

ORIGINAL

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

STAKEHOLDERS MEETING

Pages 1 thru 216

Washington, D.C.
August 17, 1998

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STAKEHOLDERS MEETING

Monday, August 17, 1998

9:05 a.m.

Hubert H. Humphrey Building
Penthouse Conference Room (Room 800)
200 Independence Avenue, S.W.
Washington, D.C. 20201

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1 all of you who are interested would come to that meeting as
2 well--we will have a Federal Register notice out to announce
3 that meeting--to talk about what are the recurring themes
4 that we're hearing from the center-specific meetings and to
5 try to focus a little bit more on what should be in the FDA
6 plan that we will be submitting to Congress on November
7 21st.

8 As you know, the FDAMA Section 406(b) has six
9 objectives, and these objectives are what we will be
10 focusing on for the plan, and these objectives include
11 maximizing the availability and clarity of information about
12 the process of review of applications and submissions;
13 maximizing the availability and clarity of information for
14 consumers and patients concerning new products; implementing
15 inspection and postmarket provisions of the act; ensuring
16 access to the scientific and technical expertise needed for
17 the agency to meet its obligations; establishing mechanisms
18 for meeting established time periods for the review of all
19 applications and submissions by July 1, 1999; and
20 eliminating the backlog in the review applications and
21 submissions by January 1, 2000.

22 These will be the main areas of focus for the
23 406(b) plan. We are hoping to have input from all of our
24 constituents on these six objectives.

25 In addition to that, the agency has identified six

1 areas of concern that we would like to have input in as
2 well. I think Dr. Woodcock might be speaking to some of
3 these more specifically from the CDER perspective, but I
4 would just like to highlight these six and point you to the
5 FDA message that is, in fact, in your packet of information,
6 and it is also on our Web site, which addresses these six
7 areas in greater detail.

8 We have identified these six areas as areas where
9 we need to identify more of our focused activities. The
10 first of these is adverse event and injury reporting. There
11 are many aspects to this. It affects all of our product
12 lines, but I think the JAMA article that spoke to the many
13 thousands of unreported drug-related injuries is one that
14 gives credence to the fact that we need to focus more on
15 this particular activity.

16 We also feel that product safety assurance, which
17 is really the basic activity of the Food and Drug
18 Administration, is one that we have not spent as much time
19 focusing on and now need to direct how are we doing this
20 work and how can we possibly meet our statutory obligations
21 for this activity.

22 Product application reviews we have been spending
23 time on, and this is an area where we have been incredibly
24 successful when we have had user fees. I think the
25 Prescription Drug User Fee Act points out to us how

1 important it is when an activity is funded at the level that
2 we feel it needs to be funded, and that will then give us
3 the resources we need to meet the statutory obligations. So
4 we would like to have your input on product application
5 reviews as well.

6 In addition, there are four other activities that
7 we are focusing on. One is food safety. As you know, this
8 is a presidential initiative and one we are undertaking with
9 the Department of Agriculture as well, and we believe we
10 need to focus more on the food activity.

11 The next is outreach. We are looking to spend
12 more of our time talking to people about how we do our job
13 and getting input into the deliberations that the FDA has to
14 make about products and to get information out to consumers.

15 Scientific infrastructure and research is one of
16 the building blocks of the FDA, and we believe we need to
17 spend more time and resources on that. It is something that
18 we have neglected in the past in order to put our focus on
19 our mandatory workloads.

20 Tobacco is listed on this slide because it, too,
21 is a presidential initiative, but given the most recent
22 court ruling, I'm not sure what the FDA focus might be in
23 the future.

24 I'd like to now share with you a few numbers that
25 I think are important. This particular slide shows to you

1 the resource issues of the FDA as we see them, and what is I
2 think apparent from this slide, you will see the top line
3 running from 1993 to 1999 shows that there has been an
4 increase in the resources available to the agency, and that
5 as one looks at the FDA budget in a sort of generic sense,
6 one would think that we had grown a lot since 1993. In
7 fact, if you look at going from \$800 million to \$1.264
8 million, it is, in fact, a significant increase. But what
9 one doesn't realize is that there is, in fact, a huge
10 portion of that that has been devoted to priority programs
11 where we must by law assign resources to those activities.
12 And some of those activities have been the Prescription Drug
13 User Fee Act, the Mammography Quality Standards Act, the
14 Food Safety Initiative, and even tobacco was a line item in
15 our budget last year.

16 So, as a result, the agency has, in fact, shrunk,
17 and I think you'll see from the next chart that, in fact, in
18 addition to the mandatory programs, we have taken out those
19 and put the constant dollars in. And you will see that we
20 have, in fact, an unfunded workload in this agency that is
21 extremely important and significant in its size. So as an
22 agency, we are in a quandary of how are we to do the work
23 that is being presented to us with the shrinking resources
24 over time.

25 I would like to now tell you that we are very

1 serious about hearing from all of you in this 406(b)
2 consultative process. We have established a docket for
3 comments, and we would like you to comment, and we have, in
4 fact, established three ways of commenting. These three
5 ways of commenting are by mail, by e-mail, and then online
6 on the Internet. So we believe that this is an effective
7 process. We are looking forward to hearing from each of you
8 today. I know that we're going to learn things, and I hope
9 we're able to ask some questions that can clarify your
10 points of view and that we will be able to come to some good
11 conclusions about how we can deal with our increasing
12 workload and our shrinking resources.

13 I'd now like to introduce Dr. Janet Woodcock, who
14 will talk to you about the Center for Drugs and its
15 activities and also how it is faring in terms of resources
16 as well.

17 DR. WOODCOCK: Thank you, Linda, and good morning.
18 I'd like to welcome you all to this day. We really do look
19 forward to your input, and we very sincerely want to hear
20 from the people in this room, those who are signed up as
21 speakers and those who are just attending, about your
22 thoughts and issues of how we can do drug regulation as well
23 as possible.

24 What I'm going to talk about this morning is the
25 state, the current state of the U.S. drug regulatory system.

1 If I could have the next one?

2 Now, as you have just heard from Linda, the
3 purpose of this meeting is to get input from our
4 stakeholders. And so you may wonder why am I talking, why
5 are you going to hear from the FDA first. One of the issues
6 that we face as an agency at FDA is that we have a myriad of
7 tasks and expectations, and our stakeholders are never in
8 agreement about what we should do. And when we have a
9 meeting like this and we all come together to have input, I
10 think it's important for everyone to hear the different
11 activities that FDA is engaged in and the kind of resources
12 we put against those activities. I think that will help
13 when you comment from your point of view as you see the
14 other priorities that the drug regulatory system faces, and
15 you can see that those are important priorities to certain
16 stakeholders as well.

17 Our issue in the climate of not boundless
18 resources available, one of our issues is: How do we
19 prioritize against all of these compelling needs for drug
20 regulation in various areas? How can we best spend the
21 resources of the American taxpayers to get the best possible
22 result for drug regulation? And the best possible result
23 means, in part, what you and all our stakeholders think are
24 the most important activities that need to be accomplished.

25 Could I have the next one?

1 Now, what I'm going to do, I'm going to talk about
2 the current drug regulatory system that we have in this
3 country and the expectations that that system should
4 accomplish, all the different things that our stakeholders
5 would like us to accomplish. Then I'm going to talk about
6 the scope of activities and resources available to us to
7 accomplish these, the current level of performance that we
8 have, what are we achieving with these resources against the
9 expectations; and I'm going to go over issues that
10 stakeholders have identified for us already in each of these
11 areas. And these are many. Finally, I'm going to
12 summarize.

13 Now, the U.S. drug regulatory system, as many of
14 you know, has been in evolution for much of the 20th
15 century. We've had various acts and modifications to the
16 acts, and expectations I think were fairly low in the
17 beginning of this century because there was a terrible
18 situation out there, and that was improved and then
19 additional expectations were put on the system and so forth.

20 Our mission, as we see it now, is to promote and
21 protect the public health by assuring that safe and
22 effective drugs are available to Americans. This is a very-
23 -it's a succinct mission, but it encompasses a lot of
24 activities. This type of mission was also reiterated in the
25 Modernization Act that's just been alluded to.

1 The most recent modification to our mission in a
2 sense and to the evolution of the drug regulatory system was
3 the Modernization Act that just passed, that added
4 priorities for the agency, that added new tasks that needed
5 to be accomplished, and basically sent a message to us about
6 what Congress felt was important for us to accomplish.

7 Could I have the next one?

8 Now, when we talk about the drug regulatory
9 system, you have to remember it has multiple components.
10 The FDA more or less operates the system, and within the
11 FDA, the Center for Drug Evaluation and Research is one
12 component, is a major component of the drug regulatory
13 system and doing review is sort of the lead for drug
14 regulation. But the Office of Regulatory Affairs, known to
15 you many of you as the FDA field operation, is a key,
16 essential component which is practically--maybe half as
17 large as the Center component. Representatives of the FDA
18 field are here today, and this meeting today is about the
19 entire regulatory system, not just the Center for Drugs.

20 The Office of Chief Counsel in FDA is very
21 important in drug regulation, which in many of its aspects
22 is a legal operation, and the Office of the Commissioner has
23 many, many supportive functions for drug regulation.

24 Now, outside of FDA--and I have by no means listed
25 all the components of the system here, but we have the state

1 and local officials. We have all the state licensing boards
2 that we work with: pharmacy, medicine, dentistry and so on.
3 These are crucial components of the regulatory system that
4 was set up a long time ago, that prescription drugs are only
5 to be dispensed by licensed practitioners and through
6 pharmacies and so on. So these groups are essential parts
7 of the drug regulatory system that we have.

8 The Institutional Review Boards that operate all
9 around the country are a key component in investigational
10 work for investigational drugs. And even the Drug
11 Enforcement Agency we deal with on a regular basis for
12 scheduled drugs. So there are many other components that we
13 rely upon for drug regulation in this country, but I think
14 it's fair to say that the FDA has the lead.

15 Now, what expectations exist? And we may hear
16 more today. That's one of the reasons I'm bringing this up.
17 But what expectations exist? What is the drug regulatory
18 system supposed to accomplish for the country? Well, the
19 basic accomplishment is that all marketed drugs are
20 effective and they're safe in the context of their use, that
21 we don't have unsafe or ineffective drugs on the market.
22 That was the basic assumption that was started out early in
23 the century and has been built on. And that human drugs are
24 of high quality; this was also a very early component of
25 drug regulation because quality was an enormous problem

1 early in this century, killing many people because it had
2 the wrong ingredients and so forth.

3 A more recent imperative is the request that the
4 system allow that generic competition keep drug prices
5 reasonable and that there be a flourishing generic industry,
6 and that that have an effect on drug pricing in the United
7 States. And that is clearly an expectation that various
8 groups have of the drug regulatory system.

9 From the get-go, also, there was an expectation
10 that advertising and promotion of drugs be informative and
11 not false and misleading, because, again, at the beginning
12 of the century and all through this century, there have been
13 cases of flagrant claims made for drugs, of false claims and
14 so forth, false advertising. The system is supposed to take
15 care of that.

16 But things have evolved, and a new expectation
17 over the past decade or so that's very important to many of
18 our stakeholders is that patients who lack alternatives
19 should have access to investigational drugs because it is
20 believed that they may represent hope for those patients.
21 And the system has to be flexible enough to allow
22 investigation of drugs and drug development, and at the same
23 time try to allow access to investigational drugs for
24 patients who don't have alternatives.

25 Another expectation that is becoming more and more

1 acute is that all patient groups should have information for
2 them on how to use approved drugs so that children--there
3 should be information available on how to use drugs in
4 children. Drugs should be studied enough in children that
5 that information is available and perhaps formulations are
6 available for children. This wasn't the huge imperative in
7 the past that it is now, although it's always been very
8 important. Elderly patients, women, all kinds of various
9 subgroups, there are growing expectations that information
10 will be available that is targeted to the individual.

11 Next one?

12 And that the drug regulatory system will somehow
13 make this happen.

14 And, finally--and this is really enshrined in the
15 Modernization Act--there is a realization that at the same
16 time we keep unsafe drugs off the market, ineffective drugs
17 are kept off the market, we need to have robust drug
18 development research programs in this country, in the United
19 States, that gets drugs through the pipeline and gets them
20 available to patients, while at the same time providing
21 wonderful protection for the human subjects who are enrolled
22 in those investigational programs. And that is an
23 expectation, again, of the drug regulatory system, that we
24 will have a system that will allow drug development and
25 investigational development to flourish in this country,

1 while at the same time human subjects will be protected and
2 all investigation on human subjects will be ethical and
3 safe.

4 Now, that is, I think, some of the scope of the
5 expectations. You may be able to tell us more during today,
6 but those are some of the overarching expectations that we
7 hear for the drug regulatory system.

8 Now, just to give you an idea of the scope of the
9 activities, I'd like to go through the current processes
10 that exist to try and make these expectations happen.

11 First, as Linda was saying, we have application
12 review, and much of our work is structured around
13 application review, both the IND review, new drug
14 evaluation, and generics, which are called ANDAs, so generic
15 drug application review. But, in addition, the FDA is very
16 heavily involved in setting standards. It's a crucial
17 activity. It's less easily tracked and evaluated than
18 timeliness of application review, but in some ways, it is
19 more important.

20 We set standards, for example, for OTC drugs
21 through the monograph process. We set marketing standards:
22 How safe does a drug have to be? What is the standard for
23 effectiveness in this country? What is the standard for
24 drug quality, for chemistry and manufacturing? What is the
25 format and content of these applications that we have to

1 review? All of these require setting of standards. It's a
2 major activity.

3 Another activity that we're heavily involved in
4 that has already been mentioned is postmarketing safety
5 surveillance, also called pharmacovigilance. We sometimes
6 require postmarketing trials or registries, and we operate
7 the spontaneous reporting system that many of you are
8 familiar with. That is where doctors, health professionals,
9 others, can send in reports to the FDA about problems with
10 medicines, adverse reactions, medication errors. We have a
11 reporting system for quality problems for medicines.

12 This postmarketing safety surveillance is a
13 separate activity from application review but, again, is
14 critically tied to it because the comfort you have in
15 approving a drug through an application review process is
16 linked to the comfort you have that problems will be picked
17 up postmarketing if they occur, if they were not apparent in
18 the premarketing system. So this is an extremely important
19 process that we operate.

20 A very large number of compliance and enforcement
21 activities are done by this regulatory agency as part of the
22 drug regulatory system. Inspections have been extremely
23 important over this century in ensuring that drugs are
24 manufactured in a safe way, ensuring that clinical trials
25 are performed safely and reported accurately, and ensuring

1 that animal testing is performed correctly and is reported
2 accurately and so forth. So the inspectional program, which
3 is partly a deterrence program, partly an actual enforcement
4 program, has been extremely important.

5 We do surveillance activities, looking at a wide
6 variety of activities of pharmaceutical firms and other
7 regulated entities. There's drug sampling out in the world
8 to make sure those drugs that are out there are what they're
9 supposed to be. There's surveillance of advertising to make
10 sure that advertising is not false or misleading. There's
11 also education activities that go along with compliance and
12 enforcement, and this has long been a focus of FDA, but it
13 is more widely accepted nowadays in government that an
14 important part of ensuring compliance is working with
15 regulated entities to make sure they know what they're
16 supposed to do. But the FDA field component and CDER have
17 long worked with regulated parties to try and educate them
18 to how you have to comply.

19 But if you think of the scope of the people who
20 need to be reached, it is very mind-boggling: clinical
21 investigators, contract research organizations,
22 pharmaceutical manufacturers, hospitals, pharmacy
23 organizations and so forth.

24 Finally, if all else fails, we take regulatory
25 actions in all areas, and these sometimes are one of the

1 more high profile activities that we do.

2 Those are the core activities that you think of in
3 producing the results, but there are key, essential
4 supporting activities without which we won't get the correct
5 results in our application review or our enforcement
6 programs. One of these is research. The world keeps
7 changing. Science keeps changing. We can't be static. We
8 must continue to keep up with what's happening out in the
9 world. We have to do a certain amount of laboratory
10 research, particularly in analytical methodologies, and we
11 do laboratory research in toxicology, in animal testing.
12 Regulatory science, which is a term we use for all the paper
13 kind of scientific analyses that we do, an extremely
14 important component. And policy development, we must do a
15 lot of legal and policy research to have the correct
16 policies and make sure they're consistent with our previous
17 policies, because, believe me, if we come out with a policy
18 and it's not consistent, somebody will figure it out very
19 quickly and let us know.

