

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

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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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 representing the US Office of Science and Technology
2 Policy, of the European Commission and Health Canada.

3 Subsequently, at 10:00 a.m. and ending this afternoon
4 at 4:25 there will be six different sessions of
5 presentations by public speakers who signed up in
6 advance to speak at this meeting. If you haven't
7 already checked in today, please do so at the table in
8 the hall.

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

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

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

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

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

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1 find some restaurants other than the cafeteria within
2 the building.

3 Finally, any member of the public who
4 doesn't receive an opportunity to speak today or who
5 would like more time than is available given today's
6 filled schedule, is more than welcome to submit
7 written comments to the public docket at our website.

8 Written or electronic comments may be submitted by
9 November 10th. Note that the submitted comments will
10 be available to the public, so please do not include
11 confidential business information. I'd like to now
12 introduce the members of the task force, who are
13 sitting the front rows facing the stage. Please stand
14 as I call your name; Dr. Rick Canaday, Dr. Mitchell
15 Cheeseman, Matt Eckel, I think is absent, Eric Flamm,
16 Dr. Flammang is absent, Dr. Steve Fleischer, Dr. Paul
17 Howard, from the National Center for Toxicological
18 Research, Dr. Linda Katz, from the Center for Foods
19 and Safety in Applied Nutrition, David Kelly from the
20 Office of the Commissioner, Mark Kramer, from the
21 Office of the Commissioner, I think, is absent, Pat
22 Kuntze from the Office of the Commissioner, Dr. Subhas
23 Malghan from the Center for Devices and Radiological
24 Health, Dr. Nakissa Sadrieh from Center for Drug
25 Evaluation and Research, Dr. Jeff Shuren, Dr. Jan

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

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

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

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

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

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

25 Although the purpose of the meeting is to

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

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

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

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

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

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

25 Now, in fact, this guidance from the

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

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

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

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

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

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

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

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

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

25 Well, this is just a step, albeit an

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

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

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

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

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

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

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

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

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

25 Well, I see I have just about one minute

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

7 (Applause)

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

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

25 Representatives from Japan's Minister of

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

12 DR. MARTIN: Well, thank you, Norris, and
13 thank you very much to -- on behalf of the European
14 Commission to FDA for inviting us at what we believe
15 is a very important meeting. You will immediately
16 note from my slides we did not trade notes with Celia,
17 that there's a lot of convergence of views in
18 particular with respect to international cooperation.

19 And the other aspect which -- on which everybody
20 agrees is that safety is a prerequisite to the
21 development of nanotechnologies. Finally, I very much
22 look forward to listening to the public, to you today.

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

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1 already mentioned and Celia in her talk. I'll say a
2 few words about the European Action Plan on
3 Nanoscience and Nanotechnologies which was adopted in
4 2005. Then I will mention international cooperation
5 and I here immediately insist on the fact that it's
6 not just governmental or inter-governmental
7 cooperation but cooperation between all stakeholders.
8 Then I have to say a word about corporate
9 responsibility because industry has a major role to
10 play in this area and finally, I'll conclude with
11 steps forward.

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

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

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

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

20 (Laughter)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 And we're also working on - the Scientific

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

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

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

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

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

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

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

25 (Applause)

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

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

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

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

3 DR. KARKAN: I want to thank you for
4 inviting me. It's a pleasure to be here. And I want
5 to thank the FDA team for a very well organized event.

6 Having seen the slides and being the third speaker, I
7 find my slides, some of them are a copy of the
8 European Commission's slides and so I'm wondering now
9 if the Office of Applied Technology actually copied
10 some of your slides because they're identical. But I
11 hope to find something new among my slides that would
12 be of interest to the audience.

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

25 As we know and this is how we see it in

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

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

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

10 And here is a copy of that slide, really
11 what's so special about nanomaterial? If you look at
12 how the property -- do you remember I said size and
13 then properties. This is more related to the
14 property. If you look at how nanoscaling a product
15 can change its property, it can actually be dramatic.

16 If it's insulator turning to nanoparticles can be a
17 conductor. If it's insoluble, it can be soluble such
18 as solvents that are used for drug delivery. If it's
19 opaque, it can become transparent, such as the
20 products in sun screen, and of course, the famous
21 gold. What I will add here to what Dr. Martin said,
22 is that if you look at this piece of gold and
23 actually, we have received some drugs submissions
24 based on gold particles recent to Health Canada, a
25 piece of gold has a surface area. If the same

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

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

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1 If you look at this slide it's showing you
2 actually the worldwide government nanotechnology
3 funding. This is from 2004 and it's from an
4 Australian report. If you look at 2004 and, of
5 course, the United States, the amount of funding of
6 1.6 billion and if you look at -- sorry, I'm using
7 this instead of the laser. If you look at Canada,
8 it's about 200 million. Considering the fact that
9 Canada has a tenth of the United States' population, I
10 think per capita, we're doing fine. It shows that
11 really the Government of Canada is considering
12 nanotechnology as a very important project. We are
13 spending a lot of money both on research and this is
14 governmental funding, both on research as well as
15 health and safety assessment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 (Applause)

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

18 Welcome, please, everybody today. And I
19 have -- our schedule allows for eight-minute
20 presentations. I think you can choose to speak from
21 here at the podium or from there. It might be easier
22 if you speak from here, especially if you have slides.

