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5 "Leveraging - Collaborating with Stakeholders"

6 Building Effective Partnerships

7 FDA and Stakeholders Public Meeting

8 Stanford Law School, Room 290

9 559 Nathan Abbott Way

10 Stanford, California

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12 Thursday, March 23, 2000

13 6:00 p.m.

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23 Reported By:

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PANELISTS

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PANELISTS (continued)

SHARON SMITH HOLSTON  
Deputy Commissioner for International &  
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California Medical Review, Inc.

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Executive Director  
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PANELISTS (continued)

KATHRYN C. ZOON, Ph.D.  
Director  
Center for Biologics Evaluation and Research  
Food and Drug Administration

MODERATOR

MARK BARNETT  
Director of Communications  
Center for Devices and Radiological Health  
Food and Drug Administration

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1 PROCEEDINGS

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3 MR. BARNETT: If I could have your  
4 attention, please, we'll get started.

5 I'm Mark Barnett of the FDA. I'll be  
6 serving as your moderator for this evening's meeting  
7 on "Leveraging with the FDA," which really means  
8 ways in which the FDA can work with outside  
9 organizations to better perform its mission.

10 Let me first introduce tonight's panel.

11 This gentleman here met me before the  
12 meeting, and he challenged me to work without a  
13 Teleprompter.

14 Anyway, let me do tonight's panel.

15 Since most of you probably can't see these  
16 little name tags I'll ask each panelist to give a  
17 sign as I call the names, so you could match the  
18 name to the face.

19 Let's start with someone whose name and  
20 face is probably already matched. That's Dr. Jane  
21 Henney who is Commissioner of the Food and Drug  
22 Administration.

23 Dr. Kathy Zoon is Director of Center for  
24 Biologics Evaluation and Research.

25 Dr. Susan Alpert is Director for Food

1 Safety in FDA's Center for Food Safety and Applied  
2 Nutrition.

3           John Taylor is Senior Advisor for  
4 Regulatory Policy in FDA's Office of Regulatory  
5 Affairs.

6           Sharon Smith Holston is FDA's Deputy  
7 Commissioner for International and Constituent  
8 Relations.

9           Dr. Dan Casciano is Acting Director and  
10 also Deputy Director for Research in FDA's National  
11 Center for Toxicological Research.

12           Jane Axelrad is Associate Director for  
13 Policy in FDA's Center for Drug Evaluation and  
14 Research.

15           Dr. Andrew Beaulieu is Deputy Director in  
16 FDA's Center for Veterinary Medicine.

17           We have three folks on the panel that are  
18 not with the FDA. They are here for a special  
19 reason which I'll tell you about in a minute.

20           They are Ms. Erica Jones, who is Senior  
21 Medicare Beneficiary Relations Benefit Specialist  
22 with California Medical Review, Inc.;

23           Dr. Tobias Massa, who is Executive  
24 Director of Global Regulatory Affairs with Eli Lilly  
25 and Company; and

1           Dr. Charles Sizer, who is Director of the  
2 National Center for Food Safety Technology, also  
3 known as the Moffett Center in Chicago.

4           Let me tell you a little bit about the  
5 format we are going to use for tonight's meeting.

6           We'll start out with a few introductory  
7 words from Dr. Henney in which she'll set the stage  
8 for tonight's meeting, talk about why it's  
9 important, and particularly why it's important at  
10 this juncture in time.

11           Then we're going to ask the three non-FDA  
12 members to talk about -- they have something in  
13 common, that is, that they have all worked with the  
14 FDA in leveraging projects in the past. So because  
15 we hope that many of you in the audience are  
16 professional leveraging partners with us, we thought  
17 it would be interesting for you to hear about their  
18 experiences in working with the FDA. You can see  
19 from their smiling faces that they survived the  
20 experience. Happy and prosperous. Or in any case,  
21 they survived.

22           Then we're ready to dive into the main  
23 portion of the program, which is to hear from and  
24 respond to some of our potential leveraging partners  
25 who are here in the audience.

1           Let me back up for a moment and describe  
2 how that happened.

3           Dr. Henney and her staff got together and  
4 came up with five areas in which they felt that  
5 leveraging was particularly important and which was  
6 likely to succeed, and they published those five in  
7 the Federal Register and at the same time announced  
8 this meeting and invited people to come and talk to  
9 us and explore with us ideas for leveraging.

10           We were delighted with the results.  
11 Several organizations and individuals decided they'd  
12 like to come. They're here with us tonight, and  
13 you'll be hearing from them.

14           As they speak and intermittently I will  
15 ask the FDA folks and the others on the panel to  
16 respond and hopefully we can get a good dialogue  
17 going here.

18           We are somewhat in a time crunch. Lots of  
19 people want to speak. We're eager to hear from all  
20 of them. That means we are going to have to keep it  
21 brief. So I am going to issue an FDA guidance on  
22 the length of talks. If you've dealt with the FDA,  
23 the FDA guidance is not strictly enforceable under  
24 the law specifically, but on the other hand, it's  
25 not just a suggestion, either. We need to -- so,

1 you get the idea.

2           Anyway, that's okay, though. Brevity is  
3 okay, because what we want tonight is not proposals.  
4 What we want is ideas. We want to explore things  
5 with you. We want you to give us a sketch, not a  
6 complete painting. So I think the brevity part is  
7 fine, and we will respond.

8           Anything we hear tonight about leveraging  
9 projects we will get back to you on, and obviously,  
10 these five items we've chosen are not the only  
11 things you can leverage with us on. There are other  
12 things as well.

13           As you sit here and hear these things, if  
14 ideas come to you in the days and the weeks and  
15 months to come, let us know. Your packet contains  
16 the names and addresses of the key FDA people who  
17 are going to be dealing with this. If you have  
18 ideas, we want to hear from you, and we will  
19 respond. So that's how things are going to play out  
20 this evening.

21           One more quick piece of housekeeping. The  
22 packet contains an evaluation form, and we would  
23 like you to fill that out because we hope to do more  
24 of these meetings, and your feedback, what you like  
25 and what you didn't like, is going to help us in

1 planning future meetings.

2           Okay. So much for the beginning and the  
3 housekeeping.

4           Now, let me call on Dr. Henney to talk  
5 about why everything is so important.

6           DR. HENNEY: Well, thank you, Mark.

7           Let me say, welcome to all of you, and  
8 thank you for coming this evening.

9           I will give you a little fair warning, I'm  
10 not as loose as Mark.

11           I'm still on East Coast time, so I went  
12 ahead and wrote down the remarks that I want to say  
13 to you just to make sure that I got them all in. If  
14 you'll forgive me, I am going to use a text rather  
15 than just be able to talk so informally to you.

16           I also want to thank not only you in the  
17 audience, but Toby, Erica and Chuck, really for  
18 joining us on the panel tonight.

19           I think that they have made time available  
20 on their schedules to be out here, to give you more  
21 of a concrete glimpse about their experience in  
22 terms of and commitment to leveraging activities.

23           There are many reasons why this meeting is  
24 important to us. It's important to us, I think,  
25 because we have tried to make a consistent effort to

1 listen, to listen to what our stakeholders think  
2 about the Agency, be it regulated industry, be it  
3 consumer groups, be it people in academia, so that  
4 we really hear what's on people's minds. So we're  
5 anxious to hear your thoughts.

6           But I'm also very much thinking that it is  
7 important to us, because we are a bit at a critical  
8 juncture in terms of how we best use our resources  
9 at the Agency and how we use our resources in  
10 partnership with others.

11           I think it's fundamental to our Agency as  
12 a regulatory agency that we be strong  
13 scientifically. But one of the ways that we feel  
14 that we can further enhance our own scientific  
15 expertise is by working with other individuals,  
16 either as individuals or with organizations that  
17 really share our goals of public health and safety.

18           They really help us enrich our scientific  
19 expertise, and thereby get our work done.

20           Last fall I asked Linda Suydam, the Senior  
21 Associate Commissioner of the FDA, who couldn't be  
22 with us tonight, but I had asked Linda to establish  
23 a workgroup of senior FDA officials and managers  
24 that would specifically look at leveraging as a  
25 concept and at opportunities that might be available

1 to us.

2           The results of this particular effort has  
3 really intensified our commitment to leveraging at  
4 the Agency, and we're putting in place a more formal  
5 structure for building such effective partnerships.

6           The system would enable us to identify  
7 projects suitable for collaborative action and find  
8 appropriate partners who share FDA's interest in  
9 performing this needed work.

10           We need to use our resources in  
11 collaboration with others, to really help us get our  
12 job done faster and with expertise that we might not  
13 now have in house.

14           We don't intend that this be a "this year"  
15 kind of activity, but really that it become a very  
16 primary and central strategy for us, because it will  
17 bring us a wider range of scientific thinking to  
18 bear on our own decision-making regarding public  
19 health issues.

20           We think it's not just a smart way to do  
21 our business, but we think it's really critical in  
22 order that we have an ability to really protect the  
23 public health.

24           Clearly, you all know better than any how  
25 much money this country is investing in biomedical





1 other than the ones mentioned tonight, please feel  
2 free to contact us. There is a list of those FDA  
3 contacts in your packet, as well as an open docket  
4 referring to these stakeholder meetings on our web  
5 site.

6           We're looking forward to your comments and  
7 the opportunity to work with you in the future.

8           MR. BARNETT: Thank you, Dr. Henney.

9           Let me ask now our three non-FDA panelists  
10 to start telling us a little about their own  
11 experiences in setting up and carrying out  
12 cooperative programs for the FDA.

13           I'll call first on Dr. Tobias Massa of the  
14 Eli Lilly Company. He worked with the FDA on  
15 developing a project called the Product Quality  
16 Research Institute or PQRI.

17           DR. MASSA: Thank you. It's a pleasure to  
18 be here tonight.

19           PQRI, or the Product Quality Research  
20 Institute was incorporated as a not-for-profit  
21 organization seven months ago.

22           It took, however, four years of debate by  
23 the founding members to decide what the institute  
24 should do and how we should do it.

25           But good things are worth waiting for, and

1 we think this is really a good thing.

2 PQRI gives us a unique opportunity for  
3 industry, academia and the Food and Drug  
4 Administration to work together in a neutral  
5 environment to conduct pharmaceutical product  
6 research. It gives us the opportunity to combine  
7 our intellectual resources to attack problems that  
8 we mutually decide upon.

9 The goal is to develop a scientific basis  
10 for good regulation and guidance.

11 We want to have good regulation coming  
12 from good science.

13 Hopefully, the end result will be a  
14 reduction in regulatory burden, not only for the  
15 regulatory industry but also for the Agency.

16 But that might not be the case. The work  
17 that we do may show that the existing regulations  
18 have to remain or that additional regulations may  
19 have to be developed. But that's okay because it's  
20 going to come from good science.

21 As I said, PQRI offers a unique  
22 opportunity.

23 First of all, all of the relevant players  
24 are at the table.

25 The family members included the trade --

1 the three trade organizations that represent the  
2 generic industry; PhRMA or the Pharmaceutical  
3 Research and Manufacturers of America, representing  
4 the innovator industry; FDA, of course; the Consumer  
5 Health Products Association; the Parenteral Drug  
6 Association; and the American Association of  
7 Pharmaceutical Scientists.