20 International collaboration is an essential
21 activity. Ten years ago, I wouldn't be standing up here
22 telling you this, but the world has changed remarkably in
23 the last decade, and the industries we regulate are
24 globalized. We work extremely closely with regulators
25 around the world. Roger Williams is our liaison with

1 different activities, especially the International
2 Collaboration for Harmonization of the technical
3 requirements for pharmaceuticals, also known as ICH, where
4 we're trying to work with other regulators to make sure we
5 have the same requirements worldwide. This takes a
6 tremendous amount of effort and time, both of our technical
7 people and our management folks, to make this happen. But
8 it has become essential. It's an essential supporting
9 activity. We can't regulate in a vacuum, an international
10 vacuum.

11 Next one?

12 Communication. Now, you wouldn't think that was
13 an essential, perhaps--maybe you're going to tell us it is;
14 I'll be interested to hear--activity for a regulatory
15 agency, but it turns out to be crucial for the drug
16 regulatory system to communicate to all its various
17 stakeholders. The Center for Drugs formed an office that's
18 headed by Nancy Smith here, the Office of Training and
19 Communication. We've put a tremendous amount of effort over
20 the past five years into communicating better with the
21 outside world.

22 We have to do drug information. We are a source.
23 We have all the information because we review everything
24 with a fine-tooth comb. We need to get it out to health
25 professionals, pharmacists, all the different people who

1 need that information. Consumers want that information.
2 The freedom of information process is something we're trying
3 to improve and make information available to the public.

4 Dispute resolution is another part that we must--
5 is a supporting activity that we must do. The agency has
6 had a reputation in the past for being, quote, a black box.
7 If you disagreed with the agency, you didn't know what to do
8 about it. Well, we've tried to develop very transparent
9 channels for those who have disagreements to come in and get
10 disputes resolved. We have an ombudsman at the Center for
11 Drugs that people can call up, a very heavily used function,
12 and we have our citizen petition process that we're trying
13 to make as open and as responsive as possible. That's very
14 challenging. We may hear more about that today.

15 The Office of Regulatory Affairs has embarked over
16 the past four years on an extensive program of stakeholder
17 feedback, and they've gone all around the country and heard
18 from stakeholders about drug regulation, among other things,
19 and I think that's been an extremely important process.

20 Another supporting activity without which these
21 activities people really want us to accomplish couldn't get
22 done right is information management. That's a new activity
23 in the past decade, really. It used to be all our
24 information was in paper and you just had to slog through
25 it. That was the only approach. We're trying to use

1 information technology to manage all these processes. We
2 have no choice given the scope of the information that we
3 get, the actual physical magnitude of it.

4 Our medical library is now state of the art and
5 has put up some of these Web pages you've heard about. It
6 manages our Intranet and Internet, the information on those,
7 as well as the medical information that people need.

8 We're moving toward electronic submissions in all
9 areas. We must do this. This will help in our
10 communication with others as well, because we will have the
11 information in an easily transmissible form, and, again, the
12 Intra- and Internet has really transformed our ability to
13 interface with the outside world. But all of these take our
14 resources. We can do these or we can put more on some other
15 activity, and we need you to tell us what's most important.

16 Training. As the world changes and all these
17 things happen, we have to have adequately trained staff, and
18 we must tell the outside world and help them. We've been
19 told by the President of the United States that we must work
20 in partnership with regulated entities and not have a
21 "gotcha" mentality. So we must be out there training people
22 on our requirements and our standards and policies, and our
23 staff has to be adequately up to date and up to speed on
24 everything that we require.

25 Now, how do we do all this, and what resources do

1 we have to put against it? Well, within the drug regulatory
2 system directly, there are about 2,500 people. About 1,700
3 of them are in the Center for Drugs, and about 853 are in
4 the Office of Regulatory Affairs or the FDA field. And
5 there are other people who help support who are in the
6 Commissioner's office, and then all these other folks around
7 that I talked about: IRBs, licensing boards, and so on.
8 But these are the people we have to put against all these
9 myriad tasks and processes I was just talking about.

10 We feel pretty stretched. Just like your own
11 budget at home, you put a little bit here and a little bit
12 here, and pretty soon you've run out before you reach the
13 end of your budget. And we have the same kind of problem.
14 We feel stretched.

15 The budget, the overall budget--that's wrong.
16 Yes, three more zeros. Three more zeros. The person who
17 typed these up probably couldn't believe--you know. Yes,
18 \$283 million, \$284 million, much of that is in salary
19 dollars because of the nature. We're a people-intensive
20 organization. \$206 million of that is within the Center for
21 Drugs alone, again, primarily in salary.

22 There is an orphan products grant process, and the
23 orphan products group within the agency is very supportive
24 of the Center for Drugs and has made a tremendous
25 contribution toward getting orphan drugs developed and

1 through the system for that constituency, for the patients
2 who need them. And then the field organization also has
3 money. This includes the user fee funding that we get,
4 which is fairly substantial, this money.

5 Now, how have we distributed this amongst the
6 various components and activities that we have? Well, I
7 don't want to bore you to death this morning, so I'm not
8 going to go through chapter and verse on how much money goes
9 to patient review and how much to this and that, because we
10 really want to hear from you where you think the emphasis
11 should be. Suffice it to say, though, that a large fraction
12 of the budget is in application review, a very large
13 fraction. And a lot of this, there are historical factors
14 for how FDA and CDER and the field have allocated their
15 resources. There are direct statutory mandates. We tend to
16 try to accomplish things the law tells us to do, and we give
17 them a higher priority than things that are important but
18 aren't written in the law.

19 I want to mention that the user fee program, the
20 prescription drug user fee program that was recently signed
21 into law, again, as part of the Modernization Act,
22 constrains the allocation of resources within the Center for
23 Drugs and to some extent within the field, because for us to
24 obtain the user fee resources, we must dedicate a specific
25 amount of appropriated dollars and level of effort to the

1 prescription drug user fee process within the agency. We
2 can't drop down below that level. So that constrains a
3 large amount toward application review, toward new drug
4 application review.

5 Then I think advocacy has played a factor, and
6 that's an important thing for you to hear. Advocacy has
7 played a factor in how resources are devoted within the
8 agency. There's a misprint here. I have orphan drugs.
9 Orphan drugs is a very good example. The orphan drug--the
10 folks representing patients with orphan indications talk to
11 Congress; they talk to the agency. They got a program
12 going. That was sometime ago. They are vigorous in support
13 of that program, and that money is allocated for orphan
14 drugs.

15 This is supposed to be AIDS here. I think AIDS is
16 a good example. Everybody knows about that example, but has
17 allowed--resources have been devoted at many levels in the
18 Federal Government, research levels as well as regulatory
19 levels, to ensuring that AIDS drugs get high priority and a
20 lot of attention is paid to them.

21 Now, I would like to go through some of these
22 processes in a little bit more detail and talk to you about
23 what we perceive some of the issues today are. What is the
24 level of performance of the Center and the field in this
25 area, and what are the major issues? This may help you in

1 your comments today.

2 In the IND review, I think the current performance
3 level from our point of view is that the IND review process
4 is well managed. It is timely. We have resolved--there was
5 a large issue of trials going overseas, first-time-in-human
6 trials going overseas because of perceived requirements.
7 That issue has been resolved. We have oversight of things
8 such as clinical holds on INDs to ensure that we apply
9 requirements consistently and in a timely manner get back to
10 people if they are put on clinical hold.

11 Next one?

12 Now, many of the standards for drug development
13 have been worked out as well, as part of the ICH process, so
14 that those drug developers who are working on
15 investigational drugs are not working in the dark. There's
16 good clinical practices, which is how you conduct clinical
17 trials, that's an example, has been internationally
18 harmonized. Toxicology protocols, how to do the animal
19 testing, what should be done, harmonization there. Clinical
20 testing, a lot of parts of clinical testing have been
21 internationally harmonized. So there's a fair amount of
22 guidance out there for those who would do drug development
23 and how to do.

24 One area that isn't current and up to date in all
25 areas is for the specific indications, and it certainly is

1 not internationally harmonized. What do you have to do to
2 get an osteoporosis drug approved? What do you have to do
3 to get an AIDS drug approved? What do you have to do for
4 this indication, arthritis, dental work, et cetera? What do
5 you have to do? What are the standards? This needs to be
6 worked out right now between the particular drug developer
7 and the agency in meetings, and some of that will always
8 happen. But it is an area there is not international
9 agreement or harmonization in right now.

10 What are the issues that we're hearing about the
11 IND process? Well, we know there are new and extensive
12 performance goals under the User Fee Act, under PDUFA.
13 These have to do with the timeliness of interactions with
14 FDA and drug developers and have to do with us giving
15 advice. What are the standards? What will be required and
16 so on? So that's a challenge that we're facing, and we'll
17 be a resource consumer, but resources are provided for this
18 under the Prescription Drug User Fee Act.

19 Access is mentioned in the Modernization Act as an
20 issue, and as we put out publicly, we are working on
21 clarifying access issues and having an overall standard, an
22 approach that everyone can understand and that is
23 transparent. If people want to specifically talk to us
24 about access, they are welcome to contact me or someone else
25 in the agency, and we can set up a meeting or telecon or

1 whatever. We have been doing this.

2 The status of Institutional Review Boards and the
3 IRB system in this country, the IRBs have been coming under
4 a lot of stress over the past five years, and with the
5 change in medical care and the change in medical centers and
6 how they're supported, there's just a lot of stress in that
7 system. And I think that's an issue we're going to have to
8 try and deal with in the upcoming year or two.

9 Pediatric drug development, that's mentioned in
10 the FDAMA, and there is an incentive put in for developing
11 pediatric indications, indications for children. It still
12 remains a very hot topic in investigational drugs.

13 Now, more research needs to be done as well, and
14 as Linda said, this is something that a lot of effort hasn't
15 been put into because of all these other things. But
16 there's been a lot of call for shortening drug development
17 times, for making drug development more efficient, for doing
18 it better, for better quality. We can't do that without
19 research. The Center is working with academia and others in
20 a collaboration called the Collaboration for Drug
21 Development Improvement, or CDDI. We hope that will get off
22 the ground and will help us to do collaborative research
23 with others on how to improve drug development. It's a
24 topic that needs attention.

25 Now, what about new drug review? This has always

1 been the hottest topic, especially during the times when new
2 drug review took a very long time and was very
3 unpredictable. Well, right now, under the user fee program,
4 the new drug review is very timely. It's meeting all the
5 user fee goals that were stipulated under the act. It is a
6 much more open process than it used to be, I think. Right
7 now we have over 50--is that right, Mac?--over 50 advisory
8 committee meetings a year. These are open public meetings
9 where we have experts from all around the country in the
10 various areas. The companies present and then the experts
11 talk about whatever they want to say about that application
12 and answer questions, and the public can contribute at these
13 meetings. So the process is pretty open about both
14 controversies and successes.

15 We're also trying to improve the efficiency of
16 this process because if we keep doing it as a paper-based
17 process, it will suck up all our resources and we won't be
18 able to do anything else. So we are very successfully, in
19 collaboration with the industry, moving toward electronic
20 submission.

21 In standards, there are requirements or guidance
22 or studying children, on studying women, elderly, ethnic
23 groups, so there are standards for what you have to do in
24 getting a new drug on the market. I think these are listed
25 as standards, but these are really issues. These are

1 issues. What should be the standards for studying women,
2 for studying children? How much a requirement should that
3 be to get a drug on the market?

4 What about antibiotic resistance? This is
5 something you're going to be hearing about in the upcoming
6 years. FDA is getting to the point where we have new,
7 effective antibiotics coming up that may be the only
8 antibiotic that could treat a certain bug. Should that just
9 be allowed to be spread out through the country to the point
10 where it, too, has resistance developed to it? What should
11 be the national approach to this upcoming problem of
12 antibiotic resistance? There are going to be opinions on
13 every side of this.

14 Over-the-counter switches is another controversial
15 area. What should be the policy for making a drug over-the-
16 counter? We have been working very carefully over the past
17 couple of years, and more and more drugs are available over-
18 the-counter for people to use. But that envelope is
19 constantly being pushed or being tested. What should the
20 standard be for getting drugs over-the-counter?

21 Chronically used drugs. More and more in drug
22 development, you know, we've hit the easy diseases, the
23 acute illness and so forth. Now it's the time of the
24 chronic disease, treating chronic diseases. We can't ask
25 drug developers to study a drug for the entire lifetime of a

1 chronic disease. They may study it for one year or two
2 years, patient years total per patient. So what should we
3 do after that drug is approved? How much information should
4 be collected, and what happens if you take the drug for five
5 years or ten years or 20 years? What should we do? And
6 what power should FDA have to compel that kind of
7 information to be collected? I think this is also going to
8 be a very controversial issue.

9 Let's see. These are more issues. These are more
10 issues on standards. This has been one of the most
11 controversial areas over the past 30 years, is what should
12 be the standards for drug approval and so forth. And so
13 it's no surprise this continues to be an extremely hot topic
14 today.

15 With drug safety being a big topic right now in
16 the news, people seem to think it relates to FDA review, but
17 drug safety, one part of it relates to how many patients
18 have you studied before you put the drug on the market.
19 Have you studied a thousand patients and then it's going to
20 be taken by ten million? Is that the right ratio? How many
21 people should be studied before a drug is put on the market?

22 There's an issue of benefits to the many versus
23 risks to the few, and that's played out lately, and there
24 have been debates about this. Most drugs have serious side
25 effects, maybe a very small number of serious side effects.

1 They may benefit many, but a few people may be seriously
2 damaged, and that may be unavoidable. Where do you draw the
3 line? What is the point where that risk to the few becomes
4 unacceptable? These are issues we're struggling with.

5 Drug-drug interactions. This has been the cause
6 of taking some drugs off the market recently. They had
7 unacceptable interactions with other drugs. If they could
8 be used perfectly safely, if the doctor were able to follow
9 a 20-page instruction list, and the patient, on what other
10 drugs and whatever foods and so forth should be avoided--but
11 where do you draw the line there? That's an issue.

12 The Modernization Act has asked us to sort out the
13 standards for radiopharmaceuticals and drugs used for
14 positron emission tomography, and we're engaged in that
15 right now because that's a requirement under the
16 Modernization Act that we figure that out.

17 Now, moving to generic drugs, another area that's
18 often full of controversy, what is our current performance
19 level? Well, Doug is here. You can help me with this. But
20 currently we are reviewing more than 50 percent of reviews
21 within the statutory deadline, which is 180 days to perform
22 a generic drug review. But at the same time, the time to
23 marketing a generic drug from the time of application to the
24 time it's marketed has dropped from about 40 months in 1993
25 to 19 months in 1997, while at the same time the number of

1 generic drugs approved has gone way up. So this program is
2 performing extremely well right now. And they're doing
3 additional streamlining to try and make the process more
4 efficient.

5 However, the issues are generic manufacturers
6 would like us to put more resources into the generic drug
7 program to bring the times down even further. The Congress
8 is interested in that as well, and they've been sending us
9 letters about decreasing the time of review for generic
10 drugs. In addition, they're interested in what are the
11 barriers to generic competition, particularly innovators who
12 petition us and do other legal maneuvers to try and avoid
13 generic competition, and Congress would like to know what we
14 can do about that.

15 For research in generics, we've been engaged in
16 research over the past five or so years because if it isn't
17 a pill, it's hard to figure out how to do bioequivalence and
18 how to make sure that that generic is identical, in fact, to
19 the innovator drug. And so we need to do scientific
20 research to develop the methods to approve generic drugs
21 that aren't pills. It's a very important message, but it's
22 a thorny scientific issue.

23 I'm bringing all these things up--some of these
24 are policy, some of these are research. They all take
25 resources for us to accomplish, each one of these.

1 Now, what about new uses for approved drugs? We
2 had a new use initiative that we spent quite a bit of time
3 on, so the status of this program is we have guidance out
4 there right now. So if you have an approved drug on the
5 market and you want to bring a new use in, we have this
6 guidance document that tells you what you need to do, how
7 much data you need to develop.

8 We also have one for cancer that is a draft, FDA
9 approval of new cancer treatments and how to get cancer--new
10 uses for cancer drugs out there because the problem is that
11 many cancer drugs have many off-label uses that aren't
12 approved uses.