23 And at the end, there will be a very short
24 opportunity for the members of the task force to ask
25 you questions. So, without further ado, we'll do this

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

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

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

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

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

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

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1 marketing recall authority and voluntary industry
2 activity.

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

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

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

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

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

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

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

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

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

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

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

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

21 Thanks.

22 (Applause)

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

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

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

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

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

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

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

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

10 The CTFA press release and associated
11 reports shared with the FOE report a similar level of
12 technical depth but draws very different conclusions.

13 As in the Friend of the Earth report, there are
14 disconnects between the CTFA's short public statements
15 and the longer technical report. For example, the
16 press release holds that the overwhelming weight of
17 the scientific evidence states that these substances,
18 referring to nanotitania are safe and un toxic, yet the
19 full report from the same organization cites several
20 publications that demonstrate oxidative damage in
21 biological systems from nanoscale titanium.

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

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

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

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

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1 any possible loss to business due to confidentiality.

2 We urge companies to not only make available toxicity
3 and testing data ideally through peer review but also
4 to provide data to support the efficacy of
5 nanopigments compared to comparable organic materials.

6 And finally, non-governmental organizations should
7 continue to monitor the technical literature and
8 highlight areas where more focused research is needed.

9 Data bases such as the one offered by ICON on EHS
10 publications should help and in time will contain even
11 more integrative information.

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

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

3 (Applause)

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

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

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

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

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

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1 toxicity information concerning these materials.

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

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

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1 cosmetics.

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

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

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

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

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

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

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

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

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

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

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

6 (Applause)

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

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

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

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

4 We had participants, government agencies,
5 non-governmental agencies, companies, industry
6 associations, universities, and we find that
7 nanotechnology gets people to react in very distinct
8 ways to nanobenefits and nanofears. Some find it a
9 desirable destination, some find it a gathering storm,
10 some find it awful and terrifying, a challenge and a
11 threat, and others find it a clear and present danger.

12 All are present. We entertained in our group the
13 representations of proponents and opponents of
14 nanotechnologies. We have had that in all of the
15 meetings and we put together a group of people, put
16 them into small work groups where we debated a number
17 of themes relevant to nanotechnologies and standards.

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

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

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

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

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

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

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

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

5 Next, regarding engagement between the
6 public, the scientific community and standard-setting
7 bodies, timing is critical. I should note here that
8 I'm a co-author with a senior research scientist at
9 Shell and it is his point that early engagement is
10 historically put, if you do a history of science,
11 quite unreliable, that the ability to predict impacts
12 at the very early level of scientific discovery
13 doesn't work very well. Partially, the issue is that
14 resource allocators in firms require a series of
15 research statements and then they make go/no-go
16 decisions. The early statements are very, very brief.

17 They are just relevant to whether or not the product
18 or the scientific idea fits with the strategic work of
19 the company but are certainly not yet explicit enough
20 for upstream engagement.

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

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1 engagement alienated the public. It was just looked
2 at as a marketing exercise. Timing, and here's
3 something, perhaps to be considered by business people
4 in the room, it's also critical regarding business
5 competitors and international standard-setting bodies.

6 If you wait too late to get in on the standard
7 setting process, you allow competitors to get there
8 first and that may rule you out, set up competitive
9 barriers and the same point, as I said before, works
10 towards working with international bodies such as ISO.

11

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

22 (Applause)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 Now, we've started running some of these
11 toxicity assays and compiling structure/activity
12 relationships for a well-defined library of gold nano
13 particles. I'm glad some of the introductory speakers
14 spoke of gold nanoparticles, so I won't have to get
15 into that at all. Thus far we have 1.5 nanometer and
16 .8 nanometer core sizes and we have a whole variety of
17 surface functionalizations on them. And using this
18 iterative approach, we are going through and trying to
19 figure out what are the common things when we get a
20 toxic response, what are the common things among those
21 particular materials? So now I want to give you a
22 very specific example, just to illustrate some of the
23 key components of our research strategy.

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

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

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

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1 So size does matter in this case.

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

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

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

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1 nanomaterials and nanomanufacturing initiative.

