UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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NANOTECHNOLOGY TASK FORCE

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PUBLIC MEETING ON NANOTECHNOLOGY MATERIALS IN FDA REGULATED PRODUCTS

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Tuesday, October 10, 2006

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The meeting came to order at 9:00 a.m. in the Natcher Auditorium, Building 45 of the National Institutes of Health, Bethesda, MD. Dr. Norris Alderson and Dr. Randy Lutter, co-chairmen, presiding.

PRESENT:

NORRIS ALDERSON CO-CHAIRMAN
RANDY LUTTERCO-CHAIRMAN

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

9:04 a.m.

CHAIRMAN LUTTER: Ladies and gentlemen, good morning. I'd like to welcome you to this public meeting on nanotechnology. I'm Randall Lutter, Co-Chair of FDA's Nanotechnology Task Force and my Co-Chair, Dr. Norris Alderson and I are delighted to have the honor of chairing this meeting today.

The presence of all of you suggests that we'll benefit from a large number of comments about nanotechnology and FDA-regulated products and today we're looking forward to an informative and wide-ranging discussion. I'd like to sketch briefly FDA's efforts to protect and promote public health in a world where nanotechnology is no longer a topic only for basic research, then I'll lay out some procedural points for our meeting today and after that, we'll begin the different sessions.

By way of scientific background, nanotechnology materials often have chemical or physical properties that are different from those of their larger counterparts because of their small size and extremely high ratio of surface area to volume. Such differences include altered magnetic properties, altered electrical or optical activity, increased

structural integrity and increased chemical and biological activity. Because of these properties, nanotechnology materials have great potential for use in a vast variety of products. Also because of some of their special properties, they may pose different safety issues than their larger counterparts.

Of particular interest to FDA, nanotechnology materials may enable new developments in implants and prosthetics, drug delivery and food processing and may already be in use in some cosmetics and sun screens. FDA also is interested in learning if there are opportunities for it to help overcome scientific hurdles that may be inhibiting the use of nanotechnology in medical product development. FDA generally is responsible for overseeing the safety and effectiveness of drugs for humans and animals, biologics and medical devices for humans and the safety of foods including dietary supplements, food and color additives, cosmetics and animal feeds.

It does so under a variety of laws and regulations and depending on product class under a variety of pre-market and post-market mechanisms. While most, if not all, of the key laws and regulations under which FDA operates were written before the advent of nanotechnology, most are general

in nature by design. They, therefore, usually are able to accommodate products made with the use of new technologies or containing new kinds of materials. At this time, we're not aware of any adverse safety issues associated with the use of nanotechnology-based materials in FDA regulated products.

In fact, for some cancer drugs under development, the opposite may be true, with better targeting and lower doses of toxic drugs needed through use of nanotechnology delivery methods. Nanotechnology is also offering advances in things like lab on a chip, clinical diagnostic testing and I'm told that nanotechnology materials may soon greatly enhance our ability to see inside the body using MRI or other non-invasive techniques that would reduce the need for exploratory surgery.

As noted below, we're evaluating the effectiveness of the agency's regulatory approaches and authorities to meet any unique challenges that may be presented by the use of nanotechnology materials in FDA-regulated products. We look forward to gathering more information today and through submissions to the docket for this meeting to assist our evaluation, including information on safety considerations for use of nanotechnology materials in FDA-regulated products.

Because of the generality of laws and regulations, FDA often finds it useful to develop guidance documents tailored to specific issues posed by new kinds of products or processes. Such guidance documents, while not binding on industry or the agency, can illustrate how the agency interprets existing law and regulation with respect to new products or processes. It may also describe the kinds of information FDA considers appropriate to demonstrate the safety or effectiveness of products made with new kinds of materials or processes or describe new procedures for interacting with the agency to help facilitate the safe entry into the marketplace of new products.

We've not yet developed guidance for products using nanotechnology materials but part of the work of FDA's task force on nanotechnology is to evaluate whether such guidance might be useful for particular product areas. We're holding this meeting today because we're interesting in learning about the kinds of new nanotechnology material products under development in areas of food, including dietary supplements, food and color additives, animal feeds, cosmetics, drugs and biologics and medical devices. We're also interested in learning whether there are

new or emerging scientific issues that should be brought to FDA's attention, including issues related to safety of nanotechnology materials.

Finally, we're interested in any other issues about which the regulated industry, academia, and the interested public may wish to inform us concerning the use of nanotechnology materials in FDA-regulated products. This meeting also helps us comply with tasks assigned to the FDA's nanotechnology task force which I will introduce shortly by Acting Commissioner Dr. Von Eschenbach on August 9th. Those tasks are as follows; first, assess the current state of scientific knowledge pertaining to nanotechnology materials for purposes of carrying out FDA's mission; second, evaluate the effectiveness of the agency's regulatory approaches and authorities to meet any unique challenge that may be presented by the use of nanotechnology materials in FDA-regulated products and; third, explore opportunities to foster innovation using nanotechnology materials to develop safe and effective drugs, biologics and medical devices and to develop safe foods, feeds and cosmetics; fourth, continue to strengthen FDA's collaborative relationships with other federal agencies, including the agencies participating in the National

Nanotechnology Initiative, such as the National Institutes of Health, the Environmental Protection Agency, and the US Department of Agriculture, as well as with foreign government regulatory bodies, international organizations, and private parties.

Fifth, consider appropriate vehicles for communicating with the public about the use of nanotechnology materials in FDA regulated products and finally, Dr. Von Eschenbach asked us to submit the initial findings and recommendations to him within nine months of this public meeting. So there will be a public report. Clearly, today's meeting is a key part of FDA's ongoing efforts to gather and evaluate information relating to the use of nanotechnology in the manufacture of FDA-regulated products.

While products made using nanotechnology like those made using any new technology, may pose risks, FDA recognizes that nanotechnology has great potential to promote public health through advances in medical products, including in implants and prosthetics and other FDA-regulated products.

Let me turn now to some procedural points. The meeting today is divided into three distinct parts. Immediately following my remarks will be presentations by three government officials

representing the US Office of Science and Technology Policy, of the European Commission and Health Canada. Subsequently, at 10:00 a.m. and ending this afternoon at 4:25 there will be six different sessions of presentations by public speakers who signed up in advance to speak at this meeting. If you haven't already checked in today, please do so at the table in the hall.

I realize the mike is now louder than it used to be. I hope everybody's been hearing me throughout my remarks. Would anybody like me to start again at the beginning? After your -- at the end of each session, members of FDA's task force may pose questions to speakers, at the end of each of these sessions, where needed as clarification for their statement. So there will be an opportunity for task force members to ask questions and the speakers to provide answers. We plan to post to our website any written or electronic materials used by speakers in the next week or so and recognizing that the speakers have limited time for their talks, we encourage you to provide more extensive comments and information in submissions to the docket.

In particular, we would appreciate submission of any published or unpublished studies

that you cite in support of your statements. And if you're unable to provide copies now, we'd appreciate any available abstracts and would encourage you to send the full studies as soon as they can be made publicly available.

The third part of our public meeting today is that at 4:25, we will have an open microphone session for additional speakers. Because of scheduling constraints, only the first 25 people who sign up for this period may speak. People may continue to sign up until 11:15 at the end of the last break before lunch unless 25 people have already signed up before that time. This way we can announce immediately before lunch the time available for each of these speakers, so they may use lunch to adjust their remarks to fit the available time. These speakers will speak in the order they sign up.

Of course, we ask all speakers to limit their remarks to exactly the allotted time. Dr. Alderson and I aim to stick to the schedule today. The number of people seeking lunch at noon will likely outstrip the capacity of the local cafeteria to serve everyone in the available time. We sent out via e-mail some maps to local restaurants. I think there are maps outside this auditorium describing how to

find some restaurants other than the cafeteria within the building.

Finally, any member of the public who doesn't receive an opportunity to speak today or who would like more time than is available given today's filled schedule, is more than welcome to submit written comments to the public docket at our website. Written or electronic comments may be submitted by November 10th. Note that the submitted comments will be available to the public, so please do not include confidential business information. I'd like to now introduce the members of the task force, who are sitting the front rows facing the stage. Please stand as I call your name; Dr. Rick Canaday, Dr. Mitchell Cheeseman, Matt Eckel, I think is absent, Eric Flamm, Dr. Flammang is absent, Dr. Steve Fleischer, Dr. Paul Howard, from the National Center for Toxicological Research, Dr. Linda Katz, from the Center for Foods and Safety in Applied Nutrition, David Kelly from the Office of the Commissioner, Mark Kramer, from the Office of the Commissioner, I think, is absent, Pat Kuntze from the Office of the Commissioner, Dr. Subhas Malghan from the Center for Devices and Radiological Health, Dr. Nakissa Sadrieh from Center for Drug Evaluation and Research, Dr. Jeff Shuren, Dr. Jan

Simak from the Center for Biologics Evaluation Research, Dr. Steve Vaughn from the Center for Veterinary Medicine, John Weiner, Office of Chief Counsel, Helen Winkle, Center for Drug Evaluation and Research. And we hope that everyone today will provide us with information that will increase our awareness of both the challenges and the opportunities that nanotechnology may provide and how we can best meet those challenges and opportunities. And without further ado, Dr. Norris Alderson will start our first session. Thank you very much. Look forward to enjoying discussions today.

CHAIRMAN ALDERSON: Well, good morning again. I'm Norris Alderson, if you hadn't figured that out. And we are delighted that you're here today and the next three speakers, as Randy indicated is to indicate both the national and regional perspectives on nanotechnology because it is truly that issue across all of the governments in the world and we are all working together in many ways.

And we're going to start today with the US perspective by Dr. Celia Merzbacher. Celia is currently on assignment to the Office of Science and Technology Policy, OSTP, and Executive Office of the President of the US Naval Research Laboratory. In her

position at OSTP she is acting assistant director for technology research and development and handles issues related to nanotechnology and the National Nanotechnology Initiative. She also co-chairs the inter-agency Nanoscale Science, Engineering and Technology, NSET, Subcommittee of the National Science and Technology Council's Committee on Technology.

As part of her responsibilities at OSTP, she serves as Executive Director of the President's Council of Advisors on Science and Technology. That's PCAST. As an advisory body to the President, PCAST is a national nanotechnology advisory panel called for by the 21st Century Nanotechnology Research and Development Act of 2003. This body provides periodic assessments and recommendations for strengthening the Federal Nanotechnology Program. Celia.

DR. MERZBACHER: Good morning. Thank you all for coming out on a nice fall day. As Norris and Randy indicated, I'm here to talk about the US National Nanotechnology Initiative. I want to thank both of them for inviting me to speak. I hope you can hear me. This seems a very receptive microphone. And I want to thank the FDA for organizing today's meeting.

Although the purpose of the meeting is to

help the FDA further its understanding of developments in nanotechnology materials that pertain to FDA-regulated products, it will, in fact, inform all of the agencies that participate in the National Nanotechnology Initiative, so I want to thank the speakers for participating as well, because those of us who are from other agencies and organizations are interested in hearing what you have to say.

What I'd like to talk about today is the Environmental Health and Safety or EHS research under the National Nanotechnology Initiative and how that's being coordinated and managed. And I just thought I would sort of put right on my first slide the four points that I want to make so that you'll get those up front and if nothing else, I hope you'll take these away from my presentation.

The first is that nanotechnology EHS research is a priority. And in fact, nanotechnology or NNI agencies are already doing a considerable amount of research in this area and the investment that's being made is in fact growing. And finally the inter-agency coordination process, I will, I hope convince you, guides the agencies that are part of the NNI. It effectively leverages the investment by each of the agencies across the entire government and going

forward, it should, I think ensure that we avoid gaps in this area of research.

So starting with the first point, let's see, which -- in fact, nanotechnology is one of just a handful of priority areas of research that's called out in a document that's sent out each year. This is the top of the memorandum sent by the Directors of the Office of Science and Technology policy, Dr. Marburger and the Director of OMB, Mr. Portman. This is an annual research and development budget priorities memo that's sent to the heads of the departments and agencies indicating what the Administration's priorities are for the coming budget cycle.

And so this is the budget that was sent out as part of the planning for the fiscal year 2008 budget and if you scroll down, to the section on nanotechnology, it reads as follows, "To ensure that nanoscience research leads to the responsible development of beneficial applications, high priority should be given to research on societal implications, human health and environmental issues related to nanotechnology". It goes on to say, "Agencies should develop, where applicable, cross-agency approaches to the funding and execution of this research".

Now, in fact, this guidance from the

Administration is completely aligned with the goals and priorities of the National Nanotechnology Initiative. In the strategic plan of the NNI which was released in 2004, the plan calls out four high level goals and the fourth of these goals is to support responsible development of nanotechnology. And the plan goes on -- the report that spells out the plan goes on to say that responsible development includes addressing potential risks to human health and the environment of new nanomaterials and the products that they are incorporated in.

Well, activities and investments aimed at achieving these goals are reported each year in an annual budget supplement that's sent to Congress and is publicly available, and all of these reports of NNI are available if you go to www.nano.gov. So this table is taken from the most recent annual budget supplement and we report each year now, the amount that's being spent by each of the agencies participating in the NNI on EHS research. So this table shows, and probably the people in the back can't see it, but it shows for all of the participating agencies that fund nanotechnology research the investment in EHS research in 2005, the amount that's being spent this year, 2006, and the amount that's

being requested for 2007. And for the purposes of making these estimates, the definition of EHS research is research that is, and I'm quoting here, "primarily aimed at understanding and addressing potential risks to health and to the environment posed by nanotechnology". Now, I think if you just take a look at this, even if you can't read the numbers, you'll see that EHS research is in fact, being performed by a number of different agencies across the government and I sort of have made the bottom line bigger so that hopefully you can see it, the total NNI investment has been steadily growing. It was just under 34 million in 2005 and the plan is to spend just over 44 million in 2007. I want to reiterate that these estimates do not include research whose primary goals are not risk-related but that may, in fact, advance understanding and the ability to measure and characterize risks associated with nanomaterials. So it's really a low estimate, if you will.

The budget supplement also provides highlights of the current and planned activities in all areas of research, including EHS. So I encourage you to go to the nano.gov website if you haven't already read this and take a look at it. Actually let me stay with that slide for a moment. The inter-

agency group that I co-chair felt that, in fact, greater coordination was going to be needed for EHS research and in 2003 it established the NEHI, Nanotechnology, Environmental and Health Implications working group. Norris Alderson is the chair of that group and its membership includes representatives from both the research agencies and the regulatory agencies.

A purpose of that group is to facilitate the identification, prioritization and implementation of the research required for the responsible development and oversight of nanotechnology. It has served as an invaluable forum for discussion and exchanging information about EHS issues related to nanotechnology and I don't think I've overstating it when I say that it has been unique, I think, among interagency activities in addressing EHS issues at such an early stage of development of an emerging technology.

So more recently the NEHI working group prepared and the National Science and Technology Council released a report entitled "Environmental Health and Safety Research Needs for Engineered Nanoscale Materials", a fairly self-explanatory title, I think. This report which just came out last month,

identifies five broad areas for research and those are shown here, I won't read them to you. And these are the research -- these describe the research that's needed in order to support federal government risk assessment and risk management activities. For each area, the report describes selected current NNI research, detailed research needs within the area, and options for research approaches to address those needs.

The purpose of the report is primarily from our point of view, to serve the federal agencies. It identifies research and information that's needed for the regulatory agencies to be able to assess and manage risks and it also will inform and guide the research agencies as they plan their programs and budgets. But it's not really a government-specific document and we hope that industry may find it useful, in particular users and producers of nanomaterials may find it useful and informative for their own EHS activities and another audience is the nanomaterials and EHS research community which we hope will read it and be stimulated to submit proposals to the research agency solicitations that address the topics that are identified in this report.

Well, this is just a step, albeit an

important step in identifying the research that's needed and the report goes on to say what the NEHI working group will do next. There's a need initially to further prioritize the research. This is a very broad compendium of the research that's needed and the report includes principles by which the agencies are going to do that prioritization. We also need to evaluate in greater detail what we're doing now and then do a gap analysis to see here those gaps exist and then take steps to coordinate with the agencies that invest in research to address any remaining gaps.

And finally, this is a very fast-moving area. And the NEHI feels it's important to establish a process by which we first of all, assess how much progress we're making towards addressing the research that's needed, and also to update this document periodically. Well, so far I've just been talking really about the NNI and what's going on among the federal agencies, but in fact, there are many others who are doing research in the area of nanotechnology EHS.

First of all, industry and in particular manufacturers of nanomaterials are doing their own EHS research, of course. Many of those data are proprietary. I just want to note that the

Environmental Protection Agency has announced a public meeting on risk management practices within the scope of a possible stewardship program that the EPA is exploring. That's scheduled for October 19th and 20th here in Washington, DC and you can find more from the EPA website.

There are also non-profit research organizations that are spending money on nanotechnology EHS research and examples are the International Council on Nanotechnology and the International Life Sciences Institutes, Health and Environmental Science Institute. These organizations, perhaps, aren't spending as much as some of the other groups but I think they represent an important interface between many of the stakeholders, government and industry for example, and so they have an important role. And next, there are, of course, other governments that are spending money in this area and we're going to hear from representatives from the European Commission and Canada today, but many other nations are spending money in this area as well, which begs the question, we don't only need to coordinate perhaps, among the agencies of the government, but also with others around the world who are working in this areas and how might we go about doing that.

I'd like to just touch upon two international organizations that I think are going to be important and in fact, I think I'm safe in saying that every international organization that has a scientific or technological mandate is probably looking at how nanotechnology is going to impact its program of work. But two that I want to mention today are the Organization for Economic Cooperation and Development or OECD, which has established a new working party on manufacturing nanomaterials and that group is going to meet for the first time at the end of the month in London, and the International Organization for Standardization or ISO, which has created a technical committee on nanotechnologies to develop standards for nanotechnologies. They are focusing initially on three areas of standardization, terminology and nomenclature, instrumentation and metrology and health, safety and the environment. And in fact, I would argue that standards in all three of these areas are going to be critical to the successful advancement and realization of the benefits of nanomaterials in a safe and responsible manner.

So I can't really emphasize enough the importance of standards in going forward with the safe development and regulation of nanotechnology. So to

recapitulate what I said in the beginning, I hope I've convinced you that nanotechnology is a research -- EHS research is a priority of the Administration and of the NNI. We already are doing quite a bit in this area. The NNI agencies are investing and the amount that they're spending is growing year by year. And finally, inter-agency bodies don't set the budgets. That's done at that agency level; but the work of the inter-agency bodies through their coordinating activities, guide the agencies. They ensure efficient investment and leveraging across the agencies and especially, I think going forward, they help to ensure that gaps in research will be filled.

We really need to be smart about how we spend our limited resources. Some research needs to happen in sequence and spending more money won't accelerate the process particularly. If we can't characterize nanomaterials, then we don't know what we're testing. And researchers and business people alike are clamoring for standards. So again, I want to emphasize the importance in that area. There's much to be done and the NNI, in coordination and collaboration with others around the world, is taking steps to protect human health and the environment.

Well, I see I have just about one minute

left, so I'll wrap up. In closing, I'll note that the response to this public meeting exceeded expectations, I think and although I had the honor of being the first speaker today, like you, I'm really here to listen. So in behalf of OSTP and the NNI, I want to welcome everyone and thank you for your attention.

(Applause)

CHAIRMAN ALDERSON: Thank you, Celia. For those of you who didn't notice, I really want to point out that FDA was not one of those agencies listed for funding. Please note that and I'll try to bring it up as many times today as possible.

Our next speaker is part of our commitment to regional aspects of nanotechnology and FDA is continuously seeking to cooperate with its international regulatory partners in addressing nanotechnology issues both bilaterally and through multinational efforts such as the Organizations for Economic Cooperation and Development and the International Organizations for Standardization and Celia had mentioned both of those. We appreciate that Health Canada and the European Commission were able to send representatives to present today their views on nanotechnology.

Representatives from Japan's Minister of

Health, Labor and Welfare and the European Agency for the Evaluation of Medicinal Products have also joined us for today's meeting. Our first speaker is Dr. Philippe Martin and he's the principal administrator for risk assessment and nanotechnology policy development in coordination with the European Commission's Directorate for Health and Consumer Protection and that's part of DG SANCO. And DG SANCO works to insure that food and consumer goods sold in the European Union are safe and that its citizens' health is protected. Dr. Martin.

DR. MARTIN: Well, thank you, Norris, and thank you very much to -- on behalf of the European Commission to FDA for inviting us at what we believe is a very important meeting. You will immediately note from my slides we did not trade notes with Celia, that there's a lot of convergence of views in particular with respect to international cooperation. And the other aspect which -- on which everybody agrees is that safety is a prerequisite to the development of nanotechnologies. Finally, I very much look forward to listening to the public, to you today.

And to give you an idea of what I will briefly talk about, I'll say a few words about nanotechnologies, things that actually Randy has

already mentioned and Celia in her talk. I'll say a few words about the European Action Plan on Nanoscience and Nanotechnologies which was adopted in 2005. Then I will mention international cooperation and I here immediately insist on the fact that it's not just governmental or inter-governmental cooperation but cooperation between all stakeholders. Then I have to say a word about corporate responsibility because industry has a major role to play in this area and finally, I'll conclude with steps forward.

So we have many benefits that were evoked and coming from the health and consumer protection area, I am especially interested in health and medicine but clearly there are many other areas, including information technology, energy production, storage and distribution, material sciences, clearly, food, water and the environment is another area and finally instrumentation, especially sensors which in this day and age are becoming very important.

Then, just to give you my summary of what I see as the defining characteristics and I will admit to a risk assessment bias, what I see as the characteristics of nanotechnologies. So small is small. Small is different and small is hard to

predict. So small is small, what do I mean? I mean that this absolute size of a billionth of a meter is also small with respect to the natural barriers to the entry and the movement of particles in the human body, not that we have not been submitted to such nanoparticles before, but not the kind that our bodies have learned to accept and handle. In particular, I have to stress the crossing of cell membranes and the possible crossing given special coatings on the nanoparticles of the blood/brain barrier, which, as you will note, both present a risk and may be an opportunity in the treatment of disease.

Then to demonstrate that small is different and also show that public servants can have a sense of humor, I took the idea, the metaphor used in National Geographic. You take -- they said that nanotechnology was you take something -- you take a cat, you shrink it, you shrink again, you shrink it yet and it turns into a dog.

(Laughter)

And here it's no mistake that I chose an angry looking dog, because if I don't know which kind of dog I'm facing, I have to assume as somebody who protects public health and consumers, that it could be an angry dog. And then the other aspect is that small

is hard to predict. And for instance, a number of people wear rings, like myself and we know that gold is yellow, melts at 1,200 degrees and is completely inert. It doesn't leave stain marks. Well, if you take a one nanometer particle of gold, it's blue. It has low reactivity and now melts at 200 degrees C. And if you take a three nanometer gold particle, it reddish, catalytic and melts at 200 degrees. Catalytic means that it triggers reaction and is itself, very reactive. And this is a property that is very difficult to predict. Basically, you have to run the test to know what is happening for several reasons.

One of them because of the equations that you would need to solve and second, because it's very expensive in terms of computer time. However, I have to say that there is hope that we may be able to use structure-function relationships and so-called QSARs in the future to help us.

Now, a few words about the European Action Plan; the message I want to deliver is that it seeks -- - and that message was blessed by the 25 ministers of Europe, of the European member states, that Europe chooses a safe, integrated and responsible approach to the development of nanoscience and nanotechnologies.

And what are we trying to achieve? Well, economic prosperity, social well-being and environmental quality. And if you're really interested in the action plan, you can use a search engine like Google to find more about it, but basically, it's got eight chapters.

One of them, probably the most important one in terms of direct funding is R&D which includes R&D on risk research. And we are presently finalizing what we in Europe call the Seventh Framework Program which is going to run from 2006 to 2013 and it includes very detailed research on safety and HSI aspects. The other chapters include clearly support to innovation, examining the societal aspects, the ethical aspects, and clearly risk assessment research as well as an international component.

Now, to do its policy, the European Commission relies on science as much as it can. It's policy is built on science. And to do that, it has actually three scientific committees that handle non-food areas. There's one that handles products, another one that handles the environment and one that handles emerging and newly identified risks in which we've placed nanotechnologies. But there are also other committees that help us in approving products.

For drugs it's going to be European Medicines Evaluation Agency and for food, it's going to be the European Food Safety Authority.

The one aspect that I have to stress is that the EU is not one sovereign nation-state but actually a collection of 25 nation-states. Even though now everybody can vote where they live in county elections, that's as far as it goes and therefore, there is underlying those committees, very often a network of national committees that support the work as well.

The Scientific Committee on Emerging and Newly Identified Health Risks delivered an opinion on nanotechnologies looking at the appropriateness of existing risk assessment methods. And the conclusions were that risk assessment methods may require modification. It was not a blanket statement saying we've got nothing. No, we've got something but we have to be very careful, in particular because we cannot assume that what we know about the bulk substance applies to the nanosubstance or the substance in nano form, and therefore, we have to operate on a case by case basis.

Then it stressed -- it pointed out adaptations to the methods. Well, we need to examine

the methodologies, the tests and the equipment because if you don't have the right equipment, you're not able to go anywhere. You will be blind to nanoparticles in particular. Knowledge gaps, and this has been the focus on both sides of the Atlantic and elsewhere of much effort recently and especially characterization mechanism and toxicokinetics are stressed as very important. But they're not the only aspect. As you well know, there is a risk only if you have both a hazard and exposure to the hazard. So measurements are needed on exposure because if, for instance, I consider the nanoelectronics in the computer here, they're sunk in a solitary state piece which means that I and you are not being exposed in any significant manner to whatever nano there is in this computer.

So that's one aspect and we need portable equipment to be able to monitor both human and environmental exposure and we need also to understand the severity of unknown – better of what happens in the environment, how do things move in the environment, how do they change, how do they accumulate, how do they degrade.

And now moving onto the more regulatory part of my talk, the EU has undertaken -- has started

a legislative review and it is not -- there are no public documents yet on it and I'm actually accompanied -- we're both from the European Commission here today. I'm here with my colleague Case Brekelmans who oversees the writing, who's actually the pen behind this legislative review and we're both available for questions outside of this meeting if you wish.

But anyway, the main message is that the framework looks okay and that is a message that has been relayed at national level elsewhere. It has also been pointed out that there are some gaps and for instance, in its review of UK legislation, the Food Standards Agency has called out a series of local gaps in the regulation that can, should and will be handled. The other message is that the real priority is implementation. Maybe do we not need better regulation, maybe, but we certainly need better implementation. In support of this work, we're now having the committee that delivered the opinion on the methods applicable to risk assessment work on, as Celia mentioned, the technical guidance documents, basically those non-legal documents that make the application of the law possible.

And we're also working on - the Scientific

Committee on Consumer Products which in particular considers authorization of cosmetics, is working on an opinion on nanomaterials in cosmetics and this work has started in February this year and obviously, it -- later developments in this area have shown that it was a very timely thing to examine. But I also would like to insist and that's where it's not only a matter of producing new research, it's also a matter of sharing data. Regulators need the data that is available today and there is data and for this we need really to partner with industry in the area of cosmetics for instance.

The committee really needs support from industry and confidential private information can be handled by those committees at least in the European system. Then international cooperation, the reason I put it between brackets is that it really is cooperation worldwide and this international business is actually -- is de facto. Everybody is talking to everybody. There are informal dialogues like the NSF sponsored international dialogues, like those initiatives, like the International Risk Governance Council. There are formal dialogues like the ones that are taking place at the OECD as mentioned by Celia as well as in ISO or UNESCO. And there is

dialogue between stakeholders, between government and industry and representatives of the civil society and academia, obviously. Here I put the little thumbnails of the OECD, the ISO and the sandwich is the European equivalent of ISO.

A word about corporate responsibility; we feel in Europe that the catch-me-if-you-can paradigm is not appropriate for nanotechnologies. Rather, we applaud the efforts toward product stewardship like the ones that are being fostered by Dupont and Environmental Defense and here I've clearly, for those of you who know this -- the work of Dupont and Environmental Defense, I've really borrowed from them. I've added one step. The first step being for me very important, at the research stage to build in safety; the second stage to describe the material and its use, then analyze its life cycle, evaluate the risk, hazard, plus exposure, assess the risk management strategies and then clearly have a record. Decide what you want to decide but then document and act and periodically monitor and review so that you may adapt appropriately.