13 So if we move to product quality assurance,
14 another topic identified by the agency as a topic, a core
15 issue for the agency, something we need to focus attention
16 on in this stakeholder input. Quality assurance means that
17 basically when you get a medicine, when you take it home
18 from the pharmacy, you know what's in there is what is
19 supposed to be, and it's in there in the right amount and
20 it's not going to crumble up and be a little film at the
21 bottom of your pill bottle or whatever. Those products are
22 high quality; they're usable. If you have an injectable
23 epinephrine pen, we recently had a problem with that, if
24 people remember. Well, you have to rely on that if you have
25 anaphylaxis. That has to be a high enough quality that you

1 know if you get a bee sting or whatever that that's going to
2 work. That's product quality. The FDA over the past
3 hundred years, almost, has put a tremendous amount of effort
4 into improving and assuring the quality of pharmaceuticals.

5 Right now, for the most part, we see problems,
6 they're always going to occur, but marketed drugs for the
7 most part, you can rely on that drug to be of high quality
8 when you get it at the pharmacy. That shouldn't be one of
9 your worries if you're sick.

10 We've also gained efficiency because quality can
11 come at a very high cost, as everyone knows, and the
12 manufacturers have said let's try to work together to try
13 and make this as reasonable as possible, maintain quality
14 but at the lowest possible cost. And we have the SUPAC
15 process, as we call it, which is Scale-Up and Post-Approval
16 Changes. It's a whole process where we are working with
17 industry to try and make sure that when they change a
18 product, that the testing they have to do is reasonable and
19 appropriate to ensure quality.

20 However, we do have a statutory requirement in
21 product quality that we inspect pharmaceutical manufacturers
22 every two years, that we're in every plant at least every
23 two years. We're not meeting that requirement right now, is
24 my understanding. Is that right, Stephanie?

25 MS. GRAY: Yes.

1 DR. WOODCOCK: Yes, we're not quite meeting that
2 requirement because of resource issues.

3 Now, the issue for us in product quality, I would
4 say, is first of all maintaining adequate inspectional
5 coverage in the United States. How many inspectors--you
6 know, how often and how many need to be in the plants and
7 for how long to maintain that level of quality? And we've
8 thought of--various things have been suggested, having third
9 parties do some of the auditing inspections. We, CDER, have
10 suggested what we call first party, which is relying in part
11 on the quality assurance units within the firms, if they're
12 of very high quality, and that's a suggestion that we have
13 floated out for discussion. So that's one issue. How do we
14 maintain the inspectional coverage in the United States?

15 The second issue is: What about inspection of
16 foreign establishments? More and more and more
17 pharmaceuticals, bulk pharmaceuticals, are made all over the
18 world. They're made in China. They're made in countries
19 you never heard of. And how do we make sure that we--how
20 can we police all of those? How can we be in those every
21 two years? What are we going to do?

22 One thing that has been approached as trying for
23 countries that have an established regulatory apparatus is
24 mutual recognition of inspections, and we're doing that. We
25 have a mutual recognition agreement with the EU, and we will

1 be working over the next several years to see if the
2 Europeans have an equivalent inspectional process, one that
3 gets equivalent results to the United States, in which case
4 we could accept European inspections if that turned out to
5 be true. That's one method of assuring the quality of
6 foreign establishments, but it's a big challenge for us.

7 Other issues in pharmaceutical quality, the
8 standards for manufacture of bulk pharmaceuticals, which is
9 just the drug--not the pill but the chemical drug itself.
10 These are particularly made all over the world, and we are
11 working under the ICH process to try and develop standards
12 for manufacturing these. This would be extremely helpful to
13 have a common worldwide standard for quality of
14 manufacturing processes around the world.

15 Under the Modernization Act, another very large
16 effort that we are undertaking right now has to do with
17 pharmacy compounding, pharmacists making drugs in the
18 pharmacy for a specific patient because it isn't available
19 commercially. And we are attempting to follow the
20 requirements of the Modernization Act and develop a
21 regulatory scheme that will allow pharmacy compounding but
22 maintain quality.

23 Now, moving on to the area of surveillance and
24 compliance--and, Nancy, how am I doing for time? I'm fine?
25 Okay, good. There are many issues in addition to inspecting

1 firms that we need to have surveillance and compliance
2 activities on. Some of these have gotten somewhat short
3 shrift over the past few years because of higher priority
4 items.

5 Health fraud is one of them. There is a very,
6 very flourishing industry in health fraud with drugs. Most
7 of it is somewhat low level or local. We do not right now
8 put a large number of resources against various health
9 frauds. We will give them high priority if they have health
10 or safety implications.

11 A lot of people ask us about dietary supplements,
12 and I just want to remind everyone we would be interested to
13 hear your opinions. But there was an act of Congress
14 passed, and as long as dietary supplements keep within
15 certain claims, they are not considered drugs and they are
16 not regulated within the drug regulatory system. They have
17 their own system. So that is why you may see dietary
18 supplements on pharmacy shelves. They are not supposed to
19 be making drug-like claims, however.

20 There is also a large number of unapproved drugs
21 that are marketed in the United States through various
22 means, and this is another activity that FDA has not had a
23 real high priority on that we need to deal with at some
24 point. They are marketed through various mechanisms.
25 They're older drugs or have some other way they've escaped

1 the drug regulatory system. And, again, they don't--only
2 where they have health risks have we given them a high
3 priority because we have so many other needs for our
4 resources.

5 Now, another hot topic and of greater interest, I
6 think, especially to consumers, is drug marketing and
7 advertising. There are a lot of issues around this. I
8 think we have a very good program right now. Its
9 performance is vigorous and adequate, but there are issues
10 and policy issues that need to be resolved. Most people
11 cannot have missed the fact of the increased prominence of
12 direct-to-consumer advertising recently, and we'd be
13 interested in people's thoughts on this. The Modernization
14 Act has a provision for dissemination of scientific reprints
15 by pharmaceutical firms, and we have been in the process of
16 implementing. We issued a draft regulation about this.
17 It's very controversial.

18 There's a whole process going on, and I think some
19 people in this room are involved in it, in having consumer
20 information available at the pharmacy for prescription
21 drugs. So when a consumer fills their prescription, they
22 will get an information sheet. This is a voluntary process.
23 It's being watched over by the FDA to ensure that it happens
24 adequately. This is a very important issue for drug safety,
25 that consumers get adequate information on how to use their

1 drugs, and that the information they get is correct, which
2 is another step.

3 Then pharmaceutical firm's role in the whole new
4 managed care industry, how do pharmaceutical firms fit in,
5 and how does that fit with FDA's traditional method of
6 regulating what pharmaceutical firms can say about their
7 drugs? This, again, is a very controversial issue, and, of
8 course, the public has a lot of issues around switches of
9 prescription medicines and having their medicines switched
10 and so forth and the role of managed care in that and the
11 role of pharmaceutical firms, and the FDA marketing and
12 advertising regulatory scheme is right in the middle of
13 this.

14 Next one?

15 Another issue that is sort of an ongoing issue--it
16 isn't extremely hot right now, but it's human subject
17 protection. If we have a vigorous program of drug
18 development in this country, that means all the people who
19 are the subjects in these trials need to be protected, and
20 their rights and their safety need to be overseen. FDA
21 performs audits of clinical trials after they're completed,
22 and in doing so sometimes we uncover fraudulent
23 investigators. We uncover people who don't get informed
24 consent out of subjects and so on. We perform audits of
25 Institutional Review Boards that oversee these trials to

1 make sure they're doing their duty by the subjects.

2 We train the IRBs and we try to train the clinical
3 investigators. We recently had an Institute of Medicine
4 meeting on clinical trial data integrity, and one of the
5 issues that came out of that is that there needs to be more
6 training of clinical investigators. Who's going to do this?

7 International clinical trials are really going to
8 be the future. We're going to see larger trials, and
9 they're going to be done all around the world. And how do
10 we ensure consistency? How do we make sure the data from
11 those foreign clinical trials, which is usually--not always,
12 but usually of lower quality than the data we've seen in the
13 United States, where we've been working with clinical
14 investigators and pharmaceutical firms for many years to
15 improve the quality, how are we going to bring that quality
16 up to a good standard?

17 And, again, just like the rest of the world, the
18 whole clinical trial process is moving toward being
19 computerized. How do we deal with that? That's another
20 challenge that we have to face.

21 Now, right before I move on to the next section, I
22 want to talk about a subject that I think is really
23 important. That's the issues of marketed drugs, drugs that
24 are already on the market, and their safety, and how is that
25 safety assured. Everybody has to be aware that the clinical

1 testing, the premarket testing of drugs will not detect all
2 the problems. It just can't. It won't detect some of the
3 problems with the drug or some of the toxicities with some
4 drugs. And this fact is something that the public and the
5 medical and pharmacy community really needs to understand
6 better.

7 Why won't testing detect them all? Well, it isn't
8 because the review process breaks down. It's because, first
9 of all, some of the events are rare. They may occur in one
10 out of 10,000 people. And so if you test 5,000 people in
11 your clinical development program, you probably won't see
12 it. Even if you test 10,000, you may not see it; or if you
13 see it, you wouldn't believe it was related. You'd only see
14 one event. So what do we do? We know this is going to
15 happen sometimes after a drug is approved. Everybody needs
16 to know that.

17 Second of all, some problems with drugs are caused
18 by the way they're used outside of the parameters they're
19 approved for. I think phenfloramine was a good example.
20 It caused these heart valve problems. It was only approved
21 for three months' use, but it was used for longer periods of
22 time. And we see this in various ways. It may be sometimes
23 in the clinical trials people were excluded who were at
24 greater risk for some problems. So for a variety of
25 reasons, you may not see the problems before marketing.

1 In addition, sometimes we encounter errors in the
2 use of the drug, medication errors that were hard to foresee
3 prior to approval. Maybe that name, even though we look at
4 the names, maybe the name was too close to another drug
5 name, and once they get out on the market, they get mixed
6 up. We've seen cases where there was an overwrap on the
7 package and it fell down, and you couldn't see it through
8 the window, and so people mixed it up with other
9 medications. They were IV bags, and they gave the people
10 the wrong IV bags. You know, these things sometimes are
11 hard to anticipate. So for all these reasons, we need to
12 have a vigorous program after drugs are marketed, detect
13 these safety problems, and correct them as soon as possible.

14 Now, what we have right now, we have this
15 spontaneous reporting system I alluded to earlier where
16 people can report to the agency, report in all these
17 problems. We get a tremendous number of reports, about a
18 quarter a million a year. So it isn't like people don't
19 report. A lot of them are not serious events, however.

20 We are upgrading this system. Because it's very
21 large numbers of reports, it's hard to deal with them all.
22 We're totally computerizing this, and with the industry
23 we're trying to move to electronic submission of all the
24 reports. This will help us analyze these faster and get the
25 information out better.

1 But that's a passive reporting system, and so
2 we're dependent on people sending stuff in and detecting it.
3 Many people on the outside have suggested--and we'd be
4 interested in your comments--that a more active surveillance
5 is needed of different kinds; people have different
6 suggestions. But it may well be true, and we think that
7 would be a benefit to the system if there were other kinds,
8 additional types of surveillance of drug safety in this
9 country.

10 Now, finally, communications. In my opinion,
11 effective communications is linked to drug safety. If we
12 can get the information out to doctors, to patients, to
13 those people who need it about what the problems are with
14 drugs, then drugs are going to be safer. If people are in
15 the dark, then they're going to--misuse of drugs is going to
16 occur more frequently. So it's extremely important. We are
17 working on a prescription drug--improving prescription drug
18 labeling and improving OTC drug labeling. We'd be
19 interested, of course, in people's input on this. This is
20 an important resource priority for us.

21 Another thing we don't have that I would like to
22 have and the outside world is always asking us for is drug
23 development statistics. The CDC keeps health statistics;
24 other places keep statistics on this and that. But we can't
25 tell you how many cancer patients are enrolled in trials

1 right now or this or that or any other thing like that
2 because we don't have--we haven't had the resources, again,
3 to devote--we haven't devoted the resources. They haven't
4 been a high enough priority to that area, to developing
5 those kind of statistics. But as drug development becomes
6 very open and people are really interested in drug
7 development and how is it going and what are we seeing, I
8 think it would be important. It is important for us to
9 develop these kind of drug development statistics. I'd like
10 to hear what people think of that.

11 Finally, we need to do communications research.
12 We do this. We need this in the regulation of advertising,
13 and we need to do it in determining the impact that label
14 changes have on the public or other communication efforts.
15 For example, we are trying to change the pregnancy part of
16 the drug label. Why? Well, right now we have the
17 categories of--pregnancy categories, and they, we've
18 determined, do not communicate the right message to the
19 people who read them. They frighten people, and they make
20 people maybe do decisions that are not optimal. So we are
21 trying to change this pregnancy category on the label, but
22 the only way we can develop the right pregnancy label is by
23 doing communications research and doing focus groups and
24 getting out there and seeing how people actually respond to
25 different versions of the prescription label for pregnancy.

1 Doctors and even patients, what information does it
2 communicate to them? This is the kind of research we need
3 to do.

4 Now, to wind up, in summary, I would say--and
5 maybe this is self-serving, and we'll hear otherwise from
6 you all, but we think the drug regulatory system in the
7 United States right now is very effective, and it's
8 performing well against its myriad expectations for it,
9 everything from fostering drug development to providing
10 access to patients, to getting effective drugs out on the
11 market, to ensuring the quality of those drugs, and to
12 making sure they are safe and effective.

13 But there are many expectations for improvement,
14 and there are many competing priorities about what we should
15 do next, what steps we should take, what are the most
16 important unfilled needs or gaps in our regulatory programs.

17 We need to hear from stakeholders, but we need to
18 hear from informed stakeholders. I'm sorry this took so
19 long, but I hope that it gave you an idea of the scope of
20 the activities that the drug regulatory system is engaged in
21 and the meaning, the impact of shifting resources from one
22 area to another within FDA.

23 Thank you.

24 [Applause.]

25 DR. SMITH: We will now have a 15-minute break.

1 The restrooms are down the hall along your left. There are
2 two sets. And the cafeteria is on your right.

3 Immediately following the break, we will have our
4 first panel of presenters, and if they could all come up to
5 the front about five minutes before, we would appreciate it.

6 [Recess.]

7 DR. SMITH: If we could take our seats, we're
8 going to try to get started within the next few minutes.

9 [Pause.]

10 DR. SMITH: Good morning. We are now to the stage
11 where we're going to be listening to our stakeholders and
12 what they have to tell those of us at CDER. The procedure
13 we're going to be using through the morning is: Each of the
14 speakers will have 12 minutes to present their ideas.
15 Following the four presentations, we have a panel of CDER
16 leadership who will be questioning the panelists and trying
17 to help clarify and prioritize the ideas that they have
18 presented for us.

19 For the benefit of the speakers, there's a little
20 timer over here which will be green for 10 minutes and then
21 yellow for 2 minutes. Try to wrap it up. After it turns
22 red, we would like you to finish as soon as possible after
23 that.

24 I did want to say that there will be a time at the
25 end of the day for other people who would like to give us

1 comments to do so. So if you have remarks that you would
2 like to make, we would appreciate hearing them later on.

3 Also, we do encourage any of you who do not have
4 the opportunity to speak today to write your comments and
5 submit them to the docket in any of the three ways that
6 Linda Suydam mentioned at the beginning of the morning.

7 So our first speaker is John Gans from the
8 American Pharmaceutical Association.

9 DR. GANS: Good morning.

10 DR. SMITH: Would you like to go up to the podium?

11 DR. GANS: I'm not sure I want all these people
12 from the FDA behind me while I'm talking. I wasn't quite
13 used to this formality this morning.

14 Everything is sort of a little stuck together.

15 Good morning, again, and thank you for the
16 opportunity to provide ideas regarding the priorities for
17 the Center for Drug Evaluation and Research. You've heard
18 who I am. The American Pharmaceutical Association is the
19 national professional society of pharmacists, and we
20 basically speak and try to represent over 190,000 of
21 America's pharmacists. We thank you for the opportunity to
22 present today and the openness of the FDA and CDER to
23 basically hear from our members.

24 I have four or five areas that we think need to
25 basically be addressed as we move into the year 2000 and

1 beyond, and our primary focus is on trying to improve the
2 use of pharmaceuticals and to try to improve information
3 flow. We see the FDA, for the lack of a better term--and
4 this is my term--as a data warehouse, as an information
5 source. And we would like to try to figure out ways in
6 which we could unchain the bonds between practitioners who
7 utilize information, who have information for the FDA that
8 they need in decision making, and to try to open up the flow
9 back to us.

10 The first issue of priority is the need for a new
11 classification scheme for prescription pharmaceuticals. I
12 am not talking about a third class of drugs. I'm talking
13 about a new scheme for prescription pharmaceuticals.