2 CHAIRMAN LUTTER: Thank you very much.

3 (Applause)

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

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

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

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1 reputation for reliable policy advice and has helped
2 to shape international regulations and expand market
3 access for US products and services around the world.

4 For example, through our membership in the Business
5 and Industry Advisory Committee, that's BIAC, USCIB
6 provides industry leadership on key OECD activities,
7 including critical work now being undertaken by the
8 OECD's Science and Technology Policy Committee, and
9 Chemicals Committee on nanotechnology policy and
10 regulatory activities.

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

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

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

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

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

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

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1 my last point.

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

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

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

12 (Applause)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 (Applause)

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

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

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

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

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

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

25 My primary area of research includes

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

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

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

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

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

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

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

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

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1 clinical chemistry in any of the tissues examined and
2 we looked at 32 tissues. And this is a nanoscale
3 polymer. So generalizations are generally unhelpful.

4 If, however, we loaded that material, the benign
5 nanomaterial, with iron oxide which we know produces
6 superoxide, then the toxicokinetics profile changes
7 but at very high doses. In fact, we saw toxicity in
8 an intact animal, this is an in vivo model, and we see
9 toxicity in the kidney and liver after exposure to
10 these very high levels.

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

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

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1 prevent -- or present adverse health risks. The
2 benefits derives from nanomaterials are far-reaching.

3 For example, NCI has invested in the University of
4 Michigan and other academic centers to develop cutting
5 edge technologies that will change dramatically our
6 ability to detect the earliest stages of cancer and to
7 manage and cure diseases for which the current
8 standard of care is inadequate. The key is to manage
9 the risk while deriving the maximum benefit from the
10 use of these materials.

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

25 That is that the blood/brain barrier

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

10 It would be wrong for us to over-regulate.

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

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

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1 (Applause)

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

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

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

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1 cosmetics, 10 food products.

2 Most of you know that there's a lot at
3 stake here. Over \$10 billion is not being invested
4 annually by the public and private sector in nanotech
5 R&D and here's some of the market numbers and
6 projections in areas that FDA regulates including
7 nanotherapeutics, drug delivery devices and also food.

8 I'd point out the number of nanobased drugs and
9 biomedical devices is, according to some estimates
10 gone up about 70 percent in the pipeline, clinical
11 pipeline over the past year, again, obviously a lot at
12 stake.

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

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

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

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

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

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

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1 marketplace and to be a watchdog.

2 What they expect from industry is honesty,
3 essentially to cut out the hype about nanotechnology.

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

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

25 The converge, again and again, essentially

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

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

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

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

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

21 (Applause)

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

25 DR. TAYLOR: Thank you very much and I do

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 (Applause)

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

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

25 That MOU sets out a number of goals and

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

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

25 The Act requires that the agency using

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

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

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

25 DR. WETTER: Thank you for the opportunity

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1 to present the view of ETC Group. We are an
2 international civil society organization based in
3 Canada and our work focuses on the social and economic
4 impacts of emerging technologies and their
5 implications, especially for marginalized communities.

6 I'm based in ETC Group's North Carolina office.

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

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

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

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

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

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

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

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

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

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

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

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

19 (Applause)

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

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

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

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

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

8 We put together something we call the
9 Tower of Babble which is just a list of what the
10 labels say and it's almost indecipherable. So -- but
11 this -- one of the things that I want to make sure
12 that I emphasize is this is the face that the public
13 is seeing. The public basically looks at the labels.

14 There's nobody in between the public and their
15 interpretation. There's no scientists, there's no FDA
16 officials, there's no EPA officials. There's nobody.

17 This is the face of nanotech. This is what's
18 appearing on the website around the world. This is
19 what appears on the label that comes out of the boxes.

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

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

12 CHAIRMAN ALDERSON: Rick?

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

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

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

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

23 CHAIRMAN ALDERSON: Paul?

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

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

9 DR. PHILBERT: I would continue the heresy
10 insofar as expressing my personal opinion that there
11 is no such thing as nanotechnology as far as the FDA
12 is concerned and that what we need to get a definition
13 on is the interaction between the product and the
14 biology. The NNI has arbitrarily drawn the line at
15 100 nanometers. Does that mean that something that is
16 101 nanometers is no longer toxic. I would suggest
17 otherwise. But that we need to get away from labeling
18 things and get down to the business of hazard
19 identification, exposure assessment and risk analysis.

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

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

25 CHAIRMAN ALDERSON: I have a question.

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1 Putting aside cosmetics for the time being and we
2 could have a debate on the food additive issues that's
3 just been discussed, but let's talk for a minute about
4 drugs, biologicals and devices. And again, getting
5 back to this issue of generalization, that we don't
6 have the correct framework as a generalized statement.