Before closing, I want to say a few words about the recent conference that was organized by the Finnish Presidency of the EU, for you to know every

six months it's like Europe has a new government and one of the member states actually takes charge of the leadership. And that was a conference organized under this leadership. So the objective was to ensure the safe, integrated and responsible development of nanotechnologies. There were about 200 people, a very balanced representation of stakeholders from 20 countries including the USA and the conclusions were very straightforward. It's imperative to demonstrate safety and make it a standard. To advance R&D definition standards and instrumentation, regulation and data, to strengthen coordination and stakeholder dialogue and to produce a roadmap to know who does what, where and when.

In conclusion, I think everybody agrees nanotechnologies hold great promises. They do entail risk like those cadmium selenite quantum dots, that really are proof of concept but probably should not be used on humans. They could be used in vitro, maybe, or probably, and that this requires strengthening cooperation, advancing risk research, filling the data gaps with the data we have or by generating new data and setting international safety standards. Thank you very much.

(Applause)

CHAIRMAN ALDERSON: Thank you, Philippe. It's pleasing for me as Chair of NEHI which you talk about to see, many of the things that Philippe identified in his presentation are the same issues that NEHI's been talking about as related to risk assessment, particularly environmental and health risk. So in that respect, we are on the same page, if you will or our thinking is and that's always great to hear, but he also points out there's opportunities for cooperation that we must take advantage of.

Our next speaker is Dr. Delara Karkan. She's the Associate Director of the Center for Evaluation of Radiopharmaceuticals and the Biotherapeutics and the Biologics and Genetic Therapeutics Directorate at Health Canada. That's a mouthful. She has been with this directorate for two years. She is a clinical pharmacologist from the University of British Columbia, has worked as an Associate Director for Drug Development in publicly traded Canadian biotechnology companies and contract research organizations in the field of drug delivery and nanotechnology.

Previously, she worked at AstraZeneca and Glaxo Wellcome as a Research Fellow in drug development. She is also a visiting scientist at the

National Research Council of Canada, working on nanotechnology, based imaging agents. Dr. Karkan.

DR. KARKAN: I want to thank you for inviting me. It's a pleasure to be here. And I want to thank the FDA team for a very well organized event. Having seen the slides and being the third speaker, I find my slides, some of them are a copy of the European Commission's slides and so I'm wondering now if the Office of Applied Technology actually copied some of your slides because they're identical. But I hope to find something new among my slides that would be of interest to the audience.

I'm going to actually, before that I'm going to give you an overview because I don't have a slide for an overview. I'm going to give you an overview of activities currently in Canada in the area of nanotechnology that's not only the Ministry of Health but other ministries and non-governmental organizations, what's happening in Canada and where we think we are heading to as well as some specific initiatives at Health Canada that may be of interest to you. And I'm going to start with some overview of nanotechnology again. I'll try not to repeat what was said before.

As we know and this is how we see it in

Canada, that there is no official definition really for nanotechnology and it's generally described as the science and technology that creates, manipulates and manages material. Two specific features are the size and the property of these material. And that's what we're focusing on in terms of our research as well as in terms of setting up new regulations for these products. I'm again repeating here very briefly. The nanometer scale which is related to the size, a billionth of the meter, in Canada we're still using the old metric system, so, yes, a billionth of a meter, 1/80 thousand of human hair as well as one hundredths of the size of a virus and as my colleague on the European Commission said, half the diameter of a DNA double helix.

What we are dealing with in Canada in terms of products that have been submitted to us for review or products that are entering the market are both the fine particle products as well as the manufactured nanomaterial, and we find that they're different and dealing with them needs different set of skills, especially in terms of health assessment, risk assessment and toxicology. For example, I'm just going to give one example as the ability to find particles if you look at their chemical complexity,

they're complex and they are less reactive but if you look at manufacturing nanomaterial and you're getting more and more -- and our research centers are producing more and more manufactured nanomaterial, and you see that they're chemically well-defined and they're highly reactive. So basically, you're dealing with two different types of products or particles in manufactured material and we have to be able to set up regulation for both.

And here is a copy of that slide, really what's so special about nanomaterial? If you look at how the property -- do you remember I said size and then properties. This is more related to the property. If you look at how nanoscaling a product can change its property, it can actually be dramatic. If it's insulator turning to nanoparticles can be a conductor. If it's insoluble, it can be soluble such as solvents that are used for drug delivery. If it's opaque, it can become transparent, such as the products in sun screen, and of course, the famous gold. What I will add here to what Dr. Martin said, is that if you look at this piece of gold and actually, we have received some drugs submissions based on gold particles recent to Health Canada, a piece of gold has a surface area. If the same

piece of gold is turned into one nanometer gold particles, the surface area would increase by four million times, so, yes, you're dealing with a totally different property. And the surface area may be related to the reactivity of gold and so how do you assess such a tremendous difference in property. We are also doing, as I mentioned, research and we're producing products in Canada, a whole range of products, very diverse. Just some examples of products that are being currently manufactured or worked on at different institutes around different provinces in Canada, fullerenes, carbon nanotubes, quantum dots, dendrimers and nanomushrooms. And they have a whole range of other products coming up.

And not many of these products have actually held safety assessment or any type of initiatives associated with them, so they are being produced currently without any proper health risk assessment requirements. And this is something that we're currently looking into, is how can we classify them and encourage industry to at least provide us some of their own suggestions as how they want to go about the health safety assessment of these products and I'm going to show you in some slides how we're going about to do that.

If you look at this slide it's showing you actually the worldwide government nanotechnology funding. This is from 2004 and it's from an Australian report. If you look at 2004 and, of course, the United States, the amount of funding of 1.6 billion and if you look at -- sorry, I'm using this instead of the laser. If you look at Canada, it's about 200 million. Considering the fact that Canada has a tenth of the United States' population, I think per capita, we're doing fine. It shows that really the Government of Canada is considering nanotechnology as a very important project. We are spending a lot of money both on research and this is governmental funding, both on research as well as health and safety assessment.

So we are encouraged to set up new initiatives, ask for new funding and participate in international cooperation. So going into international activities that we are currently involved with, again, some of them are repetitious, but I can emphasize on some of the areas that Canada is actually leading in terms of research and setting standards. If you look at the OECD, we have been active with the OECD, working on manufacturing nanomaterial for a number of years now and we have

subcommittees in Canada who work on specific subjects that OECD thinks that Canada can lead or can provide extra information. Same with Committee on Science and Technology. ISO, we've been very active with ISO and we have also subcommittee reports on some of ISO's priorities. Right now we have in Canada, we've considered setting up as -- we just heard from Celia that we consider setting up standards for new materials and classifications of these new nanomaterials, very, very important. This is our first step and so we are putting a lot of effort into working with ISO and setting up standards.

We're working with the International Risk Governors' Council, International Council of Nanotechnology as Canada's policies require. We're also very interested in global dialogue on nanotechnology with the Meridian Institute, US Science Foundation, international dialogues as well as Global Nanotech Network. So these are our current areas of international activities. If we go into Canadian federal activities, I'm just going to provide you with a few of the new initiatives and if you have questions later on, I can be available to answer.

We have, of course, the Public Service of Canada's Nanonetwork which is trying to put different

ministries together and make connections between Industry Canada, Health Canada as well as some other non-profit organizations. We have a Nanotechnology Federal Action Plan which came out of a nanotechnology working group. The action plan is helping to set up the standards for classification and nomenclature and also trying to set up Health Canada with new regulations.

We've got granting councils in Canada overall. They've considered nanotechnology as one of their priorities and so a lot of grant money is actually going into nanotechnology research. That includes health research and safety and risk assessment. National Nanotechnology Strategy, which comes out of Prime Minister's Advisory Council on Science and Technology has actually been issued recently so we do have a strategy in place as how to go forward with nanotechnology and with the Federal Action Plan.

We continue here with our federal activities. We have a brand new national Institute for Nanotechnology which was set up. We just had a grand opening in June 2006. And here we do different types of research, ethical research, research on nanomaterial as well as risk assessments research.

It's in Edmonton, Alberta. It's part of actually the National Research Council of Canada. The Institute for National Measurement Standards, this is the institute that works directly with the ISO and they are a lead on a number of projects as setting standards for nomenclature and classification of these nanoproducts. Standard Council of Canada, which is again, established a new ISO committee to work on terminology, nomenclature and metrology as well as risk environmental issues. And we've done public opinion research in 2005 and we're continuing to do new public opinion research. The main reason is to find out about integral issues conducted with the research.

Focusing on Health Canada, Health Canada is not a regulatory agency such as if you compared the FDA to Health Canada, Health Canada has a much broader mandate. It deals with a lot of other issues than food and drug, such as consumer product safety, disease and conditions, emergency environmental workplace health, air quality, climate change and contaminated sites, environmental contaminants, environmental health assessment, noise, occupational health and safety, radiation and water quality. And among these, I think the Federal Action Plan that I

just mentioned is focusing more on the occupational health and safety at this time because we understand that a lot of researchers who are working on nanomaterial may be exposed to these substances, so we thought that this would be a good start to look at how these workers or researchers are working with this nanomaterial and what kind of procedures should we put in place to ensure safety of the workers.

So as you see, we not only have a food and drug -- responsibility for food and drug regulation, but also a very strong environmental mandate and because of that, Health Canada is now moving into looking at product cycle development more and more and to full cycle development of a product. And it's not only for nanotechnology, it's a general approach that Health Canada is taking under a new initiative called Progressive Licensing. And that means that we are -- if I give you an example of a medical kit, a diagnostic medical kit that has nanomaterial in it, if that kit is now being brought up to the market, we should be involved into the very early stage of development knowing what kind of nanomaterial is used.

We should assess it, do a review on this kit and ensuring that it's safe to use and then when it's disposing to the environment, we have to make

sure that the disposal to the environment of this kit is not causing any harm to the environment. So we are looking at the full cycle development as well was you know, the disposal of this kit and this is a life cycle approach. If you're trying to apply to the majority of new material that's being -- coming to Health Canada for review, that's not only food and drug but hopefully the consumer products such as cosmetics.

We currently don't have a federal act regulating cosmetics but if a full cycle approach is approved and we're going into progressive licensing, those will come into effect, so they would apply to cosmetics as well. So in this connection, we have a few new nanoactivities at Health Canada. Just recent activities and what's happened recently to inform you about such as the fact sheet. We are going to set up a fact sheet and put in on our website shortly. We have an issue identification paper at Health Canada that's identifying all the gaps and all the research priorities that we need to look into. This paper has been now under revision, the last revision.

Health Canada's public agency working group to have an agency which does surveillance in Canada, surveillance of disease and surveillance of

side effects of products that have already been approved. And there is a working group that's been formed between Health Canada and the public health agency. Research on assessing and characterizing toxicological effect of nanoparticles and that's basically what I told you about concerning our health and safety, worker safety, that's where we're doing our toxicological research. We find that ethical issues are of importance. We have an ethical research group in our new Center for Nanotechnology Research. Especially when it comes to new product development, we find that ethical aspects of new product development is to be very well looked into, so we have a few researchers in the new center working on ethical research.

Federal lead in nanotechnology, Health Canada is actually the federal lead in nanotechnology proposal to the Council of Canadian Academics, Academies and we're also -- we've been the federal lead in a workshop that we recently set up trying to coordinate nanoactivities across all ministries and non-governmental organizations. We have -- I'm not going to go through everything but we have a list of acts and regulations here that are currently supporting our review and assessment of nanotech-based

products. Were using these acts and legislations to look into safety of nanoproduct, new nanoproducts. However, I must mention that we are also going, like the European Commission, through a legislative regime renewal process. That's another initiative at Health Canada. We're trying to reclassify the products and making sure the products that we're reviewing are in the right class and we're hoping that this legislative renewal will help us to better place nanotech products. And of course, we recognize that we have gaps in science. We don't have adequate science capacity. We have -- we don't know the impact on human health. We have lack of information on exposure. We don't know the appropriateness of our existing tools and as well as the rapidly evolving nature of the technology is not helping us.

I'm just going to conclude here with two points. Canada's current regulatory system regime can provide a framework for the advancement of nanomaterials and nanoproducts but there will be a need for modified regulatory and risk assessment approaches to better understand and that the international cooperation is extremely important and we need to be an active participant to minimize our duplicative effort. There is a list of websites, if

you have a handout of my presentation in terms of the different ministries and organizations that are involved with nanotechnology research.

(Applause)

CHAIRMAN LUTTER: Thank you very much for the enlightening presentation. Our next session is the first of public stakeholders. It's entitled "General Science, Policy or Use of Nanotechnology Materials in FDA Regulated Products". And for expediency, we invite all six speakers to join us here on the stage. In alphabetical order, they are Dr. John Balbus of Environmental Defense, David Berube from the International Council on Nanotechnology, Carolyn Cairns from the Consumers Union, Kenneth David from Michigan State University and Dr. Stacey Harper from Oregon State University and Matthew Jaffe from the US Council for International Business.

Welcome, please, everybody today. And I have -- our schedule allows for eight-minute presentations. I think you can choose to speak from here at the podium or from there. It might be easier if you speak from here, especially if you have slides. And at the end, there will be a very short opportunity for the members of the task force to ask you questions. So, without further ado, we'll do this

in alphabetical order, so Dr. John Balbus from the Environmental Defense is first.

DR. BALBUS: Thanks very much, Dr. Lutter and I'd like to thank the FDA and especially the Nano Task Force for giving me the opportunity to provide comments today. My name is John Balbus. I'm a physician and public health professional and Director of the Health Program for Environmental Defense. Environmental Defense is an organization formerly known as EDF or the Environmental Defense Fund. We're a large non-governmental environmental advocacy organization focused on science-based pragmatic solutions to environmental problems.

One of the hallmark of our work -- hallmarks of our work is our industry partnerships such as our partnership with Dupont on nanotechnology which Dr. Martin alluded to previously. Before I actually get into my slides, I just want to summarize my main points for the FDA.

The first is that as an organization, we very strongly support the safe development of nanotechnology because if its promise for tremendous advances for clinical medicine and energy production and material science and other critical societal needs. So our basic stance is promoting the safe

development of nanotechnology. We are concerned, however, that because of limited authority and limited resources, that the FDA may not be able to effectively identify and manage risks from nanomaterials especially things like cosmetics, personal care products and sun screens. And lastly, we don't believe that the FDA's public communications to this point and other agency-wide responses really reflect the urgency and potential seriousness of nanotechnology risks and call on the FDA to devote more resources to improving its handling of nanotechnology concerns.

We'll see a slide like this many times today, I'm sure, pointing out the many different applications that all fall under the FDA's jurisdiction. My main point in showing this slide is not so much the variety of applications but to highlight the variety of legal authority and legal mandate that the FDA has in these different applications, ranging from very extensive pre-market testing and pre-market screening of pharmaceuticals, high risk therapeutics, medical imaging devices, and many food additives, to no pre-market screening and just post-market surveillance for things like cosmetic sun screens, and a reliance only on this post-

marketing recall authority and voluntary industry activity.

The urgency I allude to is underscored by the fact that we have numerous products out on the market, people are using them. The materials are getting into water supplies, et cetera -- or waste water streams, et cetera. This is an old slide that shows that there were several dozen cosmetics, personal care products out on the market. I'm sure we'll see an updated slide later today from the Wilson Center showing these numbers increasing rapidly. And unfortunately, the FDA's public stance on this as at least alluded to the website, I think that we're seeing a different tone today here, but from the website, the public communications really don't inspire confidence in the process. The website states few resources currently exist to assess the risks and then kind of states flat out that particle size is not the issue and kind of long statement explaining how the FDA if very familiar with nanotechnology risks because all drugs, when you take them, go through a nanophase.

This is really not what we've heard from the other speakers today. It's not what we heard from Professor Ann Dowling and the University of Cambridge

in the UK Royal Society Report who said quote, "Where particles are concerned, size really does matter and I think that we all recognize that it's the size of nanoparticles that makes us have to revisit the status quo". We will see other slides like this today. I'm not going to stay on this very long except to stress the point that because of the unique size of nanoparticles, they are a unique -- have a unique ability to interact with our biological proteins, essential biological machinery.

The top slide is just a modeling study of Javet, et al. showing that buckyballs are just the right size to be able to bond with and reconfigure DNA. We know that carbon nanotubes are used in DNA sometimes to separate them. There are unique interactions that we don't see with non-particulate bulk materials. One critical and yet, I think insufficiently answered question is the extent to which nanoparticles are able to penetrate the skin because this is really going to determine whether topically applied kinds of products will have systemic risks and be able to interact with DNA and so on like we were just talking about. Aside -- these slides here are just a study of quantum dots. The quantum dots which are going to be increasingly found in

clinical settings, not so much in the personal care products, showing some modest penetration into the dermis depending on the coating that's used. The ME coating is a little more likely to penetrate deeper.

Critical questions of durability of these particles and other particles, fates of coatings as well as the persistence in excretion of absorbed particles are really going to be key to understanding the potential toxicity but as yet these questions are just starting to be pursued and we really think this needs to be a great focus.

And lastly, most studies that have been done so far on nanomaterials in the skin have been using in vitro preparations. And what's of most concern to me is the public health professional is not what these particular studies of cell culture show but the way in which these studies can be used and in some cases have been used to make fairly sweeping conclusions about the safety of the products for human use. Obviously, if you're just using skin cells in Petrie dishes, you really are unable to comment on the potential effects and the propensity of particles to get into systemic and lymphatic circulation and disrupt distant systems like the immune system, get into the brain, reproductive systems, et cetera. And

so I just want to -- again, we need to answer these questions of where these particles go in the body, whether or not they can penetrate the skin in any kind of appreciable way and if so, then we need to be looking at systemic effects.

Environmental Defense has been working with regulatory agencies and industry partners to develop tools and methods to effectively manage the risk of nanotechnology products based on these four principles here. I'll get to the specifics for the FDA in a second, but I just want to underscore that really the hallmark of his is what Dr. Martin pointed out, is significant pre-market assessment, pre-market scrutiny, designing products with safety in mind up front and if you don't look, you won't be finding the potential risk that can be just engineered out from the start.

For the FDA, I think it's pretty clear we need to increase the level of risk research. As an organization, we've been calling for $100 million federal budget. There's discrepancies between different estimates. The government estimate is around 44 million now. I'm not exactly sure why the FDA showed up as zero, whether that was an oversight or -- because I know that the FDA is certainly

involved in research. I'm not sure to what extent it's funding it, but we need to have a very significant ramping up in the near term to try to catch up with what's already on the market.

I think it would be very helpful for the FDA to seek pre-market authority for cosmetics and personal care products which it does not now have. Obviously, a long shot but there's no reason why we should just be counting the bodies and use that as our regulatory system. In the meantime, we can call on the FDA to maximize existing authorities. I think we need to revisit some of the weight-based exclusions under NEPA. Some of the considerations of NEPA are based on mass concentration. We can beef up the voluntary information programs that are currently used in cosmetics and I'm running out of time, so I'll just end that this is a great start that we have today. We have a great turnout. I think that we need to continue to increase meaningful stakeholder involvement and I look forward to being a part of it. Thanks.

(Applause)

CHAIRMAN LUTTER: Thank you very much. Our next speaker is David Berube of the International Council of Nanotechnology.

DR. BERUBE: First of all, I'm here today representing the Center for Biological and Environmental Nanotechnology. Vicki Colvin wanted to be here. She's on her way to India. She's a good friend of mine. I was on sabbatical writing a new book, and she says, "David, please do this for me," and I am.

Sun screens represent a multi-million dollar market and their consistent use is thought to reduce substantially the incidents of skin cancer. There will be no PowerPoint. I teach a course at Hatcher Electric called the Tyranny of PowerPoint. Titanium dioxide has been used as a sunblocking pigment since the mid-1990s and advances in nanotechnology just permitted the size of the pigments to be reduced below 100 nanometers. Similar advances were also applied to different materials, zinc oxide and today the estimate is about 30 percent of sun screen sold commercially contain these inorganic particles. The issue addressed here refers to two recent technical reports and in this month's FDA public commentary is whether shrinking the size of the pigments leads to any new toxicological properties.

A non-governmental organization, Friends of the Earth, released a report in May of 2006

characterizing the level of regulation of components of these sun screens as one of the most striking failures since asbestos. This September, the Cosmetic, Toiletry and Fragrance Association, the CTFA, a trade association, released a statement claiming, "The general scientific consensus is that there is no risk to human health". The statements from both these organizations demonstrate selective use of scientific literature and set the stage for an ineffective and polarized public dialogue on nanotechnologies risks and benefits.

The Friend of the Earth report presents a reasonably complete accounting of the recent technical literature but the technical review does not connect well with the ultimate recommendations. At several points in the report, the authors acknowledge conflicting technical data in the literature on nanomaterials' health effects but these nuances are not apparent in the report summary. For example, the report admits insufficient information about particle translocation across skin means the jury is still out, yet the report concludes regulatory negligence.

The Friends of the Earth analysis also generalizes from the specific cases of nanostructures found in one formulation to the behavior of all

nanoproducts. Thus, the report cites groups of papers in one nanomaterial type, e.g. carbon 60, and then later in the report, refers to these results as the basis for taking action on all nanoparticle types. This tendency to over-generalize is particularly apparent in the report summary and in the more extensive policy recommendations laid out in the CTA legal petition to the FDA on behalf of FOE and the coalition of other advocacy groups.

The CTFA press release and associated reports shared with the FOE report a similar level of technical depth but draws very different conclusions. As in the Friend of the Earth report, there are disconnects between the CTFA's short public statements and the longer technical report. For example, the press release holds that the overwhelming weight of the scientific evidence states that these substances, referring to nanotitania are safe and untoxic, yet the full report from the same organization cites several publications that demonstrate oxidative damage in biological systems from nanoscale titanium.

In contrast with the FOE report, the CTFA report does capture the diversity of nanoparticle composition and the related diversity and biological response. In their analysis, however these data are

used to justify a different over-generalization, namely, the size of these nanoparticles does not make them inherently different in terms of toxicity. The toxicity of nanoparticles will likely be cause for several physicochemical properties but this fact does not preclude size as being an important factor in defining biological properties for some systems.

Interestingly, both reports were in good agreement that the technical literature in many areas is equivocal. This is perhaps why the detailed reports are not substantially different and cover much of the same literature. What is striking is how each organization reacted differently to the current studies. Uncertainty was an argument not to regulate in one case while equivocation of the technical data was a sign that regulation must proceed quickly in another.

Vicki makes these recommendations. First, we urge all stakeholders permit the debate about nanotechnologies, risks and benefits to occur at the highest possible technical level. Secondly, all technical information used to form the basis for the first policy decisions in this area should be publicly available. The benefits of an open review at such a critical time in nanotechnologies development outweigh

any possible loss to business due to confidentiality. We urge companies to not only make available toxicity and testing data ideally through peer review but also to provide data to support the efficacy of nanopigments compared to comparable organic materials. And finally, non-governmental organizations should continue to monitor the technical literature and highlight areas where more focused research is needed. Data bases such as the one offered by ICON on EHS publications should help and in time will contain even more integrative information.

Whether the benefits of using sun screens containing nanoparticle pigments outweighs their risks is a question not yet resolved in the peer review literature. We hope that while the science remains uncertain, government organizations like the FDA will base their policy decisions on a balanced analysis of peer reviewed and publicly available scientific literature. General principles of risk management which rely on good monitoring programs and investments in research are well-suited to these necessarily uncertain technical times. And as I mentioned, this statement was not approved as an official document of the International Council on Nanotechnology by its Editorial Board and should be considered the opinion

of its author and the Center for Biological and Environmental Nanotechnology. Thank you.

(Applause)

CHAIRMAN LUTTER: Thank you very much. Our next speaker is Carolyn Cairns of the Consumers Union.

DR. CAIRNS: Thank you. My name is Carolyn Cairns and I'm a Senior Researcher in the Product Safety Department of Consumers Union's Technical Division. I also won't have any slides today, I'm afraid. As the non-profit publisher of Consumer Reports magazine, we appreciate the opportunity to share our views about the need for strong regulations to manage unique risks that can accompany nanoengineered substances and products within FDA's jurisdiction. We recognize the important benefits that these materials can bring to certain product sectors such as more effective medicines, safer drinking water and energy savings, but we also know that these benefits depend entirely on responsible development of nanotechnology.

We're deeply concerned that the unregulated widespread use of many nanoengineered substances, may generate the types of irreversible, unintended consequences seen before with other

innovative materials such as PCBs and pesticides like DDT pushed to market before their risks were characterized. In cases like these, risk-based standards lag some 20 years behind their entry into commerce, often resulting in a long difficult and sometimes unsuccessful process to remove them from commerce, foods and the environment. That's what we don't want to see happen with nanoengineered materials.

It's precisely because of the potential benefits of nanotechnology are so heavily promoted even hyped in some cases, that FDA must increase its commitment to characterize and manage their hazards. We encourage FDA to revise its priorities to put greater emphasis on protecting consumers from nanotechnology's adverse effects than on removing hurdles that inhibit its use in commerce. Our comments today will focus on three basic points, many of which have been mentioned already. First, that FDA must understand that risk at the nanoscale can be size- and structure-dependent. Two, that regulations and standards based on mandatory pre-market assessments are sorely needed, and finally, the FDA must require disclosure through labeling of the use of nanomaterials in consumer products and transparency of

toxicity information concerning these materials.

Although our concerns span a range of applications under FDA jurisdiction, my comments today will focus primarily on foods, dietary supplements, cosmetics and food and color additives. In our view, the first steps toward a coherent policy on nanotechnology is to recognize that risks of the nanoscale are often size- and structure-dependent and uniquely different than those of their larger counterparts. As has been mentioned already, experts in nanotechnology are virtually unanimous on this point and we think FDA needs to structure its approach to regulating these materials accordingly.

Scientists from academia and industry alike have raised many concerns about the impact of different chemical and physical properties that chemicals take on at the nanoscale, for example, their ability to cross the blood/brain barrier. Size and structural differences can also enable nanomaterials to migrate to different tissues and organs than their larger counterparts and elicit biological responses unique to their shape, worsen effects seen with larger particles. We're also concerned they may synergize adverse reactions with these or other substances and possibly impact the efficacy of conventional drugs and

cosmetics.

Characteristics like increased bio-availability are particularly worrisome for substances for which no toxic effects levels have yet been defined or for substances like selenium where there's a narrow margin between the nutritive and minimum toxic effect level. Though many studies suggest that dermal penetration of nanomaterials is -- of some nanomaterials is limited, critical factors such as movement, exposure duration, and condition of hair and skin can influence findings. Researchers at National Institution of Occupational Safety and Health, for example, found that physical activity can move beryllium oxide into skin where it can activate cell mediated immune response which may lead to beryllium sensitization at lower concentrations.

Such findings may have implications for other immunologically active nanoscale compounds. FDA should also recognize the importance of size and structural differences on detection methods needed to find these substances in products, the human body and the environment. Accurate exposure and risk assessment and the consumer's right to choose all depend on such protocols, yet already -- such methods already required for food additives should also be

required for nanoengineered substances. However, our own research suggests that some manufacturers have yet to develop reliable protocols for the nanoengineered ingredients they already sell.

Given the safety of nanoengineered materials cannot be predicted from their larger counterparts, we agree with the Royal Society and others who call for nanomaterials to be regulated as new chemical substances subjected to a full battery of safety tests and approval by government agencies before they're use. FDA needs to lead the effort to define this minimum battery of appropriate tests and work in coordination with other agencies like EPA and OSHA to insure that life cycle analysis -- life cycle impacts are fully characterized. Such protocols need to consider things like oxidative stress, C-reactive protein, platelet aggregation and other immune and inflammatory responses and genetic toxicity.

We're particularly concerned with now engineered ingredients in food, dietary supplements and cosmetics, products that completely lack pre-market safety testing requirements. Likewise, nanoengineered food and color additives currently require no special testing because FDA currently considers then equivalent to their non-nano

counterparts. We think these products should be held to reasonable certainty of no harm standard that's already applied to food additives and pesticides.