14 All of us are aware of the steadily mounting
15 evidence of morbidity and mortality attributable to underuse
16 and misuse of prescription pharmaceuticals. This evidence
17 has recently spilled over from its historical confinement in
18 the pages of medical journals to play out every day in the
19 lay media. The media, with the public not far behind, are
20 demanding more and more accountability from manufacturers,
21 pharmacists, and physicians.

22 Part of the problem is the fact that health
23 professionals are being pushed by economic pressures into
24 spending less and less time with each patient. In addition,
25 the now ubiquitous use of formularies puts prescribers in a

1 particular position of being pressed to prescribe
2 pharmaceuticals which they have less and less familiarity
3 with than the original product that they have gained great
4 experience. These marketplace trends make it difficult for
5 prescribers and pharmacists alike to remain alert to the
6 risks. Let me give you a few examples of this.

7 In the nine years that I have been in Washington,
8 I started out with Closuril (ph), we dealt with Acutane, not
9 probably too well, and we've just recently dealt with
10 Talbudomide (ph), which I hope does work very well. And in
11 the middle somewhere along the line, we took anabolic
12 steroids and made them a controlled substance.

13 Essentially, the FDA has very tightly controlled
14 hands from the standpoint of where it can classify a drug.
15 Yet on the approval side, they can classify a new
16 breakthrough product and move it through the approval
17 mechanisms very, very quickly. Yet at the same time, the
18 way we classify them is one category or maybe a controlled
19 substance. We think it's time that a new categorization be
20 done where products with particular problems could be
21 categorized not from a lack of distribution or anything like
22 that, but to then be put into our computer systems to alert
23 pharmacists, physicians, and consumers about a particular
24 health problem with a drug or a communication problem. We
25 think this would improve the flow out of the FDA of

1 information and would improve the flow back, would improve
2 the educational process, which is one of the major future
3 roles of pharmacists.

4 The second major issue, drug advertising and
5 marketing issues. Number one is sampling that I want to
6 discuss just briefly. Direct-to-consumer advertising is
7 two. And, three, distribution of peer-reviewed articles on
8 unapproved uses. And, four, the FDA's Draft Guidance on
9 marketing by health organizations such as PBMs.

10 First of all, sampling. The distribution of
11 costly drug products to prescribers is an archaic way of
12 inducing sales of pharmaceuticals that undermines the few
13 existing safeguards in today's drug distribution system. It
14 deprives the patient of pharmacist counseling and pharmacist
15 information, which is thought to be sufficiently important
16 to the health and safety to warrant statutory mandates by
17 the U.S. Congress and over 40 state legislatures. It cheats
18 the patient of even more basic written information that they
19 require and that the "Medguide" proposal was intended to
20 use. It adds costly packaging and record keeping to drug
21 distribution, with no corresponding benefit. CDER should
22 seek authority to ban the practice and replace it with a
23 system that can facilitate starter doses through the normal
24 distribution mechanisms. That way a prescription could be
25 written, it could be paid for by the manufacturer, and all

1 the information safeguards could basically be put in place.
2 These systems are available. They are utilizable, and
3 they're ready to be facilitated. It is time to end sampling
4 as it's done today.

5 Direct-to-consumer advertising. The cornerstone
6 of the FDA's DTC policy is the physician's ability and
7 willingness to decline to prescribe a product if and when
8 the consumer requests a prescription that may or may not be
9 appropriate. Yet the literature is replete with evidence
10 that physicians do not receive a comprehensive education in
11 pharmacology in medical school. Physicians are taught to
12 focus on a relatively few number or small number of products
13 which they believe are important and that they use every
14 day, and they become familiar with the side effects, dosing
15 considerations, et cetera. This is important because
16 direct-to-consumer advertising, like the constantly changing
17 demands of formulary systems, has the effect of asking
18 physicians to prescribe outside their zone of familiarity
19 and safety.

20 This is worthy of your attention because there is
21 evidence that DTC ads work. All you have to do is pick up
22 Reader's Digest or any sports publication and realize that
23 they are in a major way being supported by the
24 pharmaceutical industry. We have done a study that was
25 completed with Prevention Magazine right before the current

1 loosening up of the advertising policy of the FDA. Let me
2 give you some data that we got from that study.

3 Seven percent of all consumers report seeing a
4 direct-to-consumer ad for a dyslipidemia product, but 22
5 percent of patients with dyslipidemia report seeing that
6 same advertisement. So they are able to focus right in on
7 the patient population, and it's obvious. If you happen to
8 have a disease and you hear about a new product, you tend to
9 focus in on that or you listen to that. The rest of the
10 time we basically screen it out.

11 The second major discovery of the APhA/Prevention
12 survey is that if one projects our survey respondents to the
13 entire U.S. population, about 35 million Americans spoke
14 with their doctor about a product that they had seen as a
15 direct consequence to direct-to-consumer advertising. About
16 10.2 million asked for a prescription product which they saw
17 in a direct-to-consumer ad. Now, remember, this was before
18 they could promote the name of the product and the changes
19 that we are now seeing every day.

20 We think that CDER needs to re-evaluate this
21 policy. It's almost impossible to stay ahead of Madison
22 Avenue. And if you think you can, you really can't.

23 The second area, information about unapproved uses
24 of pharmaceuticals. Under the FDAMA, manufacturers can
25 distribute peer-reviewed articles about unapproved uses

1 directly to prescribers. We believe this is a meaningful
2 reform and enhances the knowledge base of practitioners.
3 CDER should submit a formal proposal to the administration
4 for delivery to Congress that would permit such information
5 to be shared with pharmacists as well. This would help
6 pharmacists to know more about the uses that physicians are
7 currently prescribing medications for.

8 Draft guidance on marketing by PBMs. We have been
9 on record on this. We believe the policy is important to be
10 clear that marketing is occurring through PBMs directly to
11 physicians and pharmacists, and we believe the FDA should
12 stay the course and try to control this.

13 Postmarketing surveillance. There are two
14 important problems in this area for the Center. First, the
15 FDA does not receive sufficient number of adverse drug
16 reaction reports. If we are to believe the published
17 reports regarding the amount of morbidity and mortality
18 associated with drug use are correct, the agency needs to
19 work more effectively and proactively with prescribers and
20 pharmacists to promote swift reporting of all adverse
21 effects.

22 Second, passive reporting is insufficient as a
23 strategy to identify adverse effects and problems with
24 appropriate prescribing and use of pharmaceuticals. FDA's
25 current system for identifying unknown adverse effects of

1 prescription drugs suffers from a lack of resources to
2 analyze and respond to reports by the agency. We now
3 currently have around 416 places in the body where we can
4 have drugs work. When the Human Genome Project is finished,
5 we'll have 80,000 more. We're on the eve of a rapid
6 escalation in the number of pharmaceutical products to be
7 used. These systems for postmarketing surveillance will be
8 overrun if they're not changed. And if you loop back to my
9 earlier comments about developing a new classification
10 system for prescription drugs, we think that would aid in
11 facilitating information back to the agency and out of the
12 agency to physicians and to pharmacists.

13 Recalls is the last area. Pharmacists often have
14 difficulty receiving accurate and timely information about
15 drug product recalls, even class 1 recalls. CDER should
16 take steps to encourage manufacturers to utilize the latest
17 notification technology, such as telephonic notification
18 followed up by overnight mail notification. APhA would be
19 pleased to work with the Center in this area.

20 We appreciate the opportunity to comment, and we
21 look forward to discussions with the panel. Thank you.

22 DR. SMITH: Thank you.

23 Our next speaker is Cynthia Culmo from the
24 Association of Food and Drug Officials.

25 MS. CULMO: Good morning, everyone. My name is

1 Cynthia Culmo, and I am the Director for the Drugs and
2 Medical Devices Division within the Texas Department of
3 Health. I currently serve as the Chair for the Drugs,
4 Devices, and Cosmetic Committee of the Association of Food
5 and Drug Officials. We're pleased to be able to present the
6 comments this morning regarding a most important endeavor
7 and a challenge for FDA and one that we consider AFDO to be
8 an important stakeholder in.

9 Before I get started on the rest of my comments,
10 Dr. Woodcock stated that one statement was self-serving, and
11 that was the bullet up there that FDA is very effective in
12 performing well. Let me say that AFDO supports that
13 position, but we too believe, like all agencies and
14 associations, there is room for improvement.

15 Before I address each of the specific CDER
16 questions, for those of you who may not be familiar with
17 AFDO, I'd like to explain who we are and explain our
18 mission. AFDO is a non-profit professional association
19 that's consisting of state, federal, and local regulatory
20 officials as its members, but it also includes industry
21 representatives participating as associate members. From
22 its inception more than 102 years ago, AFDO has recognized
23 the need for consumer protection and uniformity of
24 regulations. It was established in 1896 and successfully
25 fosters the uniformity in the adoption and enforcement of

1 food, drug, medical devices, cosmetics, and product safety
2 laws and regulations. AFDO provides the mechanism and the
3 forum where regional and national issues are deliberated and
4 resolved uniformly to provide the best public health and
5 consumer protection in the most expeditious and cost-
6 effective manner.

7 There are six regional affiliates, and through
8 those, a partnership process has been created which has
9 resulted in the significant improvement of consumer
10 protection in our country. The uniformity is achieved by
11 education, communication, and cooperation among the states
12 as well as with the Food and Drug Administration. We
13 routinely provide comments to federal agencies on public
14 health matters such as those before us today.

15 AFDO depends upon and extensively associates with
16 the leadership of FDA and specifically with the Centers.
17 Its members work closely with CDER and rely upon their
18 expertise and guidance. CDER has requested that
19 stakeholders address six specific questions and any other
20 objectives related to the agency's statutory obligations or
21 the public expectations. The suggestions we offer are a
22 result of current concerns of the state and local
23 regulators.

24 It's important to remember that state and local
25 regulatory officials as well as industry must act

1 immediately to address complaints, illnesses, injuries, and
2 trends, even if it means developing interim policies. Some
3 time may be useful in developing strategies during a debate,
4 but it's a curse for those of us who must act immediately.

5 Anyway, accordingly, AFDO is pleased to offer the
6 following comments:

7 On the drug and marketing and advertising, AFDO
8 recognizes the important and yet difficult task that this
9 challenge presents. AFDO believes that the best direction
10 for this oversight would be through utilization of a
11 consumer panel to assess reactions to advertisements. The
12 review should be utilized both prior to the public
13 advertising and post-advertisement. Do not depend upon
14 scientists to review the direct consumer advertising.

15 Additionally, it would seem important that
16 appropriate messages need to be defined and recognize that
17 this could be different for individual drugs. Solicit the
18 input and directions from the health care professionals and
19 the ethnic communities in this process in the review as
20 well.

21 Inspections. There is still some confusion
22 regarding CDER's inspections and the field inspections. It
23 is our understanding that the field inspectors respond to
24 CDER, yet there is still evidence that these are separate
25 inspections. There needs to be clearer understanding of

1 CDER's relationship to the districts and the regions, a
2 relationship that should be commuted down to the consumer's
3 level, or at least to the state and the local regulatory
4 levels.

5 Other appearances are that CDER directs
6 inspections to the user fee activity, the NDAs and the
7 ANDAs--and Dr. Woodcock addressed that--and not the complete
8 inspection. It's a product-specific inspection, and we
9 would suggest that more time be devoted to the inspection
10 process to allow for a more comprehensive inspection.

11 Additionally, the district inspections are
12 directed to the black and white of the regulations, not the
13 health impact of the regulations, an example being process
14 validation. It's theoretically based. How are smaller
15 companies to comply? Is every aspect of the process
16 validation critical in a smaller company with one simple
17 product?

18 Current FDA inspections could be improved if
19 augmented by the state's inspectional data resources and
20 partnerships that included the continuation of the state's
21 contracts. Realizing this would require improved resources
22 and budgets, it would still seem appropriate to perform
23 periodic quality assurance inspections and laboratory
24 analyses for identity, potency, and purity to ensure the
25 quality of the drugs manufactured in foreign countries do,

1 in fact, equal ours. In this same realm, partnerships are
2 only as effective as the regulatory program and the
3 standards in each country. While the MRA is attempting an
4 honorable and desirable result, we would like to stress that
5 the foreign countries should not only have equivalent
6 standards but effective regulatory programs as well. FDA
7 could expend more time in foreign oversight and utilize the
8 states to cover domestic regulatory oversight at their
9 level.

10 Regrading the drug information, FDA is now
11 providing regulatory information on drugs, not for the
12 patient information. It's this information for the
13 consumers as well as the clinical trials information to the
14 regulatory and health care professionals that AFDO believes
15 could be improved. Currently, the regulatory and health
16 care professionals must search and seek published
17 information. Many are utilizing the Internet for these
18 purposes, and we believe many consumers are also adept at
19 searching the Internet for their drug information. This
20 brings to question the validity and integrity of that
21 information, but that's another subject at another
22 discussion.

23 Methods that AFDO believes effective in improving
24 communications and improving the information dissemination
25 would be FDA articles in professional journals, Internet

1 messages, consumer articles, and all news media. Counter
2 some of the direct consumer advertisements by utilizing
3 radio and television advertisements, particularly in
4 episodes of "The Simpsons" since "Seinfeld" is gone--I
5 didn't put that in there--consumer magazines, and the health
6 and/or trade magazines. And information in some format
7 should be placed in physicians' offices, patients' rooms in
8 the hospitals, and in the emergency rooms for consumer
9 access. This too could be considered a great improvement.

10 Improved access to package inserts for both public
11 and the regulators would be appreciated. I don't believe
12 anybody would debate the fact that the majority of these are
13 thrown away. An FDA Internet board could be the cost-
14 effective way to provide the information to many of these
15 entities.

16 Concerning surveillance and adverse event
17 reporting, although we acknowledge that the two systems are
18 intertwined, we believe that emphasis should be directed to
19 decreasing the number of adverse events and then secondarily
20 concentrate on the passive reporting system. If information
21 is increased to the consumers, professionals, and
22 regulators, if there is an increase in effort and expediency
23 in removing harmful drugs from commerce, then we would
24 expect that the numbers of adverse events would decrease.
25 Consideration should also be given to mandatory reporting in

1 hospitals similar to the medical device reporting
2 requirements.

3 By increasing resources in CDER, priority given to
4 the MedWatch system, and better utilization of assets in the
5 states could improve response to death and injuries from
6 medicines. Additionally, the FDA might consider regular
7 continuous reminders to health care professionals and
8 regulators. It's not uncommon to only receive one message
9 from FDA on a critical outcome associated with a drug, and
10 most people need more than one notice to associate a recall.

11 AFDO also believes that one important improvement
12 in the MedWatch report would be better exchange of
13 information with the states and the industry, such as
14 reports to the states on a continuous basis and the states
15 report to FDA on a continuous basis as well.

16 Premarket reviews should be emphasized, and
17 postmarket surveillance may be strengthened through the use
18 of the state's resources, and, as already mentioned,
19 consideration of the drug reporting requirements similar to
20 the medical devices reporting requirements.

21 On priorities, we believe that the highest
22 priority should be to continue to improve the drug approval
23 process and to expedite the removal of unsafe products.
24 Both of these would seem critical to consumer safety.

25 Next, the review of the grandfathered drugs, such

1 as ephedrine, which were never subjected to the drug
2 approval process should be considered. This could lead to
3 improved monographs and result in a much needed
4 reclassification of some drugs. Over-the-counter monographs
5 need to be finalized, too, with periodic reviews to update
6 and clarify the finalized monographs pursuant to new
7 technologies and drugs.

8 Additionally, CDER should consider non-traditional
9 drugs and the ethnic use in these monographs or as a new
10 category of medicines. AFDO emphasizes that greater
11 interaction with the states to include joint work planning
12 and areas of shared responsibilities would be an
13 improvement. There are several models for this in the FDA
14 regional offices which could serve the Centers.

15 Imports definitely need attention. We know that
16 there are alleged complaints on equivalency of standards,
17 yet the states continue to receive complaints and injuries
18 concerning inferior import products. The personal use
19 policy should be reviewed and updated due to concerns and
20 complaints related to the quality of these products and the
21 probability of diversion into normal commerce.

22 Additionally, I'd like to point out that FDAMA has
23 supposedly induced the modernization of FDA. It's our
24 position that the public and the industry's expectations of
25 FDA needs to be modernized as well. I didn't include the

1 states and the local governments since we too experience the
2 same political pressures and limitations as those set upon
3 FDA.