8           These represent many of the organizations  
9 that are involved in pharmaceutical product quality.

10           However, in the short time that we've been  
11 in existence three additional organizations have  
12 joined us, and they include the International  
13 Pharmaceutical Excipients Council, the International  
14 Society for Pharmaceutical Engineers, and most  
15 recently, the United States Pharmacopoeia.

16           We have also started to get an  
17 international flavor in that the European version of  
18 PhRMA, IFPMA, has expressed interest in joining us.  
19 So clearly, people are seeing that this is a very  
20 worthwhile opportunity.

21           The other thing that we think makes us  
22 unique is that we think we have a process that will  
23 work. All of the relevant players, both the  
24 regulators and the regulated, sit at the table to  
25 decide what areas of research we will undertake.

1 All of the players decide what the  
2 research plan will be and how that research plan  
3 will result in a recommendation that will  
4 specifically address a particular guidance or  
5 regulation.

6 All of the players will be involved in the  
7 evaluation of the data and putting together a  
8 recommendation to FDA.

9 So, the fact that FDA is participating in  
10 this gives us a hope that we will come out with a  
11 recommendation that will be accepted.

12 But as Dr. Henney said, FDA has to remain  
13 a little bit apart from this. So there is no  
14 guarantee that all of our recommendations will be  
15 accepted.

16 If that is the case, they have agreed,  
17 however, to provide us in writing why the  
18 recommendation does not result in changing the  
19 guidance, so that we can take that back and rework  
20 the research that we've done.

21 All of this will be very public. We have  
22 a PQRI web site, pqri.org. All of the proceedings,  
23 all the minutes, all of the study protocols, will be  
24 up on that web. So there is a commitment from  
25 industry, there is a commitment from the Agency, to

1 make this work.

2           We don't have any positive proof to show  
3 you that this does work yet.

4           We've just started picking off a few  
5 topics. But we think by the end of the year we will  
6 have at least two projects that have gone through  
7 the system that we can show that we do have proof of  
8 concept here.

9           We're very excited about this, and we  
10 think this will work very well.

11           MR. BARNETT: Thank you very much.

12           I should mention to the audience, feel  
13 free to question these folks. After the three of  
14 them have spoken I'll open the floor. If you have  
15 questions, by all means, ask them.

16           Our second speaker is Miss Erica Jones of  
17 California Medical Review, Incorporated. She worked  
18 with the FDA on a consumer education program about  
19 taking medication safely called "Take Time to Care."

20           Ms. Jones.

21           MS. JONES: Thank you.

22           It's a pleasure to be here this evening.

23           Moreover, it's a pleasure to talk about a  
24 worthwhile project that the FDA launched that  
25 provides comprehensive education to the consumer

1 base for which I target. Working not only in the  
2 private sector and the public sector, I work  
3 directly with educating Medicare beneficiaries,  
4 seniors, who are, as you know, the primary consumers  
5 of medication.

6           Nonetheless, in working in the capacity in  
7 the non-profit sector I have been able to partner  
8 with organizations on a very grass-roots level that  
9 also have direct contact with Medicare  
10 beneficiaries, with seniors, those persons who use  
11 medication.

12           What we've been able to do is train  
13 professionals to talk about medication utilization  
14 as well as implementing the tag lines that "Take  
15 Time to Care, Use Medication Wisely" campaign  
16 implemented as well as health care interventions  
17 that the Medicare program now offers.

18           We've been able to target not only  
19 specifically the elderly, but also those who are  
20 underserved within the elderly populations; those  
21 who are shut-ins, those who are disabled, perhaps,  
22 and those who find themselves consistently out of  
23 the loop of information and thereby finding  
24 themselves compromised by not having those messages,  
25 not having that education.

1           Working also with a group of volunteers at  
2 the organization that I'm employed with now, I train  
3 them not only on the Medicare project but also on  
4 "Take Time to Care, Use Medication Wisely."

5           Just last year, from 1999 to January 2000,  
6 they've done face-to-face outreach; they've done  
7 face-to-face education; with over 60,000 Medicare  
8 beneficiaries throughout the State of California,  
9 not only using face-to-face counselling, but also  
10 the media and dropping articles into senior center  
11 newsletters.

12           The feedback that we've been getting is  
13 that our program provides comprehensive information  
14 to the target population in the State of California.

15           I'm looking forward, not only do I find  
16 this of value added to my organization and it  
17 complements the services that we provide, but it's  
18 also value added clearly to the constituency which  
19 we serve.

20           I look forward to continuing this program,  
21 "Take Time to Care, Use Medication Wisely," on a  
22 very grass-roots level.

23           Too often these messages kind of get over  
24 the heads of those people who really tactically can  
25 use them on a day-to-day basis, and often those

1 people who are defined as underserved find  
2 themselves out of the loop. So by getting that  
3 face-to-face contact, by hearing those messages  
4 consistently, you are more apt to get a behavioral  
5 change.

6 Thank you.

7 MR. BARNETT: Thank you.

8 Our third example of leveraging comes from  
9 Dr. Charles Sizer of the National Center for Food  
10 Safety and Technology, otherwise known as the  
11 Moffett Center. His organization worked with the  
12 FDA to carry out the objectives of the President's  
13 Food Safety Initiative.

14 Dr. Sizer.

15 DR. SIZER: Thank you, Mark.

16 Commissioner Henney, ladies and gentlemen,  
17 thank you for the opportunity to speak tonight.

18 I'd like to tell you a little bit about  
19 the Illinois Institute of Technology National Center  
20 for Food Safety and Technology. I'd like to share  
21 with you some of the opportunities we have for  
22 leveraging at our Center.

23 The National Center for Food Safety and  
24 Technology is a unique consortium of leading food  
25 companies, the U.S. Food and Drug Administration and

1 university-based food scientists working together to  
2 establish the criteria to ensure the effectiveness  
3 of processing and packaging technologies.

4           By bringing together key players in food  
5 safety regulation and technology development the  
6 NCFST provides a sound scientific basis for policy  
7 decisions affecting the nation's food supply. The  
8 food industry and consumers benefit from the  
9 improved processing and packaging systems that  
10 assure food safety.

11           This is a picture of the building we've  
12 got. Our complex has five buildings that were  
13 donated by Corn Products Company in 1988, and our  
14 current level of funding is about five and a half  
15 million dollars.

16           We have about 76 commercial members, and  
17 in addition, Illinois Institute of Technology, the  
18 FDA Division of Food Processing Packaging, Lab  
19 Quality Assurance Branch, University of Illinois and  
20 other universities participate. It's a resource  
21 available to industry, academia, and all of FDA's  
22 scientists, investigators and staff members.

23           The Center was founded in 1988 with a \$7  
24 million gift of five buildings and a start-up grant  
25 from FDA. At the present time scientists from FDA,

1 IIT, and the University of Illinois and 76 member  
2 companies participate in activities at the Center.  
3 Scientists at other universities and government  
4 agencies also participate in the research and  
5 outreach activities.

6           The mission of the Center is to conduct  
7 research on food safety and communicate the results  
8 of that research. Research is divided into four  
9 areas: biotechnology, food safety/HACCP, processing  
10 and packaging. This evening I'd like to demonstrate  
11 how leveraging is the core of our collaborative  
12 research program, symposia, workshops, short  
13 courses, task forces and pilot plant activities.

14           The collaborative research program  
15 utilizes scientists from industry, academia and  
16 government, with each project having at least one  
17 investigator from each branch.

18           Each project has oversight, accountability  
19 and deliverables to the working groups of the  
20 members. The best available expertise is identified  
21 and utilized for each research project. Work at the  
22 Center is conducted in state-of-the-art pilot plant.

23           The FDA's research dollars are leveraged  
24 by utilizing external expertise, industry-matched  
25 funding, shared facilities and research equipment.

1           Industry leverages their dollars by  
2 participating in the establishment of the criteria  
3 of producing safe foods which streamlines the  
4 approval process.

5           Academia benefits from the research  
6 funding and the educational opportunities provided  
7 by the program.

8           The results of our research program are  
9 communicated using various outreach tools.

10 Leveraging is accomplished by tapping into the best  
11 available expertise, sharing of resources, defraying  
12 of costs by charging participant fees and increasing  
13 the flexibility of timeliness of the events.

14           One of our newest leveraging tools is what  
15 we call a "Task Force." A task force is formed to  
16 address a rapidly emerging food safety issue by  
17 involving interested parties.

18           An example of this is the task force that  
19 we just recently completed, the "Alfalfa Task  
20 Force."

21           Alfalfa sprouts have been linked to  
22 numerous outbreaks and were considered to be the  
23 riskiest product in the supermarket.

24           Contamination was thought to come from the  
25 seeds, and a 5-log reduction in pathogens of

1 interest was thought to be necessary to improve the  
2 safety of the product. The task force was formed  
3 coordinating the efforts of the FDA, USDA, EPA,  
4 University of Massachusetts, University of Georgia,  
5 IIT and the International Sprout Growers  
6 Association.

7           The ISGA contributed \$23,000 to conduct  
8 research on the intervention processes including  
9 chemical disinfection, gamma irradiation, electron  
10 beam irradiation and thermal processing of the  
11 seeds. Sampling methods were also developed with  
12 FDA researchers to identify seed lots containing  
13 pathogens and also for testing of sprout irrigation  
14 water for pathogens.

15           As a result of that task force, FDA issued  
16 new guidance that was scientifically based on  
17 research done at the Center.

18           What does leveraging do? It increases the  
19 resources available to conduct research. It gives  
20 the participants ownership and imparts  
21 accountability to the scientists conducting the  
22 research. Communications with the stakeholders is  
23 facilitated, and the best expertise is made  
24 available. Timeliness is also mandated since the  
25 task force by definition must be completed within a

1 12-month period of time.

2           A second task force was held last year,  
3 and it was done on plastic irradiation. Although  
4 red meats and poultry had been approved by FDA and  
5 USDA, most producers wanted to use electron beam,  
6 and for electron beam there wasn't any packaging  
7 material that had received other approval than EBA.

8           So a task force was put together. We  
9 looked at ten different polymers and submitted a  
10 petition. Just a couple weeks ago we got a letter  
11 back from FDA saying they have no objection. We  
12 have a one-year time to introduce these materials  
13 while the petition is being reviewed. The entire  
14 project was supported by the industrial members. It  
15 was a very successful task force.

16           Leveraging at the National Center for Food  
17 Safety and Technology is an integral part of all of  
18 our activities, from the identification of a food  
19 safety issue, the research, the outreach activities  
20 and the outcomes.

21           For the NCFST leveraging is a way of life.

22           It maximizes what can be accomplished with  
23 limited resources. It gives projects accountability  
24 and deliverables. It allows for access to the best  
25 expertise balanced by the common sense of the people

1 who know the process on a day-to-day basis.

2           Communications are improved between the  
3 regulators and the regulated. The safety of the  
4 food supply is a common goal of the public, the  
5 industry, academia and the FDA. Leveraging is a  
6 better way of making it happen.

7           Thank you.

8           MR. BARNETT: Thank you, Dr. Sizer.

9           Let me ask you now anybody in the  
10 audience, or for that matter on the panel, who wants  
11 to ask a question of these folks or make a comment?