7 And then assuming that you know about the extensive
8 regulatory regime of testing that drugs, biologicals
9 and devices have to go through to get approved, where
10 do we need to change that quote "framework"?

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

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

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

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

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1 pre-market handle that's perfectly satisfactory.

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

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

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

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1 This afternoon we have six speakers, we'll
2 follow the format of this afternoon, I mean, of this
3 morning, so everybody gets eight minutes and then
4 we'll reserve the questions and answer after that
5 time. One other administrative announcement is that
6 at the open microphone session, I believe it begins at
7 4:25, the number of registrants for that is such that
8 everybody will have an opportunity to speak for eight
9 minutes. So I'll make introductions as we go along
10 and the order is alphabetical. So Pascal Delrieu of
11 Kobo Products, Incorporated is first. Thank you.

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

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

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

4 So if we talk about the manufacturing
5 process, in fact, they are different processes that
6 can be used for both titanium dioxide and zinc oxide.

7 I'm not going to describe all this but all of them
8 are basically two-step processes. In the first step,
9 there is a purification of the raw material, whatever
10 the raw material will be. And the second -- in the
11 second step, the crystal or primary particle is grown
12 to the desired size. This second step is made at high
13 temperature and the crystals can be grown to 200
14 nanometers and above to make pigmentary grades pigment
15 or finer than 200 nanometers for attenuation grades.

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

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

16 It can also be said that for particle
17 size, the maximum scattering occurs when the size
18 equals -- the size of the particle equals half the
19 wavelength when particles are uniformly disbursed.
20 That means if you want to attenuate UV light, UVB or
21 UVA light between 290 and 400 nanometers, then, what
22 you really need is particles ranging roughly between
23 100 and 200 nanometers, even larger than that. You
24 certainly don't need smaller particles than that
25 because you don't want to attenuate UVC. It's not

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

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

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

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

5 This table pretty much summarizes this
6 idea of the difference in size where a list of primary
7 particle size in the second column, particle size in
8 the dispersions in the second column and on the right
9 the transparency. Small particle size TiO_2 can make
10 very transparent dispersions and that's what we need.

11 However, this very small particle size will give a
12 product that is -- that will attenuate mostly UVB,
13 much less UVA, and you need larger particle size, TiO_2
14 to attenuate also UVA.

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

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1 same processes are larger primary product pigmentary
2 grades. Small particle size are necessary to produce
3 dispersions that are transparent. Larger TiO₂ can make
4 efficient dispersions against UVA and pigmentary
5 grades too big to scatter efficiently in UV light and
6 are too opaque. Thank you very much.

7 (Applause)

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

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

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

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1 our findings from the systematic evaluation of
2 ingredient labels, directions for use and package
3 details for more than 25,000 products that we're
4 currently uploading into our next annual update of
5 Skin Deep. So these products represent about a
6 quarter of what FDA estimates to be on the market,
7 100,000 products all together. And our search
8 encompassed common nanoscale terms like fullerenes
9 the prefix nano, lipizomes and even the term
10 micronized.

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

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

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

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

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

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

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

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

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

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

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

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

3 (Applause)

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

7 MR. KIMBRELL: Good afternoon. I'd like
8 to say, I'm George Kimbrell, International Center for
9 Technology Assessment. I am an environmental
10 attorney. I'd just like to say to start, I'm going to
11 zip through this at about 20,000 feet. I've got a lot
12 of slides to cover and eight minutes, just like
13 anybody else. But our full presentation will be
14 available both on our website, I think from FDA as
15 well. So when we talk about nanotechnology what are
16 we talking about? Well, there's lots of different
17 bell weathers, yardsticks people use. We talk about
18 \$9 billion in research and development numbers. We
19 talk about the term itself a buzz word, approaching
20 ubiquitous status in median society. We talk about a
21 gold rush on patents for the fundamental building
22 blocks of this technology and perhaps most
23 importantly, we talk about the rapid
24 commercialization.

25 Thousands of tons of nanomaterial is being

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3 So conclusions; number one, learning from
4 the past; I think that we tend to get a sense of
5 cultural amnesia sometimes about these things. I've
6 heard this already today and I'd like to reiterate it.

7 This isn't the first wonder substance or wonder
8 technology that we've seen, asbestos, CFCs, DDT, PCVs,
9 it's an alphabet soup of lessons to learn from. FDA
10 must act quickly but hopes to avoid repeating the
11 mistakes of past regulatory failures.

12 Second, adequate regulation. A framework
13 is needed that protects workers and the environment
14 and the general public from the impacts of
15 nanomaterials throughout their life cycle. And
16 finally, much more robust EHS study, adequate publicly
17 available independent peer reviewed safety studies on
18 the environmental and health impacts of nanomaterials.