4 This concludes our comments, and once again we'd
5 like to express our appreciation for the opportunity to
6 provide comments on the program priorities in the Center for
7 Drug Evaluation and Research, and as a stakeholder, we are
8 prepared to work with FDA to improve these processes.

9 Thank you.

10 DR. SMITH: Thank you.

11 Our third speaker in this session is Bert Spilker
12 from the Pharmaceutical Research and Manufacturers
13 Association.

14 DR. SPILKER: Members of FDA, ladies and
15 gentlemen, good morning. I am Dr. Bert Spilker, Senior Vice
16 President of the Pharmaceutical Research and Manufacturers
17 of America. My comments this morning must of necessity be
18 condensed in order to fit the allotted time. Further
19 details and substantiation will be submitted to the docket.

20 PhRMA appreciates the opportunity to provide input
21 as FDA considers how best to achieve compliance with the
22 agency's various statutory obligations. It is important,
23 however, to underscore that consultation with stakeholders
24 like PhRMA does not relieve FDA from the ultimate
25 responsibility to manage and, as necessary, reallocate its

1 resources to achieve the statutory timelines and other goals
2 of the FD&C Act in a timely manner.

3 On the first question of drug marketing and
4 advertising, we wish to make three points.

5 We applaud the FDA's new policy on direct-to-
6 consumer advertising. We believe direct-to-consumer ads
7 serve the public health interest, particularly with an
8 increased movement to self-care management. These ads
9 empower patients with information about health conditions
10 and treatment options. They prompt patients to seek medical
11 help. They promote informed discussion between physicians
12 and patients. And they promote treatment of underserved
13 populations.

14 We look forward to working closely with the FDA as
15 you evaluate the guidelines; meanwhile, industry takes
16 seriously the responsibility of reaching patients with this
17 information and acts in good faith to follow FDA's already
18 precise and thorough guidelines.

19 The second point, a recent comprehensive DTC
20 survey by Prevention Magazine, already alluded to, has
21 clearly demonstrated that DTC information promotes public
22 health by prompting physician-patient dialogue. DTC is
23 particularly valuable in prompting patients to seek
24 physician advice about previously undiagnosed medical
25 conditions. DTC information also improves compliance by

1 patients with their physician's advice about Rx drugs.

2 The third point, the question FDA posed--"How can
3 we better assure that drug advertisements communicate
4 appropriate messages?"--overstates the responsibility and
5 authority of the FDA.

6 The second question, on inspections. In regard to
7 FDA's inspectional programs for pharmaceutical Good
8 Manufacturing Practice compliance, or GMPs, PhRMA believes
9 that CDER should take a more comprehensive approach in the
10 management and coordination of this activity. Our members
11 see a need to involve all of the different parts of the
12 agency along with the regulated industry in a collaborative
13 effort aimed at assuring an effective and an efficient
14 program.

15 In order to achieve this, we have eight specific
16 points to make that will be discussed in response to the
17 docket. These eight comments are in the copy of this
18 statement that is in the back of the room, if anyone wants
19 to see what these eight statements are. But I am not going
20 to go into any of these now in the interest of saving time
21 or we wouldn't get through the rest of the comments.

22 The third question is on drug information. There
23 is a need for health care providers to have access to the
24 latest scientific information on medicines.

25 One, dissemination of information is distinct from

1 promotion--a very important point. For example, see the
2 text and legislative history of FDAMA section 401, and PhRMA
3 comments submitted to the rulemaking docket. Information on
4 off-label use, such as peer-reviewed scientific journal
5 articles, is appropriately provided to health care
6 professionals by research pharmaceutical manufacturers, who
7 are perhaps the most knowledgeable about such information.
8 FDA must assure that any regulatory limitations on the flow
9 of such information is (a) as minimally intrusive as
10 possible, (b) consistent with both constitutionally
11 guaranteed speech rights, and (c) FDAMA.

12 The second point is that electronic package
13 inserts are a positive means of spreading information to
14 consumers and health care professionals.

15 The fourth question was on surveillance and
16 adverse event reporting, and we wish to make five points.

17 First, there is nothing that is more important to
18 the pharmaceutical industry than the safety of our products.
19 Every day, worldwide, our companies are monitoring the
20 safety of their products. We have extensive systems in
21 place today to collect safety data, and we report to the FDA
22 all adverse reactions according to the regulations.

23 The second point, the FDA should stress to
24 Congress, the press, and the public that the current safety
25 standards for new drug approval are significantly higher

1 than in the past. For example, in 1980 there were an
2 average of 1,500 patients studied in 34 clinical trials in
3 an average NDA. These numbers have risen to over 4,000
4 patients in 68 clinical trials. The amount of safety data
5 is related to the number of patients exposed to a new drug.

6 The third point, we support the views of 21
7 patient organizations who wrote to USA Today last week to
8 emphasize that "the FDA has not compromised its world-class
9 standards for the safety and effectiveness of new medicines"
10 and "fear that in overreaction to a small number of recent
11 drug withdrawals, policy makers may decide to slow down the
12 drug approval process. This would hurt public health and
13 harm the patients we represent by denying them the new
14 treatments and cures they are so anxious to receive."

15 Fourth point: Both FDA and the pharmaceutical
16 industry must educate Congress, the press, and the public
17 about the vast amount of safety activities already in place.
18 Recent drug withdrawals demonstrate the systems are
19 basically working, not that they are broken.

20 Fifth point: To the extent that the system for
21 monitoring the safety of medicines after they are on the
22 market can be improved, the pharmaceutical industry is eager
23 to work with the FDA, patients, doctors, pharmacists,
24 hospitals, Congress, and anyone else to achieve that goal.

25 The fifth question on balance will be addressed in

1 comments to the docket.

2 The sixth question is on priorities. More
3 interaction and collaboration is highly desirable between
4 FDA and the regulated industries to avoid issuing guidances
5 that do not adequately take into account useful perspectives
6 that can be provided by industry to the FDA.

7 The agency rarely says, "Here's an issue. What do
8 you think about it and how should we proceed?" A positive
9 model was that used by the FDA for pregnancy labeling. An
10 unproductive model was the guidance on gender, because it
11 was issued as a final rule without any industry input.

12 Thank you for the opportunity of addressing you st
13 morning.

14 DR. SMITH: Thank you.

15 Our final speaker for this morning's session, this
16 morning's panel, will be Hiroshi Mitsumoto from the ALS
17 Association.

18 DR. MITSUMOTO: Distinguished members of the
19 panel, ladies and gentlemen: I am truly honored to be here
20 in the front of this distinguished panel of the FDA, CDER,
21 and to present our concerns and, if possible, suggestions
22 regarding the implementation of the FDA Modernization Act
23 and how it might change the drug approval process for ALS.

24 My name is Hiroshi Mitsumoto, the director of
25 Cleveland Clinic ALS Center, head of the neuromuscular/EMG

1 section, and professor of neurology at the Cleveland Clinic.
2 I am also a chair of the Medical Advisory Board of the ALS
3 Association. I am a clinical neurologist, see a large
4 number of patients with ALS, and I am actively participating
5 in several ALS clinical trials.

6 At this hearing today, I represent the ALS
7 Association, but I believe I also represent the entire ALS
8 community, which includes patient voluntary organizations,
9 patients and family, ALS experts, and pharmaceutical
10 industry.

11 First, I would like to briefly describe ALS and
12 its current status in its treatment. ALS is a
13 neurodegenerative disease that leads to death within three
14 to four years.

15 ALS is called Lou Gehrig's disease by lay people.
16 Patients lose the ability to move their bodies, to swallow,
17 to speak, and eventually to breathe. A patient with ALS is
18 described as "a live body in a glass coffin." It is worse
19 than the majority of cancers and AIDS because ALS is
20 invariably fatal in three to four years in the majority of
21 patients.

22 It is roughly estimated that there are 5,000 new
23 patients and 30,000 patients present in the United States
24 per year. The impact on patients and families are
25 unimaginable, and thus society is gravest.

1 For treatment, only riluzole, the first
2 prescribable drug for ALS, is available but is of modest
3 effects. There is no cure, and only symptomatic treatment
4 is available.

5 Increasing numbers of novel therapeutic agents are
6 considered based on very plausible hypotheses of
7 pathogenesis in ALS. Some are already in pipeline. FDA is
8 extremely helpful and their commitment in developing ALS
9 therapies is very clear. They participated in the two
10 Airlie House meetings in the past as I explain shortly.

11 With this opportunity, I would like to present our
12 concerns about the guidelines for fast-track product and the
13 Scientific Advisory Panel. Our concerns are specifically
14 related to the CDER's specific question 6, Priority. What
15 should be CDER's highest priorities for action? What
16 changes at CDER would have the most beneficial effects for
17 the American people?

18 Because almost all neurologists agree that ALS is
19 the most devastating disease, we in the ALS community
20 believe that there is no higher priority for all FDA
21 centers, especially CDER and CBER, than to continue to
22 expedite the development of the review of drugs for treating
23 serious and rapidly fatal disease such as ALS.

24 Thus, it is imperative that FDA guidelines be
25 explicit regarding fast-track diseases. The FDA should

1 solicit from both AMA sections and specialty organizations,
2 such as American Neurological Association, American Academy
3 of Neurology, or World Federation of Neurology, a
4 recommendation for properties of fast-track diseases. The
5 current guideline described in the FDA Modernization Act
6 (Section 112) is still not specific and explicit,
7 particularly on ALS. Therefore, we anxiously await the
8 agency's release for a guidance document for the section,
9 which must be released within one year of enactment of the
10 law, which will be November 21, 1998.

11 We do not believe that the ALS drug approval
12 process has benefited equally from accelerated approval. We
13 are hopeful that proper implementation of this section of
14 fast-track products will increase and expedite the
15 availability of new therapies for ALS.

16 As the former FDA Commissioner Dr. Kessler stated
17 some years ago, "when dealing with serious and life-
18 threatening conditions, we cannot wait for all the evidence
19 to come in." For truly life-threatening diseases such as
20 ALS, the FDA can expedite the availability of therapies to
21 patients in desperate need, by providing greater authority
22 to approve drugs that strongly suggest effectiveness as
23 stated in the public law. By permitting greater use of
24 Phase IV post-approval confirmatory trials, and yet adhering
25 to its own standard, the FDA should be able to acquire

1 substantial evidence of effectiveness. This procedure has
2 worked well in the AIDS and terminal cancer areas, and we
3 believe that fast-track products were intended to expand
4 that procedure to all drugs to treat serious and life-
5 threatening conditions, such as ALS. After all, 17 of the
6 20 Subpart H accelerated approvals since 1992 have been in
7 AIDS and cancer and only three have been in other life-
8 threatening conditions, according to the Drug Information
9 Journal.

10 A need for controls in the Phase I and II studies
11 is obvious. However, for a disease such as ALS that has no
12 surrogate markers, but is relentlessly progressive and
13 results in continuously cumulative physical impairments, a
14 need for controls in the Phase III needs to be reassessed,
15 although the placebo-controlled design is still the gold
16 standard for the Phase III trial.

17 In this context, the members of FDA, including Dr.
18 Paul Lieber, have been most gracious to attend the WFN
19 meeting and supportive of the effort in ALS clinical
20 researchers and the pharmaceutical industry for revising ALS
21 Diagnostic Criteria and ALS Clinical Trial Guidelines. Such
22 meetings already took place twice, in 1995 and this spring
23 at the Airlie House. Therefore, the FDA team understands
24 what issues are involved in ALS clinical trials very well.

25 The FDA should consider efficacy relative to

1 safety. Large exposure to a drug such as IGF-I which has
2 minimal side effects should weigh heavily even if there is
3 only a small benefit. In particular, if two studies show
4 safety and only one shows efficacy, in diseases such as ALS
5 where long-term exposure is probably not an issue we need to
6 press ahead. An approval of such safe, yet modestly
7 effective drugs ensures the Phase IV studies for long-term
8 efficacy. Many cancer drugs and immunosuppressive drugs for
9 organ transplant are approved based on efficacy relative to
10 safety. Again, ALS has not been treated similarly by FDA as
11 other life-threatening diseases.

12 ALS has, at present, no surrogate markers as
13 cancers and AIDS do. Although there is an urgent need for
14 developing surrogate markers for ALS, continuously
15 cumulative physical disability, shown by quantitative muscle
16 strength testing, pulmonary function tests, and a well-
17 validated ALS scale, must be sufficient to evaluate the
18 efficacy of a drug or biological product into the fast-track
19 approval process.

20 Next, I would like to discuss the Scientific
21 Advisory Panel in Section 120 of the Modernization Act.

22 Only two drugs for ALS, riluzole and IGF-I, have
23 ever come before an FDA Advisory Panel, and both were highly
24 controversial and often given contentious reviews. Given
25 the great deference that FDA places on Advisory Panel

1 decision, it is absolutely critical that true experts be
2 represented on these panels of the actual disease under
3 review.

4 Public Law Subsection 120 states, "two or more
5 members who are specialists or have other expertise in the
6 particular disease or condition for which the drug under
7 review is proposed to be indicated." Undoubtedly the
8 members of the Scientific Advisory Panel are the most
9 capable and reputable members of the medical community;
10 however, the ALS community feels that there are no true ALS
11 experts represented within the Panel.

12 It is apparently difficult to invite experts who
13 have no conflict of interests to pharmaceutical companies.
14 Nevertheless, there are still numbers of senior neurologists
15 and other ALS experts who are not involved with clinical
16 trials or pharmaceutical companies. Again, the
17 participation of ALS experts in Scientific Advisory Panel is
18 imperative.

19 In this context, the World Federation of
20 Neurology--WFN--and the Committee of Motor Neuron Disease
21 may be able to provide expertise in this review process.
22 There are approximately 100 neurologists worldwide who have
23 formed the International ALS Clinical Trial Consortia. This
24 group has set the ALS Clinical Trials Guidelines and has
25 broad expertise with ALS clinical trials.

1 One solution may be the use of ad hoc reviewers
2 from experts in such diseases. The International ALS
3 Clinical Trial Consortia, again, may be helpful when acting
4 as such an outside ad hoc panel.

5 I would like to discuss the current forum of a
6 publicly open Scientific Advisory Panel meeting. In this
7 forum, the patient testimonial is allocated and is, in fact,
8 extremely important. However, these testimonials are so
9 powerful and highly emotional that I personally wonder how
10 the panel members can make their judgment based purely on
11 scientific grounds. On other occasions, it appeared that
12 the panel had made prior discussions, leaving patient
13 testimonies to have little influence. This type of forum,
14 although extremely important, may need to be more
15 effectively incorporated in the entire process. The FDA and
16 the Advisory Panel should explore further options.

17 Next, I would like to point out some confusion I
18 have as regards to CDER and CBER. Obviously, my confusion
19 is derived from the lack of my knowledge and springs from
20 recent experiences with IGF-I. IGF-I is a recombinant
21 biological product; however, this approval process was taken
22 by CDER that requires two independent clinical trials. All
23 other neurotrophic factors, such as CNTF, BDNF, or GDNF,
24 were to be evaluated by CBER that requires only one clinical
25 trial. I do not understand how such a decision is made.

1 I believe that the FDA should aggressively educate
2 patients' advocacy groups, disease-specific organizations,
3 disease experts, and new biotech companies that have never
4 filed their product to the FDA about the FDA's function,
5 process, and scope more than ever, because recent progress
6 in therapeutics will increase drug approval applications
7 even exponentially.

8 Regarding the future direction of fast-track
9 approval, the FDA should solicit from the disease-specific
10 groups information regarding potentially effective drugs in
11 such diseases. The FDA should proactively plan the future
12 drug approval process for fast-track diseases and should
13 then formalize and implement those plans.

14 Currently, the FDA supports some research in new
15 drug development; however, I propose that FDA should also
16 fund new research for developing surrogate markers in fast-
17 track diseases that have no surrogate markers at present.
18 It is of great urgency to help American people who suffer
19 from this most devastating disease. Since the NIH budget
20 was increased in the past year, I believe the FDA budget
21 should echo such an increase. Without such a federal budget
22 increase, the FDA will not be able to meet the need of the
23 American people.

24 I greatly appreciate this opportunity. Thank you
25 very much for your attention.

1 DR. SMITH: Thank you. We really appreciate the
2 input from all of our stakeholder groups.

3 We're now going to move into the discussion phase.
4 I would like to ask both our stakeholders and the CDER
5 panelists to speak directly into a microphone when you have
6 a question. Our questions will be concerning clarification
7 of the issues that have been presented by the stakeholders
8 and also priorities as they see it.