12           Yes. In the back. Because you're not  
13 miked, can you come up front and speak into the --  
14 do you mind coming down from the aisle.

15           AUDIENCE MEMBER: I just wanted to ask, on  
16 PQRI, how you are funded.

17           Obviously, one of the issues on leveraging  
18 is a sort of potential conflict of interest, and  
19 it's unfortunate, because the program has  
20 potentially a lot of money which could help to fund  
21 a lot of these projects but would be accused of  
22 conflict of interest. How do you get round that or  
23 is it something that you face?

24           DR. MASSA: Funding is of paramount  
25 importance to PQRI. Right now the member



1           Now, the Board of PQRI is -- in addition  
2 to the scientific steering committee, there is also  
3 a Board which is independent of the steering  
4 committee, and their obligation is to raise monies  
5 for the research that the Steering Committee decides  
6 is necessary to occur.

7           The way they are going to do that is to  
8 request the member companies or the member  
9 organizations -- like PhRMA, of course, is made up  
10 of numerous innovative pharmaceutical companies.

11           What they're asking for are donations to  
12 go into a general fund, not directed toward any  
13 particular project.

14           However, if a company would like their  
15 dollars to go to a specific project, we'll let that  
16 happen as well.

17           But that goes through the Board. It does  
18 not go through the Scientific Steering Committee.

19           The Steering Committee, nor any of the  
20 contributors, are allowed to -- rather the Board nor  
21 any of the contributors are allowed to comment on  
22 any of the scientific aspects of what happens.

23           We're trying to separate that as much as  
24 possible.

25           MR. BARNETT: Thank you. Good question,

1 and good answer.

2           Anyone else?

3           Yes. Step up, please. Identify yourself,  
4 if you don't mind, before you start.

5           MS. BRENNER: Barbara Brenner from Breast  
6 Cancer Action.

7           Also, a question about PQRI. It seems  
8 that the voices missing here is the public's. You  
9 talk about what research this -- the industry would  
10 like to see and FDA is partnering with. Where does  
11 the public's voice come into this and what the  
12 public would like to see done in pharmaceutical  
13 research?

14           MR. BARNETT: I'm going to ask you, also,  
15 we've got a big program. Keep the answers brief, if  
16 we would. We'll take one more after this.

17           DR. MASSA: That's really a great comment.  
18 It's one that we just started to look at on the  
19 Steering Committee and the Board. How are we going  
20 to reach out to get public comment into this?

21           One of the ways in which we're doing that  
22 is by getting the academicians, who are probably our  
23 best voice of the public right now, they interact  
24 with us through the American Association of  
25 Pharmaceutical Scientists. They are individual

1 members of that organization.

2           But we do recognize that we are not  
3 getting some of the other consumer groups, the  
4 comments, into our research, and we're looking at  
5 ways to try and do that. Just haven't figured out  
6 how to do that yet.

7           MR. BARNETT: Yes.

8           DR. SHAPIRO: My name is David Shapiro.  
9 I.Q. Resources and Scripps Clinic. I'll address  
10 this comment to Dr. Henney.

11           I would like to ask about what it takes to  
12 form a group for a leverage operation. This week I  
13 speak as a pulmonary physician, not as a lawyer.

14           Given the Supreme Court's decision on FDA  
15 regulation of cigarettes I would ask you what it  
16 would take for a group to form a leverage group with  
17 FDA and other stakeholders to address the issues and  
18 health concerns relating to nicotine addiction.

19           DR. HENNEY: I think that we have a number  
20 of activities related to interest groups in any  
21 area, whether it is groups of oncology patients to  
22 people who are interested in issues of addiction to  
23 individuals or groups that are interested in  
24 nicotine.

25           We tend to have most of those activities

1 that relate to Sharon Holston's part of the  
2 organization. So that is the point of contact that  
3 I would steer you to.

4           In terms of the tobacco issue, I think  
5 where the dialogue, discussion, and hopefully action  
6 will come is from the Congress at this point. FDA  
7 by the decision, as you well know, has essentially  
8 been told that the regulation promulgated does not  
9 stand, and so it is what will be squarely joined  
10 with the Congress for further action.

11           DR. SHAPIRO: As a response, I welcome the  
12 response. I hope the FDA would be a little bold in  
13 taking some initiative. My confidence in the  
14 Congress in dealing with tobacco is not great.

15           Thank you.

16           MR. BARNETT: Let's do one more, one more  
17 quickly.

18           Come on up. This is the last one.

19           MR. GRILL: Thank you. Good evening. My  
20 name is Christopher Grill.

21           I was wondering what, if any, efforts the  
22 FDA has made to start leveraging with consumer  
23 groups concerned about the safety of dietary  
24 supplements.

25           We've heard words like "science," "good

1 science," and we know -- assurances. There is  
2 nothing like that that applies to these products  
3 which millions of Americans take. I would like to  
4 know what would be required to get some dialogue  
5 going.

6 Thank you.

7 MR. BARNETT: Let's make this a quick  
8 answer. We want to have questions that apply to the  
9 items that the folks have been talking about. But  
10 let's get a quick answer to that. Anybody want  
11 to --

12 DR. ALPERT: I would be happy to answer  
13 the question.

14 One of the things that we're doing in  
15 looking at dietary supplements is in fact we've  
16 recently published a long-term plan for addressing  
17 the concerns on dietary supplements, including  
18 things like manufacturing practices, labeling and  
19 communications.

20 We have a number of meetings coming up  
21 where dietary supplement issues will, in fact, be  
22 discussed. The next one is next week to talk about  
23 the pregnancy -- concerns about dietary supplements  
24 and pregnancy. There will be other open meetings as  
25 well. So we have started that dialogue.

1           MR. GRILL: Is there any leveraging that's  
2 going on? That's my question. I've been at these  
3 meetings. We can talk all we want, but until  
4 something is actually done we are -- all just a  
5 waste of time.

6           DR. ALPERT: Again, we are open to  
7 obviously hearing about specific suggestions about  
8 with whom to leverage and how to do that in all  
9 areas, including dietary supplements.

10          MR. GRILL: Who do I talk to about that?

11          DR. ALPERT: You can get in touch with the  
12 Center for Food Safety and Applied Nutrition. My  
13 name is there. I am Dr. Susan Alpert, and I am the  
14 Director of Food Safety at the Center.

15          MR. GRILL: Thank you.

16          DR. ALPERT: You're welcome.

17          MR. BARNETT: Okay. Let's go on now to  
18 the meat of the program really which is to hear from  
19 the folks who have come here tonight to talk to us  
20 about leveraging ideas.

21                 Remember, we said there were five basic  
22 areas, and the first one was Safety Review for New  
23 Products, specifically Safety Assurance in Clinical  
24 Trials, and we have several speakers there. The  
25 first one is Dr. James Nickas from Genentech,

1 Incorporated.

2           Is Dr. Nickas here? You are. Okay. Do  
3 you want to come up.

4           DR. NICKAS: Thank you.

5           First of all, on behalf of Genentech I  
6 would like to thank the Food and Drug Administration  
7 and the Stanford Law School for sponsoring this  
8 forum for exchange of ideas between stakeholders.  
9 We think this type of communication, collaboration,  
10 between the FDA, between the academic community, the  
11 consumer groups, the industry, will result in great  
12 things for patients.

13           So my topic is safety assurance in  
14 clinical trials.

15           What I'd like to do is just make a few  
16 base statements to set the frame and then kind of go  
17 into some of the leveraging ideas that we have.

18           I think most people in this room will  
19 agree that recent publicity surrounding the safety  
20 in gene therapy trials and the recent withdrawal of  
21 the diabetes drug Rezulin have caused a breach in  
22 public confidence as well as stimulating a  
23 reevaluation of the safety process that we have to  
24 assure safety in clinical trials.

25           Acknowledging that there may be breaches,

1 the reality, and I think it's important to point out  
2 here, the reality is that needed therapies are  
3 getting to patients quicker than ever, and the  
4 relative rate, I think, of product withdrawals is  
5 actually -- has not increased and may, in fact, be  
6 on the decline. We have to kind of see how new  
7 drugs play out over the years.

8           So from my perspective I like to frame the  
9 question posed to the stakeholders as: How he can  
10 we improve upon systems that are working already?

11           So, in probing ways to refine our current  
12 safety monitoring systems I think it's important to  
13 point out that safety assurance in clinical trials  
14 requires informed -- informed risk-benefit decisions  
15 by not only the stakeholders, the people who try to  
16 study these drugs, but the FDA, as well as the  
17 patients; and also that these informed decision  
18 making is dependent on good data. Okay.

19           So, herein lies two important points that  
20 we want to point out here. That with that,  
21 considering those dependencies of risk-benefit on  
22 data we think that breakthroughs in the way we  
23 collect and review safety data may add value to our  
24 current systems, as would developing metrics for  
25 benefit-risk so that new adverse reactions that are

1 identified in the post-marketing realm or even in  
2 the clinical trials are put into proper perspective.  
3 It's important.

4           We think that those two areas are areas  
5 where the FDA can focus more attention, resources  
6 and guidance.

7           What else can FDA do to leverage it's  
8 limited resources in hopes of assuring safety in  
9 clinical trials?

10           I think fundamental to this is to promote  
11 and negotiate with sponsors product life cycles  
12 safety monitoring plans. Okay. What that will  
13 require is that we acknowledge and communicate to  
14 the public, it's important, limitations of clinical  
15 trials; and on top of that, to utilize the entire  
16 spectrum of safety and monitoring modalities that we  
17 have. A lot of the work is already happening in  
18 that regard, linking databases and other things that  
19 we've seen the FDA working on.

20           I think -- but the point here is to really  
21 promote that life cycle. We are not done after  
22 clinical trials. We have a lot to do, and to use  
23 those different modalities effectively and  
24 efficiently, and do what makes sense at each stage.

25           We think another thing the FDA can do is

1 to co-sponsor with nationally recognized thought  
2 groups, if you will, more educational programs on  
3 developing hypothesis-driven, science-based  
4 monitoring plans, safety monitoring plans, during  
5 clinical trials, so that the best science and the  
6 best practices get incorporated into clinical trials  
7 regardless of who does them. Because I think where  
8 we're going here is outsourcing and studies being  
9 done at academic centers and sponsors and what have  
10 you.

11           Another area -- this is the big one, and  
12 actually it was a -- a threat to show my book here,  
13 but it was an actual topic of an important  
14 conference of -- I think last year, on data quality.  
15 That is, to create guidance documents that identify  
16 and promote practical data quality standards, so  
17 that information critical to safety evaluations is  
18 gathered or are gathered.

19           This will facilitate more rapid collection  
20 of information used which is what I think all the  
21 stakeholders want.

22           Another thing that we struggle with or are  
23 challenged with in clinical trials is to get our  
24 arms around the huge amount of data that is  
25 generated in these trials so we can make heads or

1 tails. That applies to the sponsors, the FDA,  
2 consumer groups, what have you. It's a challenge.

3           Here, and this relates to the -- the  
4 breakthroughs in data management, if you will, is I  
5 think that we need guidelines on dividing, quote,  
6 "safety data" that we collect in clinical trials  
7 into logical buckets that we can collect and  
8 evaluate in logical periods of time.