Given the number of products that have already been in the marketplace, we think that new regulations also should be retroactive to cover existing products. Where critical gaps do limit the development of test methods, however, FDA should not be passive but should act quickly with expert stakeholders to lead and accelerate the development of appropriate test protocols relevant to new applications as they're being developed. We urge FDA to err on the side of caution rather than commercial expediency where scientific uncertainty is concerned.

Though we appreciate industry's need for realistic protocols and standards that don't impede innovation, we feel that safe new foods, including dietary supplements, cosmetics and food and color additives are worth waiting for and most importantly, FDA should not take the lack of evidence of harm as a proxy for reasonable certainty of safety. We urge FDA to require labeling of nanoengineered ingredients and the products in which they are used and to act to fully inform and engage stakeholders in a debate over their use. Recent survey data show that consumers are

not well-informed about the presence of nanomaterials in consumer products. Growth and demand for organic foods increasing at a rate of nearly 20 percent a year shows that many consumers already want to limit the use of synthetic materials in the products they buy and survey data suggests that many may feel the same about nanoengineered substances. Labeling is also crucial to facilitate exposure assessment and product tracing in the event of unanticipated effects and to enable assessment of cumulative effects that occur over exposure to multiple products. As a basis for labeling, FDA should undertake the difficult but important step to develop clear definitions and nomenclature for nanoengineered materials and nanotechnologies both for regulatory purposes and for minimizing consumer confusion.

We also urge FDA to develop mechanisms by which to fully inform and engage consumers and other stakeholders in meaningful dialogue about risks, benefits and unknowns associated with nanomaterials in consumer products. Consumers Union appreciates the opportunity to share our views today on this important consumer safety issue and we urge FDA to act quickly to adopt the recommended priorities and take a leadership role in developing the scientific research

and regulatory tools needed to effectively assess, manage and communicate the risks associated with nanoengineered materials and to enable consumer choice in the marketplace through product labeling. Thank you.

(Applause)

CHAIRMAN LUTTER: Thank you very much. Our next speaker is Kenneth David from Michigan State University.

DR. DAVID: Good morning. This is a preliminary report indeed. We held our meeting on September 11th and 12th and I note from the slide that it's really characteristic of this team that I didn't even put my name on it. This is a well-integrated team. We have a sociologist of standards, Larry Busch, a philosopher of science and technology, Paul Thompson, myself, I do organizational analysis, organizational anthropology, an engineer, a mechanical engineer, Jack Lloyd, an applied anthropologist, John Stone, Susan Sulke in packaging and this is a team effort.

Now, this, I repeat is a preliminary report. We do have a website and we have already work from our previous international conference on that site and if you want this, I hope you will look at it

by about November 15th and give me a business card if you want a reminder. Let's get at some overall findings of the workshop.

We had participants, government agencies, non-governmental agencies, companies, industry associations, universities, and we find that nanotechnology gets people to react in very distinct ways to nanobenefits and nanofears. Some find it a desirable destination, some find it a gathering storm, some find it awful and terrifying, a challenge and a threat, and others find it a clear and present danger. All are present. We entertained in our group the representations of proponents and opponents of nanotechnologies. We have had that in all of the meetings and we put together a group of people, put them into small work groups where we debated a number of themes relevant to nanotechnologies and standards.

First, let's get a second finding. When one hand standards are considered convenient, neutral and benign means for handling issues of technical compatibility, they are then a social construction of reality. We wonder, the group did, whether the effectiveness of this social construction will be tested by processes of knowledge transfer among the governing agencies. Of course this is something that

Celia Merzbacher addressed. We wondered where is the coordinating framework for nanotechnology with evaluating regulatory teeth as was developed more for genetically modified food.

It's not just a social construction of reality standards are also power construction of reality, you know, setting rules that others must follow. Standards are a form of codified social power that reflect interests of group with the greatest access to the standard-setting process. It is thus a source of strategic advantage at the local, at the national and at international levels. We recognize power processes at work among countries, sometimes of collaboration and cooperation and sometimes of competition. We note the impact of the CEN influence, one country, one vote in forwarding proposals to the ISO. We note that the US was not the earliest in responding to ISO 9000 and I don't think that makes a difference. We note that China also was slow in responding in building its own answer to Codex in food definitions and then adopted them wholesale.

So if you get there first, it makes a difference. And we did analyze the topic of nanotechnologies and standards in five themes; read quickly, timing in standard, product standards and

process standards, very tricky one, international harmonization of standards, integration of operational standards, a very good topic. Wish I could spend more time on that, and finally participation and transparency. And as I tell my students, if you have too much to say, choose just a bit, and that's what I'm going to do, just something on the timing.

Timing relates to the public, to competitors, and to international standard-setting bodies. Should the standard setting process begin early in the knowledge development process, or later as such knowledge is applied to products and processes. The uniqueness of nanotechnologies, of course poses problems. Maximum residue levels have not firmly been established. We know already that ANSI and ISO are developing nomenclature to describe nanotechnologies and of course, we heard earlier instrumentation metrology directions are being developed. It's all on the way.

We note also that that progress is hindered because resources for risk assessment are low. The supplement to the President's 2006 budget recommends 1.05 billion for overall NNI investments and as we heard earlier, only 82 million of this is for societal dimensions, specifically environmental

health and safety, R&D, education, ethical, legal and other social issues. This is perhaps a big figure in one sense but compared to the overall investment, it's not the biggest.

Next, regarding engagement between the public, the scientific community and standard-setting bodies, timing is critical. I should note here that I'm a co-author with a senior research scientist at Shell and it is his point that early engagement is historically put, if you do a history of science, quite unreliable, that the ability to predict impacts at the very early level of scientific discovery doesn't work very well. Partially, the issue is that resource allocators in firms require a series of research statements and then they make go/no-go decisions. The early statements are very, very brief. They are just relevant to whether or not the product or the scientific idea fits with the strategic work of the company but are certainly not yet explicit enough for upstream engagement.

It becomes possible when a scientific idea is developed and becomes closer to the notion of applications, products and processes. There's also a late barrier. As we saw in Britain when they summoned the GM nation, genetically modified nation, the late

engagement alienated the public. It was just looked at as a marketing exercise. Timing, and here's something, perhaps to be considered by business people in the room, it's also critical regarding business competitors and international standard-setting bodies. If you wait too late to get in on the standard setting process, you allow competitors to get there first and that may rule you out, set up competitive barriers and the same point, as I said before, works towards working with international bodies such as ISO.

Now, I'm just going to show you something that is a conclusion, an analytic diagram that describes findings just described as other findings to be reported in our full report. It is complicated but the idea is here for the FDA and for all other agencies we consider the standard-setting and regulation to not be considered by itself but is one of four major issue areas that is we are underway to explore and my time is just up. I thank you for your attention.

(Applause)

CHAIRMAN LUTTER: Thank you very much. Our next speaker is Dr. Stacey Harper from Oregon State University.

DR. HARPER: Do you start this or do I start this?

CHAIRMAN LUTTER: Can you control the slides from the control room at the back of the auditorium, please?

DR. HARPER: Thank you. Sorry. Okay, I'm here on behalf of the Oregon Nanoscience and Microtechnologies Institute to tell you a little bit about the safer nanomaterials and nanomanufacturing initiative that we've developed and I want to present to you our proactive approach to actually designing nanomaterials that are both safe and have enhanced performance. Now, it's undeniable that there's going to be widespread applications associated with the nanotechnology industry but given this exhortation, there's growing concerns about the biological activity and toxic potential of these novel materials. The unique properties the industry sometimes wants to see in a material may pose serious health risks but the lack of data in this area makes this completely unpredictable at this point.

And then the last issue is, even if there are no inherent risks or toxicities associated with nanomaterials, the public's perception of that is not going to be realized until the toxicological studies

are promoted in concert transparently with the development of novel materials. Nanotechnology offers us the opportunity to use the precision engineering to both modify the properties that industry wants and to make sure that they are safe and benign for the environment and human health.

In the Pacific Northwest we have about 26 researchers working on the safer nanomaterials and nanomanufacturing initiative. Our main goals are -- what did I do? Okay, sorry. Our main goals are to develop safer and better nanoparticles using less wasteful nanomanufacturing methods. And I want to talk about this for just a second, but I'm going to focus on the better and safer nanoparticles for the most part. But the less wasteful manufacturing is also one of the key elements of the safer nanomaterials and nanomanufacturing initiative where we're trying to reduce waste using the 12 principles of green chemistry to actually direct the manufacturing portion of nanoparticle synthesis.

And then we're developing ways in which we can integrate these into high performance devices without the use of excess solvents and such. So here's our design strategy for developing these safer nanomaterials and up here on the right we have

nanoparticle -- average nanoparticle. It has a core, some sort of stabilizing shell and then some functional groups on the outside. Basically, the chemicals or the synthetic chemists give us materials that they have produced that have the properties that they desire. They give them to us and we test them in a multitude of biological systems to assess their toxicity.

And we feed the information back to the synthetic chemists. If we get something that's highly toxic in the first assay that we run or the first in vivo exposure that we do, we send it back to the chemist and say, "This isn't going to work". They resynthesize it and we're trying to get this to a point where we can actually develop some of these structure/activity or structure/property relationships to use -- to then direct the development of safer nanomaterials.

And these structure/property relationships, the goal then is going to be link the physical chemical properties of the material, either surface area, structure, charge, things we probably haven't even thought of yet, with any hazards that are posed by the material. Okay, nanoparticles have widely tunable properties. So it is feasible to

enhance performance and safety at the same time and that would probably be my biggest take home point.

Now, in order to test the biological impacts of these new engineered nanoparticles, we take a tiered approach where we start by doing screening level toxicity evaluations and at this level we test in cell cultures, tissues and in whole organisms, using a multitude of platforms and assays both in vitro and in vivo, so that in the end we aren't just looking at what one animal's response or what one's cell types response was to these nanoparticles. We can look across a whole suite of assays and get at the basis of, is this going to be harmful or not and use kind of a weight of evidence approach.

Now, if these materials are found to be potentially toxic at this screening level, then they go on. We send them back and they go on and we have people that work in the group that are mechanistic-type people so they want to identify some of the cellular targets and get more information about these materials. We define these in vivo using whole animals using fluorescently labeled nanomaterials or very targeted assays where we can look in vivo. And then finally, the nanomaterials are grouped either based on some chemical property of the material or

some effect that it elicits and when they're grouped then we take the groups together and determine gene expression profiles for those materials and see if there's any consistency across there.

All of this information is then stored in a nanomaterial effects data base and it's used primarily to feed back to industry in order to hopefully in the future to be used to direct this development of safer nanomaterials.

Now, we're started running some of these toxicity assays and compiling structure/activity relationships for a well-defined library of gold nano particles. I'm glad some of the introductory speakers spoke of gold nanoparticles, so I won't have to get into that at all. Thus far we have 1.5 nanometer and .8 nanometer core sizes and we have a whole variety of surface functionalizations on them. And using this iterative approach, we are going through and trying to figure out what are the common things when we get a toxic response, what are the common things among those particular materials? So now I want to give you a very specific example, just to illustrate some of the key components of our research strategy.

So this is an example of how the toxicity assessments can be used to help identify the relative

importance of various parameters for the toxic potential of the material. And for simplicity's sake I'm just limiting this to size and surface functionalization and we're just going to look at it in reference to a positively charged versus a negatively charged and two different sizes. And keep in mind that I'm just going to be showing you mortality in whole animal embryonic zebra fish assay, so this -- if you add this to all of the suite of experiments that we've done on these, there is some consistency with these ones, but there are some materials that you see no mortality and you see a lot of tratogenicity and it's more in-depth than that.

Okay, so this first figure shows us mortality of the embryonic zebra fish that have been exposed for five days to the 1.5. size nanoparticle that has positively charged surface groups. And you can see here at 10 parts per million, this is highly toxic and kills the animals. Now, if we look at the smaller size, the 0.8 nanometers, we see that this toxicity curve moves down to the left and at 400 parts per billion, we're seeing toxicity. So the smaller nanoparticles that are these particular nanoparticles with this particular positive surface functional group, are actually more toxic when they're smaller.

So size does matter in this case.

Now, let's look at the same size nanoparticles but with a negatively charged surface group. So this one shows that these are practically benign. They're not highly toxic to -- in this particular assay. And when we shrink these down to the smaller level, any guesses? Nothing. They're benign also. And how general and how we're going to be able to figure out what generalizations we can make about these nanomaterials is going to be, I think, more difficult than it has been for chemicals because we do have this core, this surface functionalizations and the stabilizing shell.

CHAIRMAN LUTTER: Could you please finish up in just the next few --

DR. HARPER: Yes. Our general -- our recommendations are that characterization and purification need to be done very carefully so that these structure activities are very robust and we need to identify the biological and environmental impacts for safety and design and then finally the toxicological evaluations need to be incorporated early on in the research and development scheme. Here's our contact information. I'm going to leave some brochures out on the table, too, for the safer

nanomaterials and nanomanufacturing initiative.

CHAIRMAN LUTTER: Thank you very much.

(Applause)

CHAIRMAN LUTTER: Our next speaker is Matthew Jaffe of the United States Council for International Business.

MR. JAFFE: Good morning. Again, my name is Matthew Jaffe. I'm a partner in the law firm of Crowell and Moring here in Washington DC and it's my privilege today to appear and present the views of the US Council of International Business on this important subject. My presentation today will address three points stemming from FDA's announcement. First, I will provide a brief outline of USCIB's involvement and initiatives in the area of nanotechnology. I will then speak to our understanding of current efforts and needs related to understanding the environmental health and safety implications of nanoparticles. Finally, I will address the important role that USCIB anticipates the FDA will play in promoting and protecting public health with respect to FDA regulated products that use nanotechnology materials.

Founded in 1945, the membership if USCIB now includes over 300 multi-national companies, law firms and business associations. USCIB has built a

reputation for reliable policy advice and has helped to shape international regulations and expand market access for US products and services around the world. For example, through our membership in the Business and Industry Advisory Committee, that's BIAC, USCIB provides industry leadership on key OECD activities, including critical work now being undertaken by the OECD's Science and Technology Policy Committee, and Chemicals Committee on nanotechnology policy and regulatory activities.

As you may know, the OECD just recently established a working party on manufactured nanomaterials under the jurisdiction of the Chemicals Committee. The working party's first meeting will be held later this month in London and USCIB members will be there as part of the BIAC delegation. Why the interest? That's simple. For USCIB and its members, for the business community at large, nanotechnology looks to be a critical driver of innovation and economic growth in the 21st Century. As important, it potentially represents a transformative set of technologies.

The dynamic nature of nanotechnology thus makes it imperative that governments, businesses, academia and the public at large get the policy

framework right to realize the enormous economic, technological and societal promises offered by nanotechnology, which brings me to my second point. Most of the attention that has been paid to nanotechnology to date has centered on its tremendous possibilities and thus, issues generally related to the research and development for practical applications. Lately, there has been a shift toward a recognition that we need to know more about what this research, what this development will mean in the context of environmental health and safety effects. Last month's hearing before the House/Senate Committee certainly highlighted the importance of a shift but it did not constitute the first steps in that direction. We've heard already today and in the international arena the International Risk Governance Council surveyed government, industry, non-governmental and risk research organizations and published results that split nanotechnology product development into two broad frames of reference for which it suggested separate yet complimentary research and decision making pathways.

Well, of course, then the OECD is also considering a draft program of work on the safety of manufactured nanomaterials which is likely to

establish priorities. In the United States there are inter-agencies and agency studies, research studies and industry studies like the NNI chemical industry's roadmap of important issues to consider during the first phase of nanoparticle research. And then there are other groundbreaking efforts in the private sector, like Dupont and Environmental Defense's collaboration. In other words, to borrow from Dr. Alderson's response to the House/Senate Committee, we have all heard the cause for greater research about the possible EHS effects of nanoparticles loud and clear. With that said, we should not draw conclusions about nanoparticles before we conduct the research. We have been surrounded by natural nanoparticles for eons. The European Commission reports that a room like this one may contain 20,000 natural nanoparticles per cubic centimeter. And in this context, humans have developed natural response mechanisms to nanoparticles.

It is thus, critical that in this process of developing a policy framework that we strike a balanced approach to questions concerning the effects of nanotechnology, that we do not generalize, that we measure benefits along with risks and that we base our conclusions on verifiable science, which leads me to

my last point.

What is FDA's role in all of this? What regulatory approaches should it take to encourage the continued development of innovative, safe and effective FDA-regulated products that use nanotechnology materials? The FDA already has in place a comprehensive regulatory system founded on scientific principles and evaluations. These systems allow the FDA to review regulated products in a manner that safeguards the public against risks at the same time it recognizes the need for our society to benefit from the enormous potential that these products have to offer.

We, thus, strongly encourage FDA to regulate applications that use nanotechnology according to the same guiding scientific principles that have already allowed this agency to effectively protect, promote and improve public health. Again, the dynamic and complex nature of nanotechnology makes it imperative that governments, that all of us get the policy framework right. Like any new technology, there's some uncertainty, uncertainty over environmental health and safety effects. The USCIB believes the OECD is prepared to play the critical role at this juncture and we invite the FDA to

actively participate in the OECD process together with your colleagues at other agencies. Building on the significant expertise and chemicals policy and regulation, the OECD is ideally placed to develop internationally agreed science based methodologies, definitions and mechanisms for managing products and for protecting environmental health, human health and safety. FDA's internationally knowledge and expertise in public health makes it well-suited to interface with OECD and others to share its knowledge. Thank you.

(Applause)

CHAIRMAN LUTTER: I'd like to take a few minutes to ask the members of the FDA's task force whether they have a couple questions that they'd like to put to members of the panel here and then after that we can turn to a break. So we have benefitted from six very informative presentations and I wonder if somebody would be brave enough to put a question to the speakers. Eric? If the mike doesn't work just ask the question, Eric and I'll repeat it.

DR. FLAMM: Thanks. I'd like to direct a question to Mr. Jaffe. In light of the earlier speakers' comments on the lack of knowledge of how certain materials work at the nanosize and lack of

pre-market oversight of certain areas of FDA jurisdiction, and in light of your statement that FDA should maintain its science-based approach to regulation of product, what is your view of the adequacy of FDA's authority over products like cosmetics?

CHAIRMAN LUTTER: If you could take just a minute, thank you.

MR. JAFFE: This is Matthew Jaffe again. I'm appearing on behalf of the USCIB, so obviously, I don't have the authority to speak on behalf of the USCIB in response to your specific question because it's a large organization. However, I would note, again, reference my comments which we said specifically that we believe the regulatory process that is in place currently is significant and adequate to address the issues that are currently before the FDA on issues of cosmetics and other items as well.

DR. CANADY: Hi, this is Rick Canady with the Office of Commissioner of the FDA. Actually, I have two questions. The first one I don't think folks are going to be able to answer very quickly so I'm probably going to go to the second one real quickly. The question is with regard to presentations by Ms. Cairns, I think, John Balbus, even David Berube, there

was -- there were questions about uncertainties and questions about definitions and so on with regard to what we can label, where we can label it and so on. And I just wondered if you had any further insight about how we start that process of developing definitions that allow us to label, for example, allow us to know when nanotechnology begins and how to inform consumers and then Ms. Cairns, if you could respond and then I have a question for Dr. Harper.

DR. CAIRNS: Yeah, that's really, obviously, a complex and very important question, where do we start, and I think we're thinking about it from the standpoint of somewhat the way the folks in the University of Oregon are taking it, there's a tiered approach. I think there's a lot of -- a lot that we know now already from some of the work that's already been done. It's very limited but it's not zero. And I think if we can take that tiered approach and start with some basic get -- pull this information together, and really see what do we know.

I mean, I think just at the bottom line, if a product is being engineered at the nanoscale, that right there opens the door that you're specifically manufacturing something to have these properties. We need to know what those properties

are, where that chemical is being used and how people are being exposed to it, so that, I think is the first step.

DR. BALBUS: You're really asking two questions. The first is what are we going to use as a definition of whatever it is we want labeled, whether that's nanotechnology, nanoparticle. That's proving to be pretty thorny and there's a lot of different venues in which that debate is going on, whether it's ASTN, ANSI, EPA, et cetera, and I don't have an easy answer on that.

The second part is, should manufacturers be disclosing to the agencies when they have whatever ultimately gets determined to be the definition of a nanoparticle. And we saw kind of the down side of loose labeling with the Nano Magic episode last April where companies are allowed to put the word "nano" on the product, not the three different industries of companies involved. The disclosure wasn't good. It took them months to actually figure out if there was anything that was anybody's definition of a nanoparticle in the product and ultimately there wasn't. So I think the FDA has the ability to call for claims and marketing claims and you know, it would be incumbent on you to define exactly what would be a

nano, you know, marketing claim and not, drawing from the work that's going on in a lot of standard setting organizations.

DR. DAVID: Richard, the only thing I want to add is that I'm a big fan of research needs assessment anyways and I think everybody realizes that needs to happen, but when we do this, we also have to throw a threshold parameter into it because scientific research is boundless. We all know that. We could always be waiting for more information. We just have to figure out when enough is there to actually make a decision. And the last thing, since I'm a professor of risk communications that you know, you're going to have to communicate this to the public while it's going on, I mean, because the public is getting a lot of bits of information right now and they're trying to ferret their way through it and having an incredibly difficult time.

And so we don't just need to figure out, you know, what's safe and not safe. We also have to try to figure out how to be able to communicate that to the public while all this is going on.

CHAIRMAN LUTTER: Please join me in thanking the panel for this very enlightening presentation.

(Applause)

CHAIRMAN LUTTER: We have a break of about five minutes and then after that, we'll start again.

(A brief recess was taken at 11:11 a.m.)

(On the record at 11:22 a.m.)

CHAIRMAN ALDERSON: Well, this follows -- this is our second session and I just want to remind the speakers that you have eight minutes and at seven minutes the yellow light will go on. At eight minutes, Randy and I will get itchy over there and if you continue on we'll then beep you. So you know, if you've reached that point you're in trouble. So let's get started.

Our first speaking of the second session is Martin Philbert, from the University of Michigan, School of Public Health.

DR. PHILBERT: Good morning and thank you for the opportunity to speak with you today regarding the science of nanotechnology. I'm Martin Philbert, Professor of Toxicology and Senior Associate Dean for Research at the University of Michigan, School of Public Health. I also serve as the Executive Director for the Center for Risk Science and Communication or CRSC.

My primary area of research includes

development of nanosystems for measurement of physiological processes within living systems, including cells and for the early detection and treatment of brain tumors. I look forward to assisting the FDA in furthering its understanding of nanotechnologies that fall under its purview. Nanotechnology holds great and varied promise in contributing to significant improvements in public health. However, as with all emerging technologies there are inevitable risks accompanying the development and deployment of nanomaterials that must be considered. As we continue to explore this emerging science, issues surrounding health and safety are certain to arise. But what I want to emphasize to you today is that the scientific community is not completely ignorant with regard to hazard identification, risk analysis and to the management of those risks associated with the deployment and the use of nanoscale materials.

And the take-home message is, essentially, there is no need to panic. In fact, over-reaction is likely to stifle innovation, prevent advancements in nanotechnology and rob the public of potential dramatic improvements in health and the amelioration of suffering. Simply stated, at present the benefits

of using nanomaterials greatly outweigh the risks. Any steps in policymaking must be based on a sound foundation of scientific evidence and in my opinion the science does not yet mandate Draconian action.

I want to describe in brief what I view as the state of the science of demonstrable adverse effects induced by nanoscale materials. We've known for some time from the published evidence, the peer review published evidence that comes from exposure to ultra-fine materials and to some of the more novel materials that high aspect ratio materials, i.e., long thin fibers tend to make things more reactive and more damaging. If these materials are also bio-persistent, and have reactive points that are also associated with transition metals or other metals that are capable of producing reactive oxygen species, that greatly enhances the likelihood of toxicity.

Now, it is not -- at the risk of being heretical, it is not the nanoscale necessarily that confers toxicity. It may enhance toxicity but nano is just a scale. In fact, one has to wonder whether or not as the cadmium, selenium or arsenic associated with a quantum dot-like material that is the toxicant or its size and whether one needs to reduce the overall exposure to those materials. We also know we

have learned a great deal of lessons from manganese exposure and welding fume with materials at that nanoscale. We also know how to manage these risks. Coating materials with bio-compatible chemicals or other polymers greatly reduces their toxicity and this has been published with regard to Dextran and silica titanium dioxide and zinc oxide, et cetera.

We've also known for many years that polyethylene glycol alters the pharmacokenetic and toxicokinetics profile of materials in drug delivery vehicles. Nano is just a scale. The nanoscale does not per se or of necessity confer any uniform or specific physical property. Neither does it automatically denote advantageous or adverse health effects. It is important to note that it is not the nanometer scale of the material per se that can pose the potential for toxicity as evidenced by work performed at the University of Michigan CRSC.

What you see here is essentially negative pathology produced by a 60 nanometer polymer. This is a polyacrylomide hydrogel that was delivered in doses of either on the left two panels, 10 milligrams per kilogram or on the right 500 milligrams per kilogram, half a gram per kilogram intravenously into a rat without any evidence of toxicity by pathologic or

clinical chemistry in any of the tissues examined and we looked at 32 tissues. And this is a nanoscale polymer. So generalizations are generally unhelpful. If, however, we loaded that material, the benign nanomaterial, with iron oxide which we know produces superoxide, then the toxicokinetics profile changes but at very high doses. In fact, we saw toxicity in an intact animal, this is an in vivo model, and we see toxicity in the kidney and liver after exposure to these very high levels.

In fact, there was no credible scientific evidence at this time demonstrating that in the current mode of use in the current mode of use engineered nanoparticles pose an uncontrollable or eminent threat to the health of the public. Any assertion otherwise simply does not stand the test of scientific scrutiny. We need to be vigilant in pursuing these scientific endeavors but we can also build on what we know to be true. Nanoscale materials have been with us for a very long time and human exposure to these substances provide us with valuable lessons.

Nanotechnology will soon be a trillion dollar plus global business enterprise with a potential for enormous health benefits but may also

prevent -- or present adverse health risks. The benefits derives from nanomaterials are far-reaching. For example, NCI has invested in the University of Michigan and other academic centers to develop cutting edge technologies that will change dramatically our ability to detect the earliest stages of cancer and to manage and cure diseases for which the current standard of care is inadequate. The key is to manage the risk while deriving the maximum benefit from the use of these materials.

For example, the very same material that at 500 milligrams per kilogram produces that frank necrosis of the renal cortex and the hemorrhagic change in the liver gives us unprecedented views of an orthotopic tumor in the second panel, you can see the tumor highlighted, after a single intravenous injection of 1/100 -- actually it's 1/500 of the dose that produces the toxicity. And as you can see in Panel C, you not only see the tumor itself but you get very clear views of the vasculature immediately adjacent to the tumor and this highlights a very interesting and contradictory point here or a point that contradicts much of what has been eluded to in earlier presentations.

That is that the blood/brain barrier

prevents access of this nanomaterial into the brain tumor and so it is not fair to say that this would automatically gain access. If we use exactly the same material, we can ablate the tumor as seen in this live/dead panel only within the radius of the laser that illuminates these cancer cells do we get cell death and in a tumor model, which is uniformly lethal at about 10 days, we see that we get about 40 percent survival and these animals are alive at about 50 days.

It would be wrong for us to over-regulate. As we saw in the case of ALR, consumer panic was later found to be unwarranted and it is now being called one of the greatest unfounded health scares of the last five decades. This is a constant reminder that we, as scientists, policymakers and regulators, need to engage in the business of protecting the health of the public with all due diligence, urgency and caution. I've spoken about the state of the science, the benefits of nanotechnologies to human health and we need to avoid over-regulation while remaining vigilant.

I look forward to working with you, with my other colleagues and with the CRSC at the University of Michigan in further exploring this interesting and important issue. Thank you.

(Applause)

CHAIRMAN ALDERSON: Our next speaker for this session is David Rejeski from the Project on Emerging Nanotechnologies.

