. They have to do periodic reporting to FDA and include in this all information that comes to their attention, under the law, to address these kind of issues. And we, of course, have epidemiologists on staff at our headquarters in Rockville to look at this kind of information.

As we've looked over time, though, and looking -- I just looked at these numbers in the last few days because I was preparing a talk on safety, in

fact, the recall rate has been fairly stable for the past many years. It holds at about 2 percent of products that are approved by FDA, fluctuates somewhat between -- around 2 to 3 percent. And I think this is just something that's intrinsic, that you can't obviously get all of the information you need from clinical trials alone. This is why it's so important, of course, that clinical trials represent the populations in which the products are going to be used, of course, because if they're not representative, if we don't have the means of being able to detect how the product exists in some subpopulations, clearly, we increase the probability that those problems will show up in reality after the product is approved in those subpopulations begin to use the product.

INQUIRER: Also, you had mentioned earlier that sometimes in an effort to meet a deadline, that you might pull a product off of the protocol. Does that ever -- do you ever find that that might compromise, you know, the health of the public if that is done?

DR. LEPAY: I think we use our time very well and, in fact, we take tremendous care to be sure that no study is going forward from FDA without provisions in place to assure the safety of subjects. Having reviewed -- having gone to sponsors after

reviewing a particular protocol and giving them a list of additional safety measurements that I would want seen in the study or additional increased frequency of some safety measurements, these are some requirements and this is part of what we tried to build in.

I don't think the time frames have compromised that at all. The time frames that have come from this, in fact, have supported the hiring of additional people to FDA so that, in fact, we are able to use those people to better ensure in the time frames available that we are, in fact, making the same levels, same high-quality safety decisions that we always have.

MR. DYKSTRA: We're kind of watching the time here. I want to remind people who are riding the buses back to the hotel that you have to board the bus by 9:30. Okay? So everybody is going to jump up and leave now, right? Any last-minute comments, questions, or concerns? We're thinning out rapidly here.

DR. LEPAY: I'll just make one addition, for anyone who wants additional information about the drug development process, there's actually a very good article that was written by an FDA magazine, FDA Consumer, that we've linked to our website under "Educational Materials". It's called from "Test Tube To Patient". And it -- you know, again, it's not for the

level necessarily of individual subjects that -- in all cases, but I think it provides a very good ground in about six or seven pages about how this whole process is conducted. And I think it's very good reading.

MR. DYKSTRA: Before everybody leaves, I want to thank our panel for sitting patiently.

(Applause.)

MR. DYKSTRA: And I thank Meharry for hosting this -- this very interesting discussion tonight. I want to remind you that we are transcribing this. Is that correct, Sandy? And it will be available on our website. If anybody needs a copy, again, call our Nashville office and they will assist you in getting a copy of the transcript of this -- this meeting.

I want to thank Sandy Baxter down here in the front, as well as the rest of the folks who have worked so hard to put this meeting together.

Any further comment before we call it a night?

(No response.)

MR. DYKSTRA: Okay. Have a good evening and thank you very much.

(Applause.)

(Whereupon, the meeting was adjourned on August 22, 2002, at 9:25 p.m.)

STATE OF TENNESSEE)
) ss:
COUNTY OF DAVIDSON)

I, Cheryl F. Buchanan, Notary Public in and for the State of Tennessee at Large,

DO HEREBY CERTIFY that the foregoing proceedings were taken at the time and place set forth in the caption thereof; that the proceedings were reported by me in machine shorthand constitute a true and correct transcription of said proceedings to the best of my ability.

I DO FURTHER CERTIFY that I am not a relative or employee or attorney or counsel of any of the parties hereto, nor a relative or employee of such attorney or counsel, nor do I have any interest in the outcome or events of this action.

IN WITNESS WHEREOF, I have hereunto affixed my official signature and seal of office this 10th day of September, 2002, at Nashville, Davidson County, Tennessee.

_____
Cheryl F. Buchanan, RPR, CCR
Notary at Large
State of Tennessee

My Commission Expires: November 31, 2002