9           Under this recommendation we have a few  
10 sub-suggestions. One is to partner with thought  
11 leader groups, whatever they may be, and develop  
12 standards or list, if you will, of important  
13 clinical outcomes to monitor during clinical trials  
14 as well as disease-symptom endpoints that can be  
15 actually compared across trials.

16           Another important point, and it's actually  
17 overlooked, it may seem obvious, but it actually was  
18 borne out in some of the gene therapy issues that  
19 come out in the press, and that is, I think it's  
20 real important for the FDA to partner with clinical  
21 pharmacology and safety monitoring experts. This  
22 may sound basic. But to develop some practical  
23 guidance on recognition and actually reporting of  
24 treatment-emergent adverse events during clinical  
25 trials.

1           We read in the gene therapy documentation  
2 that despite a lot of the regulations that are  
3 written there is still confusion about what it is  
4 that people should be reporting. So I think some  
5 practical guidance would be helpful.

6           MR. BARNETT: Remember the three-minute  
7 guidance.

8           DR. NICKAS: Sorry?

9           MR. BARNETT: Remember the three-minute  
10 guidance.

11          DR. NICKAS: I only have a few more  
12 comments. Okay.

13          I think issuing guidance on safety and  
14 monitoring boards is another.

15          Then lastly, I really have a pitch, please  
16 finalize the document that was very valuable, issued  
17 in '96, of how to do a safety review. There was a  
18 lot of insight in that document.

19          So, I think the common thread through our  
20 suggestions here are that we need more education,  
21 not more regulation.

22          So with that, thank you.

23          MR. BARNETT: Thank you, Dr. Nickas.

24          What I'll do here, we have several  
25 speakers on this topic. Let's go through them all,

1 and then perhaps ask the FDA panelists to do some  
2 general responses. Okay.

3           Our next speaker is Dr. Siegel from Ground  
4 Zero Pharmaceuticals.

5           DR. SIEGEL: Thank you for the opportunity  
6 to speak tonight. I'll be brief. The panel has my  
7 remarks.

8           There are several critical key clinical  
9 development issues that need to be thought about in  
10 this topic.

11           First is the critical planning versus time  
12 constraints necessary in clinical trials.

13           Another is the scientist-versus-clinician  
14 identification, that is, the clinician who is  
15 performing a clinical trial needs to think of him or  
16 herself as a clinician and a scientist. Sometimes  
17 one predominates more than the other, and there is  
18 some confusion in the actual clinical trial process.

19           Training of investigators and staff is  
20 critical.

21           Proper data management at the sites which  
22 will lead to appropriate safety reporting in a  
23 timely fashion.

24           The sponsor has a number of  
25 responsibilities. The protection of the

1 participants in the trial.

2           Financial accountability for the  
3 corporation.

4           Corporate management pressures.

5           Communication of results.

6           The protection of the regulatory status of  
7 the project.

8           These regulatory concerns obviously  
9 involve the regulations which are well known: Parts  
10 50 and 56, 21 CFR 312, 314, the 600 series.

11           The issues of disbarment.

12           Effects on the system of voluntary  
13 compliance which we operate under should there be a  
14 failure in the clinical trial process.

15           The investigator has a responsibility for  
16 protection of participants, regulation versus the  
17 clinical practice, as was said earlier, the  
18 information assessment and appropriate reporting.

19           There are inherent risks and benefits to  
20 patients. The personal responsibility for one's own  
21 health does take place within a clinical trial as  
22 well as outside of it. If you participate in a  
23 clinical trial there is some inherent risk and you  
24 should be aware of it and should be willing to  
25 accept it.

1           The necessity for continuing therapeutic  
2 innovation versus the personal safety of each  
3 participant in a clinical trial.

4           The sacrifice of participating in a trial  
5 versus the potential benefit personally from a new  
6 therapy.

7           There needs to be a compact or an  
8 agreement among the parties in all clinical trials.

9           The congruency of the regulatory process  
10 and clinical innovation.

11           The recognition of economic political and  
12 public health changes which lead to importance for  
13 the proper conduct of clinical trials.

14           The requirement for both participant  
15 safety and data quality.

16           We have some solutions.

17           One is to recognize the need for faster,  
18 more cost-effective product development. This has  
19 been occurring through marvelous strides at the FDA  
20 for a long period of time.

21           A collaborative team to be formed amongst  
22 the FDA, the sponsors, investigators and others.

23           Third-party certification, similar to the  
24 medical device third-party review system. That is,  
25 consultants and others can add to the review of

1 safety data and the reporting of safety data, and  
2 the proper conduct of clinical trials which can  
3 protect participants.

4           The mandating of a faster and more  
5 complete reporting of safety data.

6           It is an absolute utter scandal to see  
7 that safety data, despite the regulations and the  
8 admonishments in place for many years, have not been  
9 reported in a timely fashion for both important and  
10 small, relatively unimportant clinical trials.

11           The assurance of communication without  
12 fear. If a safety problem is noted early on in drug  
13 development that should not kill the drug, the  
14 device or the biologic, but rather a cooperative  
15 arrangement should allow for the continued clinical  
16 study of appropriate new medical products along with  
17 a stepped-up safety monitoring regime.

18           Some conclusions:

19           The assessment of early- through  
20 late-phase development programs must occur in the  
21 safety arena in a continuous fashion.

22           The there must be an improvement in both  
23 strategic planning and execution of clinical trials,  
24 and better education of both investigators and  
25 patients.

1           There must be an assessment of the  
2 critical responsibility for the safety of the  
3 clinical trial and the patients involved.

4           A compact must be arranged among all  
5 parties to assure that these initiatives occur.

6           Finally, the establishment once again of a  
7 third-party review function.

8           FDA cannot monitor every single clinical  
9 trial, either during the trial or ex-post facto. It  
10 is obvious that sponsors do a good job but not a  
11 great job.

12           It is also obvious that many investigators  
13 are really falling down in their responsibilities  
14 for the proper scientific conduct of the clinical  
15 trial and the inherent safety of the patients that  
16 must be preserved.

17           Thank you.

18           MR. BARNETT: Dr. Siegel, thank you.

19           Our next speaker is Miss Barbara Brenner  
20 of Breast Cancer Action.

21           Ms. Brenner.

22           MS. BRENNER: Thank you very much for  
23 coming to the "left coast" and for the opportunity  
24 to address with you tonight issues related to how to  
25 leverage Safety Review for New Products and Safety

1 Assurance in Clinical Trials.

2           As the Executive Director of Breast Cancer  
3 Action, which is a national education and advocacy  
4 organization, one of the things we do on behalf of  
5 our more than 6,000 members is to work to assure  
6 that the needs of women with and at risk for breast  
7 cancer are addressed appropriately by the various  
8 entities working in this arena.

9           We frequently present testimony to the  
10 Oncologic Drug Advisory Committee on matters related  
11 to breast cancer. My remarks today focus on things  
12 that have come out of that Committee.

13           FDA's approval in September of epirubicin,  
14 September of '99, which is a new breast cancer  
15 treatment drug, and on compassionate access to  
16 trastuzumab, better known and more easily pronounced  
17 as Herceptin.

18           These two examples point toward steps that  
19 can be taken to improve the process of safety review  
20 and safety assurance.

21           Epirubicin was approved by the FDA for  
22 treatment for women with early-stage node-positive  
23 disease. The approval was based on data that showed  
24 that the drug improves chances of survival when  
25 compared to a combination chemotherapy referred to

1 as CMF, cyclophosphamide, methotrexate and  
2 fluorouracil.

3           However, women with early-stage  
4 node-positive breast cancer are not normally treated  
5 with CMF. They are treated with combinations of  
6 drugs that usually include adriamycin.

7           Comparing epirubicin to CMF was not a  
8 relevant comparison, and approving the drug based on  
9 that comparison did nothing to improve outcomes for  
10 women with breast cancer.

11           All breast cancer drugs have side effects.  
12 We know that.

13           In many cases, the long-term side effects  
14 are unknown, and because of the need for speedy  
15 approval in light of the life-threatening nature of  
16 breast cancer the side effects will not be known  
17 until long after drugs are approved.

18           Under these circumstances, new breast  
19 cancer drugs should not be approved unless they do  
20 one of they three things:

21           First, improve overall survival when  
22 compared to currently used treatments;

23           Or improve quality of life for breast  
24 cancer patients;

25           Or significantly reduce the cost of

1 treatment.

2           Ideally, any drug would do all three.

3           While safety is and should be the first  
4 consideration, it cannot be the only consideration.

5           Breast Cancer Action would be happy to  
6 collaborate with the FDA in the educational aspects  
7 of any clinical trial when these three criteria are  
8 made central to the guidelines under which trials  
9 are administered and their results are approved.

10           The Herceptin story reflects these  
11 criteria and also highlights the possibilities of  
12 collaboration in advancing the interests of all  
13 concerned.

14           When Genentech asked Breast Cancer Action  
15 to help recruit patients for its Phase III trials,  
16 of Herceptin we agreed, provided that the drug be  
17 made available on a compassionate basis to women  
18 who, based on the biology of their cancer, might  
19 benefit, but who are otherwise ineligible for the  
20 trial.

21           While some women who were desperately ill  
22 questioned the structure of the compassionate access  
23 program, there is no doubt that the existence of the  
24 program both helped many women who otherwise had no  
25 hope and advanced the completion of the clinical

1 trial in record time.

2           Herceptin, which actually improves both  
3 overall survival and quality of life for some  
4 patients, was approved with record speed.

5           Genentech's willingness to work with the  
6 advocacy community to make compassionate access  
7 available came after long and often contentious  
8 battle. It is clear now, however, that the model  
9 works.

10           The FDA can and should facilitate this  
11 kind of collaboration by requiring that a  
12 compassionate or expanded access program be part of  
13 Phase III clinical trials for breast cancer and  
14 other cancer drugs.

15           Thank you.

16           MR. BARNETT: Thank you.

17           Our final speaker in this section is  
18 Dr. June Fisher of the Trauma Foundation.

19           Dr. Fisher.

20           DR. FISHER: I would like to thank  
21 Dr. Henney and the FDA staff for giving me the  
22 opportunity to present our project's perspective in  
23 regard to Safety Assurance in Clinical Trials.

24           I believe I will be presenting a unique  
25 perspective, one that was presented to the FDA as

1 the invited panel speaker in August and again in  
2 December when we did a seminar for the FDA college.

3 I speak to you from the perspective of an  
4 internist and occupational health practitioner who  
5 for the past ten years has conducted an NIH-funded  
6 research project involving line health care workers,  
7 industrial hygienists and project designers to  
8 promote the development of safer medical devices to  
9 prevent health care worker exposure to blood.

10 I would like to say, the workers we worked  
11 with are the ones who never have a say in the whole  
12 process, and today, although I am speaking as a  
13 professional, I hope I can present also their needs  
14 and their perspectives.

15 Some of the outcomes of our research  
16 project are actually now being widely used by  
17 manufacturers as benchmarks and performance  
18 standards and by health care organizations and  
19 unions for evaluation and selection of devices.