DR. REJESKI: Well, thank you. It's a pleasure to be here. I'd like to thank the FDA for inviting me. Why do public perceptions matter with nanotechnology? Let me sort of take you through some arguments. Public perceptions matter right now because the public is coming in contact with more and more products that are at least according to manufacturer's claims, based on nanotechnology, and many of these are under FDA purview. Our inventory on nanobased consumer products now has over 320 products in it from 17 countries, an increase of 100 products in less than six months.

The largest increase is in the area of cosmetics. Dietary supplements are also up. Food has remained level except products that are now in contact with food have increased dramatically. There's also a number of drugs and biomedical devices that are emerging and we started a separate inventory just to cover those. We recently met with some researchers in Japan who have launched a similar inventory. Theirs contains over 200 products. Almost half of those are

cosmetics, 10 food products.

Most of you know that there's a lot at stake here. Over $10 billion is not being invested annually by the public and private sector in nanotech R&D and here's some of the market numbers and projections in areas that FDA regulates including nanotherapeutics, drug delivery devices and also food. I'd point out the number of nanobased drugs and biomedical devices is, according to some estimates gone up about 70 percent in the pipeline, clinical pipeline over the past year, again, obviously a lot at stake.

So what can we say about public perceptions in the FDA and nanotechnology? I think the first important piece of data is that public confidence in the FDA is down. And it's down precisely at a point in time when more and more nanotech products are beginning to penetrate the marketplace. This is six years of data. However, the story is, I think, a little bit more complicated and somewhat more subtle. In August we conducted a national survey of over 1,000 adults and asked people who they trusted to maximize the benefits and minimize the risks of scientific advancements. The FDA came out below the USDA but it came out above EPA and far

above industry. People are fairly ambivalent about industry's abilities, so trust in FDA is down. However, the agency is nevertheless, I think has a lot of standing, especially when compared to industry and I think that's standing that can be used over time to build trust.

We asked people specifically who should monitor cosmetics for safety and effectiveness. People chose the government and independent researchers again above industry. In fact, only 12 percent trusted companies alone to monitor safety which is essentially what happens now. The survey also pointed to some important differences in risk/benefit perceptions, I think, which are relevant to FDA or anybody that's introducing nanotech into the marketplace. I think one of the most important ones is related to gender. After we provided participants with information on nanotech applications and potential implications, women were far more likely to focus on risks than men. Okay, this is something called the white male effect. It's been known for years. It's nothing new or surprising.

One expert in risk research once noted that a substantial percentage of white males see the world as so much less risky than everyone else sees

it. Maybe this is a plea for gender balance in our regulatory agencies. However, I think this is important because a lot of the nanobased products on the market FDA has some oversight on, why, cosmetics are purchased primarily by women. Also, women are also, I think, primarily responsible for many of the food purchases in the home and nanobased or nanoengineered food is coming and it's coming very quickly. In August we ran two focus groups right in Baltimore just with women to probe their attitudes toward nanotechnology, especially in relationship to cosmetics. One of the most stunning findings was that none of these women realized out little oversight FDA has on cosmetics, none of them.

They all overestimated the level of FDA's oversight on cosmetics, exactly what they could do, what kind of test they could do, whether they could recall products, and at the end of the two hour sessions, we asked them what they would say to FDA or industry if they got them in a room and these are some of the remarks, and I think these are fairly representative of what we've seen in a lot of other focus groups. You can see, what they expect from FDA is they want the agency to be responsible, to oversee, to look before the products are introduced into the

marketplace and to be a watchdog.

What they expect from industry is honesty, essentially to cut out the hype about nanotechnology. That's something that came up again and again. At this point in time, we've conducted over 30 hours of focus group work around the US on nanotechnology. And I just want to share with you the bottom line messages. Once people learn about nanotechnology, once we give them information, they show very little support for any kind of moratorium on nanotech R&D. In fact, I'd say almost -- usually 10, maybe 10 or 12 percent will actually support that idea. They get excited about the applications, especially about the medical applications which I think has enormous implications for FDA. This is what really excites people in these focus groups, the medical applications of nanotechnology.

They also show virtually no support of industry self-regulation of a new technology. They show virtually no support for voluntary programs. I think voluntary programs are very important, especially in terms of getting information, but you need to know that the public shows very little support for these things.

The converge, again and again, essentially

when we ask them this question, how can public confidence be supported or improved in nanotechnology around three recommendations; greater transparency, pre-market testing and third party independent testing and research. And the most important one that they keep talking about again and again and again and that's why this meeting is important, is disclosure and transparency, disclosure and transparency. I'll read you a recent article that came out. This is just the headline.

"Nanotech out of the lab into the store shelves." There's stealth revolution going on in nanotech today. As companies quietly integrate nanomaterials into more than $32 billion worth of products worldwide. Stealth might be great for jet fighters, but it's not the strategy that you want to use for new technology like nanotech. Why, because avoiding disclosure and transparency is exactly what raises public suspicions and generates mistrust. So we don't want a stealth revolution here. Industry might believe that's the best technique, that's the best strategy, but this is not something that we want.

I'll end with this one comment from Lincoln, but I think as we introduce nanotech into the marketplace, the most important variable is going to

be trust. Trust is extremely fragile. It takes years to build. You can destroy it in a few days. And with low level of trust, basically, you can undermine all attempts at communicating either risks or benefits, whether you're the government or whether you're industry. So the question I would ask today is, is the FDA and the US Government doing enough to build public trust, to engage the public because under-investing will surely cut the promise of nanotechnology short. I believe that the FDA needs significantly more resources because it can function essentially as a critical trust building organization at this point in time. This is one of its most important functions right now and I believe it's radically under-resourced.

So I want to thank the FDA for inviting me here and allowing us to share some of our comments. Much of the data that I've essentially cited could be found on our website. We also have a bunch of publications outside in the hallway, thank you.

(Applause)

CHAIRMAN ALDERSON: Our next speaker will be Michael Taylor from the School of Public Health, University of Maryland.

DR. TAYLOR: Thank you very much and I do

appreciate the opportunity to participate in this meeting and I do applaud FDA for convening it. I also want to thank the Project on Emerging Nanotechnologies which Dave leads commissioning the report we issued last week which really provides the basis for my statement this morning. I think we can all agree that nanotechnology has tremendous potential to benefit public health and the nation's economy with applications to virtually every product category under FDA's jurisdiction. The successful development and introduction of nanotechnology products is thus in my view a matter of great public interest.

The success of nanotechnology will depend to a large extent, however, on how FDA plays its oversight role. Americans expect a lot of FDA. They expect the agency to protect public health by keeping unsafe products off the market and to promote public health by insuring safe and effective new products reach the market promptly. And industry and consumers alike expect FDA, by doing its job well, to provide the basis for public confidence in nanotechnology and the products it will generate.

This is a tall order and it comes at a tough time. As many are beginning to realize, FDA simply does not have the resources it needs to do what

people expect and partly as a result of this resource crisis, public confidence in FDA is on the decline, as reflected in the Harris poll last spring showing a sharp drop in the percentage of Americans holding a positive view of FDA's drug safety efforts.

Loss of public confidence in FDA is a matter of real public health concern. In the case of drugs, obtaining the benefits on innovative medicines depends on sound prescribing by doctors and good compliance by patients both of which depend on confidence at the risk that the products are well-understood and being properly managed. This, of course, requires FDA being fully on top of information about the risk of products, not only pre-market but also after products are marketed and that requires resources to obtain and analyze the information needed to make good and timely public health decisions.

The fact is, however, that going back many years over successive administrations FDA's funding to perform core public health tasks such as overseeing drug safety and reducing food-borne illness has been inadequate. Funding constraints also hamper FDA in developing products and providing developers, I should say, of new products with the testing and regulatory guidance they need so that innovation will not be

slowed. Now, this unfortunately is the resource context that awaits nanotechnology and within which FDA is now expected to oversee the wave of new products nanotechnology will produce.

Ironically, FDA's resource problem may have its most immediate impact in an area less central than drugs to FDA's public health mission, namely cosmetics. Numerous cosmetic products claiming to incorporate nanomaterials or otherwise be based on nanotechnology, are already on the market. FDA has no pre-market authority over cosmetics, however, and thus no built in mechanism for gaining knowledge about new products or evaluating their safety prior to marketing. FDA and the industry have compensated for this by collaborating on voluntary industry self-regulatory mechanisms that I believe generally work well for conventional cosmetic ingredients.

These include the requirements that cosmetic companies either develop adequate substantiation for the safety of their products or declare on the label that safety has not been substantiated. But what constitutes adequate substantiation of safety for a cosmetic product containing engineered nanomaterials. Does FDA know the composition and function of the nanomaterials

being used in cosmetics today? What information do manufacturers have about their safety? These are questions, it seems to me that FDA should be able to answer when the public turns to the agency for assurance that nanotech cosmetics are safe.

But how will FDA do this? Where will it get the resources to develop scientific guidance on safety substantiation? How will it mount the effort to gt detailed knowledge of products being marketed and in the pipeline especially in the absence of legal tools for obtaining this information? Now, let me be clear about one important thing; I don't pose these questions to raise an alarm about the safety of nanotech cosmetics or to claim that other nanotechnology derived products entering the market today are unsafe. What we do know about nanomaterials, however, is that their safety cannot be assumed based solely on knowledge about the safety of larger scale versions of the same material. So what we know about the safety of any particular application of nanotechnology is that we just don't know unless and until we have the data and analysis that reasonably answers the safety question.

And this brings me to my central message today, which is simply this; FDA must have ways to

obtain the information it needs to provide the oversight people expect both before and after nanotechnology enters the marketplace. In the report we issued last week, I've offered a number of recommendations for meeting FDA's information needs, some of which FDA could pursue under current law and some of which require congressional action, but all of which require resources FDA does not have. I hope the Administration, Congress and the larger stakeholder community concerned about the success of nanotechnology will come together to give FDA the tools it needs to do its job.

Now, realistically, FDA's resource picture and legal tool kit will not change overnight which makes near-term collaboration and information sharing between FDA and the regulated industry all the more important. Particularly for cosmetic, dietary supplement and food applications, FDA and the industry must immediately find ways to provide FDA detailed information about the specific applications of nanotechnology that are in the pipeline or emerging in the marketplace. This can and should be done in ways that protect legitimately confidential business information from public release while meeting FDA's information needs.

Now, the information flow should run both ways, to bring a measure of order to the marketplace and provide the basis for public confidence in some of the early applications of nanotechnology, FDA should provide guidance on such questions as these; first, what is the regulatory status of nanoscale versions of food use chemicals including packaging materials, whose conventional form is currently listed in FDA's food additive and grass regulations? Is additional safety testing needed for these new versions of previously approved materials? Does FDA expect developers to come to FDA prior to marketing the nanoscale versions? Similarly, FDA should address when nanoscale versions of dietary supplements are properly deemed new dietary ingredients and what bearing the evaluation of a conventional ingredient by the cosmetic ingredient review properly has on the safety substantiation of the nanoscale version.

These are not easy questions and any answer FDA gives today may properly be considered preliminary. But if it does not provide its best guidance on these questions soon, I'm concerned the FDA risk becoming a bystander as nanotechnology enters the consumer product marketplace and this would not be good for anyone. I again, thank FDA for convening

this meeting and for the effort that it's putting into preparing for oversight of nanotechnology. I have great faith in the commitment of FDA's staff to the agency's public health mission and I sincerely hope that this meeting really is just the first step in a broad collaborative effort to give FDA the tools it needs to do its job. Thank you.

(Applause)

CHAIRMAN ALDERSON: Our next speaker in this session will be Bruce Levinson from the Center for Regulatory Effectiveness.

DR. LEVINSON: Well, it turns out it really is a small world after all. I'd like to thank FDA for convening this task force and holding this meeting. The agency's work to develop an effective framework to support the development and marketing of safe nanoparticle containing products is one of its most important initiatives. FDA has demonstrated its leadership in nanotechnology regulation in many ways including not only this task force, its previous experience in nanotechnology in drugs, and also in signing an inter-agency memorandum of understanding with the National Cancer Institute and the National Institute for Standards and Technology.

That MOU sets out a number of goals and

principles that will guide this task force's work. The document calls for the FDA, NCI and NIST to leverage resources and expertise for multiple sources, including the private sector, toward the goal of facilitating the development of nanotechnologies that constitute novel research tools and safer, more effective cancer therapies by establishing a framework for effective risk identification, assessment and evaluations of emerging products based on nanotechnology.

Of course, all of FDA's work and that of other agencies is going to have to comply with the framework of the good government laws that regulate the regulatory process. These good government laws include the Paperwork Reduction Act, which governs any contemplated information collection or labeling requirements, the National Technology Transfer and Advancement Act which promotes government use of private voluntary consensus standards and the Data Quality Act. The Data Quality Act, along with the OMB and FDA's implementing guidelines, sets standard for virtually all information disseminated by the agency, including reports, regulations, and responses to citizen petitions.

The Act requires that the agency using

pre-dissemination review process to insure that the information they disseminate meets agency and OMB data quality standards before it is disseminated. The Data Quality Act also includes an administrative process allowing effective parties to seek and obtain correction of information not complying with data quality standards. And I'd like to note that the Data Quality Act applies not only to government sponsored and initiated information but also to third party data on which the agency seeks to use or rely. Third party studies, comments and other data need to comply with the Act in implementing guidelines if the government is to make use of them.

Therefore, FDA needs to apply their pre-dissemination review process to all substantive third party data. Additional information on the Data Quality Act may be found on our website, www.thecre.com. CRE in its role, is a regulatory that looks forward to monitoring the FDA's -- this task force and other FDA work on nanotechnology and we may intervene as appropriate. Thank you.

CHAIRMAN ALDERSON: Our last speaker for this session is Kathy Jo Wetter and she's from the ETC Group.

DR. WETTER: Thank you for the opportunity

to present the view of ETC Group. We are an international civil society organization based in Canada and our work focuses on the social and economic impacts of emerging technologies and their implications, especially for marginalized communities. I'm based in ETC Group's North Carolina office.

ETC Group has been monitoring the development of nanoscale technology since 2000. Though we focus on the socioeconomic impacts of technologies, in the case of nanotech, we couldn't ignore the potential health and safety impacts. Five years ago, we were stunned to realize that there were no internationally accepted scientific standards governing lab research or the introduction of nanomaterials in commercial products. There were virtually no toxicology studies devoted to synthetic nanomaterials. There were no standards for describing or even measuring nanoscale materials. There were no labeling requirements. In short, there was a regulatory vacuum and that regulatory vacuum persists today despite the fact that hundreds of products containing engineered nanomaterials have been commercialized.

The reality is that the discussion of nanotech regulation is at least a decade overdue. We

can't congratulate ourselves on being proactive or for getting it right this time. Instead, let's focus on the urgent need to address the situation. The first generation of nanotech products, those that incorporate engineered nanoparticles, have slipped through the cracks of the existing regulatory framework. In the summer of 2002 ETC Group urged governments to establish a moratorium on the commercialization of new products containing novel engineered nanoparticles until lab protocols could be established to protect workers and until regulations were in place to protect consumers and the environment. Our proposal received a less than enthusiastic response from nanotech proponents but our call for a moratorium was not motivated by a desire to rain on the parade of exciting new consumer products.

We saw that public debate was non-existent and that current regulatory framework inadequate to address these novel materials and their unknown effects on human health and the environment and until their safety could be assured for consumers and for workers, the technology could not develop in a healthy and transparent way. As everyone in this room is now aware, substances produced at the nanoscale can behave as if they were all together different substances from

their familiar larger scale counterparts. Their novel properties are precisely why there is so much scientific and commercial interest in nanoscale materials and why the US patent and trademark office has been swamped by nanotech patent applications, so much so that one market research firm estimates that there are more than 2700 outstanding nanotech patent applications.

As the 1998 Nobel laureate in physics explained, with nanotechnology the possibilities to create new things appear limitless. That limitlessness has reacted and will continue to create daunting challenges for FDA as the regulatory agency responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics and products that emit radiation. Every one of these categories includes or will soon include products that incorporate engineered nanoscale substances.

And the onslaught of nanotech products won't stop. A second wave of products, those that result from the convergence of nanotech and biotechnology or nanotech and synthetic biology will soon be on FDA's doorstep. I'll give just one small

example, of the challenges facing FDA, the example of titanium dioxide in foods. FDA approved titanium dioxide as a food color additive in 1966 with the stipulation that the additive was not to exceed one percent by weight. Titanium dioxide in micron form is white in color and it can be added to icings on cookies and cakes. The FDA approved titanium dioxide as a food contact substance as well, meaning that it's safe to incorporate it into food packaging. Titanium dioxide is now being formulated to nanoscale and these transparent particles are being used in clear plastic food wraps for UV protection.

Because titanium dioxide has already been approved as a food contact substance, this nanoscale use in packaging will not trigger further regulatory scrutiny. This is also true for nanotitanium dioxide's use as a food additive which is relevant because companies are exploring the use of nanoscale titanium dioxide in foods. For example, foods are being coated with nanoscale titanium dioxide to keep out moisture and oxygen. The percent by weight limit set back in the 1960s aren't necessarily relevant to today's nanoscale formulations since tiny amounts can produce large effects. But nanoscale titanium dioxide in food is just one example.

Market analysts predict that the nanotech market for food and food packaging could be $20 billion by 2010. We've been told that every major food corporation has a nanotech R&D program or is looking to develop one. Today there's a virtual consensus among scientists that the toxicology of engineered nanomaterials is largely unknown and that toxicity data cannot be extrapolated from existing toxicology studies conducted on larger scale materials. In short, we don't know what accumulated amounts of any human made nanomaterial will do in our lungs or our livers or our guts even if we do know how bigger particles of the same material behave in our bodies. The closest thing we have to go on is our experience with similarly sized ultra-fine particulate matter, like that found in air pollution and not toxicologist in the world is arguing for the benign nature of air pollution.

Unfortunately, so far, the US Government has acted as a cheerleader, not a regulator, in addressing the nanotech revolution. In the all out race to secure economic advantage, health and environmental considerations have taken a back seat and socioeconomic impacts are a distant concern. There's no doubt that FDA is under-staffed, under-

funded and currently ill-equipped to deal with the nanotech revolution but that has to change. FDA must be given the resources it needs to address the challenges posed by nanoscale technologies. We urge the FDA to embrace the scientific consensus that size matters. Because engineered nanomaterials behave differently from their larger scale counterparts, they should be regulated as new substances. FDA must take a precautionary stance and not fall back on the notion that a lack of evidence of harm is an adequate assurance of safety. Probably adequate, as FDA now considers its current framework with regard to nanoscale materials is not good enough. Regulations must be mandatory, not voluntary. Products containing engineered nanomaterials should be labeled as such. The FDA must fulfill its responsibility to protect public health rather than the health of the companies that pay it user fees.

(Applause)

CHAIRMAN ALDERSON: I would ask the task force member if they have any questions. Linda?

DR. KATZ: Linda Katz. I have actually a question for a point of clarification. This is for David Rejeski and this is really with regard to the survey that was done, the product classifications and

the classification of nanotechnology. It's unclear to me as I listen to your presentation, as I've heard the presentation before and as I've read through what's published on the Woodrow Wilson Report, that all of the products that are listed as cosmetics are truly cosmetic products. It's also unclear to me that by definition what's being defined as nanotechnology products and if in fact, all of these products that are being classified as nanotechnology products again, in your survey and your report, are nanotechnology products an and of itself and contain nanoparticles, so could you please clarify those two points for me, please?

DR. REJESKI: In terms of kind of what's in and what's out, we only put products into the inventory where the manufacturer has made a claim either on the website or the label and we try to sort of ask the question, is it reasonable. So we came across a nanokayak that didn't make it in. So we sort of give it the reasonableness test. One of the things we don't do, we're not in the position to do is actually test, you know, are there really nanomaterials in there? Again, we're going basically on the claims of the manufacturer. In terms of are they cosmetics or are they over the counter drugs,

we've gone through the labels of all of the -- we've bought probably 20 or 30 of these cosmetics and I can tell you in certain cases, it's not clear at all. There are cosmetics there that are making health claims on the labels. I think that's one of the big issues I think the FDA is going to have to grapple with is exactly what are they saying.

We put together something we call the Tower of Babble which is just a list of what the labels say and it's almost indecipherable. So -- but this -- one of the things that I want to make sure that I emphasize is this is the face that the public is seeing. The public basically looks at the labels. There's nobody in between the public and their interpretation. There's no scientists, there's no FDA officials, there's no EPA officials. There's nobody. This is the face of nanotech. This is what's appearing on the website around the world. This is what appears on the label that comes out of the boxes.

There's no control. There's no common definitions and so I think that there's an enormous opportunity there for somebody, obviously to try to come up with some definitions that make sense. But it's incredibly -- I think we did this consumer group with women and we passed these around and they were

totally confused. So I think that there's a real issue right now in terms of how these things are being presented but I can tell you that there's no intermediary. There's no consumer's union. I mean, somebody was here from consumer's union. This is an important kind of function for somebody to step in between the manufacturers and the public and say, what is this, what does it mean that nanotechs are in there? What are these claims, both the benefits and the risks? So there is an incredible amount of confusion there.

CHAIRMAN ALDERSON: Rick?

DR. CANADY: Rick Canady, FDA, Officer of the Commissioner. I want to ask a question of Dr. Philbert and also Dr. Harper from the earlier panel possibly. I mean, there's data that you presented in your slides, Dr. Philbert and that I think Dr. Harper related to that I hadn't seen before, that I don't know is in published literature. It may well be but I haven't seen it yet, and it brings me to the general question of how do we collect all this information that's sitting in laboratories that may or may not be published, that is relevant to understanding the physical characteristics of nanoparticles and relevant to understanding the toxicity? How do we get it all

together? How do we you know, snowball it together and help us use this information? If you have any insight to that, I'd appreciate it.

DR. PHILBERT: Fortunately for me and unfortunately for society at large, perhaps, is the academic structure of having to produce manuscripts that are accepted by the peer review literature. It is, therefore, very, very difficult to publish negative data. It's nye on impossible. So being an academic I'm rewarded for the number of published peer review manuscripts that I produce every year and so there are very few incentives other than good -- being a good citizen in public service for releasing that data. If, however -- and I believe the folks at Rice are developing the system, there is a structure to which data, high quality data can be submitted, then I think more academics will participate in that.

On the industry side, there -- I believe those industries that participate in product stewardship will release data as it comes on line, but it's difficult to see how you would make that other than a voluntary system.

CHAIRMAN ALDERSON: Paul?

DR. HOWARD: Paul Howard, a point of clarification for either of the speakers right now or

the ones from this morning; I like what Martin said, by the way. In general, it's good not to generalize but do any of you see a distinction between very solid nanoparticles such as titanium dioxide crystals, semi-solids, such as dendrimers or very fluid particles such as liposomes? Do you see a distinction between those because they have all been lumped together so far in the pods?

DR. PHILBERT: I would continue the heresy insofar as expressing my personal opinion that there is no such thing as nanotechnology as far as the FDA is concerned and that what we need to get a definition on is the interaction between the product and the biology. The NNI has arbitrarily drawn the line at 100 nanometers. Does that mean that something that is 101 nanometers is no longer toxic. I would suggest otherwise. But that we need to get away from labeling things and get down to the business of hazard identification, exposure assessment and risk analysis.

DR. HOWARD: So you're implying case by case basis? So you're implying case by case approach.

DR. PHILBERT: Until we have enough data to draw meaningful extrapolations, I think that's what you have to do.

CHAIRMAN ALDERSON: I have a question.

Putting aside cosmetics for the time being and we could have a debate on the food additive issues that's just been discussed, but let's talk for a minute about drugs, biologicals and devices. And again, getting back to this issue of generalization, that we don't have the correct framework as a generalized statement. And then assuming that you know about the extensive regulatory regime of testing that drugs, biologicals and devices have to go through to get approved, where do we need to change that quote "framework"?

DR. TAYLOR: I'll take a stab at that. My view is that with respect to the legal and basic regulatory framework for drugs and devices and biologics, there is no need to change the basic framework. In fact, the thrust of the report that I did is that there's no general need to change the structure of the statute or the basic regulatory framework. It's really a matter of implementing that in a thoughtful way. I mean, drugs and devices, FDA has, you know, full authority and indeed, every product, every specific application of nanotechnology or any other technology in a device or drug product must be presented to FDA prior to marketing.

So the question is whether FDA has the basic scientific knowledge and the tools to evaluate

safety as well as efficacy and then there are also the issues about post-market oversight but it's not a structure issue or framework issue. In my view, it's a resources issue for those categories. I think for -- you know, there are different issues with respect to cosmetics but even there, I don't think it's a matter of changing the structure of cosmetic regulation. I mean, cosmetic regulation is based on the premise that -- and the statute is based on the premise that cosmetics go on the surface of the skin and more or less stay there and don't effect the structure or function of the body, and that's a pretty sound concept and there probably isn't a legitimate need for systematic pre-market oversight review of conventional cosmetic ingredients.

If there's dermal absorption and if there's effect on the structure or function of the body, these become drugs. I think that's the reality of the cosmetic world and there is a drug/device line or cosmetic/drug line. That's not a matter of changing the framework. That's a matter of implementing the framework and it is a costly thing to do for FDA to go ahead and police the marketplace for cosmetics and be able to judge, you know, what's a cosmetic and what's a drug. If it's a drug, FDA has a

pre-market handle that's perfectly satisfactory.

CHAIRMAN ALDERSON: If there are no other comments, we will adjourn for lunch and we will start back promptly at 1:30.

(Whereupon at 12:11 p.m. a luncheon recess was taken.)

CHAIRMAN LUTTER: Would everyone please take their seats? We're going to start in about a minute. Good afternoon. I'd like to welcome everybody to the afternoon session of the FDA Public Meeting on Nanotechnology. This is Session Number 3, Science, Policy or Nanotechnology Material Use in Cosmetics, Personal Care Products or Topically Applied Products. Before beginning I thought I'd make one remark based on the observations and messages that we heard this morning. There were references by the various speakers to a need for transparency, a need for data, a need for trust and a need for resources. To keeping in mind transparency, data, trust and resources, I suggest that any speaker scheduled to talk this afternoon think about what might be arrangements by which data could be shared more broadly with the government or with other parties outside the government so as to insure a trust and transparency while economizing on resources.

This afternoon we have six speakers, we'll follow the format of this afternoon, I mean, of this morning, so everybody gets eight minutes and then we'll reserve the questions and answer after that time. One other administrative announcement is that at the open microphone session, I believe it begins at 4:25, the number of registrants for that is such that everybody will have an opportunity to speak for eight minutes. So I'll make introductions as we go along and the order is alphabetical. So Pascal Delrieu of Kobo Products, Incorporated is first. Thank you.

MR. DELRIEU: Good afternoon. My name is Pascal Delrieu. I work for Kobo Products, which is a supplier of ingredients for the cosmetic industry. And I'm going to give you this presentation to show you perspectives on supplying attenuation grades of titanium dioxide and zinc oxide and show how and why they can be used in sun screen applications.

There are two different types of pigments that can be used for UV filters and are commonly used in personal care, titanium dioxide and zinc oxide. And they are used to provide protection against UVA and UVD. They both attenuate light by absorption and scattering. They are usually available surface coated to minimize their photo-catalytic activity and they

are typically produced as finer crystal from the same feed stocks and with similar processes as pigmentary grades.

So if we talk about the manufacturing process, in fact, they are different processes that can be used for both titanium dioxide and zinc oxide. I'm not going to describe all this but all of them are basically two-step processes. In the first step, there is a purification of the raw material, whatever the raw material will be. And the second -- in the second step, the crystal or primary particle is grown to the desired size. This second step is made at high temperature and the crystals can be grown to 200 nanometers and above to make pigmentary grades pigment or finer than 200 nanometers for attenuation grades.

I mentioned that these pigments are usually surface treated so you can see on the pictures on the left a surface treatment on -- this is alumina on top of the titanium dioxide pigment. The table on the right shows the weight constant of a reaction of oxidation of astalete taken as an example for the photo-catalytic activity of the pigments, and you can see that for Pigment Grade TiO_2, attenuation Grade TiO_2 and attenuation Grade zinc oxide, the treated pigments are much less reactive than the non-treated ones.