19 Much more information about our work, including this
20 presentation and our legal petition is available at
21 our website, www.icta.org. Thank you very much.

22 (Applause)

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

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1 MR. PICA: Thank you. Good afternoon. My
2 name is Erich Pica and I'm the Domestic Policy
3 Director at Friends of the Earth. Friends of the
4 Earth is a national non-profit environmental advocacy
5 organization and we're a member of Friends of the
6 Earth International. Friends of the Earth
7 International is the largest grassroots environmental
8 organization in the world and we have member groups in
9 71 countries around the world. And I'm here today to
10 talk about the nanomaterials, cosmetics and sun
11 screens and our recent report, "Small Ingredients, Big
12 Risks". Friends of the Earth comes at nanotechnology
13 from a precautionary principle point of view. We
14 believe these products should be tested and proven
15 safe before they are out on the market. The problem
16 is, is as George has mentioned in his last
17 presentation, we've had an alphabet soup of bad
18 chemicals and bad products that have entered the
19 market and they have, over 20., 30, 40 years have been
20 recalled and we're still cleaning up the messes.

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

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1 cosmetics, sun screens, as well as personal care
2 products. And so we published a report in May of 2006
3 that did a survey of websites products and we found
4 116 cosmetic, sun screen, personal care products that
5 contain nanomaterials, and this was despite the
6 absence of safety testing and independent of
7 regulation.

8 Of the 116, there's 71 cosmetics products,
9 23 sun screens and 22 personal care products that all
10 contain nanoparticles and this is a little bit lower
11 than the Wilson Study and what Jane has come up with
12 but, you know, there are all conservative numbers. I
13 think there's a lot more out there than what we know.

14 So our methodology, we looked at both the
15 manufacturer's labels. We looked at what retailers
16 were claiming as well as other claims to see if we
17 could find nanotechnology. The problem is -- or
18 nanoparticles. The problem is that there's no real
19 standardized function or way that these are all talked
20 about on the label. So it's a very difficult research
21 product to have.

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

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

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

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1 levels have killed human liver cells.

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

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

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

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

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

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

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

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

9 (Applause)

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

13 DR. ROBERTS: Thank you, Mr. Chairman.
14 Good afternoon, everybody. It's a pleasure to be
15 here. I want to thank both the FDA and the CTFA who
16 encouraged me to come over and speak to you today. I
17 hope you can understand me with my Australian accent.

18 If you've heard Steve Irwin, perhaps you will
19 understand me. I come from Queensland, where he came
20 from and of course, you probably know, that's the sun
21 cancer capital of the world. We have the highest
22 instance of melanoma and one of my other areas of
23 interest actually is melanoma. So one of the comments
24 I'll make is I have an interest in sun screens and
25 skin absorption and I think we need to put this in the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 (Applause)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 (Applause)

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

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

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

6 MR. DELRIEU: Well, the pigments that they
7 use as sun screen products are usually surface coated.

8 So there are different surface coatings. It's not
9 only -- in fact, to reuse the activity of the pigment.

10 It's also to ease the formulation. But yeah, they
11 are -- most of them are surface coated.

12 DR. CANADY: Most of them, thanks.

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

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

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1 would become available through that process.

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

4 DR. SANTAMARIA: Pardon me?

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

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

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

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1 agglomeration, that would be very helpful.

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

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

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

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

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

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

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

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

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

6 It is similar to the NNI's definition and
7 that of the FDA's informal definition on their
8 website. I do think there are some common ground
9 where people agree on the issue of definition and that
10 has to do with the fundamentally different chemically
11 and physical properties of these materials. So on the
12 one hand, I recognize it's a difficult issue but China
13 certainly has agreed on sanction and official
14 definition for nanotechnology and related definitions.

15 I don't see where we can't and I don't see why it
16 should stop us going forward.

17 MR. PICA: I agree with George's comments.

18 I would just add that we need the definitions for the
19 labeling because there is a desire, I think, and these
20 are the responses that we're getting from our members
21 and even the conversations that I'm having with
22 companies that are including or they are trying to
23 evaluate if there's nanoparticles within their
24 products themselves. We need at least some sort of
25 definition. We can say look, whether it's 100

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

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

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

16 CHAIRMAN LUTTER: Thank you.

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

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

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

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

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

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

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

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1 then delivers the payload to a specific area.

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

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

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

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

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

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

21 (Applause)

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

25 DR. DESAI: Thank you very much, Mr.

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

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

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

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

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

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

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1 get steric-stabilization that keeps these
2 nanoparticles stable.