20 I am an Associate Clinical Professor of  
21 Medicine, UCSF and the Senior Scientist at the  
22 Trauma Foundation, San Francisco General Hospital,  
23 and from 1990 to 1999 a lecturer in product design,  
24 School of Engineering here at Stanford.

25 I have to parenthetically tell you, I

1 can't handle any of this technology, if I had to do  
2 that.

3 I really work with need-finding with the  
4 students and not the technology.

5 Working over these years both on specific  
6 research projects and the academic area of device  
7 defining and health care we have identified many  
8 needs in these areas and present a very few today.

9 I first would like to address the  
10 erroneous but widely-held belief that patient and  
11 worker safety are at odds with each other. This is  
12 one that even most workers have. We value that  
13 workers put the patients first, but as an  
14 occupational health physician and a public health  
15 physician I feel that both of their needs to be  
16 tended, and that it is very clear that patient and  
17 health care safety needs are intimately linked. The  
18 healthy worker is one that can do a job, and  
19 certainly I think we are beginning to understand  
20 that when we talk about medical error.

21 I do not have time tonight to develop a  
22 concept and to present specific examples, which we  
23 could. I would like to suggest that the FDA create  
24 a task force to develop a physician paper  
25 that explicates such a perspective and that

1 promulgates policies to be included in both device  
2 and drug development.

3           This is not a new concept for the FDA,  
4 Your own Human Factors group has written on this.

5           To paraphrase them: Medical error is both  
6 a result of human behavior and those occupational  
7 factors of work environment, work organization and  
8 device efficacy and safety.

9           Within the critical efforts to reduce  
10 medical errors we should address these factors by  
11 support of user-based research and by regulation to  
12 assure that this is incorporated into the  
13 manufacturing process of device and drug  
14 development.

15           Specifically, I would like to recommend  
16 that all device and drug reviews include user-based  
17 design and exposure considerations.

18           As excited as I am about new ways to  
19 deliver drugs, and I must say it's very exciting  
20 that all the new areas are coming, I wish I was only  
21 20 years younger, so I could more actively  
22 participate.

23           I foresee that these may present  
24 unacceptable exposures to the health care workers  
25 unless such potentials are explored and mitigated

1 during research and development phases, and that  
2 such data be required as part of the approval  
3 process.

4           I would also like to propose that more  
5 emphasis be given and requirements mandated for  
6 better preclinical simulation studies, which you do  
7 require for the devices.

8           In our own work we have isolated a series  
9 of critical factors that should be part of a  
10 simulation so that it really approximates the real  
11 work environment.

12           Most manufacturers, I have talked to a  
13 number of them in the area, most of the area we're  
14 working in, do not include such element in these  
15 stimulations. An orange in a conference room to  
16 test a syringe is hardly a useful simulation.

17           We need standardized, systematic methods  
18 that really replicate the clinical environment.  
19 Such studies are not expensive and should be  
20 required in the FDA review.

21           We have also found a deficiency in  
22 clinical trials in regard to health care worker  
23 safety. Clear guidelines do not exist, and in  
24 general, such trials are haphazard.

25           The most common scenario is to toss some

1 samples out to workers without any training and come  
2 back sometime later, sometimes this is three weeks,  
3 sometimes six months, sometimes a year later, and  
4 ask them if they liked it or not. Most common, the  
5 user rejects it without even having tried it. So we  
6 are implementing devices that have never really had  
7 their clinical trials.

8           We would like to see the FDA promote such  
9 guidelines so that we have systematic data that can  
10 be collected and pooled so that we can evaluate both  
11 patient and worker outcomes and not have to wait  
12 five years to find out a device is not effective.

13           Given these time constraints, I can only  
14 allude to a few critical needs. There are many  
15 more, in device development and evaluation that will  
16 promote both patient and health care worker safety.

17           My final remarks is a plea that line  
18 health care workers who will be using these devices  
19 on a day-to-day basis be included in the entire  
20 process of need finding, design development and  
21 evaluation. Tapping their considerable expertise  
22 should enhance both patient and health care worker  
23 safety outcomes.

24           I also would parenthetically say, it would  
25 save some manufacturers from major disasters, which

1 we have seen.

2           This should be encouraged by the FDA.

3           I would also like to finally conclude, we  
4 are a very small project, but we would be very happy  
5 to work with you to promote this perspective.

6           Thank you very much.

7           MR. BARNETT: Thank you, Dr. Fisher.

8           Let me pause now and ask the panelists if  
9 they have any comments or questions to ask of the  
10 speakers.

11           DR. ALPERT: I recently was working in the  
12 area of medical devices, and I think the idea of  
13 looking at some way to look at the simulations of  
14 the real world, both pre- and post-market is a very  
15 interesting idea. Might be one that -- that some  
16 ideas could come out of. I think that's a -- a very  
17 fertile area for the medical device industry as well  
18 as for the Agency.

19           DR. FISHER: We are actually working on a  
20 manual that should be available --

21           MR. BARNETT: Dr. Zoon.

22           DR. ZOON: I want to thank all the  
23 presenters.

24           I think the comments were very good, and  
25 actually, many of the comments suggested are areas

1 that we have been thinking along the lines of. So  
2 it's just -- actually, my initial reaction is quite  
3 positive in terms of some of the suggestions because  
4 issues of, especially in the areas of clinical  
5 trials and the safety of clinical trials, while gene  
6 therapy has -- has been in the limelight, actually  
7 point out issues that we should consider across the  
8 board in conduct of clinical trials.

9           A great deal of effort by the Agency in  
10 recognizing this has been looked at through the  
11 International Conference on Harmonization where good  
12 guidance practices have been developed for good  
13 clinical practices.

14           But clearly, as the environment changes  
15 and the complexities of the environments change with  
16 new types of technologies and medicines and how they  
17 are developed and tested in different environments,  
18 clearly one needs to look at, more importantly,  
19 issues related to not only product development but  
20 clearly, a focus on patient safety.

21           Making sure that balance is achieved I  
22 think is very much a responsibility of FDA, but not  
23 a responsibility of FDA alone. I think the idea of  
24 leveraging in this area is important and good  
25 considerations.

1           Many of the suggestions I wrote down  
2 and will certainly take back and think about with  
3 others, because they affect more broadly across the  
4 whole Agency, and I wouldn't want to speak for  
5 everybody on that, but in the areas right now in  
6 gene therapy where we're dealing particularly in the  
7 Center for Biologics and working with our colleagues  
8 in the field the whole issue of bioresearch  
9 monitoring, good clinical practices, educational  
10 outreach, has to be done in a back-and-forth setting  
11 and with everybody participating, because in an  
12 environment where if something happens it not only  
13 reflects on the one individual who may have made an  
14 error or may have not communicated something  
15 properly that affects the patient safety, that can  
16 actually impact on a whole scientific field and the  
17 credibility of the field like gene therapy.

18           So it becomes an issue of: How do we  
19 promote good safety? How do we really have informed  
20 consent for patients? How do we really work to  
21 educate people? How do we at FDA make sure that  
22 once we've educated, those rules are abided by?

23           People do a good job at monitoring their  
24 patients; do they have plans in place, how they do  
25 that.

1           I think many of the issues you raised are  
2 very important and certainly food for further  
3 thought. So, I thank all of the presenters in that  
4 regard.

5           MR. BARNETT: Thank you.

6           Dr. Henney.

7           DR. HENNEY: I would just come back to the  
8 other part of this that was raised by a couple of  
9 the speakers.

10           Clearly, the focus on the pre-market or  
11 the pre-clinical work in terms of the proper conduct  
12 of clinical trials but -- the broader continuum of  
13 the need to really look again at the whole  
14 post-market arena, how do we learn from it, how are  
15 the feedback loops in place so that the correct  
16 decision can be made, the Agency actually issued a  
17 report in this whole area last May in terms of the  
18 risk management system, if you will, from the  
19 earliest phases of development of product all the  
20 way through post-market. It's very clear from that  
21 report that there are many individuals and groups  
22 involved in that system. It's very important that  
23 as risk management changes, particularly in the  
24 post-market arena, that a proper and strong feedback  
25 system of signal-sending analysis, and then again

1 feedback back into the post-market area, be strongly  
2 developed. So, we are working on that mightily  
3 within the Agency, but other thoughts you have in  
4 that whole paradigm of risk management, we would  
5 appreciate very much.

6 MR. BARNETT: Thank you.

7 Anyone else on the panel want to speak?

8 Very good.

9 Let's go on to the second major topic, and  
10 that is Assuring Compliance With Safety Regulations,  
11 particularly with products that are based on human  
12 cells and tissues.

13 Our first speaker is Mr. Leland Traiman of  
14 Rainbow Flag Health Services.

15 Mr. Traiman.

16 MR. TRAIMAN: Rainbow Flag Health Services  
17 and Sperm Bank.

18 The FDA Modernization Act states the FDA  
19 will work in consultation with experts and consumers  
20 and retailers of regulated products.

21 Indeed, if one wants industry compliance  
22 with FDA regulations then industry should be  
23 consulted in the formulation of those regulations.

24 However, this was violated by the FDA when  
25 it issued proposed Tissue Banking Regulations on

1 September 30th of last year. Far from consulting  
2 the tissue banking industry as the FDA Modernization  
3 Act suggests, the FDA worked in secret and  
4 systematically ignored input from the industry.  
5 This does not inspire industry compliance.

6           Moreover, the person the FDA chose to  
7 write these regulations, Dr. Ruth Solomon, by her  
8 own biography published for an FDA seminar where she  
9 outlined the proposed regulations, showed that she  
10 was a pathologist and did not have one day of tissue  
11 banking experience. This has not inspired industry  
12 compliance.

13           When this proposed regulation was  
14 presented to Secretary Shalala's office for approval  
15 the FDA denied there was any significant objections  
16 to these regulations. Secretary Shalala and  
17 Shalala's staff had to read about these objections  
18 to these proposed regulations in the press. This  
19 did not inspire industry compliance.

20           When Dr. Solomon's boss, Dr. Jay Epstein,  
21 tried to justify these regulations as related to  
22 reproductive tissue, my field of expertise, he made  
23 statements to the press, to Congressional staffers  
24 and to the public about reproductive tissue which  
25 contradicts every article in the medical literature

1 on the subject. This does not inspire industry  
2 compliance.

3           How can this be remedied? Some very  
4 simple steps. The FDA wants to leverage  
5 stakeholders. The FDA wants to use our expertise.  
6 It's very simple. All you have to do is ask.

7           Several states already require tissue  
8 banks to be licensed.

9           It would have been a "no brainer" for the  
10 FDA to have gotten a list of the licensed tissue  
11 banks and to have asked for help.

12           This is exactly what California did in  
13 writing its proposed tissue banking regulations.

14           In the spirit of the FDA Modernization Act  
15 the State of California assembled a team of tissue  
16 bankers to assist in this task. In doing so,  
17 California recognized that the issues of blood  
18 banking, organ procurement, eye banking, milk  
19 banking, and sperm banking, were very different.

20           In contrast to the FDA's secret process,  
21 California's discussions were held in public. The  
22 public viewed and participated in the discussion.

23           California now has a proposal with wide  
24 industry acceptance, and I foresee little problem  
25 with industry compliance.