So it is now common industry practice to use surface treated inorganic defensers to formulate sun screens. I also mention in the article properties that titanium dioxide and zinc oxide attenuate light by absorption and scattering. Absorption is a characteristic of the pigment and more or less the absorption, the maximum absorption for this pigments is around 400 nanometers. Scattering on the contrary is a combination of the difference in refractive index of the particle and the refractive index of the surrounding media and of the particle size. As you can see here, refracted index of titanium dioxide is much higher than the refracted index of zinc oxide, therefore, titanium dioxide is much more efficient to attenuate light.

It can also be said that for particle size, the maximum scattering occurs when the size equals -- the size of the particle equals half the wavelength when particles are uniformly disbursed. That means if you want to attenuate UV light, UVB or UVA light between 290 and 400 nanometers, then, what you really need is particles ranging roughly between 100 and 200 nanometers, even larger than that. You certainly don't need smaller particles than that because you don't want to attenuate UVC. It's not

really necessary. It might become necessary if the ozone layer actually gets thinner, but for the moment, we don't need really that.

So what are we talking about when we say particle size with these products? We have already seen the primary particles, that's the crystal that is grown during the manufacturing process. But in fact, when the product comes as a powder, it comes as a big agglomerate, agglomerate in excess of one micron and if we were using this in sun screen products, they will block completely the visible light, making a very whitening product. So we have to reduce the size of these agglomerates to aggregate of the size already mentioned between 100 and 200 nanometers in order to -- and that's what you see on the bottom right to have a product that is transparent to visible light and that will block efficiently UV light.

That's what you can see also on these electron micrograph pictures on the left with 50 nanometer TiO_2 and 35 on the right with the agglomerates for the powder and the aggregates for the dispersants. Small particle size like 10 nanometers or 15 nanometers are necessary to produce transparent dispersions that can attenuate UV light effectively. You can see here the comparison between the small

particle size, primary particle size, 10 nanometer that give 110 in this example dispersion particle size and the large ones for pigmentary on the left of each picture.

This table pretty much summarizes this idea of the difference in size where a list of primary particle size in the second column, particle size in the dispersions in the second column and on the right the transparency. Small particle size TiO_2 can make very transparent dispersions and that's what we need. However, this very small particle size will give a product that is -- that will attenuate mostly UVB, much less UVA, and you need larger particle size, TiO_2 to attenuate also UVA.

Here we have formulated different pigments and tested them using approved methods on people. So you see that with the small particle size, small primary particle size TiO_2 we can reach a very high SPFs, the PA attenuation review with UVA is much lower. Using larger TiO_2 makes the SPF lower but the PA higher so this could be a good example of a product that can be used for UVA attenuation or you can use zinc oxide that has very high PA but lower SPFs. So in conclusion, we've seen that attenuation grade titanium dioxide and zinc oxide produced using the

same processes are larger primary product pigmentary grades. Small particle size are necessary to produce dispersions that are transparent. Larger TiO_2 can make efficient dispersions against UVA and pigmentary grades too big to scatter efficiently in UV light and are too opaque. Thank you very much.

(Applause)

CHAIRMAN LUTTER: Thank you very much. Our next speaker is Jane Houlihan from the Environmental Working Group.

MS. HOULIHAN: Good afternoon and thank you to FDA for organizing this event. I'm Jane Houlihan, Vice President for Research at the Environmental Working Group. We are a non-profit public health and environmental research organization based in Washington, DC. And we've conducted research on the safety of ingredients in personal care products for the past six years. Among our work in this area is an online consumer tool that we update annually called Skin Deep and this is an interactive safety assessment guide that currently contains about 15,000 products and their 7,000 constituent ingredients.

From out product data base in Skin Deep we've completed a survey on the use of nanoscale materials in personal care products. We've derived

our findings from the systematic evaluation of ingredient labels, directions for use and package details for more than 25,000 products that we're currently uploading into our next annual update of Skin Deep. So these products represent about a quarter of what FDA estimates to be on the market, 100,000 products all together. And our search encompassed common nanoscale terms like fullerenes the prefix nano, lipizomes and even the term micronized.

And we also search product ingredient listings against a comprehensive data base of chemicals now commercially available in nanosizes. So two findings. First, we identified 256 products all together that contain one or more of 57 different types of nanoscaler micronized ingredients and we've included micronized ingredients because we know from some of our research that commercial forms of these ingredients can range down as low as 20 nanometers in diameter or even lower. Secondly, we identified 9,509 products, this is over a third of all products we assessed that contain ingredients that are now commercially available in nanoscale forms and none of these products contained information on whether the listed ingredient is conventional or nanoscale and, of

course, that's not required so we have no way to know if the ingredients we're looking at are in nanoscale form or not. But this includes everything from gold and silver to iron oxides and zeolites.

So what we're seeing are nanoscale materials used in cosmetics at what could potentially be a very broad scale. We understand that FDA and others, we've heard a lot about this, are still conducting basic research to substantiate the safety of nanoscale ingredients and we know that FDA can't require the cosmetics industry to test ingredients or products but FDA regulations do require manufacturers, as many of you know, to post a warning label on products that contain ingredients that haven't been adequately substantiated for safety, and I'll read you the implementing regulations.

"Each ingredient used in a cosmetic product and each finished cosmetic product shall be adequately substantiated for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing is misbranded unless it contains the following conspicuous statement on the principal display panel. "Warning, the safety of this product has not been determined". So none of the products we

assessed, the 25,000 products bears this warning label, so this omission means that either manufacturers aren't following this regulation or that they do indeed believe that they have the data needed to substantiate safety.

But either way, we recommend that FDA take actions that logically follow request safety studies for manufacturers and enforce the requirements for a warning label if these studies aren't adequate to substantiate safety. So there's one big change in the works. The Cosmetic, Toiletry and Fragrance Association we understand, is implementing a new program called the Consumer Commitment Code and we understand that will go into effect at the beginning of next year. So the code includes a dossier program that will make safety information more easily accessible to FDA through what CTFA is called a safety information summary. We understand this would include information on raw material specifications and presumably would also include information on particle size and form. The safety information summary would also presumably include a summary of safety information but most importantly, this Consumer Commitment Code includes the following provision according to industry reports.

Key elements of the code include companies' commitment to using ingredients that have been substantiated for safety either by FDA or the Cosmetic Ingredient Review Expert Panel. This is a big deal because we know FDA does not systematically review the safety of ingredients and the industry's own safety panel, the cosmetic ingredient review, has assessed the safety of just 11 percent of what FDA says are 10,500 ingredients used in personal care products. And we'd also note that none of the nanoscale materials currently used in cosmetics has been substantiated for safety by FDA or by the Cosmetic Ingredient Review Panel.

So by restricting the 600 member companies to the use of assessed ingredients only, you could interpret this to mean that CTFA is endorsing a moratorium on nanoscale materials. But the bottom line is that through CTFA's new Consumer Commitment Code, FDA can look forward either to nanoscale materials being removed from cosmetics or to the public release of industry safety studies that justify the continued safe use of these ingredients in personal care products.

Among our recommendations to FDA are these three. First of all, we believe FDA should establish

through a public process a definition for the adequate substantiation for the safety of cosmetic ingredient and this should include explicit consideration of the effects of particle size and form on absorption and on risk. We also recommend that FDA request from the cosmetic industry all available studies on nanoscale materials used to adequately substantiate ingredient and product safety and FDA should review these studies and make independent determinations on the safety of these materials. And lastly, we're recommending that FDA identify the presence of nanoscale materials in all personal care products and we're recommending that the agency could do this through their own voluntary cosmetic registration program, data base that the Consumer Commitment Code, now requires all member companies of CTFA to input their products and ingredients into. We're recommending that information on supplier of the material and the particle size and form also be collected as FDA is going through that massive data collection exercise.

Ultimately, we'd like to see the agency adopt a standard for safety that incorporates the idea that particle size can effect penetration, can effect toxicity and we'd like to see that explicitly in the definition of product safety. Ultimately, we'd like

to see all products tested for safety before they're put on the market. Thank you.

(Applause)

CHAIRMAN LUTTER: Thank you very much. Our next speaker is George Kimbrell from the International Center for Technology Assessment.

MR. KIMBRELL: Good afternoon. I'd like to say, I'm George Kimbrell, International Center for Technology Assessment. I am an environmental attorney. I'd just like to say to start, I'm going to zip through this at about 20,000 feet. I've got a lot of slides to cover and eight minutes, just like anybody else. But our full presentation will be available both on our website, I think from FDA as well. So when we talk about nanotechnology what are we talking about? Well, there's lots of different bell weathers, yardsticks people use. We talk about $9 billion in research and development numbers. We talk about the term itself a buzz word, approaching ubiquitous status in median society. We talk about a gold rush on patents for the fundamental building blocks of this technology and perhaps most importantly, we talk about the rapid commercialization.

Thousands of tons of nanomaterial is being

produced each year. We've heard the numbers over 32 billion in nanoproducts in 2005, twice the number of the previous year. The Wilson Center's newest estimate is 320 self-identified nanoproducts, including paint, coatings, sporting goods, sun screens, cosmetics, personal care products, clothing, food and food packaging and various electronics. There's a visual sampling of those products.

Nowhere are these products reaching consumers faster than the personal care industry, I should say the environment as well. Again, the Wilson Center's data base, the largest single category health and fitness as well as the 2006 Friends of the Earth Report, Nanomaterials in Sun screens and Cosmetics, which found at least 116 cosmetics, sun screens and personal care products containing nanomaterials. Again, a visual sampling there.

One more case study; nanosilver products, we're seeing a proliferation of these ranging the gambit from everything from food storage to refrigerator coatings. So what does all this mean? Well, FDA is charged with the overseeing the safety and efficacy of many of these products, the first wave of nanoproducts. Thus, this public meeting is a necessary development. On the other hand, it seems

dangerously overdue. The same can be said for FDA's recently created task force. What should FDA do going forward? Well, immediately prioritize human health and environmental concerns, that includes both the framework that adequately accounts for the fundamental differences of nanomaterials and protects human health and the environment as well as undertaking much more robust environmental health and safety research.

I think we heard the numbers earlier were four percent of the NNI's budget, none of which is currently going to the FDA and I think the spokesperson from NNI said that number was going to be increased to just over four percent. So I would respectfully submit that that's still quite insufficient. So the fundamental differences, well, I'm only going to briefly touch on this since I think it's been covered but in short, nano is best understood not to merely mean one billionth of a meter but rather to mean that a substance can be fundamentally different. Materials engineered to the nanoscale exhibit different fundamental physical and biological chemical properties.

These new properties, in turn, create unique and unpredictable human health and environmental risks. As far as those human health

risks, they break down into two different stems, the first coming from enhanced toxicity, from unprecedented mobility for manufactured material. I want to talk a little bit more about environmental impacts because I don't think that's going to be touched on as much today. First, when we talk about environmental impacts, we're talking about pathways to the environment of a new class of manufactured non-biodegradable pollutants through the manufacturing process, transport, use recycling and disposal.

What are these concerns that we have? Well, first, from the mobility of these materials, second from their transportation, that is their ability to absorb smaller -- larger contaminates and allow them to hitch a ride over great distances. The reaction with substances already in the soil and their durability and bio-accumulation. What does that -- what challenges do those create for our regulatory agencies going forward? Well, I think the two big ones are detection and removal. Once these are on the loose in the environment, we need new protocols and cost effective technologies for measuring, monitoring and controlling these materials. Skip over that.

When we get to FDA, well, as we've said, this is FDA's jurisdiction. Many of these products

fall under FDA's jurisdiction. FDA itself has said as much. However, up to this point, FDA treats nanomaterial product ingredients no differently than bulk material ingredients. With regard to its regulation of nanomaterial products, FDA said it believes the existing battery of testing is probably adequate and that particle size is not the issue. Well, this seems at loggerheads with the view of the scientific community at large. I have a couple of quotes up there.

The first one, "Experts are of the unanimous opinion that the adverse effects of nanoparticles cannot be predicted or derived from the known toxicity of the material at macroscopic size."

And from the UK Royal Society, "Substances made using nanotechnology should be considered new chemicals and undergo extra safety checks before they hit the market". So that brings us to what should FDA do going forward? Well, I would submit respectfully that FDA has both a blueprint as well as a legal impetus going forward on what do and I speak of the legal petition. My organization and a coalition of seven other groups filed in May of this year with FDA challenging FDA's failure to regulate human health and environmental threats from nanomaterials.

That petition calls for, among other things, comprehensive nanomaterial specific regulations, new paradigms of nano-specific toxicity testing, the classification of nanomaterials as new substances, mandatory labeling and compliance with the National Environmental Policy Act that the agency address the environmental impacts of its actions. I should also say, I don't have it listed here, but we ask for definitions which is a topic that has been brought up several times today already.

The second half of the petition focuses on sun screens which we've heard something about also today. Sun screens, as many of you, I'm sure, are aware, are classified by FDA as human drugs rather than cosmetics and should be therefore, subject to more rigorous pre-market regulation. We do have red flags regarding the free radical creation and DNA damage of these nanoparticles as well as unanswered questions about their skin penetration, the ease of their skin penetration. Currently, despite these dangers and the patented differences of these particles, FDA considers them the equivalent to bulk material sun screens. Therefore, the petition calls for a recall until manufacturers submit an FDA review, pre-marketing testing data approving the drug's safety

and efficacy. That is that they be treated as new drug products that require new drug applications.

So conclusions; number one, learning from the past; I think that we tend to get a sense of cultural amnesia sometimes about these things. I've heard this already today and I'd like to reiterate it. This isn't the first wonder substance or wonder technology that we've seen, asbestos, CFCs, DDT, PCVs, it's an alphabet soup of lessons to learn from. FDA must act quickly but hopes to avoid repeating the mistakes of past regulatory failures.

Second, adequate regulation. A framework is needed that protects workers and the environment and the general public from the impacts of nanomaterials throughout their life cycle. And finally, much more robust EHS study, adequate publicly available independent peer reviewed safety studies on the environmental and health impacts of nanomaterials. Much more information about out work, including this presentation and our legal petition is available at our website, www.icta.org. Thank you very much.

(Applause)

CHAIRMAN LUTTER: Thank you very much, Mr. Kimbrell. Our next speaker is Erich Pica of Friends of the Earth.

MR. PICA: Thank you. Good afternoon. My name is Erich Pica and I'm the Domestic Policy Director at Friends of the Earth. Friends of the Earth is a national non-profit environmental advocacy organization and we're a member of Friends of the Earth International. Friends of the Earth International is the largest grassroots environmental organization in the world and we have member groups in 71 countries around the world. And I'm here today to talk about the nanomaterials, cosmetics and sun screens and our recent report, "Small Ingredients, Big Risks". Friends of the Earth comes at nanotechnology from a precautionary principle point of view. We believe these products should be tested and proven safe before they are out on the market. The problem is, is as George has mentioned in his last presentation, we've had an alphabet soup of bad chemicals and bad products that have entered the market and they have, over 20., 30, 40 years have been recalled and we're still cleaning up the messes.

So the reason why we're here is nanotechnology is proliferating in the consumer marketplace. We heard about the Wilson Center's 320 products ranging from automobile electronic additives to what we're concerned about today, which is the

cosmetics, sun screens, as well as personal care products. And so we published a report in May of 2006 that did a survey of websites products and we found 116 cosmetic, sun screen, personal care products that contain nanomaterials, and this was despite the absence of safety testing and independent of regulation.

Of the 116, there's 71 cosmetics products, 23 sun screens and 22 personal care products that all contain nanoparticles and this is a little bit lower than the Wilson Study and what Jane has come up with but, you know, there are all conservative numbers. I think there's a lot more out there than what we know. So our methodology, we looked at both the manufacturer's labels. We looked at what retailers were claiming as well as other claims to see if we cold find nanotechnology. The problem is -- or nanoparticles. The problem is that there's no real standardized function or way that these are all talked about on the label. So it's a very difficult research product to have.

So what we found, we found carbon -- nanoscale metaled oxide, zinc and titanium oxide's carbon fullerenes or buckyballs, nanocapsules, that were designed to reach into the deep layers of the

skin. And some of the corporations that had these products, you know, these aren't all of them but you're looking at some of the biggest ones in the world, Clinique, Chanel, Estee Lauder, Johnson & Johnson, Loreal, all have products that contain nanotechnology. And this is problematic because of the human health impacts of these particles. You know, they are able to migrate through -- you know, I think some of the skin penetration stuff still needs to be decided. I think that's unproven or it's a question mark at this point but we are looking at photo-reactivity. We're looking at free radical formation, cell deaths. These are just some of the impacts that we're seeing from the preliminary science that's out there and I think a lot more needs to be done but Friends of the Earth is looking just from a precautionary principle point of view.

So what was most alarming in our survey is that we found carbon fullerenes in various face creams and anti-aging creams and some of the science that's out there is that, you know, carbon fullerenes are impacting aquatic species, they're killing brain damage in fish, killing water fleas, persistent in the water up to 15 weeks and they're being easily absorbed by earth worms moving up the food chain. And then low

levels have killed human liver cells.

The problem is, is that we even got quotes from the Nobel Prize winner who helped discover carbon fullerenes has said, you know, I take a conservative approach in avoiding using cosmetics that have buckyballs. And so we found that there are seven products that contain these carbon fullerenes. There's six now. We've been in dialogue with a corporation that's now removing their carbon buckyballs from their product and there's no regulations on this. And now we go into nanosunscreens. Nanolight titanium dioxide and zinc oxide, the problem is the labeling, you know, whether it's micronized or nano, you know, my reading of what's out there is that there isn't a truly agreed upon definition.

These are being nanonized so that you can apply it cosmetically clear which means you don't have that nice white goo on your nose when you're out on the beach. I kind of like it, but you know, it means, I'm actually applying it properly. So, you know, that's part of the reason why we're seeing these nanoized titanium and zinc dioxide. And there's been some already red flags that George had pointed out about free radical formation, DNA damage and despite

this, the FDA censoring sun screens with nanoparticles as their parent or the bulk form.

So Friends of the Earth recommendation and you know, if you take any lesson away from this, we're a precautionary organization. We -- technology is fine as long as it's done and it's tested and it's safe before it's out on the market. You know, we don't need to have humans as guinea pigs or the environment as the guinea pig for any type of new chemical or new particle product. So, immediate moratorium on the release of new products that contain nanotechnology. We would call for a withdrawal of current technologies, nanoparticles that are on the market right now, a comprehensive study, I think we've all heard about the woes of inefficient funding for the human and the health and environmental impacts of nanotechnology. I think we need more of that.

We need to classify nanotechnology under a new regulatory regime and we need a new framework that protects workers, the general public and environment from the impacts of nanotechnology. And I think the worker side of things is important and unfortunately, we haven't -- I haven't covered it a whole lot but I think the ETC Group began to talk about it but we're going to have millions of people that are going to be

impacted at the manufacturing level for these particles. So, some more of the same recommendations, assessment, you know, based on precautionary principles, a risk assessment that includes the entire life cycle of the product are determined and that's very important. You know, what happens when the nano-sun screen washes off and is in the water -- bodies of water that we're swimming in or drinking. All the studies are made publicly available, I think that's a key one.

And that the labels that nanoparticles and nanomaterials are labeled. You know, doing the survey and working with Friends of the Earth Australia, who I should give credit for who helped release this report and draft the report with us, you know, we need to make sure that this stuff is labeled and let the consumer decide whether or not they want nanoparticles or to apply nanoparticles to their skin. So that's about it. Friends of the Earth is a cosigner of the ICTA petition to FDA so I would support everything that George has said in his presentation as well as what's in the petition. And here's my contact information. And just to -- and all of our report, other nanotechnology related documents can be found at www.foe.org and this isn't just Friends of the Earth

US that's concerned. Our member groups around the world are concerned. Friends of the Earth Australia helped release the report and draft our report with us. We know Friends of the Earth European Groups are also concerned about nanotechnology. So there is from the environmental perspective, a global concern about the introduction of nanoparticles into the cosmetic supply or into the consumer products. Thank you.

(Applause)

CHAIRMAN LUTTER: Thank you very much, Mr. Pica. Michael Roberts from the University of Queensland, School of Medicine.

DR. ROBERTS: Thank you, Mr. Chairman. Good afternoon, everybody. It's a pleasure to be here. I want to thank both the FDA and the CTFA who encouraged me to come over and speak to you today. I hope you can understand me with my Australian accent. If you've heard Steve Irwin, perhaps you will understand me. I come from Queensland, where he came from and of course, you probably know, that's the sun cancer capital of the world. We have the highest instance of melanoma and one of my other areas of interest actually is melanoma. So one of the comments I'll make is I have an interest in sun screens and skin absorption and I think we need to put this in the

context of risks and benefits and perhaps enlarge in that as we go along.

And the first thing I'd sort of like to comment on is that from the viewpoint of sun protection that the two agents which I know very well, I mean, I've worked with some of the other sun screens. In fact one of them was discontinued after some of our work, is that both zinc oxide and titanium dioxide have been around for a long time. And zinc oxide, of course, ends up as sort of an essential metal. The other key comment I want to make is in terms of the scale of things, nanoparticles is in probably what my previous speakers would call the gray area. Most of the compounds which we know go through the skin very readily are usually compounds of mega- weight of less than 500. That is the size of .9 nanometers or less. So in this case we're talking about particles on the order of 10 nanometers or greater. So it's an order of magnitude difference.

So we have to think of mechanisms other than diffusion as the main process of transport. But the other comment I'd make is that when I think about safety and I think this is where the FDA needs to sort of think about this very carefully, is robust science is essential. We have to think about issues such as

what is exposure, just exactly what area, what time, and is the skin in the area being applied to more painful than some other area of the body. And that in turn will define the absorption.

So then the question becomes is, well, exactly how much gets through? You may actually have some get through but the amount present may not be sufficient to cause any major concern. And the third component is what is intrinsic toxicity that exists. So to talk about absorption on the absence of intrinsic toxicity is also a mistake. So if you've got a highly toxic material and you're placing it on the skin and you claim it doesn't absorb very much, that's a no-go area from my perspective. You should really try and have a combination of all those features together, if you can.

The other key thing to be aware of is that this is the skin structure very simply, and I've got sort of the fuller diagram here. Most compounds, when you apply them to the skin, they really are stopped by the stratum corneum. The stratum corneum is the outer most layer of the skin. It's dead layer. The whole purpose of the epidermis to some extent, is to produce this physical barrier. When we look at compounds applied to the skin, particularly nanoparticles, we

find most of them reside either on the surface of the skin, in the folds of the skin or actually in the openings of hair follicles.

And that applies for a lot of the sort of nanoparticles I'm going to refer to but there are some exceptions that I'll raise later on in my talk, just to sort of make it more controversial. The other comment I'd make is the sort of nanoparticle we've done quite a bit of work on recently has been zinc oxide and the one we've been particularly interested is one which is between 20 and 30 nanometers. This shows you the particle size distribution. This shows you some particles from the TM and the reason why we do that is you can see that the 25 nanometers actually absorbs light in the visible region but blocks -- sorry, transits lights in the visible region but blocks lights in terms of UVA and UVB. So that's really quite desirable.

And these are some of the results that we found. The first thing you can see is if you look at electro-micrographs you can actually have squami, so the outer most layers of the skin are continually coming off and you can see here, if you look carefully you can see agglomeration deposits on the surface of the skin but you'll see nothing actually in the skin

itself so most of these are actually trapped on the surface.

Since then we've actually done a lot of multiphoton work. Multiphoton allows you to look into the skin without actually sort of having to do a biopsy. And so we can look at different regions of the skin and focus in different areas.

And we've used about a 10 nanometer cerium oxide and I think there's a typo in some of the handouts we're giving out at the front as well, as zinc oxide in different sizes. And in each case, we found all the material were retained in the follicle lipons and around estimating 20 sites. Now, I need to highlight that the skin that I always use is human skin. One of the dangers you need to be aware of is when people use animal skins, you get very false results. And you'll see that I think repeatedly when you look carefully.

Rat skin sometimes can be up to 100 times more permeable. Pig skin can be up to 10 times more permeable, so they can give you impressions of potential toxicity which may not be exactly real. The other thing -- and I'm going to talk about flexing later on. The other thing we're trying to do is do some work where we actually flex the skin backwards

and forwards repeatedly. And when we do that, we also have found there's actually, none of these particles go beyond the outer most regions of the stratum corneum and the follicles. We've also measured the amount that goes through into the receptifiers and of course titanium oxide it's insoluble. With zinc oxide you can measure it in the sense that you can then take your solution dissolving acid and what you tend to find is the amount of zinc which comes through is actually sort of not different to placebo but you can see a trend here. And I think part of that trend occurs because, in fact, the skin surface is acidic and probably helps some of the zinc oxide be transferred to zinc. But human skin here, you can see the amount we have absorbed is .03 percent of what was applied. There's been only one other study I'm aware of with pig skin and they actually end up with recoveries about 100 fold greater which just highlights the difference between species.

With titanium oxide a similar story. You can show the titanium oxide agglomerates on the surface. You don't see this in deeper layers. And if we look at sort of follicular levels, there's been some work done by Literman in Germany and he's actually tried to measure titanium distribution and

you can see, in fact, it does go down with the follicles. This creates another artifact when people talk about skin penetration because I actually have a combination of this follicular levels with the skin itself and they suggest maybe the compounds are being absorbed when, in effect, they're not. It's just an artifact of sampling.

So in general I would argue that sort of most of the data I've seen suggests for zinc oxide and titanium dioxide with human skin, there is minimal total absorption. We found in some of the other studies we end up with some controversy and some of that we need to try and address. So for instance there's a study by Kohli and Alpar in 2004 with pig skin and that was suggesting that negative charged particles penetrate by 50 and 500 was 100 and 200 times. And when we have done similar studies with human skin, we find, in fact, there was no penetration at all. So the key thing I'd argue is there needs to be a body of evidence. There needs to be repeated studies and we should actually use robust science as a sort of justification for what we have.

And in fact, if we look through some of the literature, there is other studies and this is by Alpars and there's actually no penetration as well and

if you look at all the in vivo data, in vivo human data is to my view the real gold standard, there's actually been no penetration shown by a number of studies.

Let me talk about some of the controversial issues. There's been some very nice work by Jim and Nancy Rivera about quantum dots. I know you've seen this work but I actually find it's really interesting and the reason it's interesting is it raises the issue whether we can actually use nanoparticles for drug delivery in which case it should really become I suppose, a drug. One of the areas of course that one of my groups is interested a little bit in is, can you actually deliver genes by these means to treat cancer. So it's a different approach. But I think we've got to make sure we don't mix up the science involved with safety from the science involved with drug delivery. They're two different aspects. And so you need to actually engineer things to not go in or go in and understand that science has to be robust.

And you can see in Jim's work what that shows. That can show that some particles, when you apply it to pig skin, you can actually see them in the epidermis after eight hours. And so I should say

these are actually just control skins. These are actually skins with a fluorescent shine agents. This is the stratum corneum up here and this is actually the sort of the depth of the fluorescence. And what you can see is in the case of this iron compound, this material goes through to the dermis and when things go through to the dermis, that's really of great concern to me. Even the epidermis is of great concern to me because generally, you'll find if you do any epidermal injection, it ultimately will go into the lymph nodes pretty well straight away and certainly our work we've done on lymphatic transport shows that it's pretty effective.

But what I want to comment is, first of all this is pig study, so I don't know how relevant is it to man and we need to put that in context. Until it's repeated in man, I'm not sure what it really means. The second thing is I used the pH of 9 for the COOH and a pH of 3 for the peg related compounds. If you know anything about skin physiology, you'd be aware that pH's above about 8 causes the skin to become more permeable. And it's interesting how this data here really starts to appear at 24 hours.

The other comment is, of course, that they use peg overtures which, of course, is faster. I was

going to talk briefly about some of the work of Sally Tingle. I will just simply say that in fact, when you do flex and you can see material through it, in her case, she actually hydrated skin for 24 to 48 hours, so the issue becomes here that you may, in fact, have materials going through but maybe it's not on the skin. I agree with her and I've had a long chat with her, the mechanical force and particle size may be important issues in skin penetration. I'm going to flip through this quickly but what I want to really say is if you do your calculations, you can show the rates have levels of 10^{-19} based upon what you see in solution chemistry.