9 Dr. Woodcock, would you like to begin?

10 DR. WOODCOCK: Certainly. Thank you.

11 First I'd like to make a clarification on a recent
12 talk we just had. I think CBER and CDER have issued a joint
13 document on evidence, the standard for approval of drugs,
14 and it is the same standard in both Centers. So we do not
15 feel there is a different standard depending on where a
16 drug--whether a drug is regulated in the Biologics Center or
17 the Drug Center, although there may have been differences in
18 the past.

19 I wanted to ask Cynthia Culmo about a couple
20 things she said that I was interested in. I know you
21 collected these comments from a variety of people. Process
22 validation, do you have more--can you expand on what you
23 said about that and the small company?

24 MS. CULMO: The comments that came in on that are
25 from California, and we've experienced ourselves in Texas--

1 and I would say it's predominantly evident in the states
2 that have got a strong regulatory program in place at the
3 state level. And what we've seen when we've done joint
4 inspections with the FDA is the FDA investigator tends to go
5 exactly by the regs. I mean, it has to be in black and
6 white. You have to follow it. And one of the examples was
7 we were in a manufacturing site that was over-the-counter,
8 and--it's still not on or is it okay? It's okay.

9 Anyway, it was a simple product being
10 manufactured, and FDA proceeded to write up a very extensive
11 483 for deficiencies in the process validation. There was a
12 lot of discussion that went back and forth on whether or not
13 it was really critical in this simple drug product that all
14 of those steps be in place for this particular product. But
15 yet--so the same--and I've heard it voiced by industry as
16 well, particularly in our association and in other public
17 forums, where it's very difficult to come up with
18 regulations that are needed in a very large manufacturing
19 process and then the smaller companies are required to
20 follow those same process. So that's what it was.

21 DR. WOODCOCK: Thank you. That's helpful. I
22 wanted to follow up, too, about the confusion versus which
23 component of FDA is doing the inspection.

24 MS. CULMO: Correct, and that's exactly what it
25 is. It's confusion. When we'd go out and do an inspection,

1 particularly with the field investigators, there is
2 confusion on their part as to where the direction comes
3 from. Do they follow CDER's direction? Do they follow the
4 regional office's direction? So it goes back and forth.
5 And then, again, some of the emphasis from CDER is more if
6 you're involved in an inspection pursuant to an NDA or an
7 ANDA versus one that's just a routine inspection.

8 DR. WOODCOCK: That helps. Thank you.

9 DR. SMITH: Does anyone else have a question?

10 DR. LUMPKIN: I have a question, primarily I think
11 for John Gans and Cynthia Culmo, but if any of the rest of
12 you have comments on it, I'd be very interested.

13 As I've become more involved over the years with
14 the spontaneous reporting system, not only our system here
15 in this country but the system that we know of that exist in
16 some other countries, it's become more apparent to me that
17 these kinds of systems were really never designed to be a
18 registry of all adverse events that people believe have
19 happened with a drug; that they were really designed for
20 another purpose, and that other purpose was to try to
21 identify rare, serious, unexpected adverse events that occur
22 after marketing.

23 I guess really my question to you goes in two
24 parts. Number one, do you think it would be helpful, is it
25 something that we need, to have a proper registry system to

1 capture adverse events more in a statistics manner that
2 Janet was talking about, kind of as health statistics?
3 Would that be helpful to us in the long run? Because that
4 would be a totally different system, and do we need to think
5 about doing that?

6 Then on the system as it's presently designed, I
7 was very interested in both of you. I kind of got the
8 impression that both of your organizations have methods of
9 capturing adverse event data that might be helpful to us.
10 And I would be interested in what kind of data that is or
11 ways that you think that the data you get back on putative
12 adverse events might be able to be communicated to us and
13 how we might use that and share our data with the kinds of
14 databases you have with your organizations.

15 DR. GANS: Well, we would like to try to get more
16 statistical information along the lines that you are
17 suggesting, simply because some of these rapid approvals,
18 there just isn't the time out there that's needed. We are
19 beginning in some new practices in pharmacy where--for
20 example, we have a project we call Project Impact. It's
21 improved compliance with dyslipidemic patients, and we have
22 700 patients in 15 states with 25 pharmacies who are
23 monitoring and managing it because those states allow you to
24 take a little finger stick of blood, you can do a total
25 lipid profile. And the physicians enter their patients in

1 this program. The amount of information that the
2 pharmacists have on these patients and the information flow
3 because they're coming in every month, supposedly, to get a
4 prescription, et cetera, filled, back to the physicians and
5 the communication is incredible. And dyslipidemia is a
6 challenge for compliance because people don't have any
7 symptoms, obviously. It's not a challenging disease in the
8 sense of diabetes to manage with its sequelae, so it's
9 fairly simplistic. So I don't want to overstate what we've
10 been able to do. But there is a huge amount of information
11 about what's going on with these patients, and we believe
12 that that's going to be an enormous data source, okay, if
13 managed care and insurance companies see this as important,
14 okay. Drug companies see it as very important because
15 they're getting compliance rates now higher than they've
16 ever seen before in anything they've done. But, obviously,
17 they're only going to be able to support this kind of thing
18 when it's a patented product. Obviously, the generic
19 industry isn't going to be able to do it.

20 So I think that's a tremendous breakthrough, and
21 we're beginning to see that with an enormous number of
22 diseases where pharmacists are becoming actively involved in
23 the management, and they have great records and great
24 information sources, much better than we've ever seen
25 before. That's a rich opportunity for feedback, it seems to

1 me, to the manufacturer and to the FDA, because I agree the
2 manufacturer is very concerned about safety.

3 I think the other end of this is sometimes we lose
4 drugs because of a few events. We had products taken off
5 the market when they were being used for unapproved uses.
6 The intended company--I think Durac (ph) was taken off.
7 That's the first time that I think that's ever happened,
8 that I can remember that a product was taken off because it
9 was being used inappropriately. That's where we were coming
10 from with we need to have--if a product should only be used
11 for ten days and a liver test be done, we've got to have a
12 system or a category that that drug fits in so it shoots up
13 on the radar screen of pharmacists and physicians when
14 they're ordering these things that they need to do that, and
15 the system locks the patient from getting a second refill
16 until that laboratory test has been done. There's no
17 difference between Durac and Closuril in the reality of what
18 happened.

19 So those are the kinds of things that I think are
20 beginning to evolve in these systems as they become more
21 sophisticated. I think that information would feed back and
22 be statistically relevant to the agency and then could be
23 fed back to us. But we're just at the beginning of doing
24 this. We've been doing this for about five years now.

25 MS. CULMO: From AFDO's perspective, numbers,

1 statistics, percentages, would always be appreciated, too,
2 and it's one of the things that we too are requested often.

3 We still support the idea that it be required
4 reporting. I think there's been some wonderful information
5 available from the NDRs that could be of great value on the
6 drug side. One of, I guess, the biggest criticisms of the
7 passive reporting system right now is the lack of
8 information as far as the denominator. So I think you could
9 get better information if it were required.

10 Within Texas--and I can't speak for all of the 50
11 states within the association--we do have a bit of an
12 improved system in that we have six poison control centers
13 in the state that are linked by computer and Internet
14 access, so we get a lot of information there that I know
15 some of the other states are not privileged to, and it's
16 better than what's available on the DON because it's
17 immediate feedback. So we get reports from them, and those
18 are currently being provided to CDER, and then,
19 additionally, for the dietary supplements it goes in as
20 well.

21 DR. SMITH: Would anyone else like to answer Dr.
22 Lumpkin's question?

23 DR. SPILKER: There are an infinite number of
24 questions that can be asked about anything. I'm replying to
25 the comments of my panelists who were calling for collection

1 of a lot of statistics. I think what you have to do is,
2 given resources available or even resources you would like
3 to have, decide which are the most important ones that you
4 want to collect data on. I did agree with Dr. Gans that
5 when you identify a specific question--and he went into the
6 lipid area--when you're dealing with specific issues, then,
7 yes, if they're important questions, then you should apply
8 the resources and do it. But I think we shouldn't look at
9 the world of pharmaceuticals or other worlds and say let's
10 collect all statistics because maybe it will have some use.
11 I think you want to know where it's going to be used ahead
12 of time.

13 DR. WOODCOCK: Yes, I have a question for Dr.
14 Gans, if he could possibly expand on this categorization of
15 pharmaceuticals. It's very clear that the more drugs that
16 are available, the more confusing it is for the prescribing
17 community, for pharmacists, everybody, there need to be ways
18 of getting that information out. We tried this recently
19 with thalidomide, and obviously we needed every prescriber
20 and we'll need every patient who takes thalidomide to have
21 full information about the risks. It's crucial. And it
22 sounds like your association has some ideas about how that
23 could be best accomplished.

24 DR. GANS: Well, I think actually what we did with
25 thalidomide I hope works, because I think--

1 DR. LUMPKIN: So do we.

2 DR. GANS: I think there's a terrific risk, but I
3 think there are some up sides for a limited number of
4 patients. And pharmacists who wanted to participate, and
5 physicians, in the utilization of that product can
6 participate. There's no mechanism of screening people.

7 But, clearly, thalidomide, if it's ever used,
8 should somehow or another be identified as a challenging
9 product with a downside risk. Hold the mike closer than
10 that?

11 Clearly, we've had products like this in the past.
12 Downside risk with Closuril is an example, and we know--we
13 ended up at cross purposes with the agency on that, and we
14 were both working for the same thing. So I think we learned
15 our lessons, and thalidomide--clearly, the system for
16 thalidomide will be better. But there are a lot of products
17 out there--Acutane requires a warning, okay? And I don't
18 know how often that's happening. But computer systems are
19 looking for classification or organizations of products, and
20 all we have is this huge morass once it's approved. And I
21 think, when we were talking about data collection, I would
22 hope PhRMA would support this kind of thing, is when
23 something is rushed through because of need, et cetera, for
24 ALS patients or for AIDS patients, well, you know, the study
25 was on a few number of patients, it was done quickly.

1 Everybody supports that. But we don't have the net
2 underneath those patients taking that; we don't have those
3 drugs organized in a way where they take special precaution.
4 They're just basically prescribed and dispensed by anybody.

5 So I think that--we would look to maybe some
6 specific--get some researchers, the pharmacists and
7 physicians, to begin talking about this, because we haven't
8 seen anything yet. If this Genome Project is correct, we're
9 going to have literally 30 or 40 times the numbers of sites
10 for drug action. So I think it's time to begin to
11 categorize these, not limitations of use but yet in how we
12 counsel those people, how we collect data on those people,
13 and how we make sure that they know how to utilize that
14 product, because the beauty of drug products--and I don't
15 think we want to ever forget this--it's one patient deciding
16 every day how to take it and utilize it, no matter what the
17 physician has said, no matter what the pharmacist has said,
18 or sometimes it's a parent or a caregiver applying it. That
19 I think is where the challenge comes in for us, and I just
20 don't think this one sort of class works.

21 I mean, I don't know how--I know how anabolic
22 steroids ended up in controlled substances. But maybe we
23 ought to have a more tightly controlled system and better
24 record keeping, et cetera, on some of these products so we
25 know where they're being utilized.

1 So that's where we come down: safety, efficacy,
2 maybe it's information, certain education has to occur.
3 These are the kinds of things that I think the public want
4 in the way of information. But the systems treat all drugs
5 the same once they're approved in the prescription category.

6 DR. LUMPKIN: On a different topic, I had a
7 question for clarification for Dr. Mitsumoto. I was very
8 intrigued by kind at the end of your remarks when you were
9 talking about your experience with Advisory Committee
10 Panels, and particularly the public input at those Advisory
11 Committee Panels and how--I wasn't quite sure what you
12 meant, if you thought that was a good thing or a bad thing,
13 and maybe you could clarify and expand on that. You ended
14 by saying you thought perhaps we in the Advisory Panel
15 should explore further options. Do you want to expand on
16 that about what some of those options might be?

17 DR. MITSUMOTO: Well, certainly, I think it is
18 extremely important we should continue because that is the
19 real voice from patients and families. Yet I have to--in
20 conclusion, I don't have any good answer what is to be done.
21 As long as I know the first advisory board meeting was
22 testimony came first and then discussion came later. And
23 the other occasion, the other way around, discussion was
24 done first and testimony came second. So that means someone
25 can decide how you arrange these sort of things. It's

1 extremely important, and particularly like the so-called
2 experts may be in a panel or in the audience, very difficult
3 to deal with those patients who personally know them. And
4 so somehow we needed to make arrangement. It's important,
5 yet rather--I don't know. That's what I am advising you,
6 the advisory board and FDA. Make a discussion how you can
7 implement this important process in very scientific way
8 rather than so emotional. I felt if I am a panel member
9 there, it's just--I can't think anything rationally. That's
10 what I have the impression.

11 DR. GANS: I have one additional point on this
12 about information to patients and this whole area of
13 unapproved uses of drugs. We're challenged as a profession
14 and we've committed to get more information to the public,
15 more written information, more counseling to patients. It's
16 a huge challenge for the profession, and I have no doubt
17 that we're going to meet the commitment that we made to the
18 public and to the FDA. But after making comments a couple
19 of years ago, I was taken on by a lot of consumer groups
20 because they saw us as being anti that. So I sort of
21 learned my lesson. I won't do that today.

22 But we are very sincere in trying to get out more
23 and more information, but I want to make a couple of points
24 on where we need some help from the public.

25 First, the prescription blank, the information,

1 the drug order that's given to pharmacists, hasn't changed
2 in 150 years. Okay? It may have your name on it. It never
3 has your address. It doesn't have your age. It has an
4 order for ingredients, for a product. Now it's the name of
5 usually a prescription drug product. Usually there's some
6 directions there. And only 20 percent of the time is the
7 intended use on the product. And let me tell you why that's
8 really, really important.

9 If somebody wrote for the commonly used beta
10 blocker, propranolol, the range of uses on propranolol go
11 from migraine headaches to tachycardia and hypertension. We
12 have the ability in our computer systems to give you
13 information on any one of those areas depending upon what
14 you're using the product for. But we need to know what the
15 intended use is so that we can focus that, and that's real
16 important. And it's not the diagnosis and don't be confused
17 with that. It's just the intended use.

18 We'd like to know your age. We would like to know
19 some more information. Modern pharmaceuticals and how
20 they're being used, okay, all of that information that's
21 coming out of the FDA is useless unless we have more
22 information. But the first step is really intended use.

23 Now, can you imagine somebody's using a product
24 for an unlabeled, unapproved use because it's been in a real
25 good study, and they walk into the pharmacy and you give

1 them a product leaflet that has nothing to do with that
2 product and you go home and you read it, all right? Are you
3 going to use that product? I'd be on the telephone. I
4 think anybody in this room would be on the telephone.
5 That's where I think, if we're going to really go forward
6 with these studies, these refereed journal, we support that
7 at APhA. We think that's an important step forward.
8 The next step, of course, occurs so you don't get
9 any information and then we have to work through a system
10 that says we don't pay for drugs--the insurance company
11 doesn't pay unless it's approved. So all of those
12 challenges we as a profession are willing to step up to, but
13 just giving us the intended use, if we could move from 20
14 percent to 40 percent to 60 percent--it's just--sure, you
15 can make it a law, but all it is is the style of practice,
16 and we've moved from 0 percent to 20 percent, and we'd like
17 to see by the next millennium this move to 100 percent. We
18 think it would be a catch for the public. They'd look at it
19 and say, you know, this isn't an antibiotic and yet it says
20 it's for a cold, so it would help them catch errors that we
21 sometimes make. It would also really help us focus the type
22 of information people need to utilize these products
23 correctly. And just think about it, if it's an unapproved
24 use, that information is nowhere. It's in our computers.
25 We can pull it out. We can get the information, and we can

1 talk to people. But we're really talking about compliance.

2 And, remember, as someone said, a physician said,
3 the patient's waiting. They're waiting for new products,
4 new therapies, breakthrough products. But they're also
5 waiting for information on how to utilize them properly.
6 This profession that I represent wants to be the source of
7 that, and we will be the source of that. But we need a
8 little bit more information than the information we were
9 getting 150 years ago.

10 Thank you.

11 DR. SPILKER: Dr. Gans, I'd like to just comment
12 that with your last proposal, that seems like one that you
13 would want to--and perhaps you already have--talk to the
14 AMA, AAMC, APF, and quite a few other organizations that
15 could influence physicians.

16 DR. GANS: Yes, and, unfortunately, sometimes it
17 gets mixed up in the politics of our professions, and
18 they'll say things like, well, if you really want to
19 practice medicine, why don't you go to medical school?