1           In contrast, the FDA's proposed  
2 regulations ignores current scientific data, and in  
3 doing so it threatens public health and safety as  
4 well as violating the civil rights of millions of  
5 Americans.

6           The FDA failed its own mandate by refusing  
7 to leverage stakeholders. This does not inspire  
8 industry compliance.

9           Far from it, if enacted in their present  
10 form there will be outright refusal to follow these  
11 regulations, and the FDA will be challenged in  
12 court.

13           The FDA could have avoided this by  
14 following the FDA Modernization Act's mandate and  
15 simply asked for help. It clearly needed it.

16           MR. BARNETT: Thank you, Mr. Traiman.

17           Our next speaker is Dr. Daniel Henderson  
18 of Calydon, Incorporated.

19           Dr. Henderson.

20           DR. HENDERSON: My name is Dan Henderson.  
21 I am the president of Calydon.

22           I have been in the center of the gene  
23 therapy controversy as I had to present to RAC -- at  
24 the last RAC meeting March 10th.

25           We are located in Sunnyvale locally. We

1 are involved in cancer therapy using adenovirus.

2 Indeed we use targeted adenovirus, a replicating  
3 virus, to treat prostate cancer.

4           We are currently in the clinic with the  
5 virus and second virus, both for locally recurrent  
6 prostate cancer.

7           More significantly, earlier this month we  
8 received RAC clearance to treat end-stage metastatic  
9 hormone refractory prostate cancer with the  
10 intravenous administration of a replicating  
11 adenovirus we call CV787. Clearly, I feel we are a  
12 stakeholder in the field.

13           After the tragic and unfortunate death of  
14 Jesse Gelsinger, which has been referred to many  
15 times already this evening, in Philadelphia last  
16 September the adenovirus gene therapy field has been  
17 going through a significant reevaluation. Some of  
18 this reevaluation has centered on the fundamental  
19 disconnect prevalent in the field of using a vector  
20 that gives transient gene expression but limited  
21 usage due to its immunogenicity to treat genetic  
22 defects that require lifelong gene expression.

23           Some of the reevaluation has been to  
24 challenge the relationships between clinical  
25 investigators, their commitment to the therapy in

1 question and their financial interests.

2           Equally important has been the need to  
3 assure the compliance of unsophisticated sponsors  
4 and clinical investigators with the rigorous  
5 manufacturing and reporting requirements of all  
6 clinical trials. I applaud and wish to express my  
7 support of all these efforts.

8           In addition, I have approached the FDA on  
9 a scientific basis. I have really been pleased and  
10 astonished at the reception that has been so  
11 positive that I have gotten as a new company.

12           I would like to express my appreciation.  
13 Since my first interaction with Phil Nagouchi five  
14 years ago -- he came in to meet me on a federal  
15 holiday, the parking lots were empty -- to my most  
16 recent interaction with Ann Pilaro last week, I have  
17 found the FDA professional, supportive and extremely  
18 helpful. I wish to express my thanks.

19           There is a point I need to make.

20           That relates to the serious adverse event  
21 or SAE perpetrated on the whole gene therapy field,  
22 and the adenovirus field in particular, for the  
23 reckless misadventures of a small minority.

24           To quantify this, let me describe the  
25 effect on patient enrollment we have experienced at

1 Calydon. In our multicenter clinical trials with  
2 adenovirus treating prostate cancer we have only  
3 treated two men since mid-October.

4           As recently as last November we projected  
5 to have treated 54 men with this virus by the end of  
6 this month. We have not been able to enroll a  
7 single new clinical site. No IRB, including the one  
8 here at Stanford, has been willing to take on a new  
9 project.

10           The inability of local IRBs to distinguish  
11 the safety of adenovirus or the appropriate safety  
12 of the therapeutic in question for the disease in  
13 question, not a single new clinical trial has come  
14 online to treat a patient. This has cost cancer  
15 patients dearly. For them a promising new therapy  
16 has been needlessly delayed.

17           The greatest misadventures have occurred  
18 at NIH-funded sites by NIH investigators who have  
19 recently started companies. Much ado has been made  
20 of the commercial interest now seen in the field.

21           However, the misadventures have come from  
22 unsophisticated new participants in the world of  
23 business. Like youngsters in a candy store or  
24 travelers in a foreign country, mischief can occur  
25 when one does not know the limits of participating

1 in new environments.

2           With the proposals of the past few weeks,  
3 NIH investigators will come up to the necessary  
4 FDA-imposed levels of clinical conduct, a level of  
5 conduct that has been known to most of private  
6 industry for decades.

7           In the case of adenovirus-based therapies,  
8 the commercial interests, including Calydon, have  
9 treated a great number of patients with cancer  
10 without mishap.

11           Going forward, I urge the FDA to  
12 differentiate the participants in the field, so that  
13 miscreants can be more readily isolated from the  
14 whole; to use a cancer example, to separate the  
15 tumor tissue from the normal tissue.

16           Negative comments, in the absence of  
17 differentiation, brings everyone down to the same  
18 level. Perhaps some balance and positive comments  
19 would be appropriate.

20           In addition, I would just like to say that  
21 I know there are several attempts to try to come up  
22 with CMC standards for the gene therapy field, the  
23 bios involved, the American Society for Gene Therapy  
24 is involved, and I would like to see that continue  
25 at the most rapid pace as possible.

1 Thank you.

2 MR. BARNETT: Thank you, Dr. Henderson.

3 Again, I'm going to turn to the panel now  
4 and see if we can get some general responses to that  
5 group.

6 I am very sorry. Dr. Siegel, please.

7 DR. SIEGEL: You've seen me before, and  
8 here I am again.

9 I'd like to thank the panel and the --  
10 the -- for having me here today. Many of my  
11 comments will actually be similar to those I gave  
12 earlier on the general clinical trial area, and I  
13 will not repeat them here.

14 The clinical development issues that are  
15 specific to this particular topic involve something  
16 which is both very frustrating and also somewhat  
17 amusing. It's known as "Founder's Disease." We use  
18 that term in our company to relate to companies  
19 which have fantastic new-tech ideas but little  
20 opportunity from their previous histories to  
21 actually work within the regulatory system that is  
22 so critical for proper development of products in  
23 this area.

24 As a result, they feel that this wonderful  
25 idea, which has such promise, can automatically lead

1 to great products and great therapies. So they  
2 pound the table and yell, "It works. It works," and  
3 try and convince the Agency in that manner that it  
4 works.

5           That is a very difficult road to hoe. So  
6 we are very empathetic.

7           My personal background involves having  
8 been a reviewer at FDA many years ago, at California  
9 Food and Drug and in a number of industry settings.  
10 So I have somewhat -- as well as being a university  
11 researcher. So I have somewhat of a mixed  
12 perspective on this area.

13           One of the things about "Founder's  
14 Disease" is that the protection of subjects and  
15 patients in the trials is considered very important.

16           On the other hand, the actual execution of  
17 the melding of the technology with the clinical  
18 trial and regulatory processes becomes very very  
19 difficult for these individuals to understand.

20           Many of these founders are the Nobelists,  
21 the prominent scientists and clinicians who are  
22 fueling the pipeline of these new products and  
23 therapies, but somehow the execution requires more  
24 guidance, more guidelines, more of a compact among  
25 the various stakeholders, including the Agency.

1           So I would suggest that the cutting edge  
2 of our vector -- research, the need for  
3 manufacturing controls as we just stated for cell  
4 substrates and the cellular and tissue-based  
5 products is very very critical. It's a difficult  
6 area. There's a lot of individual-type treatment  
7 and individual-type initiatives in the gene therapy,  
8 the cellular and tissue-based therapeutic areas, but  
9 we must somehow render the safety of patients in the  
10 clinical trials, the development of these products,  
11 the regulatory processes, congruent so that we can  
12 really have commercializable therapies and products,  
13 because that is the name of the game here is to be  
14 able to commercialize and use broadly across the  
15 patient bases that are so needy of these products a  
16 reasonably congruent, similar type of product from  
17 one back to the other, from one therapy to another  
18 in the similar areas of endeavor; and thereby render  
19 this a practicable form of treatment for patients  
20 that are out there and that are needy.

21           There are obviously many regulatory  
22 clinical concerns. I won't go over them again  
23 except as to underline my previous remarks of the  
24 need for the clinical trial process to involve much  
25 better and more rapid safety reporting.

1           There needs to be a collaboration, once  
2 again, amongst FDA, the sponsors, investigators and  
3 others. I think really that third-party review of  
4 research programs outside of the government is  
5 important.

6           I'm not sure that the NIH-based review  
7 using the RAC was a good approach, and I don't think  
8 it is today.

9           I think the collaborative approach with  
10 the Agency that's now ongoing is more effective, but  
11 very obviously there are some holes here. And the  
12 public takes one look at one incident or two or  
13 three incidents and generalizes across the industry,  
14 and that is very harmful to the Agency and to the  
15 other stakeholders in the process.

16           I think the manufacturing certification  
17 and a third-party review for cell substrate  
18 facilities and the quality control and safety for  
19 cellular and tissue-based products is important.

20           I would really emphasize the use of  
21 important state groups, such as California Food and  
22 Drug, such as the great state laboratories that are  
23 very often originally university-based or university  
24 collaborative. There is a way to harmonize the  
25 disparate therapies and the disparate technologies,

1 the adenoviral therapies and others with some form  
2 of certification so that the load can be shared  
3 between FDA and others, and so that there is some  
4 consistency given to the process of the review of  
5 safety data in this field, and also the  
6 manufacturing controls.

7           We work with many small firms, and they  
8 are fantastic intellectually, but they often do not  
9 know the first thing about preparing and providing a  
10 reasonably safe clinical trial material in a  
11 consistent fashion.

12           So I would again underline the fact that  
13 the collaborative effort could involve third-party  
14 review and some form of reasonable, cost-effective  
15 certification to render the process a bit more  
16 consistent and to take some of the load off the  
17 Agency itself.

18           Thank you.

19           MR. BARNETT: Thank you, again,  
20 Dr. Siegel.

21           Now that I got my head together, I will  
22 once again ask if the panel has any general  
23 responses to those.

24           Yes. Dr. Zoon

25           DR. ZOON: Well, one, I want to thank the

1 speakers for their comments. The first speaker was  
2 alluding to the proposed rules related to tissues.  
3 This is still an on-going process.

4           The process actually had a number of open  
5 public meetings, and the rules as they stand now are  
6 still proposed. They are not final. So there is  
7 always opportunity for comment and discussion. So  
8 I would extend that to you, and in hopes that if  
9 there are issues that you believe are important or  
10 problematic we would like to hear them, and so I --  
11 I hear your concerns, and certainly if you have  
12 specifics with respect to the rule we would like  
13 very much to --

14           MR. TRAIMAN: Oh, you've heard my  
15 specifics before.

16           DR. ZOON: And we actually -- the ones I  
17 know of are being discussed with the Center for  
18 Disease Control, and we're looking into a number of  
19 the issues surrounding it. So I think hopefully  
20 scientific data and discussion will help illuminate  
21 some of those issues.