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

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

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

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

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

4 What we were required to do as a part of
5 the approval is an extensive battery of pre-clinical
6 tests that compared Abraxene to Taxol. So now you're
7 asking the question, does a nano-drug impart and
8 untoward toxicity as compared to a conventional drug?

9 So in this battery of tests, we did intravenous
10 toxicology, looking at multiple organ systems. We
11 looked at bio-distribution, metabolism, excretion,
12 reproductive toxicology, tumor efficacy studies and
13 studies of mechanism of transport and several others.

14 And so far we have also tested more than
15 1,000 patients in carefully controlled clinical trials
16 looking for, of course, efficacy but also any untoward
17 toxicities and then since approval, more than 20,000
18 patients have been treated with Abraxene and I'm happy
19 to say that there was no new or unique toxicities that
20 were seen with Abraxene that were any different than
21 that reported for conventional paclitaxel or Taxol.
22 So what I could say from this is that currently we
23 believe that the FDA has adequate procedures in place
24 at least as far as nanotechnology based drugs go, to
25 insure the safety and adequate testing of these

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1 products.

2 Just switching gears quickly on the
3 definition aspect, we've heard the one to 100
4 nanometer definitions. If you look at published data,
5 you see that of 152 abstracts recently cited, almost
6 80 percent actually talk about nanoparticles that are
7 greater than 100 nanometers, not less than 100
8 nanometers. There's other drugs that we're working
9 on. Some of them are less than 100 nanometers. Some
10 of them are greater. So the question is, what is the
11 nanotechnology definition to apply.

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

23 Thank you very much.

24 (Applause)

25 CHAIRMAN ALDERSON: Our next speaker is

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1 Dr. Anil Diwan from NanoViricides, Incorporated.

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

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

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

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

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

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1 so far is by choosing different ligands, we can create
2 a broad spectrum drug such as against all influences.

3 We can create nonospectrum drug which we call group
4 specific against the highly pathogenic influenzas.
5 H5N1, the current influenza trait is one of those
6 special cases of high path and then there are
7 additional cases that are coming up. So we have
8 created a filter kind of mechanism here and then we
9 created another one which is extremely specific for H5
10 and one that's strain specific.

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

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

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

7 NanoViride is made specifically to H5N1 is
8 at about 20,000 which is about 200 times superior in
9 efficacy. So we are seeing extremely high efficacy
10 levels. We also have not seen any concomitant safety
11 problems, toxicity problems. We have run one
12 preliminary safety data with mouse studies. All of
13 these are injectibles and only on the on the polymer
14 and in that we have not seen any toxicities. We did
15 13 different issues as well as microscopic
16 examinations and blood pathologic. So it is general
17 consensus today and has been for awhile that
18 nanotechnology can develop very good high efficacious
19 and molecular safe drugs. And we believe that by
20 having the broad spectrum versus narrow spectrum type
21 of ligand tuning we can potentially reduce mutation
22 frequencies for two reasons.

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

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

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

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1 you've been using flexible polymers which are very
2 defined but non-particular materials. These are
3 single molecular chains but they have heterogeneous
4 molecular sizes, there is a molecular size
5 distribution. You saw even in the case of Abraxene
6 there is a size, particle size distribution. This
7 cannot be avoided in these kind of chemistries. There
8 are molecular rate averages and in the distributions
9 that can be characterized. Ligand attachment cannot
10 be quantified because no chemical reactions are 100
11 percent complete. And you don't have the ability to
12 purify only 100 percent complete type of chemistries.

13 Same problem as with Abraxene. So we don't see that
14 as a major issue. We believe that the links probably
15 are there that can be applied further.

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

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

13 Thanks.

14 (Applause)

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

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

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

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

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

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

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

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

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

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

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

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

25 But looking at the next step, which will

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

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

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

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

14 (Applause.)

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

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

25 DR. DESAI: Yeah, I would answer that in

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

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

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

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

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

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

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

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

16 DR. DESAI: Thank you.

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

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

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

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

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

25 DR. DESAI: Do you want me to comment

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1 again on that?

2 CHAIRMAN ALDERSON: Absolutely.

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

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

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

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

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

25 DR. LADENHEIM: Good afternoon, ladies

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

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

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1 Targeted therapeutics need to exhibit a
2 number of important characteristics, assuming that
3 they are either ingested orally or injected
4 intravenously. The drug if it's going to exert its
5 action outside of the vasculature needs to be able to
6 diffuse out of the endothelium. I think there is some
7 controversy about how small these particles need to be
8 in order to diffuse out of the vasculature, but around
9 20 nanometers seems to be generally accepted to be
10 small enough to get out of the vasculature and the
11 particles can then diffuse into a tumor cell or into
12 the tissues to exert their actions.