My last slide is I just really want to comment that the available data that I've seen says that the zinc oxide and titanium dioxide in nanoparticles, there isn't sufficient going through in terms of toxicity. And the theory in my country is we should do a very thorough evaluation and mainly it is the view that they remain on the surface of the skin and the outer stratum of the skin. So I would argue at the end of the day, it has to be robust science and it has to be based on the body of evidence. And I think the FDA is the right body to do that. I think we can use some of our current knowledge, and finally,

I just want to acknowledge the people that have helped me and that's my staff and the Australian National Health and Medical Research Council. Thank you.

(Applause)

CHAIRMAN LUTTER: Thank you very much. Our final speaker of this session is Annette Santamaria of the Cosmetic, Toiletry and Fragrance Association.

DR. SANTAMARIA: Good afternoon. My name is Annette Santamaria and I'm a board certified toxicologist with Environ International Corporation. I am speaking here today on behalf of the Cosmetic, Toiletry and Fragrance Association, CTFA. First, I would like to thank that FDA for this opportunity to discuss the use and safety of nanotechnology in the area of cosmetics and personal care products. Nanotechnology offers distinct and well-recognized benefits for consumers of personal care products. Moreover, it has done so safely and effectively for many years. This presentation is based on the extensive comments that the CTFA submitted to the FDA public docket on September 19th, 2006. Those comments provide documentation that supports the safety and continued use of nanoscale materials in personal care products.

Today, I will discuss four main points regarding the use of nanoscale materials in personal care products, specifically; one, there is no scientific evidence of a toxicity profile common to the various nanoscale materials. Two, the safety of nanoscale ingredients should be evaluated just as any other new -- any other ingredient. Three, available toxicological methods are appropriate for evaluating the safety of all ingredients regardless of their size and four, nanoparticles have been safely used in cosmetics and sun screens for many years.

The suggested enhanced toxicity of nanoscale materials has not been confirmed by competent and reliable toxicological tests for most nanoscale materials and an a priori assumption of greater risk from nanoscale materials does not have a sound, scientific basis. Particle size may have an impact on toxicity in some cases; however, generalizations about an increased toxicological potential of smaller sized particles are not appropriate. In fact, there are conflicting results in the scientific literature about the impact of size on toxicological potential. Most information on the toxicological effects of nanoparticles, including titanium dioxide and zinc oxide comes from respiratory

studies. However, it is essential to note that these studies have been conducted to evaluate the pulmonary toxicity of nanoscale materials. Furthermore, the results from these studies are equivocal. In some studies, smaller size was reported to be associated with enhanced toxicity while in other studies, larger sized particles induce greater toxicity or there were no differences observed. Importantly, few toxicological studies have been conducted to systematically examine the role of particle size and surface area in producing toxicity. Furthermore, studies have not reported differences in toxicity following the dermal administration of chemical substances due to particle size.

To assess the safety of an ingredient, cosmetic companies evaluate the potential of the ingredients to induce adverse effects by reviewing existing scientific studies, conducting structure activity studies and by performing toxicological studies when necessary. For example, studies may be conducted to evaluate reproductive, developmental, respiratory, dermal, ocular or carcinogenicity end points. Safety assessments consider level of exposure, routes of exposure and duration of exposure which are all essential for characterizing risk. Once

the information is obtained, recommendations are made including the identification of data gaps to insure that all toxicological end points and/or concerns have been addressed. If testing is deemed necessary to fill a critical data gap, the appropriate in vitro and/or in vivo studies will be conducted. By combining the results from the toxicological evaluation and the exposure assessment, a risk characterization can be developed to determine whether an ingredient is safe for use in personal care products. The risk characterization of an ingredient includes an adequate margin of safety to protect against unexpected toxicity or adverse effects if the product is misused or abused. The scientific methods that are currently used to insure the safety of existing and new substances that may be used as cosmetic ingredients are equally appropriate for evaluating the safety of ingredients developed in the nanoscale range. In fact, panels of scientists have concluded that traditional approaches and study protocols for the toxicological evaluation of chemical substances are appropriate and sufficiently robust to provide meaningful characterization of nanoscale materials. Cosmetic companies typically use state of the art scientific methods for evaluating the safety

of ingredients. Just as our understanding of science continues to evolve, so too will toxicological testing of all ingredients, including nanoscale ingredients, and new study methods will be implemented as necessary.

The regulatory processes that the FDA currently has for evaluating ingredients in personal care products are more than adequate for insuring their safety regardless of their size or how they were manufactured. Cosmetic companies are responsible for the safety of their products and are committed to insuring that consumers have access to safe products that not only improve health but also promote personal care and enhance beauty. The industry uses established processes and programs and recognized testing protocols to insure the safety of personal care products.

Concerns have been expressed about nanoscale ingredients because of their small size and the possibility that they may be absorbed through the skin. Cosmetic ingredients in personal care products consist of discrete molecules which have the potential for dermal absorption and personal care product companies approach the safety evaluation of an ingredient by focusing on the amount of application

and duration of potential exposure. Therefore, the dermal absorption is routinely taken into account in the safety evaluation of cosmetic and sun screen ingredients and formulations. In addition, the available studies for evaluating dermal absorption are appropriate for evaluating nanoscale materials as ingredients. The use of materials with dimensions in the nanoscale range in personal care products is not new. Nanoparticles of titanium dioxide and zinc oxide have been used in sun screens for almost two decades and their safety has been thoroughly demonstrated. In addition, in vitro and in vivo studies provide compelling evidence that nanoscale particles of titanium dioxide remain on the surface of the skin and do not penetrate the skin. The use of nanoscale particles of titanium dioxide and/or zinc oxide in sun screen products allows for greater protection against the harmful ultraviolet rays from the sun including UVA radiation.

Furthermore, the use of small particles in the formulation results in a clear protective barrier that is easier to apply. Consumers find these sun screen products more aesthetically pleasing, thus leading to increased consumer acceptance. Both of these factors contribute to a greater impact of sun

screens on public health by protecting the individuals from the harmful effects of the sun including skin cancer. Clearly, sun screens are an example of the improvements of a consumer product because of the addition of nanoscale materials.

In conclusion, nanoparticles have been safely used in sun screens for many years with no relevant evidence of adverse effects. Existing test methods are appropriate for evaluating the safety of nanoscale materials. Safety assessments are performed on nanoscale materials as they are developed for use in personal care products and lastly, current regulations insure the safe use of nanoscale materials in cosmetic and sun screen products. Again, thank you very much for this opportunity to speak on such an important matter.

(Applause)

CHAIRMAN LUTTER: Thank you very much. We have about four or five minutes to take questions from members of the task force who may wish to pose questions to our esteemed panelists here.

DR. CANADY: Yeah, I'd like to take the first if I could, Rick Canady, Office of the Commissioner. Dr. Delrieu, I'm sorry if I'm mispronouncing your name, you mentioned that it's

common industry practice to coat the nanoparticles. Could you explain what that means in terms of for example, efficiency of coating within a given batch or common practice across different manufacturers? Could you give a little --

MR. DELRIEU: Well, the pigments that they use as sun screen products are usually surface coated. So there are different surface coatings. It's not only -- in fact, to reuse the activity of the pigment. It's also to ease the formulation. But yeah, they are -- most of them are surface coated.

DR. CANADY: Most of them, thanks.

DR. SADRIEH: Hi, my name is Nakissa Sadrieh, Center for Drugs, and I have a question for Dr. Santamaria. You had a statement on your last slide saying that safety studies are done on nanomaterials and so I was just wondering, are those studies, the results of those studies available for the public and for the FDA to look at?

DR. SANTAMARIA: Well, at this point, they are not necessarily in the published literature but they would be available if there was -- through the process of the cosmetic ingredient review process. If we decided that there was sufficient evidence to support a formal review of these materials, then they

would become available through that process.

DR. SADRIEH: So what would make you do that?

DR. SANTAMARIA: Pardon me?

DR. SADRIEH: What would make you sort of then sort of give us that data? I mean, what kind of criteria do you have for determining that the results are such that they need to be elevated to a certain level?

DR. SANTAMARIA: Well, I think that would be sort of up to the individual companies if they recognize that there are some potentially adverse effects associated with these materials, then I think it's in their best interests to make those studies readily available through the published literature and/or submitting them to the FDA if there are concerns.

DR. HOWARD: Paul Howard, FDA. Dr. Delrieu, you made a point that primary particles do aggregate and agglomerate. I would encourage you to put in the docket any size distribution information you have of materials that are in sun screens and the same question would go for Dr. Santamaria, that if there's information available regarding what is truly in sun screens as far as aggregation and

agglomeration, that would be very helpful.

MR. DELRIEU: Yeah, we actually are going to prepare a more detailed presentation as well, than what I could do in eight minutes, well, nine minutes actually, but yeah, and that would be made available.

CHAIRMAN ALDERSON: I have a question for Ms. Houlihan. A number of times in our presentation you made reference to FDA should request data on the cosmetics. Now, recognizing the authority that FDA has over cosmetics, help me understand what you mean that you would have us do.

MS. HOULIHAN: Well, one thing I talked about was CFTA's new consumer commitment code and my understanding is what they're committing to do is to provide FDA with data upon request in the form of safety information summaries. And so that's progress and we understand you don't have the authority to demand data from the industry, that doesn't stop you from requesting it and certainly with the new consumer commitment code, we would hope that there would be a better process for getting data from companies to you when they have it.

CHAIRMAN ALDERSON: So with that, I would follow up to Dr. Santamaria. Could you expound on that program that's just been defined for us, what it

means, make sure I understand it? Does that mean that if we've got a list of products that we want to ask for safety data on that you will provide that?

DR. SANTAMARIA: Yes, it's something that you're requesting could be provided but this, again, is probably best answered by a member directly of CTFA. I'm here on their behalf but I don't want to speak for CFTA for that particular issue.

CHAIRMAN ALDERSON: My last question is for the two gentlemen sitting here to my left. And this is the issue of definition of nanotechnology. We've heard that from a number of speakers. And I would ask you to help FDA understand what it is you want us to define and what it gets us in terms of a regulatory posture that we don't already have in place that would serve the same purpose.

MR. KIMBRELL: I think the definition issue is a thorny one. I think we've heard that several times today. I think at some point it becomes sort of stalling issue. I've seen lots and lots of conferences on nanotech where people argue that we can't really go forward with anything until we all agree on one definition. I don't agree with that. I think it's possible to go forward on parallel tracks, that is, develop policy, recommendations and

regulatory initiatives while also fleshing out definitional issues. To the extent that we have a definition in our petition, I recommend that to the agency, that is for both nanotechnology, nanoparticle and nanomaterials.

It is similar to the NNI's definition and that of the FDA's informal definition on their website. I do think there are some common ground where people agree on the issue of definition and that has to do with the fundamentally different chemically and physical properties of these materials. So on the one hand, I recognize it's a difficult issue but China certainly has agreed on sanction and official definition for nanotechnology and related definitions. I don't see where we can't and I don't see why it should stop us going forward.

MR. PICA: I agree with George's comments. I would just add that we need the definitions for the labeling because there is a desire, I think, and these are the responses that we're getting from out members and even the conversations that I'm having with companies that are including or they are trying to evaluate if there's nanoparticles within their products themselves. We need at least some sort of definition. We can say look, whether it's 100

nanometers, if it's smaller, larger, whatever that threshold is, I think it's 100 meters in the petition, just to start giving benchmarks out and you know, to help the consumers and the various companies and corporations that are trying to -- that are trying to evaluate whether to use nano or not within their products to give them some guidelines.

CHAIRMAN LUTTER: I have one final question for Michael Roberts of the University of Queensland. You presented a bunch of data on penetration. Are those available to be shared by the -- with the Australian Government?

DR. ROBERTS: Yes, all of our data's been published and I believe in transparency as much as possible.

CHAIRMAN LUTTER: Thank you.

CHAIRMAN ALDERSON: Okay, we thank this panel and while they are departing, we would ask the next panel to join us on the stage. Mr. Buckler, Dr. Desai, Dr. Diwan and Dr. Grodzinski, please step up here, please. For this session, Phillip Buckler is our first presenter from Kereos, Incorporated.

MR. BUCKLER: Good afternoon. Thank you. I appreciate having this opportunity to speak this afternoon. I think this afternoon's session is going

to be more drug oriented, so I think we're going to switch gears a little bit, going from cosmetics to pharmaceuticals. Some of the things that I'll discuss are some of the regulatory strategies and considerations that should be made when developing a pharmaceutical product and so even though products may fall into that nanotechnology umbrella, again, as someone said earlier today, I think we shouldn't throw our hands up and assume that things are going to be bad because as I hope to show are some examples of our products, that products can actually be made to be safer. So we'll talk about that a little bit toward the end as well.

Again, I don't want to beat this to death but we've talked a lot about the definition of nanotechnology, the size issue and also the differential performance components organized on a nanometer scale typically have significantly better or a different performance than on a larger scale. And again, the different types of nanotechnologies, I won't go through all of those. One thing I do want to point out, however, is that toward the end of the list, nanoparticles are thought of normally as kind of rigid particles and whereas nanodroplets which I'll show in a little but, which are my cells or PFC

emulsions, are less rigid and may enhance the safety effects.

When you're looking at a safety framework on a nanotech scale, I think it's important to look at the constituents in bulk, the existing drug device guidelines in connection with the nanoscale. And as I've shown here, also in the nanostructure impact, if you have -- you want to make sure that you have novel activity or reactivity to make your drug something that the industry is going to use. And you also have to look then at the biodistribution. Has the addition of these materials that may be on the market already when they've been put on the nanoscale, has it effected bio-distribution and has it effected bio-availability, whether it's positive or negative?

Okay. Also there is -- so getting to the examples, our products are known as ligand-targeted emulsions, so we don't consider them nanoparticles. They're nanodroplets. So they're oil and water emulsions and the makeup of this is a per fluorocarbon center with a monolipid layer around it to help rigidity and then with this product, we were able to add different payloads for imaging or psytotoxic for cancer therapy. The other part of this droplet is a targeting ligid that actually targets the disease and

then delivers the payload to a specific area.

As I indicated earlier, we're able to place different payloads on these droplets so that you can use them again, in cancer therapeutic imaging, cardiovascular disease. There's really not a limit to the types of payloads that we can place on these products. So again, in looking at the safety of these type of products, you have to look at the distribution of the constituents in bulk and also at the loading of the material on the droplet. With the materials that we're currently using, we have a great human safety profile for the per fluorocarbon. There's been extensive human safety experience as a partnetral drug at higher doses and for again, chelate, again there are several approved products on the market at much higher doses and the targeting ligand is a new chemical entity but it's a small molecule, peptidomimetic.

So my points here are, we've taken existing products that have generated safety profiles and we're using them at a lot lower levels and because of the targeting effects of our droplets, we're able to lower those dose levels and increase the safety of the products. Some of the other things that we think about also and we've talked a lot about FDA

guidances and regulations. And in our field, in looking at our products, we feel like there are already good guidances out there to give us an indication of what we should be doing to test our products. So they're lyposomes guidances, although our products are not lyposomes, they're different than lyposomes, the agency has indicated that they would like us to use the lyposomes guidance. There are three imaging guidances to apply to our imaging product. There are other guidances for non-clinical, pre-clinical testing that will be applied to all of our products. We will be testing these products pre-clinically to get a full safety profile prior to filing an IND and of course, all that material will then be available to the agency for review.

Now, looking again at the nanostructure impacts, again, we're looking for a novel activity or reactivity but again, how will the nanoparticles impact the biodistribution? In other words, because of the targeting from the payload, how will those different constituents then react once they are injected into a human or an animal? And that would be the normal course of evaluation prior to marketing the product. We also look at bio-availability. Hopefully, because of our technology, this would

enhance bio-availability, then again, not only make the product more safe but make it much more effective.

So conclusions are nanotechnology really is a broad umbrella. I think we've established that from the discussions this morning. So with groups calling for a moratorium on nanotechnology research, that concerns me a little bit because I feel like our products are being tested properly and very in-depth, so this really argues to a one size fits all approach, against a one-size fits all approach. So again, safety considerations should be based on the non-nenotech compositions; what types of products are you adding to the nanotech product and then are there appropriate existing drug device guidances already in place that will allow the company to properly assess their products. And then once you take those materials, what are the changes that are caused by placing that under a nanostructure. And again, those are all the things that a company like ours would be doing in a full preclinical package. Thank you.

(Applause)

CHAIRMAN ALDERSON: Our next speaker this afternoon will be Dr. Neil Desai from Abraxis Bioscience Incorporated.

DR. DESAI: Thank you very much, Mr.

Chairman. It's a pleasure to be here to address this audience and the FDA on issues relating to the nanoparticle albumin bound technology which we call the NAB technology. I'm going to be talking about primarily the NAB technology, but I also want to switch gears a little bit from the morning sessions of FDA bashing on the cosmetics side to a bit of praise for the FDA for what they've done on the drug side. And then I'll allude to some definitions of nanotechnology. The NAB platform as we call it, is a means of converting insoluble drugs such as paclitaxel, docetaxel, rapamycin and there's a whole host of other drugs into a nanotechnology platform which consists of almost spherical particles of the drug coated with a protein, a bio-compatible protein human albumin.

And these are about 50 to 150 nanometers in size. One of the interesting aspects is we're able to convert these hydrophobic compounds which are normally crystalline in their bulk form into a amorphous state which is readily bio-available. And we see this example of microscopy. This is electron microscopy. Once these nanoparticles are injected and get into the blood stream, the nanoparticles rapidly dissociated into their components which is the albumin

and the paclitaxel or other drug that's bound to the albumin. And this is in a very natural like phenomenon. Albumin is a natural carrier of hydrophobic molecules in the body so we're just promoting this natural process to occur.

The first product of its kind, Abraxane which is we call nano-paclitaxel was approved by the FDA last year for the treatment of metastatic breast cancer. And this product has essentially paclitaxel and albumin by itself. There is no surfactants or solvents or other chemicals in there that help to solubilize a drug as opposed to Taxol which has been out there for many years with the same active ingredient, paclitaxel but because of the insolubility of the drug, requires a large amount of cremophor which is polyotoxilated castor oil is refractant known to have allergic and anaphylactic side effects and also the solvent ethanol. The other interesting part about now these two drugs being out in the market is that we are able to compare a nano version of the same drug to something that's been out there before, a different conventional drug version. So I've heard a lot this morning about the fears of nanotechnology and toxicology and hopefully I can address some of that in this talk.

Abraxene was approved by the FDA, as I mentioned last year in a trial that -- of metastic breast cancer patients comparing Abraxene versus Taxol. In about 460 patients it had twice the response rate in metastic breast cancer patient as the Taxol, of 21.5 percent versus 11 percent for the case of Taxol and this was highly statistically significant at the .003 level. A key aspect of the nanoparticle technology is the ability to form stable nanoparticles and these nanoparticles are characterized by special methods that are able to look at the small nanoparticle size. In this case, this is nanoparticles of paclitaxel which are about 113 nanometers in diameter.

Now, mind you, this falls outside the current definition of one to 100 nanometers and I will have a few words to say about that. The other aspect about stability is that we have -- due to the albumin coating that we have, the biocompatible human albumin on the nanoparticles, at neutral pH these particles are negatively charged. We heard some things about negatively charged particles and their lack of toxicity earlier this morning. They resist agglomeration and further more due to the presence of the polymer albumin, which is a large molecule, you

get steric-stabilization that keeps these nanoparticles stable.

Very interesting mechanism by which the drug is released, once it enters circulation, as depicted here. This is a graph of concentration in plasma versus nanoparticle size, so as the concentration decreases upon administration, once you reach about 50 to 60 microgram per mil, the nanoparticles of about 113 nanometers decrease rapidly in size and form complexes of albumin and paclitaxel or albumin and whatever drug they're administered with.

And so essentially, you've got soluble albumin bound drug floating around very soon after administration. What this does is then allows some special pathways of albumin to come into play which results in unique transport of these drug molecules into the tumor. So this cartoon shows the tumor blood vessel and these are the endothelial cells lining the blood vessel. You have the albumin bound drug which can bind to specific albumin receptors called GP60 receptors and these trigger the formation of caveolae or vessel like structures which actually transport the complex across the endothelial cell by a process known as transcytosis and into the tumor bed or the tumor

interstition. Interestingly, tumors have developed a mechanism where they secrete a protein called SPARC which is an albumin binding protein and this helps sequester the albumin bound drug into the tumor, therefore, getting high tumor levels. And this is shown here in this slide. I hope you can see this. We are injecting here nanoparticls which are fluorescently labeled into a rat containing a tumor -- I beg your pardon, a mouse containing a tumor, and very soon after administration, within a minute or 15 minutes, you'll see the tumor light up with the fluorescence of the dye that was in the nanoparticle.

These measurements have further been confirmed in radio-label studies where we actually measured the tumor concentrations over a 24-hour period to show 33 percent higher tumor levels of paclitaxel when we used nab-paclitaxel as compared to the standard Taxol. So in comparing nano-paclitaxel versus the standard paclitaxel, which is Taxol and has been out there for a long time, I would like to say a few words. This gives us a unique opportunity to do that and first of all I'd like to say that we've had a close and extensive interaction with the FDA for almost 10 years now which ultimately led to the approval of Abraxene and this was -- all our

interactions were very scientifically sound and I must say we have enjoyed our interaction with the FDA so far.

What we were required to do as a part of the approval is an extensive battery of pre-clinical tests that compared Abraxene to Taxol. So now you're asking the question, does a nano-drug impart and untoward toxicity as compared to a conventional drug? So in this battery of tests, we did intravenous toxicology, looking at multiple organ systems. We looked at bio-distribution, metabolism, excretion, reproductive toxicology, tumor efficacy studies and studies of mechanism of transport and several others.

And so far we have also tested more than 1,000 patients in carefully controlled clinical trials looking for, of course, efficacy but also any untoward toxicities and then since approval, more than 20,000 patients have been treated with Abraxene and I'm happy to say that there was no new or unique toxicities that were seen with Abraxene that were any different than that reported for conventional paclitaxel or Taxol. So what I could say from this is that currently we believe that the FDA has adequate procedures in place at least as far as nanotechnology based drugs go, to insure the safety and adequate testing of these

products.

Just switching gears quickly on the definition aspect, we've heard the one to 100 nanometer definitions. If you look at published data, you see that of 152 abstracts recently cited, almost 80 percent actually talk about nanoparticles that are greater than 100 nanometers, not less than 100 nanometers. There's other drugs that we're working on. Some of them are less than 100 nanometers. Some of them are greater. So the question is, what is the nanotechnology definition to apply.

And so ending here with this last slide, we have some recommendations. Of course, we believe that there should be some unique function, whether it be physical, chemical or biological, but a suggested cutoff, at least on the pharmaceutical side that may be relevant is 220 nanometers or .22 micron, because this is relevant for sterile filtration and insuring sterility of injectable nanotechnology products and also that special techniques of characterization are required for these products. And lastly, there should be at least a committee to discuss these definitions. Thank you very much.

(Applause)

CHAIRMAN ALDERSON: Our next speaker is

Dr. Anil Diwan from NanoViricides, Incorporated.

DR. DIWAN: NanoViricides is a new company. It's based on technologies that developed in what I call the polymeric micelle type of technologies which Dr. -- I forgot his name, he just recently referred to and we are finding similar to them that these have much greater safety potential than do particulate technologies. Because these are not particulate technologies, there are very important different problems that associated with characterization and things like that that these technologies bring out.

Then name of the company is derived from nanotechnology based viricides. Currently viricides do not really exist. We are the first ones to create viricides which is virus killing agents. Vaccines and therapeutics, I call them two wheels of a cart, and they're usable in different kinds of viruses and not in all cases.

What we have developed is a pendantized polymetric micelle based commercially flexible, specially targeted drug and we are currently working on it. It's in pre-clinical studies at present. Regulatory implications for two parts. These are the two parts of my talk today, regulatory implications

for the normal IND enabling study. We are still pre-IND. Hydroxene is already approved and the second part is a novel war-like bio-threat response mechanism that is enabled by what we have developed. What we have developed is a material that looks like that cartoon on the right side. It's like a guided missile. And the rectangles and triangles are different lignads that are attached covalently to the backbone which is shown as the blue line there, it's a polymeric chain and the pendant, slippery, oily pendants that you are seeing. These materials have extremely high capability for encapsulating the active pharmaceutical ingredients. However, so far we have not had the need to use any encapsulated IP's. That's because the materials themselves have certain attractions with the various particles. This tabulates the various particles.

So this is the chemical structure repeating it of the polymer that I described to you in a schematic form. The patents are pending on these structures and what I'm showing here is that we are not using any APIs right now. The ligands are coherently attached, single molecular chain type of structures. So these are very close to the definitions molecule identities, NC's. What we have

so far is by choosing different ligands, we can create a broad spectrum drug such as against all influences. We can create nonospectrum drug which we call group specific against the highly pathogenic influenzas. H5N1, the current influenza trait is one of those special cases of high path and then there are additional cases that are coming up. So we have created a filter kind of mechanism here and then we created another one which is extremely specific for H5 and one that's strain specific.

The dark spectrum drug, of course, has a very high commercial potential and H5N1 strain specific currently has a potential for SNS, Strategic National Stockpiling and so does the high path one. And this is a novel treatment methodology in the sense that by choosing -- targeting a ligand appropriately, we can specify the spectrum to be broad or short of metal depending upon what the needs are. It's really important from perspectives of bioshield because you want to stockpile a minimum number of drugs that can target a maximum number of diseases.

We have seen in very, very preliminary research and I'm not showing the data here, that in mouse studies we have shown that our drug, what we call NanoVirivide D, the actual name is very, very

long and complex, that one was about eight times bigger than Tamiflu, somewhere between 100 times better than Tamiflu in efficacy and if we compare that with our H5, in one base study in cell cultures, we see compared to Tamiflu, which you don't see here, when it's very, very low and you go up.

NanoViride is made specifically to H5N1 is at about 20,000 which is about 200 times superior in efficacy. So we are seeing extremely high efficacy levels. We also have not seen any concomitant safety problems, toxicity problems. We have run one preliminary safety data with mouse studies. All of these are injectibles and only on the on the polymer and in that we have not seen any toxicities. We did 13 different issues as well as microscopic examinations and blood pathologic. So it is general consensus today and has been for awhile that nanotechnology can develop very good high efficacious and molecular safe drugs. And we believe that by having the broad spectrum versus narrow spectrum type of ligand tuning we can potentially reduce mutation frequencies for two reasons.

One is because if you have a very high efficacy drug, the possibility that a mutant will arise is expedentially lower. And the second is that

because we have a broader spectrum, even if a mutant arises, for example an H5N1 mutant arises, but if you are treating with a high path drug, then it will still be sensitive to the high path drug, and if it is not sensitive to the high path drug, then in 90 percent of the cases, you do not have to worry about it because it will have symptoms inherent to common influenza. So that kind of mechanisms are now made possible and it is likely that this will reduce the resistance of strain generation. What we are looking for is what are going to be the guidelines for proving because there are -- if you know about molecular biology and pathology in particular, you can generate thousands and thousands of mutants. So where do you stop testing and how much testing is enough. Those kind of guidelines we would need for testing further.

The future of this approach is, of course, unlimited. We can target an extend to many different viruses and also to some non-viral releases. As long as a discrete pathogen particle appears in the bloodstream, this nanoviricide approach can be used against it. This is primarily a neutralization of viremia in the bloodstream. That's how it occurs. So the key differences from the drugs and biologics that are -- we have been seeing that are that we have --

you've been using flexible polymers which area very defined but non-particular materials. These are single molecular chains but they have heterogeneous molecular sizes, there is a molecular size distribution. You saw even in the case of Abraxene there is a size, particle size distribution. This cannot be avoided in these kind of chemistries. There are molecular rate averages and in the distributions that can be characterized. Ligand attachment cannot be quantified because no chemical reactions are 100 percent complete. And you don't have the ability to purify only 100 percent complete type of chemistries. Same problem as with Abraxene. So we don't see that as a major issue. We believe that the links probably are there that can be applied further.