22           MR. TRAIMAN: I want to say that you say  
23 there were a number of public meetings. I was in  
24 first contact with the FDA and the CDC about this  
25 over three years ago and was not informed about any

1 of these public meetings. So the idea that you are  
2 actually trying to leverage stakeholders, I don't  
3 understand why you simply do not adopt what  
4 California did. California did not engage in a  
5 radical process. It did it under a conservative  
6 Republican governor. And it came up with tissue  
7 banking regulations that everyone feels comfortable  
8 with and can live with.

9           For -- for one person to sit in her office  
10 and to write these regulations in secret are  
11 antithetical to a democracy, and I think you need to  
12 start over again.

13           They are not appropriate.

14           MR. BARNETT: I want to move it along from  
15 here. So let's go on to another response if we can.

16           DR. ZOON: And I -- yes. I wanted to go  
17 on to the other issues with respect to gene therapy.

18           A number of points have been raised, some  
19 of them, again, reinforcing the need for additional  
20 guidance, and also for some of the issues  
21 surrounding interactions and looking at the quality  
22 of data monitoring that's going on. And I think  
23 these are all important initiatives that we will  
24 continue, as I said earlier.

25           We appreciate the opportunity to work with

1 others and would certainly be happy if people  
2 submitted guidances, white papers, whatever, for the  
3 Agency to look at in consideration for future  
4 leveraging activities.

5           So, thank you.

6           MR. BARNETT: Yes.

7           DR. MASSA: To the issue of viral vectors  
8 and CMC controls of viral vectors, I'm not sure if  
9 you are aware that the USP is in the process of  
10 writing a General Chapter, I believe it's 1046, and  
11 that will be providing some very specific comments  
12 about how these products are -- will be manufactured  
13 and controlled even to the point of describing --  
14 because many of these products are prepared at the  
15 site of administration, what those facilities should  
16 be like as well.

17           So there has been a very collaborative  
18 process involving industry, academia and FDA to put  
19 those guidances together.

20           The other issue regarding adverse events  
21 and adverse event reporting with regard to these  
22 products is of concern for big industry, small  
23 industry, as well as the public.

24           And I think one of the things that people  
25 have to recognize is that there are very clear rules

1 out there right now about adverse event reporting.

2           And I think the key is not that we need  
3 additional regulation and guidance; what we need is  
4 education so that the current rules can be followed.

5           Because if the current rules were  
6 followed, we would not be in the situation we are in  
7 right now.

8           And I know that the challenge has been  
9 made to certainly the bigger pharm. companies to  
10 cooperate with CBER to provide some educational  
11 seminars to individual investigators and smaller  
12 companies to explain how we conduct clinical trials  
13 and how we handle adverse event reporting and CMC  
14 issues.

15           And we are going to sit down and talk  
16 about how we can leverage that relationship to  
17 provide that information to the general public.

18           MR. BARNETT: Thank you.

19           Anyone else on the panel?

20           If not, let's go on to the -- to the next  
21 area. We have one speaker here, that is on Patient  
22 Consumer Education on the Safe Use of Products.

23           Ms. Barbara Brenner, again, would like to  
24 speak with us.

25           MS. BRENNER: Thank you for the

1 opportunity to address you again on the subject of  
2 Patient Consumer Education and the Safe Use of  
3 Products.

4           As the Director of a breast cancer  
5 education organization I can tell you I know what it  
6 is to try to explain risk to people.

7           And I am aware of the challenges of  
8 educating the general public on that issue.

9           In the context of safe product use,  
10 however, the greatest challenge we now face is  
11 direct-to-consumer advertising of pharmaceuticals.  
12 The example of tamoxifen is telling for what it  
13 indicates we should and should not be doing to  
14 educate the public about both the risk of illness  
15 and the safety of drugs.

16           Breast Cancer Action has been following  
17 tamoxifen since the organization was founded in  
18 1990, and we have been concerned about the use of  
19 the drug in healthy women since its use first began  
20 in the National Cancer Institute's Breast Cancer  
21 Prevention Trial.

22           We opposed the FDA's approval of a new  
23 label permitting the marketing of tamoxifen to  
24 healthy women, and our fears are being borne out  
25 with every passing day.

1           AstraZeneca, the manufacturer of the drug,  
2 is engaged in a huge marketing campaign, to get  
3 women to ask their doctors about Nolvadex, which is  
4 the trade name for tamoxifen. This  
5 direct-to-consumer advertising is largely in print,  
6 though some television advertising has been done.  
7 The first print ad which appeared in women's health  
8 magazines was the subject of a detailed  
9 cease-and-desist letter in January of 1999. Since  
10 then, the company has developed both new print ads  
11 and television ads that are equally problematic but  
12 more subtle.

13           The print ads for Nolvadex are misleading,  
14 but not in any way that Jane Doe consumer would  
15 notice. They generally feature a young woman,  
16 though young women are at considerably lower risk of  
17 developing breast cancer than older women are.

18           The ads encourage women to know their risk  
19 assessment number, though the risk assessment test  
20 is one that has been seriously criticized because it  
21 omits key information. The ads heavily imply that a  
22 risk score of 1.7 makes you a good candidate for  
23 tamoxifen, even though in the study cited in the ad  
24 and on which the new label was based, less than one  
25 quarter of the participants in the trial had risk

1 scores lower than 2.0.

2           The numerous dangers of the drug appear  
3 mostly in fine print.

4           In the face of this advertising, educating  
5 the public about the true risks and benefits of  
6 tamoxifen takes far more resources than any one  
7 non-profit organization can muster. This is  
8 particularly so since so many cancer organizations  
9 receive funding from AstraZeneca and are  
10 consequently unwilling to put all the facts on the  
11 table.

12           Some of them, in fact, help the  
13 manufacturer by promoting the drug without any  
14 attempt to balance the one-sided information  
15 that AstraZeneca provides.

16           While tamoxifen is an egregious example of  
17 the problem, it is certainly not the only one. In  
18 the breast cancer arena, the marketing of  
19 raloxifene, known as Evista, presents some similar  
20 problems.

21           The public's health requires that the FDA  
22 take whatever measures are necessary to stop  
23 direct-to-consumer advertising by powerful  
24 pharmaceutical companies. Risk management will be a  
25 meaningless phrase so long as drug manufacturers can

1 promote their products directly to the public.

2           Breast Cancer Action believes that until  
3 direct marketing ends, the FDA should require  
4 pharmaceutical companies to submit all  
5 advertisements for approval prior to dissemination.

6           To do otherwise leaves the public in the  
7 untenable and hopeless position of trying to inform  
8 itself from misleading advertisements about the  
9 benefits and risks of powerful drugs.

10           Collaborations between the FDA and the  
11 pharmaceutical industry will not advance the cause  
12 of safe product use. In the area of risk  
13 management, the FDA must find and work with  
14 organizations that are independent of the profit  
15 motive that drives drug marketing.

16           Thank you.

17           MR. BARNETT: Thank you.

18           And let me again ask the panel to respond  
19 if there are any questions or comments.

20           Yes.

21           Ms. Holston.

22           MS. HOLSTON: Let me just say that I agree  
23 wholeheartedly with the fact that communicating risk  
24 is a very difficult and complex area. And that is  
25 really one of the reasons why it's so important for

1 us to find partners who can help work with us to  
2 share that responsibility.

3           I think that the "Take Time to Care"  
4 program is prime example of not only working with  
5 the industry in some cases, but also working with  
6 consumers and state and local governments and others  
7 organizations to help present balanced messages  
8 about the safe use of medical products.

9           And so, what we're striving for are  
10 opportunities to present those balanced messages  
11 across the board, and I appreciate your comments and  
12 would welcome an opportunity to work with your  
13 organization or similar organizations to come up  
14 with messages that you think could communicate risk  
15 as appropriately as possible for certain targeted  
16 audiences in order to make certain that the messages  
17 that get through to them are, in fact, balanced.

18           MS. BRENNER: I'll be in touch. Thank  
19 you.

20           MR. BARNETT: Okay. Our next topic is  
21 Safety Related Research, particularly chip  
22 technology, and our speaker here is Dr. Walter Koch  
23 of Roche Molecular Systems.

24           Dr. Koch.

25           DR. KOCH: Just a couple overheads, if I

1 could. I'm standing in for Dr. Tom White, Senior  
2 Vice President of Research, who unfortunately had a  
3 family emergency this afternoon, was unable to  
4 attend.

5 I am here to respond to the opportunity  
6 that the NCTR has identified for collaborating on  
7 development of DNA microarrays as addressed --  
8 applied to safety-related research opportunities.

9 There is a growing concern in this country  
10 about adverse drug effects, as evidence by  
11 numerous publications in the scientific literature  
12 as well as two recent government reports, one by the  
13 Institute of Medicine in December as well as a more  
14 recent one from the Government Accounting Office.

15 The FDA has been monitoring adverse drug  
16 effects for a long time with a spontaneous reporting  
17 system that gathers information from various  
18 sources, and in fact, it understands the need to  
19 improve this, better improve the data collection  
20 analysis, and is expanding an adverse events  
21 reporting system currently being developed.

22 I want to talk to you about how  
23 microarrays can play a role in improving drug safety  
24 and efficacy.

25 The microarrays review can do two things

1 that can help here. One is genotyping, and the  
2 other is DNA expression, RNA expression profiling.

3 I am going to use this as an example of  
4 how the genotyping can work. This is one of many  
5 such examples, but all drugs and xenobiotics are  
6 subject to transformation in the body metabolism.

7 This is an example or a depiction of some  
8 30 genes known to affect the metabolism of most  
9 drugs that are currently used. There have been  
10 genetic polymorphisms detected in each and every one  
11 of these, and in those slices of pie that are most  
12 removed from the pie that have been demonstrated to  
13 have clinical impact.

14 Now, the drugs that are affected by these  
15 enzymes are not obscure agents. They are used every  
16 day to treat millions and millions of people with  
17 cardiovascular disease, with psychiatric disorders,  
18 and many many other diseases. Just a simple example  
19 that many of you may relate to, seven to ten percent  
20 of you gain no analgesic benefit from codeine  
21 because you lack the 2D6 enzyme and can't convert it  
22 to morphine. It may not hurt too long when you go  
23 to the dentist, but you will notice it.

24 So, the impact of being a poor metabolizer  
25 as this is termed -- genetically determined poor

1 metabolizer ranges from rather benign syndromes like  
2 nausea, dizziness, excessive sedation, to far more  
3 serious, life-threatening ones such as internal  
4 hemorrhaging with Warfarin, cardiotoxicity or  
5 arrhythmias, and in fact, there are case reports of  
6 individuals who have suffered such effects.

7           I could not talk about microarrays without  
8 showing you one of these pretty images of the  
9 fluorescence hybridization patterns. This is an  
10 example of an assay that we are co-developing with  
11 Affymetrix here in Santa Clara, a CYP450 genotyping  
12 tool, which hopefully will find use in clinical  
13 practice as well as in clinical trials.

14           But this is, the same technology, the  
15 oligonucleotide microarrays, can also be applied to  
16 examine the expression of literally hundreds of  
17 genes simultaneously, and has actually allowed  
18 science to be done in a way unlike what was  
19 previously mentioned, hypothesis-driven research,  
20 one can now use data mining techniques and  
21 informatics, too, in a query-independent manner,  
22 with no preconceptions or no expectations, look  
23 at mechanisms underlying toxicity.