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

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

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

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

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

25 This cartoon shows how the dendrimers are

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1 converted to what we call Avidimers and the cartoon at
2 the bottom shows targeting ligands which I think look
3 like purple mushrooms. They're not really like that.

4 And they will seek out specific tumor cells based on
5 surface receptors. We can also attach drugs to these
6 dendrimers or imaging agents as well.

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

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

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

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

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

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

25 Public scrutiny, I was amazed to look at

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

7 (Applause.)

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

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

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

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

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

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

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

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

6 Currently, for example, diagnostics are
7 being miniaturized and we anticipate that certain
8 diagnostics will be implanted routinely in the future.

9 It's very inviting to presume that nanotechnology
10 will play an important role in accelerating or
11 sustaining this development. Similarly, combination
12 products are proliferating. The product category
13 appears to offer particularly fertile ground for the
14 incorporation of nanotechnology materials into novel
15 therapies and novel diagnostic devices.

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

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

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

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

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

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

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

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

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

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

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

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

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1 perfect opportunity for addressing any nanotechnology
2 aspects of the process.

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

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

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1 through the use of nanotechnology.

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

15 (Applause.)

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

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

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

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

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

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

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

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

15 The NCL is a formal collaboration between
16 NIST, NCI and FDA as you heard from Piotr's talk
17 earlier. We're often asked how is nanotechnology
18 different for preclinical characterization. Why do
19 you need an NCL? Can't we just do it the same way
20 like we've been doing drug discovery and development?

21 We're asked that and our answer to that is the FDA
22 requires a certain set of assays or a certain set of
23 parameters to be characterized in the CMC portion of
24 the IND, the Chemistry Manufacturing and Control's
25 portion of the IND.

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

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

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

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

11 Now it's interesting because you've heard
12 the comment about don't generalize. Now we echo that
13 very, very strongly. We're finding that it's very
14 difficult to generalize and to bend nanoparticles. We
15 see the same results for hemolysis assay. That's
16 lysis of red blood cells. PEG is a neutral species.
17 It's a negative control. PL is polysine. That's a
18 positive control. The OH is neutral species and the
19 NH₂ again would be positively charged under these
20 conditions and we do see hemolysis under those
21 conditions.

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

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

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

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

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

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

11 (Applause.)

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

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

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

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

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1 product contains nanoparticles.

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

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

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

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

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

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

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

16 (Applause.)

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

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

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

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

17 Nanoparticle formulations of health
18 ingredients have been known for a long time. If we
19 look into history, carotenoids are formulated this way
20 since the '60s. The main reason for formulation is
21 the bioavailability. Carotenoids have a zero
22 solubility in water, several orders of magnitude less
23 than normal pharmacists would say. It's really na-da.

24 Co-enzyme Q10, it's also bioavailability and this has
25 been marketed since the '90s. Vitamin A is mostly

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1 stability because you need to microencapsulate this
2 sensitive molecule against oxidation and such has been
3 marketed since the '60s. Vitamin E, it's mostly the
4 composibility (sic). Vitamin E is an oil which you
5 cannot easily formulate obviously into a tablet. You
6 have to make powders out of it that you can make hard
7 tablets and such has also been marketed since the
8 '60s. If you look into Vitamins D and K, it's mostly
9 stability, microencapsulation, yet again 30 years and
10 longer. And PUFAs it's the stability through
11 encapsulation and here these are marketed since the
12 '80s and '90s.

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

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

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

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

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

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

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

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

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

25 This cannot be taken to assess the size of

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

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

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

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

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

7 If you see comparison with, for instance,
8 in the case of lycopene with formulation based on
9 natural lycopene, then we arrive at similar
10 bioavailabilities. Here you see a continuous intake
11 of lycopene, 50 milligram per day over 18 days at 28
12 days, and then you see the serum levels for lycopene.

13 Our lycopene, ten percent achieved a similar
14 bioavailability compared to formulated to moderate
15 extract.

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

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

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

5 (Applause.)

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

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

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

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

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

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

21 DR. END: Yes.

22 AUDIENCE MEMBER: (Off the microphone) How
23 do you encompass the stability of the polyunsaturated
24 --

25 DR. CANADY: We're actually holding

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

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

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

14 (Pause.)

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

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

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1 500 companies on assessing the environmental health
2 and safety needs related to nanotechnology. We took
3 up a part in NCI working group helping to establish
4 standards and also we support government agencies. We
5 work for the EPA and actually these slides were
6 developed together with the Army Corps of Engineers
7 and the Army Corps is just starting a sizable program
8 on assessing environmental and ecological risks
9 related to nanomaterials and Jeff Stevenson and
10 Elizabeth Ferguson were part of these slides.

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

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1 they are widely used in business communities.