This is another one, operational definitions again, example made it very clear that these things are possible and these are amphiphylic materials. That causes additional problems over what abraxene and albumin type of drugs have done. For example, EM's are not useful again, amphiphylic materials cause complications and the closest cases to these kind of materials are some recipients like BEO, PPO type of polymers and things like that. So there are plenty of guidelines that are available but the

BEO PPO polymers do not have a frequency associated with them so the second -- and so I think I'll conclude here, that we are looking for as an industry guidance on the minimum experience, informative and critical amount of information that we need to create because our resources are limited and of course, FDA's point of view is going to be as much as possible and there is always going to be a tussle but I believe that we have a need for a balanced approach which would lead to speeding up of such extremely high efficacy drugs. And the second part of it I will leave for next time. It's on the slides.

Thanks.

(Applause)

CHAIRMAN ALDERSON: Our final speaker for this session is Dr. Piotr Grodzinski from the National Cancer Institute.

DR. GRODZINSKI: Good afternoon, everybody. Good afternoon, again. Thanks a lot to FDA for inviting us here. And I'm following three speakers which talked about very specific platforms, which address specific medical issues. What I would like to do here is to step back a little bit and tell you how we, at National Cancer Institute, look at development of nanotechnology in general but

specifically for cancer applications and since we all -- we certainly all know that nanotechnology carries certain benefits for biomedical applications, which I list here and from the standpoint of developing new drugs or therapeutic solutions, we certainly hope and there is strong evidence of that and some of that came across in the previous talks that these solutions will result in improved therapeutic index and improve the efficacy of the drugs but at the same time, because the drug or therapy is capable of working locally, should result in lower side effects, which again, in case of traditional chemotherapeutic treatments for cancer are quite severe.

These solutions are expected also to be capable of delivering more than one drug at the same time to the tumor locations. They can also participate in gene therapy by delivering nucleic acid and in addition, they can provide therapies which not necessarily are associated with the delivery of the drug but also are related to for instance photothermal activities when simply you aggregate nanoparticles in a given location and then you can infuse locally their temperature and kill the tumors locally that way.

So essentially, all these comments lead to the development of multifunctional platforms, and

that's why they are so attractive because the nanoparticles which are introduced to the patient can be targeted locally to the tumor location. Then deliver therapy by the means of releasing drug or other methods, but at the same time, report the location of the treatment and its effectiveness potentially through bio-sensing means. So how that differs from the traditional free drug approaches that all these functionalities can be delivered in one package. And again, that is certainly very good news from the standpoint of prospective efficacy. But it leads to certain complexity when it comes to considering the drugs from a regulatory standpoint. And as Dr. Desai already mentioned, some of the drugs which are using nanoparticulate delivery have been approved by FDA last year.

So again, to give you some of the examples here from the -- where it is maturing but hasn't reached the approval yet, on the left-hand side, you'll see delivery of methotrexate which is chemotherapeutic drug and relies on dendrimers delivery but also is capable of this multi-functional approach because it carries the tag which allows to image the presence of the particle and at the same time target it to the tumor. The right-hand side, you

look at a slightly different approach, where you're actually not using the drug itself but you are using metho nanoshells which then by being shined by the laser are capable of increasing the temperature and ablating the tumor tissue.

So again, what happens here because of this complexity and because of the multi-functional nature, what I think developers of the technology would like to see and this is already happening but may need to be clear at some point is how to approach characterization of these materials. Because of their multi-functionality, they can be classified at the regulatory stage as device or as a drug. Again, also in many cases, the nano-delivered platform is being used to deliver the existing drug, which again, differs from approval of the new drug where newer chemical analogue is being developed.

So from our perspective, we formed a large funding program which addresses essentially new technologies for development of prevention, diagnosis and treatment of the cancer using nanotechnology approaches and there is a number of funding efforts across the country, large and not so large. They are classified as centers of cancer nanotechnology excellence or which involve usually multi-institution

groups from very different walks of life, including not only medical schools and cancer centers but also engineering entities and physical scientists. The other one is cancer nanotechnology platforms. We're also developing a number of training approaches to allow for cross-disciplinary training of scientists in that area and last but not the least, and I think that's actually most important for the discussion here, we talked many times during presentations in the morning and also in the afternoon today about responsible and uniform and standardized characterization of nanomaterials.

Obviously, before these nanomaterials enter the clinical trials, they have to be characterized in-depth from the physical and biological chemical standpoint and because of that, we formed Nanotechnology Characterization Laboratory and Dr. Scott McNeil, who is Director of that lab, will talk in the next session and the charter of NCL is to develop uniform and standardized efficacy which will allow to cover a number of different steps of characterization and eventually hopefully will lead to the uniform characterization of particulates from different nanoparticulate families.

But looking at the next step, which will

go beyond physical and biological characterization but in pre-clinical stage, and this is the graph, which is borrowed, in fact, from -- I'm sorry, from FDA from the critical path, the next step will be to develop programs and some of that already is happening independently of the funding from NCI but develop the programs and methodologies which allow to push the development of the material forward and scale it up through GMP practices and eventually lead to identifying and Phase 0 and Phase 1 trials.

Again, as I said, some of them that came across in the presentations earlier is happening independently but the level of innovation in this area is very, very high and from the Federal Government perspective, we feel that developing such programs will be helpful for the community. Again, I talked already about National Character and Nanocharacterization Lab which is addressing the use of nanomaterials for biomedical application and of course, the other fairly large issue and that was touched upon in the morning session, is looking at the nanomaterials characterization from the standpoint of the exposure of the worker where, again, large quantities of these materials will be developed and there are some programs within the institute within

NIH at NIHS to work on that part but I won't touch upon that because of the focus which we have here.

So to close, you will hear the presentation from Scott McNeil in about half an hour and he will be able to discuss the NCL charter and their work in more detail but that brings us to interaction with a number of different agencies in the Federal Government. We are doing that in sync with FDA because we hope that some of this characterization methodologies from NCL will contribute to the characterization of the material in general. We're also working with NIST on physical characterization aspect. Thank you all for your attention.

(Applause.)

CHAIRMAN LUTTER: Thank you very much. Are there questions from the Nanotechnology Task Force members? Rick?

DR. CANADY: I'd like to ask one question. Dr. Desai, it seems like you were making an effort to bring the definition of nanotechnology up so it included you so you could be with us here today. Why is it important to you that the definition includes your product. I mean, you could fly above the radar, as it were.

DR. DESAI: Yeah, I would answer that in

multiple parts. First of all, let me just take the academic approach. I think there's lots of researchers out today, me included, I came from academia initially, and when you do a search of the literature and look at these references which I put up there briefly that, you know, these researchers think that they're working in nanotechnology. I think it's widely accepted that they're working in nanotechnology but here at the NNI we have this arbitrary definition of 100 nanometers which we heard about several times today so the question is now, you know, what field are they working in? You know, is it nanotechnology or is it not. So that's one of the issues. And I think it's not an easily -- I don't think we can come to an answer easily but we need some debate about that.

Secondly, in terms of for us as Abraxene to try to climb onto the nanotechnology bandwagon, I don't think we need to because if you look at the public literature and even from my colleague here, Dr. Grodzinski's presentation, I think we already regard it as a nanotechnology product. You can see several articles out in the literature in the reviewed literature in the public lay press. So I don't think that's really the issue. But as some of the earlier people mentioned, you know, labeling and defining a

product is important from the perspective of the doctor, from the perspective of the patient. So I think that should be clear and if this arbitrary definition of 100 nanometers does not allow us to label it appropriately, then I think we need to discuss that.

DR. DIWAN: I have a little bit of addition to that. What Neil Desai here had said was a very important point, that is a real standard manufacturing standard for sterile injectable materials and that can be a useful cut off for what you call nanomaterials because it is a standardized test.

DR. SIMAK: Jan Simak, Center for Biology. I have a question for Dr. Desai. Could you comment on your approach on immunologenecity assessment in your albumin track particles?

DR. DESAI: Yeah, I think we can talk about it in general terms. Typically, these drugs, because they are cancer drugs, are given repeatedly you know, in the patients, for example, week after week or every three weeks, for multiple, multiple cycles, and we've never seen any problem of immunogenecity or antigenicity, which we believe is because we do not use albumin that is denatured in any

form. We use the native albumin. And if you start cross-linking the albumin with chemicals and things, I think you might run into problems but we don't do that.

DR. HOWARD: Paul Howard, at the point of sounding repetitively redundant, thank you so much for showing the distribution of the particles from the hundred or so nanometer size down into the smaller particles. It brings up a point that characterization in these materials in the biological matrix is of critical importance because it may be nano or not nano on the outside, but once it's interactive with the body, that is where the toxicologist going to be concerned and that's where we need to know is what is the particle size in the body.

DR. DESAI: Thank you.

CHAIRMAN ALDERSON: At the expense of also being redundant, I have a question I want to ask this panel and recognizing that it's -- the bias that you represent is here, and also it was this morning the opposite extreme, but I want to ask it. In terms of the battery of tests that FDA requires in this case for drugs, and I think Dr. Desai answered this but I want to ask the other three, is a battery of tests required for a drug approval? Do you feel at this

point in time, based on what we know relative to the toxicity of nanomaterials? Is that battery of tests adequate to show safety?

MR. BUCKLER: I would say yes. I think with the current guidelines, that we're dealing with and the interactions that we've had with the agency in two divisions, I think they do -- the battery of tests that are required are very adequate.

DR. DIWAN: I believe they are adequate. Sometimes they may be overkill. For example, the current changes in the guidelines for antiviral products which are moot, a lot of information about mutational and molecular biological type of studies that were traditionally conducted after filing and IND back before filing an IND, that, I think, is an overkill especially when we already know theoretically that mutant substance suppression is going to be a primary byproduct of the technology we are developing. Although proving it is important, it may be something that can be done at a later stage, after filing the IND application.

DR. GRODZINSKI: Well, these gentlemen developed the technology, so I think their opinion is relevant.

DR. DESAI: Do you want me to comment

again on that?

CHAIRMAN ALDERSON: Absolutely.

DR. DESAI: Well, of course, I think they are adequate but you have to look at what exactly it is we're looking for in these tests and unless somebody tells me otherwise, I believe they're adequate because we look at every single organ system in the body. We're looking at mode of administration. We're looking at how the drug behaves and where it ends up. We're looking at excretion, we're looking at metabolism. I mean, we're looking at everything we can possibly look at. So unless there's some new test that I haven't heard about, I think the FDA is doing very good on that perspective.

CHAIRMAN ALDERSON: With that, we will take a break. Let's plan to be back at 25 till, promptly, please.

(A brief recess was taken at 3:23 p.m.)

(On the record at 3:37 p.m.)

CHAIRMAN ALDERSON: On the record. I think we'll go ahead and get started with this next session. Our first speaker is Deborah Ladenheim, did I get that correct, from Avidimer Therapeutics Incorporated.

DR. LADENHEIM: Good afternoon, ladies

and gentlemen. My name is Deborah Ladenheim and I work for Avidimer Therapeutics which is based in Ann Arbor, Michigan. I'd like to talk a little bit this afternoon about nanotechnology drug delivery devices that are based on dendrimers. You've already heard a little bit about dendrimers already today. So I'll give you a little bit more detail about how we use the dendrimers backbone to target both drugs and imaging devices. The technology that I'm going to talk about today was discovered and developed at the University of Michigan at Nanotechnology Institute.

I don't know whether you need an overview for an eight minute talk, but briefly what I'd like to describe firstly are the general requirements of targeted therapeutics so that you can see why dendrimers are well-suited to talk to drug delivery. I'm then going to talk about how the dendrimers backbone is used to make what we called Avidimers, these for drug delivery, specifically cancer drug delivery and tumor detection. I would like to describe why Avidimers are very beneficial for drug targeting and finally, to talk about general regulatory considerations for nanotechnology-based devices. We've heard many of these earlier today, but I would still like to talk briefly about them.

Targeted therapeutics need to exhibit a number of important characteristics, assuming that they are either ingested orally or injected intravenously. The drug if it's going to exert its action outside of the vasculature needs to be able to diffuse out of the endothelium. I think there is some controversy about how small these particles need to be in order to diffuse out of the vasculature, but around 20 nanometers seems to be generally accepted to be small enough to get out of the vasculature and the particles can then diffuse into a tumor cell or into the tissues to exert their actions.

Following diffusion out of the endothelium, the targeted therapeutics need to recognize their target cells and bind with high avidity and specificity to these cells. Once they've targeted the cells, they then need to internalize the therapeutic and reach their site of action which may either be within the cytoplasm of the cell or from some drugs they also will need to reach the nucleus.

One of the main values of targeted therapeutics is that they avoid normal tissues, so the targeting part of the molecule must be specific to the tumor cell. The therapeutic must also remain intact until it reaches its intended site of action and it's

important that the carrier that is used to be stable and biologically inert.

I would now like to talk about the dendrimers-based structures and the Avidimers and how they respond to these challenges of targeted therapeutics. This schematic shows the scaffold that we use called "a dendrimers" for our technology. The dendrimers is composed of an ethylendiamine core to which are attached layers of polyamidoamine polymer which act like layers of an onion. So they are attached sequentially to a core to produce a dendrimers structure.

There are also active surface groups on the dendrimers and, for our work, we are using what we're calling "generation five dendrimers" which have five layers of the polyamidoamine groups and these are approximately five nanometers in diameter. The size of these G5 dendrimers approximates the size of hemoglobin and this allows them to be transported easily within the blood. The size is also useful because when we add constituents to the surface of the dendrimers scaffold the size of the molecule still remains small enough for it to diffuse out of the plasma and into the tumor cells.

This cartoon shows how the dendrimers are

converted to what we call Avidimers and the cartoon at the bottom shows targeting ligands which I think look like purple mushrooms. They're not really like that. And they will seek out specific tumor cells based on surface receptors. We can also attach drugs to these dendrimers or imaging agents as well.

You may have already seen this slide in the previous presentation. This is a computer model of a trifunctional Avidimer that we have been using in our labs. The black shows the G5 PAMAM dendrimers scaffold. The folic acid is what we use to target these dendrimers to folic receptor positive cancer cells. We have about five folic acids per dendrimers.

The methotrexate is a dihydrofolic reductase inhibitor and is a cytotoxic agent that we're targeting to the cells. We have about five/six methotrexates per dendrimers. We can also attach imaging agents such as fluorescein to the dendrimers in order to visualize the tumors, to see the tumor size and shape.

So the value of Avidimers for drug delivery, firstly, we've been able to make them with uniform size and shape. They are truly nanoscale. I don't want to get into the debate about what is and what is not nano but I think five nanometers should

probably qualify. But it allows them to move in and out of the vasculature.

The targeting is affected by the ligands on the surface. The folic acid is attracted to the folate receptors on the tumors and the attachment of multiple methotrexate drug molecules allows an increased drug concentration within the cell. An improved therapeutic index is affected not only by improved efficacy by targeting the methotrexate to the cell but also by avoiding systematic toxicity to normal tissues and we believe that we have the potential for faster drug development as we're using approved drugs and well characterized targeting ligands.

Regulatory considerations, we've heard a lot about most of these already today. The characterization and heterogeneity is a problem from a practical perspective and I was delighted to hear that the NCI is developing a lab that's going to help us to characterize our products. Environmental impact is always an issue and I do agree that we should be developing nanotechnology expertise within the FDA to assist the reviewing divisions in understanding the challenges of nanotechnology.

Public scrutiny, I was amazed to look at

the Amazon.com and find this book, *Nanotechnology for Dummies*. The public knows about us. They want to know about us and it's for us as a regulated industry along with the FDA to teach them how good nanotechnology therapeutics can be. Thank you very much.

(Applause.)

CHAIRMAN ALDERSON: Thank you very much. Our next speaker is Dr. Bernie Liebler from AdvaMed General.

DR. LIEBLER: I'm going to take advantage of not having slides and being six time zones out of sync and stay right here. First, I would like to thank the FDA for having this meeting and for providing an opportunity for us to speak about this.

AdvaMed is the world's largest trade association representing manufacturers of medical devices, diagnostic products and medical information systems. Our members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent of the products purchased annually around the world.

The range of medical devices currently available for use in the diagnosis and treatment of disease conditions is extremely broad both in terms of

application and physical size and we expect that eventually nanotechnology-based products will be integral to a similarly broad spectrum of devices whether in materials used in large capital goods or in the components of very small products like stents or possibly even as medical devices themselves.

The nanotechnology aspect of a medical device could appear as the principal device component, a subsidiary component that supports the principal mode of action or it could appear in the processing or treatment of a device component in a manner to alter or otherwise improve the performance of the component by, for example, facilitating sterilization, increasing tensile strength, improving wear characteristics or electrical conduction or resistance characteristics. It could be, for example, that someone could develop a nanoparticle-based electrolyte for an improved pacemaker battery and that's purely thrown out. I don't know of anything like that.

In some cases, the nanotechnology aspect of the product will provide the most significant feature of the device's performance. In others, it will provide a slight enhancement to an already effective product. It's difficult at this point to predict with any accuracy where the bulk of the

nanotechnology-enabled development will occur. Medical device and diagnostic technology moves much too quickly to make accurate predictions particularly with respect to the application of an entirely new method and entirely new technologies.

Currently, for example, diagnostics are being miniaturized and we anticipate that certain diagnostics will be implanted routinely in the future. It's very inviting to presume that nanotechnology will play an important role in accelerating or sustaining this development. Similarly, combination products are proliferating. The product category appears to offer particularly fertile ground for the incorporation of nanotechnology materials into novel therapies and novel diagnostic devices.

Given the very early stage of current expiration and development activities, nanotechnology represents a difficult area in which to obtain precise information from manufacturers regarding possible products. Breakthrough information would tend to be considered proprietary as it could provide a company with significant competitive advantage.

For example, a coating that would reduce the coefficient of friction in a total hip replacement thereby extending the potential expected lifetime of

this prosthetic would provide the manufacturer with an enormous marketplace advantage. Even though such market advantages tend to have fairly short lifetimes, manufacturers pursue them vigorously as they can make or break a small company. I think we heard about that earlier from our previous panel. These are small companies with significant breakthroughs.

Medical devices markets rarely if ever behave the same as the markets for the so-called blockbuster drugs that can create multi-billion dollar, long-term revenue streams. Medical device marketplace is tight and minor distinctions can create major although relatively short lived effects.

Within this context, there are several aspects we need to address effectively. Ultimately the questions are how should and how will FDA regulate products that are nanotechnology-based that contain components that are nanotechnology-based or are produced using nanotechnology-based processes.

AdvaMed believes it is in the best interest of the industry and the patients it serves to work as closely and openly as possible with FDA in exploring nanotechnology, its scientific and engineering characteristics and its regulatory aspects. We also believe that it would be important

for the agency and the medical device industry to work together and in collaboration with other industries interested in this area to educate the public about the relative benefits and risks of the coming nanotechnology-based products.

Earlier today, we heard about the Woodrow Wilson studies and I won't go into them again. I was planning to, but I'd like to read two quotes from Hart Research who conducted the surveys. "The concurrent lack of awareness of nanotechnology presents an opportunity for the government and industry to establish confidence in nanotechnology-enabled products." They also said, "Now is the time to focus on increasing public awareness and understanding of nanotechnology and establish a level of trust that nanotechnology's benefits will be realized and the risks will be minimized."

We also understand that some parties and we've heard this already today advocate that FDA establish a separate approval tract for nanotechnology-based or nanotechnology-containing products. We believe this would be the wrong approach for all parties. It would -- Particularly, I speak here for the medical device industry. I'm not referring to other areas of FDA regulated products.

We believe this would be the wrong approach for all parties. It would complicate matters for the FDA and the various industries involved, a result that is rarely an improvement over the status quo. It would also likely delay the introduction of potentially highly beneficial products.

The agency currently has a robust system for addressing new medical devices. The medical device approval processes, both 510Ks and PMAs are extremely well understood by all parties and they provide ample opportunity for appropriate examination of any nanotechnology application relevant to or part of a new medical device.

I have enough time to say that here I'm realizing that I'm almost anticipating your question about what should be changed then. I hadn't thought about that at all, but in anticipation of your asking it again, as I said devices are all over the place. They're not quite the same. There's more uniformity clearly to drugs or biologics than there is to the device industry and the current process, particularly the PMA process, requires a lot of consultation between the industry and the agency to decide on what tests will be used, you know, what will be presented, how the clinicals will be run and I think that's the

perfect opportunity for addressing any nanotechnology aspects of the process.

It's already there. We already need to consult with the agency before we hand them -- I mean, we don't just create an application or create a 510K, flip it over the door and hope that it comes out okay at the other end. There's a lot of talk in advance and I think all of that talk leads to the ability to look at all issues, nanotechnology clearly being one of them.

We recognize that we need to work closely with FDA to ensure that agency personnel are fully prepared to meet the challenges introduced into this well-known system by new technologies that may require a fresh way of looking at old things. We are still learning and we are sure that FDA staff is also still learning. We can move along the so-called learning curve much faster and much more effectively if we move together. Thus, we are offering to work with the agency through continued discussion and information exchange including formal instruction at our companies or at FDA facilities. We at AdvaMed are also willing to work in partnership with FDA and other regulated industries to educate the public about the potentials and the pitfalls facing us as we pursue innovation

through the use of nanotechnology.

New technologies and novel paradigms can sometimes be delayed or rejected for reasons that appear to be mere whim. There is usually a more fundamental issue underpinning such decisions, lack of information or inadequate or incorrect information. We believe that we all have a collective duty to ensure that the public has adequate and correct information on which to base choices related to nanotechnology and by the way, all other technology. An informed public will allow us to work effectively to improve our health care system and to achieve the goal of a longer lived and healthier public. Thank you.

(Applause.)

CHAIRMAN ALDERSON: Our next speaker is Scott McNeil of Nanotechnology Characterization Laboratory.

DR. McNEIL: Well, good afternoon and let me say thanks as well for the opportunity to discuss efforts in characterization by the Nanotechnology Characterization Lab, also known as the ANCL."

So as Peter mentioned to you, the NCL provides infrastructure support to the alliance in nanotechnology. We've been around for a little over

two years now. When NCI instituted the alliance, they queried some hundred different basic nanotech researchers and asked them the question, what are some of the obstacles that would have to be overcome in order to reach the clinical trials and the clinical realm.

There were three themes that were voiced throughout the country. The first, it was very difficult to compare results between laboratories. A laboratory at UCLA might use different internal standards and different methods than a laboratory at MIT. Next was something that's been voiced several times today and that is we're not quite sure which parameters influence biocompatibility and toxicity. Is it size? Is it surface chemistry? Is it surface charge? And finally, there was definitely a perceived uncertainty in the regulatory approval process for nanomaterials and I do emphasize the word "perceived" there.

So to address these three concerns, NCI instituted my laboratory, the NCL. The NCL provides preclinical characterization of nanomaterials that are intended for cancer applications. It's a national resource. It's a free resources that's available to researchers in academia, industry or government and

that includes researchers that are not necessarily being funded by NCI.

Once a particle or strategy comes into NCL for characterization, it's subjected to a three-phase assay cascade. The first is physical characterization where we collaborate very heavily with the National Institute of Standards and Technology. NIST has the expertise in spades and the equipment in spades to look at things like size and size distribution. Next is in vitro and finally is in vivo characterization and throughout this, we're collaborating with the FDA on the scientific and policy level to make sure that the characterization that we subject the material to is in line with the IND application.

The NCL is a formal collaboration between NIST, NCI and FDA as you heard from Piotr's talk earlier. We're often asked how is nanotechnology different for preclinical characterization. Why do you need an NCL? Can't we just do it the same way like we've been doing drug discovery and development? We're asked that and our answer to that is the FDA requires a certain set of assays or a certain set of parameters to be characterized in the CMC portion of the IND, the Chemistry Manufacturing and Control's portion of the IND.

But if I present to you a GC tracing, a gas chromatograph trace of a multi-functional nanoparticle, that GC trace is going to be very ambiguous when you think about a particle that has a targeting agent, an imaging agent and a therapeutic on it. So to address these same parameters with nanotechnology, we use a different battery of instrumentation to get at the same issues. So at the NCL you'll find many of the old Legacy instrumentation, but you'll also see instrumentation such as atomic force microscopy, capillary electrophoresis, field flow fractionation. See me afterwards and I'll be happy to elaborate on how we use these tools and under what conditions and what algorithms do we follow to figure out which instrumentation to use.

You hear talk about surface activity relationships. So I just want to share with you one or two examples of some of the trends that we're seeing at NCL. To the topic of transparency, any data that's generated by the NCL will be publicly disseminated roughly three months after we disclose it to the vendor. The data that you're seeing here is from commercially available products. What you're seeing on the upper left are dendrimers with roughly

the same molecular weight, roughly the same -- It's almost identical architecture.

The only difference between those is the outer surface. The surface charge is different. So for the COOH that would be a negatively charged species under physiological conditions. We see that those particles are fairly neutral, fairly benign. But what happens if we have a cationic particle, that is a positively charged particle, under in vitro conditions, we do see cytotoxicity.

Now it's interesting because you've heard the comment about don't generalize. Now we echo that very, very strongly. We're finding that it's very difficult to generalize and to bend nanoparticles. We see the same results for hemolysis assay. That's lysis of red blood cells. PEG is a neutral species. It's a negative control. PL is polysine. That's a positive control. The OH is neutral species and the NH_2 again would be positively charged under these conditions and we do see hemolysis under those conditions.

But I also need to emphasize that these are in vitro assays done in their test tube conditions and in more than one case, we found that results that we've seen in vitro do not migrate up to in vivo

studies. They do not carry -- We do not see the same results under animal models and we are working very closely with the FDA to identify these SAR studies.

I think I heard Paul Howard say earlier that you really have to characterize material under biological conditions. Here's a specific example. The column on the left are gold nanoparticles. At the top is 50 nanometers and 30 nanometers and we monitor that size by dynamic light scattering. You can see in the yellow that the size reflects fairly closely to what the vendor's claims are.

But look what happens when we incubate those particles in serum, human serum. The size grows on average 45 to 50 nanometers in diameter. We've figured out what this is due to. It's due to optimization proteins that absorb to the surface of the particles. They are not aggregating and we find that it does require an interdisciplinary approach because a material scientist may approach you and say the size is 56.000 nanometers, but in fact as soon as that's introduced into a biological matrix, we see an increase in size. So just for any reviewers in the audience, just be aware of that particular parameter.

So in summary, we are a form of collaboration between NCI, FDA and NIST. There are

many different sets of tools and equipment that may be required for nanotechnology. We believe that the parameters are similar to the drug industry and device industry and we do need to have more thorough tests on what parameters influence biocompatibility and toxicity. Among those are going to include size, surface chemistry and we are actively conducting SAR studies to elucidate what's important for biocompatability and again avoid generalizations. With that, I'll thank you.

(Applause.)

CHAIRMAN LUTTER: Thank you very much. Do any members of the task force have questions to pose to panel?

DR. PROVOST: Hi. I'm Miriam Provost from CDRH. I have a question for Mr. Liebler. I was wondering if the device industry had any comment on the idea of disclosing in the labeling of a product that it was made with nanotechnology or that it contains nanoparticles.

DR. LIEBLER: Miriam, I missed part of that.

DR. PROVOST: I was asking about whether you had any comment on if FDA were to require that device manufacturers put on their labeling that the

product contains nanoparticles.

DR. LIEBLER: We haven't discussed that at all but again, it's the typical labeling question that comes up when you're discussing your approved product and I don't think that would be a major obstacle for the industry. In fact, I think in many cases since depending how you're using nanotechnology you may be using that as a marketing edge you would probably not mind having it in your labeling.

CHAIRMAN ALDERSON: Mr. Liebler, I -- You escaped part of my question, but I have one that's a follow-up to it and this relates to 510Ks. Do you feel that the current approach to testing product that's a 510K as compared to the testing that was on the predicate is appropriate?

DR. LIEBLER: Well, I think that over the years the amount of testing being required on the new device as compared to the testing that was done on the predicate device has been increasing and I would be very surprised if someone came in with a nanotechnology improved, so to speak, a product compared to a predicate device that they would not have to look at those aspects.