24           We believe that this technology -- or that  
25 this affords a tremendous opportunity for technology

1 and information sharing, for identification of  
2 common resources for medical and scientific studies,  
3 for participation, ongoing dialogue with public,  
4 government, private and academic groups, as well as  
5 to share educational packages to better understand  
6 the role of genetics and genomics in improving drug  
7 safety.

8 Thank you.

9 MR. BARNETT: Thank you, Dr. Koch.

10 Again, let me ask the panel if anyone  
11 wants to respond in any way.

12 DR. CASCIANO: Yes. I will.

13 I would like to thank Walter for his  
14 comments. Sounds like you are presenting work that  
15 we're developing at the NCTR, and we feel it's very  
16 important methodology that's not only applicable in  
17 drug -- design of individual drug for clinical  
18 evaluation but also in all of the various  
19 toxicological disciplines available.

20 So it has a broad spectrum of  
21 applications, and we feel that it's very complex as  
22 you -- as you've shown by -- by the amount of  
23 information that's developed from one single --  
24 single run.

25 So that there is a high requirement for

1 collaboration and leveraging between academia,  
2 industry and government, and we are pleased to  
3 respond.

4 MR. BARNETT: Thank you.

5 Yes.

6 DR. ZOON: Yes.

7 I think the whole area of bioinformatics  
8 is going to be really a major advance in the next  
9 decade in both understanding biomarkers and  
10 assessing what might be the right match for a right  
11 tumor for -- with the right drug, and all the  
12 knowledge that we can gain from some of this as well  
13 as using it as a model for toxicity is going to be  
14 very important. I think it will have major roles in  
15 drug development as well as looking at adverse  
16 events.

17 We also see it as important in looking at  
18 mechanisms of actions of molecules because of how  
19 one can induce certain proteins and signal  
20 transduction mechanisms that then can be implemented  
21 in looking at how -- some of these medicines may  
22 work.

23 So, I think it's an extraordinary  
24 opportunity in many ways to leverage, and I thank  
25 you for presenting.

1 Thank you, Dan.

2 MR. BARNETT: Anyone else?

3 Okay. Our final speaker is going to be  
4 talking to us about the role of leveraging in food  
5 safety. And that's Ms. Laurie Girand.

6 MS. GIRAND: Close enough.

7 I want to thank the previous speakers.  
8 Whenever I come to one of these meetings I learn an  
9 awful lot about pharmaceuticals and the drug  
10 industry.

11 I am an advisory member of STOP, Safe  
12 Tables Our Priority, and the mother of a child who  
13 consumed unpasteurized apple juice and developed a  
14 life-threatening kidney failure as a result.

15 While your original agenda didn't address  
16 the need for collaboration with food safety  
17 stakeholders, we felt it was important for us to  
18 come forward to indicate that there is a need for  
19 greater collaboration with consumers about food  
20 safety, and in particular, at-risk groups.

21 In the three years since I've been working  
22 with CFSAN, CFSAN has taken giant leaps forward in  
23 an effort to keep us informed of CFSAN's activities,  
24 and for this we are extremely grateful. Inquiries  
25 that went unreturned three years ago are politely

1 and promptly returned today. And even out here in  
2 California we now receive notice of Federal Register  
3 documents.

4           We credit Joe Levitt with taking enormous  
5 strides forward within CFSAN by making it responsive  
6 to parties that express interest.

7           Still, there is much more we could ask  
8 for. Consumer groups may not be able to offer FDA  
9 the funding opportunities that would make us perfect  
10 partners for ambitious research projects, but we  
11 have expertise and constituencies to offer.

12           Our ideas tonight focus on the creation of  
13 messages for consumers and the chain of  
14 communication by which they may ultimately arrive at  
15 the target audience.

16           Here are our suggestions:

17           First, it is crucial that your overall  
18 food safety publicity and education campaigns  
19 effectively target consumers.

20           FDA needs to evaluate the effectiveness of  
21 its publicity and education campaigns.

22           Last year you issued an important press  
23 release warning consumers about health hazards  
24 associated with sprouts. Today we have been unable  
25 to find any consumer that has heard of this warning,

1 small sample in California.

2           We believe that the format of your  
3 publicity about recalls and food safety warnings is  
4 not conducive toward greater publicity.

5           Similar to the situation with sprouts, you  
6 tend to issue a press release and wait for the press  
7 to call. Consumers would suggest you need a  
8 standard format, such as a chart, you can issue to  
9 newspapers weekly or biweekly. With a standard  
10 format, the press could just republish the box,  
11 instead of assigning a writer to generate an article  
12 around the data, which would subsequently be buried  
13 in the back of the newspaper, anyway. Generally  
14 readers would become familiar with such a box and  
15 would learn to look for it.

16           Second, messages directed toward consumers  
17 should be run past consumer groups before they go  
18 into print. You produce campaigns where the most  
19 critical information, like the fact that a disease  
20 is life threatening, is buried. You overpromote  
21 nutritional information, while spending virtually no  
22 publicity, time or money on warnings.

23           In my own family's sad situation, we were  
24 led by FDA promotions to believe that juice  
25 qualified as one of the daily servings of fruit and

1 vegetables that we are supposed to push on our kids.

2 No one said it should be pasteurized juice.

3           Consumer groups can offer you the broad  
4 perspective you need to understand the impact of  
5 your combined campaigns while helping to ensure that  
6 the right messages come through.

7           Here is an example:

8           You have a risk communications group  
9 developing a list of questions directed toward focus  
10 groups, pregnant women in particular, about Listeria  
11 in order to help develop messages. Though STOP has  
12 victims who have suffered the worst from Listeria,  
13 we have yet to be asked to review focus group  
14 questions to determine if they could have changed  
15 victims' behavior prior to their illnesses. We have  
16 valuable information to offer and await a chance to  
17 become involved.

18           Third, the distribution channel for the  
19 bulk of your food safety educational programs is  
20 places where nutrition and cooking are taught; yet  
21 the at-risk groups generally aren't going there.

22           Instead, you need to work with key  
23 constituents and authorities who can deliver the  
24 message, including the AARP, the National PTA, the  
25 American Academy of Pediatrics, the American College

1 of Obstetrics and Gynecologists. You need to target  
2 the audiences for when they are most receptive to  
3 information through the most popular avenues, such  
4 as the book, "What To Expect When You Are Expecting"  
5 for pregnant women.

6           Here's an example of the type of program  
7 FDA should do to target food safety messages toward  
8 parents:

9           At STOP we have developed a brochure  
10 called, "So Your Baby is Starting Solids." From a  
11 timing standpoint it targets parents at the point at  
12 which they need to be most wary and at a point at  
13 which they are receptive to new information. It  
14 describes all the foods a parent should be concerned  
15 about today, and importantly, why they should be  
16 cautious. It could be distributed by pediatricians.  
17 We have the relationship with the American Academy  
18 of Pediatrics. FDA could help us partner with other  
19 companies to help us fund this particular thing,  
20 because as with the Breast Cancer Action group, we  
21 don't have the funds to produce this brochure.

22           Fourth, if you want to use the internet  
23 most effectively, it would be very inexpensive to  
24 develop an e-mail information distribution channel.  
25 There are internet sites devoted to health targeting

1 very specific groups, parents, arthritis patients,  
2 breast cancer patients, AIDS patients.

3           The parent sites already pick up important  
4 recall information from the Consumer Product Safety  
5 Commission and the NTSI. They are thrilled to have  
6 current information of value to their  
7 constituencies. You could pay a college intern  
8 almost nothing to set up this system of notification  
9 about recalls and outbreaks, and yet you would see  
10 instant results.

11           Lastly, you should be aware that  
12 pathogenic food safety is an area of FDA that does  
13 not have a single consumer on its advisory panels.  
14 We ask that you address this oversight.

15           We greatly appreciate the opportunity to  
16 speak to you tonight, and thanks to the  
17 pharmaceutical people for listening.

18           MR. BARNETT: Thank you very much.

19           Panelists?

20           DR. HENNEY: I just wanted to have one or  
21 two responses.

22           You know, the FDA is the great divided  
23 organization into medical and edible. So we are  
24 glad to hear from the edibles.

25           We have been working very hard this year

1 in terms of developing the strategic plan under the  
2 President's Food Safety Initiative.

3           And very big portion of that particular  
4 plan is targeted, I think, right where you are and  
5 where we need to be in terms of risk communication.

6           We have, I think, been frustrated, too,  
7 about knowing just how to go about this. I'm glad  
8 our press office is here as well to hear some of  
9 your statements because just issuing the press  
10 release one time to hit or miss different  
11 publications and only a one-day phenomenon isn't the  
12 most effective way to go. But you've given us many  
13 concrete examples, and I really thank you for that.

14           I think that we really do need to do a  
15 better job, particularly for vulnerable populations,  
16 but to get the message out again and again and again  
17 for as long as it's needed.

18           This whole issue of sprouts has been quite  
19 an interesting one. At the main headquarters  
20 building where the FDA resides, our head of the  
21 emergency outbreaks has continually told our  
22 cafeteria not to carry sprouts; and they are still  
23 on the sandwich line.

24           Susan.

25           DR. ALPERT: I'd like to thank you, as

1 well.

2           I think the issues of representation in  
3 our public meetings is extremely important. This is  
4 a very opportune time as we are looking at our  
5 advisory panel process in the food center, and  
6 that's very helpful.

7           I would also like to thank you on behalf  
8 of Mr. Levitt for the kind comments and to welcome  
9 the idea of bringing the clinical community to the  
10 table with the consumer community and trying to  
11 leverage the messages. I think that's an extremely  
12 important issue. For those who are in the medical  
13 products arena, you get the medical community quite  
14 a bit. In the foods arena it has been more  
15 difficult to attract the attention, if you will, of  
16 the clinical community, and I think bringing them  
17 together with the -- with the vulnerable populations  
18 and with all of the consumers, which we all are, in  
19 this product arena, would be very helpful. I'll  
20 take all of those ideas back.

21           Thank you.

22           MS. JONES: I would just like to say that  
23 I was very pleased to hear your comments as well.  
24 Working on the front line in the community,  
25 especially with the elderly, I get that feedback

1 often that the messages aren't very clear.

2           So in working cooperatively with other  
3 organizations, that's the way you leverage, to get  
4 that feedback to the community, as you clearly said;  
5 and also get those subtle cultural nuances in there  
6 so they can grasp the concept, grasp the idea, about  
7 whether it's "Take Time to Care, Use Medication  
8 Wisely" or don't take this; this is a high risk, and  
9 changing behavior. So I was really glad to hear  
10 your comments, and I support your efforts.

11           MR. BARNETT: Let me comment as well.

12           The FDA right now is exploring ways to  
13 better use the internet as a vehicle to transmit  
14 information. So your ideas are right on target and  
15 very timely.

16           Okay. Dr. Henney, would you like to close  
17 things out with a few comments.

18           DR. HENNEY: It's been a very good  
19 evening. We are going to still be here for a few  
20 minutes once we do close this meeting. So if you  
21 have one of us that you want to have more direct  
22 comments to we'd be glad to take those now or later,  
23 you know who we are. You've got contact points now  
24 with the Agency for issues as they might arise  
25 that -- or ideas that you have subsequent to



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