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

9 So I think what they will try to do is to
10 address some of the issues that we've discussed and
11 everybody is saying we need to balance benefits and
12 risks, we need to bring together all this information.

13 So I will try to show how you can do that with a
14 couple of tools I'm familiar with.

15 Again first point, I was part of the EPA
16 peer review panel of nanotechnology. This is some of
17 our peer review panel and I know a couple of my
18 colleagues are here who were part of this panel. So
19 obviously I selected those that illustrate my points.

20 But we had many conclusions clearly. But I would
21 like to say is that current risk assessment experience
22 is for chemical unstable agents and we deal with
23 engineered nanomaterials. We can change the property
24 of this nanomaterials and this is a challenge and also
25 an opportunity. For me, the opportunity here is that

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

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

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

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

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

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

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1 we found that in regulatory databases the range is
2 like four orders of magnitude. So those, the values
3 that EPA and other government agency recommend to use
4 in risk assessments four orders of magnitude for PCBs.

5 What are we going to have for nanomaterials? I think
6 it will be even more than that.

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

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

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

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

25 Yes. So this is my last slide that shows

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

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

8 (Applause.)

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

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

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

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1 experts.

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

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

15 Another aspect is the collaboration
16 between industry and FDA. The cosmetic industry has a
17 long history of strong collaboration with FDA through
18 voluntary self-regulation programs. This includes the
19 voluntary reporting program which establishes a system
20 whereby cosmetic companies can report their
21 establishments, report products, any ingredients that
22 are used in these products. This is actually the
23 first such program ever established by FDA back in the
24 1970s. So this is a means whereby FDA and actually
25 the industry as you'll find out in a minute can get

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

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

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

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1 industry.

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

11 Another program that's just been
12 implemented or is being implemented and was mentioned
13 by Jane Houlihan of the Environmental Working Group
14 earlier has to do with CTFA consumer commitment code
15 and this is an extension again of the voluntary
16 approach, self-regulation and collaboration with FDA.

17 It provides a mechanism whereby FDA can ask companies
18 for information about the safety or other aspects of
19 the ingredients. It sets up procedures for doing this
20 and a structure for interacting, but FDA can go to a
21 company and ask for information about the safety
22 substantiation for an ingredient. It also for
23 participants provides a commitment that they will
24 participate in a voluntary registration program which
25 provides very important information again about

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1 ingredients, products and how they're used.

2 Another important part that wasn't
3 mentioned was that the consumer commitment code
4 provides for immediate reporting to the FDA of any
5 serious or unexpected adverse reaction as defined in
6 the drug part of the Code of Federal Regulations. So
7 I think that that's an important part to keep in mind.

8 This information to make a long story short will be
9 maintained in what we call the Safety Information
10 Summary.

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

18 Most uses are limited to TiO₂ and zinc
19 oxide. These are approved drug active ingredients by
20 FDA. The micronized or nano TiO₂ and zinc oxide have
21 been reviewed and found to be safe by FDA. The
22 products are used according to regulation and they
23 provide clear benefit. Any assertion that these
24 products should be pulled from the market fails to
25 take into account the fact that they do prevent skin

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

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

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

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

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

9 (Applause.)

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

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

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

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

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

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

21 (Applause.)

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

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

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

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

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

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

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

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

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1 helps safeguard the safety, but it also drives down
2 the cost and the barriers to innovation going forward.

3 We believe that that's an absolutely critical
4 development and we salute the effort of the
5 Nanotechnology Characterization Laboratory as they
6 move in that direction. We believe it's doing some
7 great things.

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

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

23 (Applause.)

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

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

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

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

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

25 MR. LUNKOV: You may use it when you put

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1 together technical information. When you do any
2 assessment as a technical expert, you use assumption.

3 We call it "weight of evidence" when we do for
4 example carcinogenicity evaluation for a chemical. We
5 have multiple tests and they are not consistent. So
6 you can use multi-criteria decision analysis to kind
7 of formalize your judgments on those issues rather
8 than discuss in like two pages of a document why you
9 decided this way.

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

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

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

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

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

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

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

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

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

24 (Applause.)

25 CHAIRMAN ALDERSON: I have the task of

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

9 In August, Dr. Von Eschenbach, our acting
10 Commissioner, charged the task force with determining
11 regulatory approaches that encourage the continued
12 development of innovative, safe and effective FDA-
13 regulated products that use nanoengineered materials.

14 This meeting that you've attended today is the first
15 major task force milestone in carrying out this
16 charge. This meeting is an example of the process FDA
17 follows to ensure transparency and public input into
18 our development of regulatory policy. We are all
19 committed to this approach at FDA.

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

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

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

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

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

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

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

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

17 (Applause.)

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