DR. CANADY: Rick Canady with the Office of the Commissioner. Dr. Ladenheim, you mentioned

that environmental concerns were one of the issues that raised at the end. I think it was your last slide or at least research with regard to that. Do you have a sense for how persistent the dendrimers are that you use?

DR. LADENHEIM: We haven't done any work on looking at the environmental impact of dendrimers as yet, but I think it's one of the issues that we as an industry as well as the FDA should be really looking at closely to see what does happen to all of these kinds of technologies when they get into the environment. So we don't have any data. No.

CHAIRMAN LUTTER: Please join me in expressing thanks for this panel for their enlightening remarks.

(Applause.)

CHAIRMAN ALDERSON: We have two more speakers for our next panel. We need one of those up on the stage. Paul Toskiso, is he here? Dr. Lutz, you're the panel.

DR. END: Good afternoon, ladies and gentlemen. The end has come to you unfortunately not yet for the whole workshop and for me only in five minutes or let me say in eight minutes. My name is Lutz End, End being a family name. I'm the head of an

R&D group within BSF. I'm heading the formulation that is the galenx for our fine chemicals, mainly catering to the animal nutrition and human nutrition industry.

I will talk today about nanoscale formulations of health ingredients. Health ingredients are products like vitamins and carotenoids which are proven by clinical studies to have health effects, health effects on humans. They are not therapeutic and they reduce the risk of diseases. As they are not therapeutic, we cannot claim that benefit in the risk/benefit consideration, of course. We are looking into foods and dietary supplements. The subject of this presentation will be BSF products, the fat soluble vitamins A, D, E and K, carotenoids, PUFAs as polyunsaturated fatty acids and co-enzyme Q10.

Nanoparticle formulations of health ingredients have been known for a long time. If we look into history, carotenoids are formulated this way since the `60s. The main reason for formulation is the bioavailability. Carotenoids have a zero solubility in water, several orders of magnitude less than normal pharmacists would say. It's really na-da. Co-enzyme Q10, it's also bioavailability and this has been marketed since the `90s. Vitamin A is mostly

stability because you need to microencapsulate this sensitive molecule against oxidation and such has been marketed since the `60s. Vitamin E, it's mostly the composibility (sic). Vitamin E is an oil which you cannot easily formulate obviously into a tablet. You have to make powders out of it that you can make hard tablets and such has also been marketed since the `60s. If you look into Vitamins D and K, it's mostly stability, microencapsulation, yet again 30 years and longer. And PUFAs it's the stability through encapsulation and here these are marketed since the `80s and `90s.

We don't want to go into the discussion which size is nano and which is not. We went by the old definition. All the years we've said we have carotenoid nanoparticles. Now we cannot come and say we don't have because they are bigger than 100 nanometers. At any rate, you will see some of the particles are because we have particle size distributions smaller than 100 nanometers.

We would rather say the distinction is it something which we can use in food and dietary supplements or which we can use only in other areas because some of the ingredients are not approved for food. If you look at the left side, then if you look

into persistent coating like really persistent nanoparticles which are loaded with vitamins and carotenoids, then we consider such for the time being as exclusively pharma because the vehicle would not be approved.

If you would go into drug targeting, let's talk about vitamin targeting, then there is something that we don't see for decades to come. So there's no reason to talk about it. This is highly invasive. The vehicle would also go into the bloodstream. So what we talk about is mostly solubilisates, emulsions and suspensions which are encapsulated.

What products do we actually offer. We have powder products which are in the range of millimeters, 0.3 millimeters, fairly coarse powders. These encapsulate in a matrix, the nanoparticles, which are several orders of magnitude smaller. This you see on the lefthand side. The nanoparticles are released, if you use them for a beverage during the application, at the beverage manufacturer or as part of ingestion in the stomach.

When the nanoparticles are released and all of them are coated as we've seen before by a hydrocolloid, this is gelatin. This can be casing. This can be modified starch and what we indicate here

are typical sizes, 300 nanometer roughly overall size smaller than the powder. The whole thing is in a way comparative to instant milk powder when you have reconstituted milk because if you homogenize milk you will have also very small droplets in your milk and the way of production it's just the other way around, spray drying or a similar procedure.

Our nanoparticles cannot exist freely, neither in water or in air. If we make a thought experiment and would extract a nanoparticle, in the case of Vitamin A and beta carotene and carotenoids, we would have spontaneous combustion. They cannot survive. They oxidize right away. Of course, we have to consider occupational hazards the dust of these powders. Vitamin A is a fairly toxic, not toxic, but a very potent vitamin and you cannot expose everybody over a long time.

We put much work into elucidating the structure of nanoparticles. As an example, I give you here only some electron photographs, electromicroscopy photographs, where we contrast the cause, in this case the beta carotene or where we can contrast the colloid protecting the nanoparticles, in this case gelatin.

This cannot be taken to assess the size of

the particle because what you see is not what you get as opposed to computer software. Because what you see here is the most common particle size by number, not the most common particle size by volume. If I would add just one particle which is double the size of this one, I would shift the average particle size well beyond the 100 nanometer threshold we talk about in nano.

We published some more literature. I will take this as one example. So we are very experienced in determining and characterizing the structure and the properties of nanoparticles.

To a certain extent, we mimic nature. Here you see carotenoid-rich food and in many of these, the carotenoid is actually stored in nano-crystallites for the very reason is that it is absolutely nonsoluble in water. Even in fat, you will see only very small solubility. So it must somehow aggregate and form crystallites.

If you look into the resorption process, then I show here roughly to scale what happens in the stomach. Here you see one of our nanoparticles in the range of 300 nanometers. What you see here is a mice cell made from bile acid which is in the range of 10 or so nanometers. So NICHA uses nanotechnology

obviously as well. The key issue which we address with our products which increases the bioavailability is the facilitated transfer of the carotenoid or of the Vitamin A for instance from the nanoparticle into this mice cell so that it can then penetrate the intestinal wall and go into the body.

If you see comparison with, for instance, in the case of lycopene with formulation based on natural lycopene, then we arrive at similar bioavailabilities. Here you see a continuous intake of lycopene, 50 milligram per day over 18 days at 28 days, and then you see the serum levels for lycopene. Our lycopene, ten percent achieved a similar bioavailability compared to formulated to moderate extract.

You can go even smaller to solubilisates which became accessible only after polysorbates were approved for foodstuffs as well during the `90s. In this case you can observe some additional increase of bioavailability.

The toxicology of our products is well established. Safety studies especially our toxicity studies are performed with formulations as marketed. Actually nonaccommodation is a prerequisite for resorption. So you can test toxicity only with

nonaccommodations. And our GRAS modification also rely on such data and very high tolerance level were observed for carotenoids. In the case of vitamins, we're not looking into now.

(Applause.)

CHAIRMAN LUTTER: Does the task force members have any questions of Dr. End?

DR. CANADY: I had just one question of clarification. The data that you presented on both bioavailability and toxicity, that's all been published or it's publicly available.

DR. END: Much of the data has been published, yes.

DR. CANADY: Okay. Was there any data that you presented that was not?

DR. END: No, most of them are published and are from scientific publications of the `90s and early 2000s.

DR. CANADY: Okay. So it's well established and it's out there for awhile.

DR. END: Yes.

AUDIENCE MEMBER: (Off the microphone) How do you encompass the stability of the polyunsaturated --

DR. CANADY: We're actually holding

questions for the task force at this point, sir. Sorry.

CHAIRMAN ALDERSON: Okay. If there are no other questions, we'll move to the open session and Dr. Lutter.

CHAIRMAN LUTTER: My understanding is we've had three people sign up to use the open mike, four people sign up to use the open mike. So since there's only four, we'll give each of them eight minutes and maybe the thing to do is for them to sit here and since there are four people we can just bring up, come up to the podium. And, Rick, do you have a list of names?

(Pause.)

CHAIRMAN LUTTER: We have four speakers and we'll proceed as announced in the order in which they signed up unless somebody is not here. So we'll have Sean Murdock first and I think he's not here. Barring that, we'll go to Igor Lunkov and if Sean appears before we're done, then he may speak at that time. So, Igor, you have eight minutes please.

MR. LUNKOV: Thank you. It's a pleasure to present and I'm with Intertox Corporation. Intertox is a small company but we have a sizable nanotechnology practice. We support several Fortune

500 companies on assessing the environmental health and safety needs related to nanotechnology. We took up a part in NCI working group helping to establish standards and also we support government agencies. We work for the EPA and actually these slides were developed together with the Army Corps of Engineers and the Army Corps is just starting a sizable program on assessing environmental and ecological risks related to nanomaterials and Jeff Stevenson and Elizabeth Ferguson were part of these slides.

My main points, obviously you've heard enough about uncertainty and problems related to toxicology and structures of nanomaterials, so my first point is redundant. But what I will try to do is I will try to show that current methods and tools that we use to use to deal with uncertainty in other areas may not be applied to nanomaterials and that will lead me to my second point that basically given uncertainty that we have in the current state of the knowledge about nanomaterials, we really need to bring tools designed to deal with uncertainty and the tools that we are suggesting are tools developed in business communities, multi-criteria decision analysis tools, that are basically designed to support making decision in very uncertain situations in the business world and

they are widely used in business communities.

And I spent a fair amount of time, well at least a few minutes, on those and finally my last point, unfortunately I don't think I will have time to go over that but adaptative management and information analysis could help in structuring decision analysis and ultimately help in making better regulatory decisions.

So I think what they will try to do is to address some of the issues that we've discussed and everybody is saying we need to balance benefits and risks, we need to bring together all this information. So I will try to show how you can do that with a couple of tools I'm familiar with.

Again first point, I was part of the EPA peer review panel of nanotechnology. This is some of our peer review panel and I know a couple of my colleagues are here who were part of this panel. So obviously I selected those that illustrate my points. But we had many conclusions clearly. But I would like to say is that current risk assessment experience is for chemical unstable agents and we deal with engineered nanomaterials. We can change the property of this nanomaterials and this is a challenge and also an opportunity. For me, the opportunity here is that

if we somehow structured what we know about toxicity and non-desired effects of nanomaterials we can influence nanomaterial developers and industry. That's actually I see the role of FDA and EPA is really providing feedback to industry about how they should structure productions so they produce benign materials rather than try to regulate after the materials are produced.

Uncertainty and exposure and risk characteristics and dose response is unprecedented, but what we need to do, clearly this presentation today shows that we have immediate regulatory needs and environmental evaluation and decisions are growing more complex and the current risk assessment paradigm may not be appropriate. Why I think that it's mainly given uncertainty current risk parameters are not appropriate, when we talk about uncertainty we talk about model uncertainty, parameter uncertainty and this is simple model uncertainty. You have sera dose and you can fit multiple functions here.

In the case of nanotechnology, we really are not sure about basic mechanism about what's going on, so what kind of model we will use. People are talking about structure activity models and I've done some structure activity modeling for carcinogenicity.

I know that those models are very sensitive and they require multiple databases with very structured and standardized information. How are we going to do that for nanomaterials is a big puzzle for me especially given that all this nanomaterials can be influenced not just by structure but also by functionalization, by coding we use and by all this multiple engineered factors.

So the methods that we have to deal with model uncertainty like combining different models, considering alternative model structures, probably are not going to be too efficient and at least at this stage of knowledge, at least using expert judgment seems to be the appropriate way to go about that and expert judgment will be very influential in model development for nanotechnology. And later on, I will show that expert judgment again should be treated with multi-criteria decision analysis tools.

Parameter uncertainty, well, when we do measurements, we have a range even for well defined parameters, what we are going to have for nanotechnology - sorry for the typos here - but I think it will be quite a mess. Actually just recently we reviewed a reported range of octinal coefficients for PCBs, one of the most widely studied chemical and

we found that in regulatory databases the range is like four orders of magnitude. So those, the values that EPA and other government agency recommend to use in risk assessments four orders of magnitude for PCBs. What are we going to have for nanomaterials? I think it will be even more than that.

So again expert estimate for parameters is probably the only option that we have now. What will be happening when we get all this information and send it to the decision maker. Obviously what we do now is we listen to stakeholders. We all express our judgments and then all this information will be submitted to agencies and obviously a decision makers will be using some kind of ad hoc process to aggregate all this information. It will be difficult and obviously it will be driven by the biases of decision makers and by aggressiveness of stakeholders and that's what we see.

Why it's bad? It's clearly bad because research shows that people are not really good in making complex decisions on the uncertainty and different papers show that individuals cannot make good decisions and other sort of papers show that groups cannot make decisions. So it doesn't seem to work.

So what we really need to do is to develop tools that help to aggregate all this information and provide framework for a decision maker to make judgment. So the tools to do that is multi-criteria decision analysis tools. Basically it looks like comparing apples and oranges, but in fact, the questions that we ask in here is how many apples you would trade for one orange, what is the value of all this factors for decision makers in making decisions.

So I guess, Lutter, that I'm running out of time, but again I have a paper actually that is based on my EPA recommendation. I will be glad to share this view with you if you leave me your business card, but it's also a multi-criteria decision analysis design to deal with situations like that. In my paper, I go through two case studies. One is how to bring together stakeholder judgment political factors with technical factors and this is one on the screen and the second case study that I went through is how to just make a scientific decision when you have multiple testing done on the same nanomaterials and you use something to bring it together. This alternative to weigh the evidence of evaluation that we widely use in areas of risk assessment.

Yes. So this is my last slide that shows

how to bring together different people involved in making nanotechnology decision and different tools to use as a scientist and decision tools that will help to bring all major players within multi-criteria decision analysis process.

And finally, these are my three points again. Thanks.

(Applause.)

CHAIRMAN LUTTER: Thank you. Our next speaker is John Bailey of the Cosmetic Toiletry and Fragrance Association.

MR. BAILEY: Thanks. I'd just like to make a few points based on the presentations today, maybe to clarify a few aspects of the other presentations.

First, I would like to talk about FDA authority. FDA authority I think has been somewhat misrepresented during the day. FDA has the authority to ensure the safety of drug and cosmetics. For drugs, FDA exercises control over all aspects of products either through the OTC drug monograph process or through NDA process that is applied to ensure that such products are safe and effective. This provides for a great deal of open public discussion, submission of data and consideration of the data by agency

experts.

For cosmetics, it's important to keep in mind that FDA may take the same actions as far as they do for other products. This includes the seizure of unsafe or misbranded products, adjoining manufacturer products, warning letters, mandate warning labels, inspect establishments, ban harmful ingredients or limit ingredients, prosecute violators and request recalls.

FDA really does not need new laws. As was mentioned earlier today by Mike Taylor, what FDA needs are the resources to enforce the laws that they have and CTFA firmly supports the allocation of sufficient resources to FDA and we've supported this in the past.

Another aspect is the collaboration between industry and FDA. The cosmetic industry has a long history of strong collaboration with FDA through voluntary self-regulation programs. This includes the voluntary reporting program which establishes a system whereby cosmetic companies can report their establishments, report products, any ingredients that are used in these products. This is actually the first such program ever established by FDA back in the 1970s. So this is a means whereby FDA and actually the industry as you'll find out in a minute can get

information that's important to understanding the ingredients that are used and the types of products that they're used in.

The second program is the cosmetic ingredient review and this may be a program that some of you are not familiar with. But this is a program that's modeled on the FDA Drug Advisory Committee process. It is set up with a panel of experts whose charge it is to review the safety of ingredients based on available data. It's an open public process. It is funded by CTFA but it has within its procedures assurances of independence and this is in part done by being an open public process. It's transparent. It includes representation by FDA Liaison as well as Consumer Federation of America which again models the FDA programs.

It reviews high priority ingredients first. Clearly, there are a lot of ingredients that can be used in cosmetics. The prioritization process started with those most frequently used based on the voluntary registration data working its way down to those that are less frequently used. To date, CIR has completed 1300 ingredient reviews. I think this is more ingredients ever reviewed by any other systematic ingredient review process and is very important to the

industry.

I do want to make one thing very clear and that is it was represented earlier that CIR has only reviewed 1300 ingredients out of 10,500 that are known to be used in cosmetics. That's not true. Based on the frequency of use and what we know about the actual use of ingredients, this process represents about two-thirds of the ingredients used and those that are used at the greatest volumes in finished products. So I think that's an important point to keep in mind.

Another program that's just been implemented or is being implemented and was mentioned by Jane Houlihan of the Environmental Working Group earlier has to do with CTFA consumer commitment code and this is an extension again of the voluntary approach, self-regulation and collaboration with FDA. It provides a mechanism whereby FDA can ask companies for information about the safety or other aspects of the ingredients. It sets up procedures for doing this and a structure for interacting, but FDA can go to a company and ask for information about the safety substantiation for an ingredient. It also for participants provides a commitment that they will participate in a voluntary registration program which provides very important information again about

ingredients, products and how they're used.

Another important part that wasn't mentioned was that the consumer commitment code provides for immediate reporting to the FDA of any serious or unexpected adverse reaction as defined in the drug part of the Code of Federal Regulations. So I think that that's an important part to keep in mind. This information to make a long story short will be maintained in what we call the Safety Information Summary.

Okay. Let's talk about use of nanomaterials and products. This has been presented as pervasive. It's actually very limited. Part of the problem is with the definition and we talked about the process of defining what nanotechnology is and there are pluses and minuses for doing that in a regulatory sense and I won't get into those now.

Most uses are limited to TiO_2 and zinc oxide. These are approved drug active ingredients by FDA. The micronized or nano TiO_2 and zinc oxide have been reviewed and found to be safe by FDA. The products are used according to regulation and they provide clear benefit. Any assertion that these products should be pulled from the market fails to take into account the fact that they do prevent skin

cancer and are very important public health products and that should be kept in mind.

Nanocapsules, this is represented as nanotechnology. I think you can make a good argument that it's not nanotechnology. It's really old technology and it really is lyposomes and I think you could make an argument that these are being miscounted as being included in cosmetic products or personal care products when you see representations of how these are apportioned in the market.

Fullerenes, these are reported to be used in some products. They are not expected I think by reasonable assessment to be toxic when used in topical products and also keep in mind that they must be declared on the label of the product. Cosmetics were the first products that required ingredient declarations going back to the 1970s. If a fuller ring is added to a product, it must be included in the ingredient declaration. So that information is available to consumers or anybody else who wants to find out about that.

I'm coming down to the end of my wire here. The science, I think the science as we've stated clearly supports the safety of nanoparticles. There have been earlier assertions that our press

release is a disconnect with the statement that we submitted to the FDA. If you look closely, our detail statement had to do with pulmonary toxicity to make the point about small is not necessarily harmful. The press release was intended to say that the weight of the evidence for dermal exposure does not present a convincing case. There is a safety concern that these materials are safe. And with that, I'll stop.

(Applause.)

CHAIRMAN LUTTER: Thank you very much. Our next speaker is, and our next and final speaker is, Jay Anderson from Vico Metrology.

MR. ANDERSON: Hopefully, Mr. Buzzer, you won't have to ding me here. I'll make this fairly short and sweet. My name is Jay Anderson. I'm with Vico Metrology. I'm sure some of you have heard of the name. Vico manufactures atomic force microscopes and I actually thank Scott McNeil for finally mentioning that instrumentation that's being used for all the discoveries that we're seeing and discussing here today along the nanoscale technology.

Coming to you as a layman, I'm appreciative of the FDA for holding and having this open forum and having this conference to where we can voice our concerns for the technology and the products

that are out there and especially from what we've learned what the aspects of the nanotechnology in the cosmetic area and other areas like that. It is a concern for me as a consumer. So I do appreciate and look forward to further research by the FDA and for taking this initiative to look into this technology.

Again, as I work with universities and institutions such as this, NIH and FDA and NIST and others, it is important that we really take advantage of the technology that is available. Vico being one of the world's largest providers of measurement tools for this, we do have some novel technology that is really advancing the aspects of being able to do this technology such as high harmonic imaging, fast imaging and imaging at high resolutions that have just not been available in the past.

So if you'd like to learn more about our technology and what we're doing, please let me know. I'll be out in the lobby after the presentation this afternoon and I'd love to talk to you. Thank you.

(Applause.)

CHAIRMAN LUTTER: And then we have an opportunity for Sean Murdock to speak. He signed up first and is taking the spot of the caboose on the train. So welcome.

MR. MURDOCK: Thank you very much. It's always fun to be the last person between everybody and the doorway, but hopefully I will be able to be sufficiently brief and to the point.

First, I'd like to thank the FDA for the opportunity to participate in this forum. We do believe that public engagement is critical not only for building trust that you've heard a lot about today but honestly for improving outcomes and getting to better answers.

As I think everyone has heard today, it's important to keep in mind that nanotechnology is not one thing. It is a collection of technology platforms, materials related platforms, tools related platforms and devices and systems that have a myriad of applications and interestingly much of the discussion today has in fact focused on cosmetics and some of the food-related products. The overwhelming majority of my membership is focused largely on diagnostics, novel therapeutics, energy solutions and electronics applications. But it is an important part for my membership as well.

We in the Nano Business Alliance want to be clear that the nanobusiness community wants to be a good partner of the agency and work closely and

openly. The Nano Business Alliance and its membership has been engaging with EPA as part of its voluntary nanomaterial stewardship program and looks forward to engaging with FDA in a similar fashion going forward.

I think it is important to notice that because of the diversity of nanotechnology and the different nanotechnology applications it's important not to try to create a separate yet one-size-fits-all approach to regulating nanotechnology. These products will need to be regulated on a product-by-product basis that looks at the benefits and risks of each one of those as they move into the marketplace.

One of the things, you know, often in these dialogues we hear a lot about the areas of disagreement and I think some areas of agreement have become very clear. I think that there's broad agreement that it's imperative that the FDA be given the resources to conduct the fundamental science to develop the scientific foundation for the future regulatory environment and in particular, the Nano Business Alliance has called over the past couple of years for increased funding for EHS research and in particular, we focused on the need to develop the foundation for the quantitative structure activity relationship database, if you will. That not only

helps safeguard the safety, but it also drives down the cost and the barriers to innovation going forward. We believe that that's an absolutely critical development and we salute the effort of the Nanotechnology Characterization Laboratory as they move in that direction. We believe it's doing some great things.

Finally, I'd like people to keep in mind that as we invest in the new science and develop new tools, methods and predictive modeling like the QSAR we believe that the existing products on the market are in fact safe and the process and methodologies which have served us well over the past several decades will continue to do so and I think, you know, as you hear the weight of what's been discussed today that has emerged. However, we think it is truly important for the FDA to communicate how those existing processes and methodologies are in fact effective and do protect and safeguard safety to maintain public confidence going forward.

With that, I'd like to thank the FDA for the opportunity and close.

(Applause.)

CHAIRMAN LUTTER: Thank you very much. Since we have only four speakers here, maybe there's a

couple minutes for the members of the task force to ask questions. Subhas has a question.

DR. MALGHAN: Subhas Malghan from CDRH. I think the last speaker mentioned something to the extent of one of the best opportunities to regulate product by product if I heard. I'm wondering if you could explain a little bit more on what you mean by that please.

MR. MURDOCK: Really what we mean is obviously the safety and efficacy isn't determined by nanotechnology per se but in the specific incarnation that is ultimately going to be developed, formulated and brought to market and so it's not a matter of the underlying technology but it's really the specific profile and characteristics of the product that will determine both its efficacy and its safety.

MR. CANADY: If I could ask a question. Rick Canady. Igor, you had a model that it seemed was applicable to situations where you're not generating data de novo to evaluate a product but rather using information that you collect from a various of sources. Is that correct? For example, you would not need a multi-criteria decision analysis approach necessarily to evaluate a drug.

MR. LUNKOV: You may use it when you put

together technical information. When you do any assessment as a technical expert, you use assumption. We call it "weight of evidence" when we do for example carcinogenicity evaluation for a chemical. We have multiple tests and they are not consistent. So you can use multi-criteria decision analysis to kind of formalize your judgments on those issues rather than discuss in like two pages of a document why you decided this way.

You can make your decision, justify it and formalize it so if somebody disagrees she can change it and change weighting of different factors. But obviously the main use of multi-criteria decision analysis is to kind of compliment experimental measurements with expert judgments when you don't have enough of technical information to make your decision.

CHAIRMAN ALDERSON: I have a couple of questions for Dr. Bailey. You can probably anticipate one of them and that's the question I asked earlier about the data sharing issue because that's come up a number of times in presentations about transparency of data and I'd like to know from CTFA's position if FDA requested on a number of nanoparticles that are being used in cosmetics, would that data be available to FDA and the public.

MR. BAILEY: I think CTFA has a history of making data available when there's an identified need to do that. So I would answer that yes. I would also point out that the cosmetic ingredient review is a mechanism whereby published and unpublished data is made available. As Dr. Filbert mentioned this morning, you can't publish negative results. So this vehicle, this method, was set up so that that information could be provided. In fact, most of the information that the CIR reviews is unpublished company studies. So this is all designed to provide the information necessary to make informed safety decisions.

CHAIRMAN ALDERSON: My second question also follows from a number of comments we've heard today and that is regarding labeling. What would CTFA's position be on labeling of cosmetics that contain nanomaterials? Granted we don't know what nanomaterials means right now and how we're going to define it, but let's say we had a definition that would be applicable to cosmetic ingredients.

MR. BAILEY: Certainly, within the ingredient declaration structure, if a fuller ring or a nanotube or something like that is added to the product, it must be on the label now. So that

information is available for viewing within the ingredient declaration. Also FDA has the authority to require warning statements or other statements on product labels when there's a public health need to do so. So if there is a public health need, then I think through the regulatory process that would be the way that the information would be presented and vetted in a public way.

CHAIRMAN ALDERSON: That leads -- That position leads me onto another question. Are you saying that your position would be the only time that you would label something that contains a nanomaterial is if there is a safety issue associated with the use of it?

MR. BAILEY: I can see really no other reason to put it on. I mean if it's not a safety issue then the need for putting on "it contains nanoparticles" or something like that would be -- I just don't think it would be supported and would actually take up valuable label space that could be used for something else.

CHAIRMAN LUTTER: Please join me in thanking these panelists and speakers.

(Applause.)

CHAIRMAN ALDERSON: I have the task of

attempting to summarize everything we've heard today in a couple of minutes. But on behalf of the task force and my Co-Chair, Dr. Lutter, we want to thank you for all of you who took the time to participate in today's meeting. We've heard a lot of information today. A lot of issues have been raised on science and policy issues that obviously FDA is working to deal with.

In August, Dr. Von Eschenbach, our acting Commissioner, charged the task force with determining regulatory approaches that encourage the continued development of innovative, safe and effective FDA-regulated products that use nanoengineered materials. This meeting that you've attended today is the first major task force milestone in carrying out this charge. This meeting is an example of the process FDA follows to ensure transparency and public input into our development of regulatory policy. We are all committed to this approach at FDA.

During the presentations today, we've heard detailed insights on nano-based specific products. We have heard issues on the science associated with these materials and their products. We've heard views on FDA policy. We've heard views on interpretation of the Food, Drug and Cosmetic Act.

And as applied to nanotechnology, these issues are very complex, involving various interpretations of science, policy and the law. And this is often the case for FDA, the input we receive is widely diverse and you've seen examples of that today. FDA's regulation of products containing nanomaterials is just no exception.

We also heard issues on public education on nanotechnology as well as transparency of the availability of data. Recognizing the issues, the Nanotechnology Task Force is committed to ensuring that our regulatory policy is aligned such that the potential benefit this technology has for health care and for consumer and medical products are realized with assurance of safety and efficacy.

The task force will be considering the information the speakers provided today along with all the other available information you and others will submit to our docket. We'll use these in assessing FDA's policy for evaluation of products for nanotechnology.

I want to remind everyone that the docket established for this issue closes on November 10th. I want to encourage all who have referred to published or unpublished data and information to make that

available to us through the docket process. This information is very important to us as are the verbal comments we've heard today both in the presentations and in the responses to our questions.

I also want to remind you that the transcript for this meeting will be placed in that docket shortly for all to use. In that respect, we've had a number of requests for the names and affiliations of the speakers today and that's the place you can get that information once that docket is posted.

But in final, we really value your input and look forward to hearing from you further on this important issue to us. Again, thank you for your attendance today and your involvement and have a safe trip to wherever you're going today. Thank you.

(Applause.)

(Whereupon, at 4:55 p.m., the above-entitled matter was concluded.)

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