20 I don't think that works anymore, and we really
21 need to have, I think, the neutral group here, the public,
22 to step up and demand a change. And all you have to do--you
23 need two things when you go to a physician's office or get a
24 prescription: A, ask them if it's on the formulary, because
25 that's going to make it a lot easier when you get to the

1 pharmacy to get it filled, number one; and, number two, ask
2 them to put the intended use on there. What is it being
3 used for?

4 It's kind of helpful maybe three months later when
5 you open up your medicine cabinet and you reach in there and
6 say I think I got something for this, and if it doesn't have
7 "for cold," for this, for that, you have no idea what it's
8 being used for.

9 So I think those things would really be helpful.
10 We will continue to work with medicine and enlightened
11 physician groups. We get good support from poison centers
12 for that kind of thing. But we need the public support for
13 it because that's the way it's going to change. And I think
14 it's just a matter of making a demand for it.

15 DR. WILLIAMS: Well, just to follow up with Dr.
16 Gans, these are certainly intriguing suggestions, but the
17 agency's always sort of stayed away from the practice of
18 medicine and pharmacy. Are you suggesting that that
19 paradigm, if you will, change a little bit?

20 DR. GANS: I knew that would happen.

21 [Laughter.]

22 DR. GANS: Since we beat up on you every time you
23 do that.

24 No, I think it's part--it just has to become part
25 of the dialogue. I don't believe that the practice of

1 medicine or pharmacy should be overseen by the FDA. But I
2 think it should be part of the dialogue. I mean, we're
3 pushing, the agency is being pushed hard. It's a real focus
4 group for more information to patients. And our hands are a
5 little bit tied, and we don't know--and I just get
6 concerned, although we're supportive of these studies that
7 are put out there and they're approved and all for being
8 distributed to physicians, it's just going to be one more
9 blind spot in the communications system. So we're just
10 trying to keep the dialogue forward. No, we don't think
11 that that's FDA's role, but FDA can use the bully pulpit to
12 begin to stimulate that, and manufacturers can start to
13 stimulate it, and I think it's in the patient's best
14 interest.

15 I see no downside. I see no downside. I don't
16 see a downside for the agency. I don't see a downside for
17 medical boards, pharmacy boards, physicians, pharmacists. I
18 see no downside for anybody. All I see is the upside, and
19 it's just one more piece of information, and they do it 20
20 percent of the time.

21 MS. GRAY: I have a question for Dr. Spilker. In
22 your comments--you didn't address it from the podium, but
23 from the written comment--number five addresses a first-
24 party audit program, and Dr. Woodcock also addressed first-
25 party audit as a first-party certification versus third-

1 party certification. And I wonder if you could elaborate
2 conditions under which you believe a first-party audit would
3 be more desirable to industry or if you think a third-party
4 audit program would be more desirable to industry.

5 DR. SPILKER: As you mentioned, I do have in the
6 written comments point number 5, the comment that although
7 intended to reward firms with good performance, we are
8 skeptical about FDA's first-party audit pilot program of
9 self-inspection because the companies would be expected to
10 share internal audit data which they are very reluctant to
11 do right now, I think for a lot of good reasons. Number
12 two, we do not see any benefit to the industry or companies
13 from this program as proposed. Three, the approach did not
14 involve the industry at all in designing the program, and we
15 are ready to help the agency design a program with practical
16 benefits for both participating firms and the agency.

17 Let me stop there before continuing and say that
18 if I have one message to stress today from the
19 pharmaceutical industry, it's that we are anxious to
20 collaborate with you and not just be in a reactive mode to
21 guidances or pilot programs or other things that come out
22 from the agency that we are forced to react to. I mean, we
23 have citizen--we've been forced to put in citizens'
24 petitions, et cetera, because we were not involved in
25 discussions on a number of issues, some of which we think

1 could have been avoided had we been involved. Actually, I
2 think most of these issues. FDAMA is a good example where
3 we worked together, and I think that's the overall message.

4 But I think that we have not really gone into the
5 third-party audit as much, and I would have to go back to
6 the people to see what their reactions are to third-party
7 audit. But I know that they are very loathe, as currently
8 designed, with the first-party audit. But my feeling is
9 overall why don't we sit down together, work out a system
10 that we both feel is fair. We're not asking you to
11 compromise in ways which you don't want to, but I do know
12 that once we sit down together, things do have a way of
13 working out better.

14 MS. GRAY: As a point of information, the public
15 meeting was intended to start a collaborative process. It
16 wasn't intended to apply a fully formulated idea, because it
17 isn't fully formulated.

18 DR. SPILKER: Oh, I appreciate that in terms of
19 this first-party audit issue, that this is far from being
20 final. I well recognize that. But we would like to sit
21 down and find ways in which the agency is comfortable in
22 doing so to discuss some of the details, and perhaps that's
23 the best way to answer the question.

24 DR. WILLIAMS: I had a question for Cynthia Culmo.
25 I was interested in some of your comments about the balance

1 between what the Federal Government does and the state
2 government does, which is always a challenge for any
3 society. Are you suggesting that that could be improved or
4 strengthened in some way? Did I hear that in some of your
5 comments?

6 MS. CULMO: Well, definitely, it could be
7 improved. One of the mechanisms has been the contracts that
8 some of the states have been awarded. Eleven states were
9 doing compressed medical gas inspections for the FDA
10 pursuant to contracts. We've been doing GMP inspections for
11 medical devices in three states.

12 It's simplest, obviously, in the states that have
13 food, drug, and cosmetic statutes that mirror or track the
14 federal statute. And that is one of the things that AFDO
15 stresses, is uniformity, so we encourage that the states do
16 try and follow models statutes which mirror the federal
17 statute.

18 But because of the food initiative, a lot of--
19 well, not a lot. In fact, all of them except for the
20 mammography and the food initiative contracts were
21 discontinued, and those will be completed September 1. So
22 through contracts, that does work. There are going to be
23 continued partnerships with the states that had contracts.
24 But, yes, it could be improved, and other states could be
25 incorporated into those arenas without the formalized

1 contracts or partnerships. Makes sense.

2 DR. WOODCOCK: Could I follow up on that? You
3 said that potentially we shouldn't be looking outside so
4 much to the EU, US, MRA as how could we domestically partner
5 to have adequate inspectional coverage. Is that feasible
6 without contracts or you think that would be required?

7 MS. CULMO: We're currently doing that in
8 California, Florida, and Texas that I'm aware of, and those
9 are the bordering states where we obviously have a lot of
10 imports. And we're doing that. We're working cooperatively
11 and in a partnership with FDA on the import issue.

12 But one of the things that we recognized is the
13 authority and the expertise lies with FDA on these imports,
14 so if they could concentrate their resources at the airports
15 and the borders, then we can handle it at the state level as
16 far as some of the domestic products, and then still work
17 jointly once we have interstate commerce established and
18 things like that. We already share reports in several of
19 the states, so some of the regulatory efforts are exactly
20 the same.

21 MR. LILLIE: I'd like to go back to ADR reporting
22 for a minute. There was some good information and some good
23 examples you both gave us, John and Cynthia. These are
24 things we've been wrestling with for some time, and more
25 acutely recently. One of the comments I took from Cynthia's

1 remarks concerned mandatory reporting, and I think there are
2 a couple of ways of approaching this. If you're talking
3 about the spontaneous system, obviously we have the
4 authority to require the manufacturers to report the
5 information to us at that level, but you still have this
6 brush border, this grass-roots issue of reporting really
7 occurring in the HMOs, among other places. Now, hospitals,
8 I think we've been more successful, using pharmacists and
9 other types of disciplines in getting that done. I'm
10 curious if you have any thoughts on how we might stimulate
11 for the spontaneous system the HMO environment, the managed
12 care environment. Things that could come to mind to me
13 obviously are things like accreditation, perhaps insurance
14 issues or other areas that clearly fall outside of FDA's
15 domain. But I'm interested in any and all creative thoughts
16 in that area where we might have a little more success in
17 actually getting the reports for the spontaneous system.

18 DR. GANS: Spontaneous reports are always a
19 challenge because sometimes they're seen as a failure of the
20 system. When someone is injured or has a problem with a
21 product, that's always a challenge to get that information
22 back into the system.

23 But things are improving, and let me give you--
24 this isn't an adverse drug reaction report, but talk about
25 drug recalls. When a couple of products were most recently

1 recalled because pharmacies are now becoming large
2 corporations, not only community pharmacies but you have
3 mail-service pharmacy, one of these companies was able to
4 contact every patient on the product, every physician that
5 wrote a prescription directly, by mail, to get the product
6 back. All right? And I think that was the first time that
7 that was done.

8 I think what you're starting to see is ease, the
9 systems at least to allow you to do that are cost-effective.
10 Now, how you stimulate flow back on that or the need to get
11 flow back on that, when many times things go underreported.
12 We have a couple of studies that talk about 10 percent of
13 hospital admissions. USA Today talked about 100,000 or
14 10,000 lives because of adverse drug problems in hospitals.
15 We have another study that says \$76 billion a year in costs
16 because people don't use the drugs properly.

17 I am continually amazed that when a failure of a
18 drug product occurs, no one seems to get blamed for it. The
19 physician doesn't get blamed, the manufacturer, the
20 pharmacist. You sort of have to sort these things out.
21 Sometimes it's considered a progression of the disease; the
22 drug product just isn't looked at. But yet when pharmacists
23 or physicians study the system, they begin to see these
24 problems.

25 I think you're going to see more and more of that

1 kind of thing as we look for--insurance companies are
2 forcing us to develop sort of a failsafe drug system of
3 distribution and use. I think you're just going to see more
4 and more insurance pressure on that, and I think you're
5 going to see more and more companies come into compliance
6 and have compliance officers in these big companies, and I
7 think you're going to see more and more of that information
8 pulled out.

9 We certainly are focusing on it because we see it
10 a way for justifying one of our major roles of managing drug
11 use, okay, with the American public and with physicians.
12 And we see it as a great opportunity for ourselves. Well,
13 obviously, we've got to make the case for that, and you
14 start by making the case for the failures, and we've got to
15 begin to feed that information back.

16 So I think you're going to see more and more of
17 that, and that's why it gets back to, I think, the FDA
18 developing systems, target drugs that they want to look at,
19 okay, that they want information back on. I think it would
20 be a good way to start. Also, I think beginning to
21 stimulate large insurers, that they have a responsibility
22 here. They're paying for these products. If there's
23 problems with them, they have a responsibility to get that
24 information back, okay, into the company and then out of the
25 company into the FDA.

1 I think that's going to start happening.

2 DR. WILLIAMS: I guess I wanted to direct a
3 comment to Dr. Spilker. Your question 6 on priorities and
4 how we could work better together in the formation of
5 guidances, I think that is a very challenging and good
6 opportunity for us, and as you know, we've tried to do it in
7 many different ways. As you work with the agency on that
8 suggestion, one of the boundaries which I see as a challenge
9 for us is sort of the FACA debate, you know, where we're
10 getting in problems with the Advisory Committee Act versus
11 good guidance practices. And I know that's of interest to
12 PhRMA, and maybe you could--as you direct your stakeholders'
13 comments to us, I think you could help us there.

14 DR. SPILKER: That certainly is a very good point.
15 I think sometimes it's a question of getting the legal
16 people together on both sides to see if they can work out
17 the details rather than the regulators or the scientists.

18 DR. SMITH: Well, I would like to thank all of our
19 stakeholders and our CDER panelists this morning. I think
20 we've had an excellent exchange of ideas, and I look forward
21 to hearing more this afternoon.

22 We will reconvene promptly at 1:15, and, again, if
23 the speakers who are going to be participating on the panel,
24 the second panel, could be here a little early, I would
25 appreciate it. Thank you.

1 [Whereupon, at 12:00 noon, the meeting was
2 recessed, to reconvene at 1:15 p.m., this same day.]

A F T E R N O O N S E S S I O N

[1:19 p.m.]

1
2
3 MS. HENDERSON: Good afternoon. Could you take
4 your seats and we'll get started for the afternoon. My name
5 is Debbie Henderson. I'm the Director of the Executive
6 Operations Staff for the Center For Drugs. I welcome you
7 back this afternoon, and those of you who were not here this
8 morning, I welcome you for the first time.

9 I'm going to start by introducing our afternoon
10 panel. Let's see. Sitting on the very end is Nancy Smith
11 who's the Director of our Office of Training and
12 Communications. Next to her is Steve Goldman. He is a
13 member of our MedWatch staff at FDA. Next to Dr. Goldman is
14 Dr. Woodcock. Janet Woodcock is the Director of the Center
15 for Drug Evaluation and Research.

16 Next to Dr. Woodcock is Dr. Robert Temple who's
17 our Associate Director for Medical Policy at the Center For
18 Drugs, and next to Bob is Minnie Baylor-Henry, who is the
19 Director of our Division of Drug Marketing and Advertising.

20 That's our FDA panel. To my left is our
21 stakeholders panel and I will introduce each of them as they
22 come up.

23 Our first speaker. I'm going to change the order
24 that you have in your handout. Our first speaker is going
25 to be Mary Rouleau from Consumer Federation of America, and

1 then the rest will follow in order as they are.

2 So we will start. I want to ask each of the
3 speakers--we've been asked from the morning, to please be
4 sure that your mouth is very close to the microphones,
5 especially the ones at the table, if you speak--even though
6 it sounds like you're projecting from here, the people in
7 the back couldn't hear this morning.

8 So with no further ado, I'd like to introduce Mary
9 Rouleau who is representing the Consumer Federation of
10 America.

11 MS. ROULEAU: Good afternoon. I asked to speak
12 first because my comments are more general in nature and I
13 just thought it'd make more logical sense to proceed that
14 way.

15 Anyhow, here we go. I'm the Legislative Director
16 of Consumer Federation of America, by the way, and these are
17 our comments, but there are other patient and consumer
18 groups with whom we work, that you will hear from, and we
19 obviously share many of the same opinions.

20 According to the Senate Labor and Human Resource
21 Committee report issued following its referral of then
22 Senate Bill 830, the Federal Food Drug and Cosmetic Act
23 provides no form of public accountability by the FDA for its
24 performance of its statutory obligations.

25 The legislation, meaning FDAMA, required the FDA

1 to develop a plan and submit an annual report which would,
2 according to the Labor Committee, improve agency
3 accountability and provide for better resource allocation by
4 setting priorities.

5 Let me first say that Section 406 of FDAMA was
6 neither sought nor endorsed by consumer or patient groups.
7 Prior to its passage, we, the industry, and Congress all
8 sought, through various methods, to hold the FDA
9 accountable. As consumers, we believe the FDA knows what to
10 do; it just doesn't have adequate staff to do it, let alone
11 worry about timeliness.

12 The irony is then that this provision will further
13 divert the time and energy of the FDA away from its other
14 statutory obligations.

15 While some of the objectives of the plan should
16 work to the benefit of patients and consumers, on balance,
17 we think the plan factors industry issues regarding review
18 of applications.

19 Once the time period for review of applications,
20 and elimination of backlogs have been charted, is there
21 really any doubt that there will be relentless pressure on
22 the FDA to meet those periods at the expense of other tasks?

23 You have asked for other objectives related to the
24 agency's statutory duties, where public expectations should
25 be included in the FDA plan.

1 We note that under the version of FDAMA passed by
2 the Senate Labor Committee, the plan included an objective
3 to minimize deaths and injuries suffered by persons who may
4 use products regulated by the FDA.

5 We think that objective should be specifically
6 built back in. Now it might be argued that under current
7 objectives B and C, regarding clarity of information and
8 post-market monitoring, deaths and injuries should be
9 lessened, and that is probably correct, but it is only part,
10 and maybe only a small part of what it will take to minimize
11 deaths and injuries.

12 As you all know, CFA bitterly opposed FDAMA.
13 Despite the claims of its supporters, we think it
14 represented nothing less than a rollback of FDA authority.

15 We cannot reopen the legislative language at this
16 time, but we can advocate that this plan not make the
17 dynamic worse. The FDA is to regulate various industries to
18 protect the public health and safety.

19 FDAMA speaks of collaboration, but it must not be
20 allowed to become a sugar-coated version of deregulation.
21 Let's face it. The trend in this country for almost the
22 last 20 years has been to deregulate one industry after
23 another--airlines, telephones, cable, and now, electricity--
24 none of which has been to the overall benefit of consumers.

25 The call has been to let the market prevail. To

1 our knowledge, no one has openly called for deregulation of
2 the food, drug, device, or cosmetic industries. This is for
3 a very good reason.

4 The public would, we believe, have a visceral
5 reaction to such a suggestion. However, is the new pressure
6 to collaborate has the effect of moving or blurring the
7 lines which define the FDA's role as regulator, the market
8 will in fact rule.

9 We know that the FDA is under pressure to bring
10 drugs and devices to market faster. As consumers and
11 patients, we benefit, too. But these drugs and devices must
12 be safe and they must work.

13 So we should, for the purposes of the FDA plan,
14 measure success not only by the number of drugs and devices
15 approved, but also by a reduction in the number of deaths,
16 adverse reactions, and recalls reported.

17 While we will offer comments today, and in the
18 future, about various provisions of FDAMA, we continue to
19 express our ongoing concern about the impact caused by the
20 lack of a commissioner. It has now been almost two years
21 since Dr. Kessler departed.

22 The lack of attention to filling this position, by
23 both the administration and Congress, is appalling, and
24 demonstrates a lack of commitment to the mission of the
25 agency.

1 Now it has been reported that we expect a
2 confirmation hearing for Dr. Hainey on September 1, but it
3 is extremely distressing to read about the number and nature
4 of questions submitted to Dr. Hainey by Labor and Human
5 Resources Committee Chair Jim Jeffords.

6 As reported, the hearing may not go forward if Dr.
7 Hainey fails to respond sufficiently.

8 This is an unprecedented effort to tie the hands
9 of the commissioner in advance of proper study of the
10 issues. According to reports, Dr. Hainey received questions
11 from industry that were, in some cases verbatim to the ones
12 received from Senator Jeffords, and the process has been
13 described as an effort by industry to work through senators
14 to pin down the agency and Dr. Hainey.

15 It is hard to read this effort other than as an
16 attempt to compromise the independence of Dr. Hainey, and by
17 extension, the agency.

18 However, there is one question that needs to be
19 asked and answered before the public, even though it is best
20 directed back at Congress.

21 What will you do to ensure that new initiatives
22 like food safety and tobacco do not draw resources away from
23 other FDA priorities?

24 We wonder why that question wasn't discussed fully
25 last year, when FDAMA was being considered, in light of the

1 new responsibilities it placed on the agency.

2 Consumer and patient groups unsuccessfully raised
3 the issue and it was also noted in the media. The agency,
4 in its message to FDA stakeholders, has admitted that it
5 finds itself severely challenged to meet all of its
6 statutory obligations.

7 The nation's chief health officer, Surgeon General
8 David Satcher, has also noted the FDA's underfunded status.

9 We wonder about the time and energy spent
10 developing this plan, if the agency simply lacks the
11 resources to adequately execute it.

12 This problem must be addressed now by all
13 stakeholders. CFA has certainly had disagreements with
14 FARMA and they will no doubt continue, but we call on FARMA
15 to work with us to secure adequate funding to implement
16 FDAMA, which industry pushed in a way that will not
17 compromise the safety of the public.

18 In general, CFA supports user fees for product
19 application reviews. One point of agreement during last
20 year's debate was that PDUFA has been, to quote industry, a
21 smashing success.

22 Congress should give serious consideration to
23 expanding the user fee program.

24 As we've said, safety goals need to be included in
25 the plan. We join with the patients' coalition in calling

1 for the creation of an Office of Drug Safety, and my
2 colleague, Scott Sanders, will describe this in more detail
3 later.

4 A particular challenge has been raised as the
5 result of a new efficacy standard in FDAMA, which will allow
6 drugs to be approved on the basis of one clinical trial.

7 We have no doubt that the agency will be under
8 heavy pressure to make this the rule, rather than the
9 exception. Indeed, there is a question to Dr. Hainey,
10 asking her views on the necessity of two clinical trials.

11 CFA unsuccessfully fought this provision last
12 year. We were especially dismayed by the lack of attention
13 paid by Congress to report about clinical trial fraud and
14 irregularities, which surfaced while FDAMA was pending.

15 In one case two researchers relied upon by many
16 drug companies were indicted on 172 charges involving drug
17 testing operations.

18 According to a lengthy article in The Wall Street
19 Journal, not exactly a liberal vehicle, prosecutors and
20 medical college officials were incredulous that none of the
21 drug companies appeared to notice that anything was wrong,
22 and they overlooked obvious signs that proper procedures
23 weren't being followed.

24 Earlier work by one of the researchers had been
25 reviewed and criticized by the agency, but that did not

1 impede future contracts with major drug companies.

2 The recent allegation involved charges of
3 unqualified personnel, inadequate supervision, and
4 ineligible patients who were misled. One former employee of
5 the researchers described the drug-testing inspection system
6 as a joke, and said that drug companies treat researchers
7 like kings because they supply the study data.

8 In this particular case, according to the journal,
9 the FDA found serious violations but had sufficient evidence
10 from other test sites to uphold its approvals of drugs the
11 researchers had tested.

12 In addition, last fall, the president and two
13 employees of a research firm pled guilty to falsifying
14 clinical data.

15 In this case, data were falsified in experimental
16 drugs for a range of conditions, including asthma and heart
17 disease. The FDA later improved some of the drugs and noted
18 that the agency, quote, always required two controlled
19 multi-center trials, perhaps true at the time, but not into
20 the future.

21 Both the FDA and the industry must ensure the
22 integrity of the clinical trial process. We believe this is
23 an appropriate subject for collaboration.

24 Similarly, given the new off-label provision, we
25 are concerned about the integrity of the publishing process,

1 both for reasons of safety and efficacy.

2 Last year, it was widely reported that a
3 university scientist's findings about a thyroid drug were
4 suppressed by the company that paid for the research,
5 raising questions about how the relationship between
6 academia and the industry impacts the reliability of
7 information given to doctors and the public.

8 A lengthy article in the New York Times reported
9 that medical leaders were concerned that the reluctance to
10 publish studies that did not show any benefits from a drug
11 skewed the public information.

12 The article claimed that little attention was
13 being paid to this relationship. According to one
14 authority, this issue is very big, and former Deputy
15 Commissioner Mary Pendergast acknowledged the discordance
16 between the full news about a new therapy, and that which is
17 published in the scientific literature in many cases.

18 We call on Congress to investigate these practices
19 and to provide the FDA with adequate resources to monitor
20 clinical trial quality.

21 Finally, we take issue with the balanced approach
22 CDER has described in its question five.

23 CDER asks how it should balance the need for
24 strong and timely pre-market review programs with the need
25 for effective post-market inspection, surveillance, and

1 enforcement programs.

2 Now "balance" can imply equality, or it can imply
3 the act of weighing, much more likely to be the case here.

4 The agency needs to approach these issues
5 independently. It is simply not acceptable for post-market
6 activities to suffer because of pre-market activities.
7 Indeed, we would never tolerate such an approach in the
8 airline industry, for example. Thank you.

9 MS. HENDERSON: Our next speaker is Cynthia
10 Pearson on behalf of the National Women's Health Network.

11 MS. PEARSON: Thank you. I'm going to read a
12 slightly shortened version of the prepared remarks I
13 submitted, and if I manage to squeak by before the lights
14 start flashing at me, I wanted to continue the dialogue
15 about public comment periods and advisory committees, that
16 started earlier this morning.

17 I'm the Executive Director of the National Women's
18 Health Network, which is a nonprofit women's health advocacy
19 organization. We are supported by a national membership of
20 over 12,000 individuals and 300 local organizations, and we
21 take no contributions from pharmaceutical companies or
22 device manufacturers.

23 We are pleased today to have the opportunity to
24 provide our perspective to CDER as you define the strategy
25 for fulfilling its responsibilities and achieving its goals

1 in the upcoming years.

2 We feel particularly happy about the opportunity
3 to comment at this point because this is an issue that's
4 near and dear to our heart. We were established nearly 20
5 years ago to provide people with information and services to
6 enable them to take action on health issues, and to serve as
7 a clearinghouse on women's health information.

8 Some of our very earliest actions were directed at
9 the FDA on behalf of women's right to have information about
10 drugs.

11 Even before the network was formally established,
12 our founders were organizing, writing, testifying, and even
13 demonstrating at the FDA on behalf of women's right to
14 patient package inserts, a consumer's version of the
15 prescription drug information available to physicians.

16 We strongly believe in the mission and the work of
17 the FDA, and the need to ensure that the agency remains a
18 strong regulator with the authority to safeguard our
19 nation's drugs and devices.

20 We also believe in the need to provide the agency
21 with comment and criticism about how the center and the
22 agency can meet the needs of consumers and patients, and
23 protect public health.

24 We've never missed an opportunity to communicate
25 to the FDA and to its stakeholders, when we believe there is

1 a need to change.

2 However, we have consistently argued that efforts
3 to reform the agency must build on, not dismantle the
4 ability of the FDA to safeguard drug products.

5 Our idea of change includes a vision of a strong,
6 well-resourced public health regulator capable of more
7 efficient review and approval of safe drugs than devices,
8 and more and better monitoring of safety and enforcement of
9 FDA regulations, and greater public access to crucial
10 health-related information.

11 We believe that this vision is currently
12 unattainable. Indeed, the FDA has submitted, as Mary said
13 in her remarks, that it is finding it increasingly difficult
14 to meet its statutory obligations.

15 As the FDA's authority has been relaxed, we feel
16 that safety has been relaxed as well. In 1997 alone, the
17 FDA received 251,000 adverse event reports, nearly 100,000
18 more than in 1996. Thirty percent of these reports were due
19 to drugs which had been approved from 1993 to '96, when the
20 FDA was coming under increasing pressure to act quickly on
21 new drug applications.

22 Further, in the last several months, five drugs
23 have been withdraw for safety reasons, including the widely
24 used, off-label combination Fen-Phen.

25 Currently, patients and consumers are more, not

1 less, in danger of drug-related injury, are more, not less,
2 likely to have a television or magazine ad be the main
3 source of information about prescription drugs, and are
4 more, not less, likely to have taken drugs which have not
5 been adequately tested for safety and effectiveness for the
6 use for which they are being used.

7 The FDA is doing less, not more, monitoring and
8 enforcement, with fewer and fewer resources.

9 As you will hear from other panel participants
10 this afternoon, the FDA simply cannot perform its core
11 functions with the resources presently available to it.

12 We believe that the FDA must fully exercise its
13 role as a regulator and protector of public health, and to
14 do this, the FDA must be its own strongest and most
15 vociferous advocate for more resources.

16 As center directors and leaders, you must carry
17 this message to the Acting Commissioner, the future
18 Commissioner, and to your own staff.

19 Nowhere is the need, we believe, more urgent than
20 within the area of direct consumer advertising.

21 Since a voluntary moratorium on advertising ended,
22 we have watched the evolution of drug advertising, and
23 believe that our worst fears have been borne out.

24 Drug companies have taken full advantage of the
25 relaxed rules, which were further loosened in August of

1 1997.

2 A recent survey discovered that spending on direct
3 consumer ads increased 42 percent in one year alone, from
4 1996 to 1997, and patient requests for brand name advertised
5 drugs increased 59 percent.

6 According to the same survey, projected direct-to-
7 consumer advertising expenditures are expected to skyrocket
8 to \$1.3 billion in 1998.

9 In 1997, just 10 drugs were advertised on
10 television. Less than three months into 1998, more than 50
11 drugs had already been advertised on TV, and magazines
12 carried many more glossy, full-page ads.

13 Yet, for all the millions of dollars drug
14 companies are spending on advertising, consumers and
15 patients are getting previous little useful information
16 about the safety and effectiveness of the drugs being
17 directly advertised to them.

18 What is being communicated in these ads is the
19 same type of information that's imparted in any other ad.
20 The brand name and a reason to use the product.

21 Most importantly, the public is being bombarded by
22 an impression about the drug.

23 For example, ads for Depo Provera birth control
24 shots convey the impression that busy women with hectic
25 lives will find Depo Provera convenient. Some women may

1 well find it convenient; however, many others may find it
2 extremely inconvenient because of a common side effect which
3 is unpredictable vaginal bleeding.

4 Even if women wade through the long columns of
5 tiny print and find irregular bleeding listed in the adverse
6 reactions section, the message communicated in that text is
7 nowhere near as compelling as the message conveyed by the
8 slick, sophisticated ad on the front of the page.

9 Consumers are facing a blitz of drug advertising
10 without any balancing flow of unbiased information.

11 Another case in point is the aggressive campaign
12 for Evista, put on by its maker, Eli Lilly Company, which we
13 believe began promoting the drug even before the drug was
14 approved by the FDA.

15 We realize our belief is a matter of opinion,
16 since the ads didn't mention the name of the drug. But we
17 believe's that Lilly was trying to create the impression in
18 women's minds, that Evista, once it was approved, would be a
19 replacement for estrogen replacement therapy, and we knew
20 that the only indication that was being requested for Evista
21 was osteoporosis.

22 We protested this ad, and thankfully, the FDA
23 acted and the ad has been revised. However, the problem
24 hasn't ended for women. Soon after, Wyeth-Ayerst entered
25 the fray with its own ad for its product, Premarin, and, in

1 our opinion, Wyeth-Ayerst's ads are also misleading. They
2 combine proven benefits which are included on the label with
3 benefits which have only been hinted at in small,
4 preliminary observational studies, and are years away, if
5 ever, from being well-enough proven to be on the label.

6 In both of these cases women have no easy way to
7 get balanced information. Although drug companies often
8 give consumers a Web site and toll-free number for obtaining
9 additional information, these resources are also controlled
10 by pharmaceutical companies and also influenced by the
11 intent to advertise rather than to inform.

12 There's no FDA Medguide program in existence,
13 right now, and the types of patient package information
14 leaflets that are available to consumers are created by for-
15 profit companies and often omit critical data about adverse
16 effects.

17 And finally, if the FDA directs companies to
18 revise an ad campaign or even orders ads to be pulled,
19 consumers have no way of knowing that the ad they used to
20 see, that they aren't seeing now, was changed or pulled
21 because of complaints about the message conveyed in that ad.
22 An entire nation of magazine readers and TV viewers have
23 been exposed to the ads and affected by them, and in some
24 cases the damage has already been done.

25 I noted earlier, that there ha been a parallel

1 rise in the budget for direct-to-consumer advertising, and
2 the number of adverse event reports submitted to the agency.

3 We're particularly alarmed by the frightening
4 evidence that Fosamax and Norplant are the top two drugs at
5 the top of this list of adverse reports, and these drugs are
6 used nearly exclusively by women.

7 They're both advertised directly to consumers in
8 campaigns that we believe do not adequately balance the
9 benefits with the risks and the side effects.

10 Many, including some in the FDA, argue that the
11 number of direct-to-consumer ads, and the number of adverse
12 event reports are not connected, and that the greater number
13 of adverse events reports is indicative of the FDA's efforts
14 to put more time into safety monitoring.

15 We disagree. As more drugs enter the market on
16 the fast-track and are approved with less data, consumers
17 are put at risk. They are further put at risk when flashy
18 ads, which glamorize prescription drugs, and minimize risks
19 are run in print and on TV, and the public health is even
20 still further compromised due to the inability of the FDA to
21 effectively monitor this direct-to-consumer advertising and
22 take action against companies that mislead.

23 In summary, we have four recommendations. The
24 Network urges the FDA to rethink its rules regarding direct-
25 to-consumer advertising. We believe the balance has swung

1 to misleading information. We encourage the agency to
2 revisit its rules and begin to find ways to strengthen
3 standards for drug advertising.

4 We also urge CDER to request more resources for
5 more aggressive policing of ad content, and part of the
6 monitoring process must include a greater emphasis on public
7 education. The public has a right to know when companies
8 have been asked to revise or pull ads, and the reasons why.

9 Finally, if direct-to-consumer advertising
10 continues, we believe that all pharmaceutical companies that
11 participate should be made to fund an independent consumer-
12 run organization generously supported with enough resources
13 to independently evaluate drugs advertised to consumers and
14 drugs claims made to those consumers.

15 The FDA must ensure that consumers have access to
16 an independent source of information on drugs that can match
17 the accessibility of savvy direct-to-consumer advertising.

18 As the FDA moves forward with its strategic plan,
19 we call on CDER to give the public more and better
20 information about drugs than can fit into a 30-second sound
21 bite.

22 Thank you and I'll take advantage of maybe 20
23 seconds that I have left, and just to continue the
24 conversation started by the physician this morning, tell you
25 that the views I think pretty commonly shared in the

1 consumer community about public comment periods during
2 advisory committees are well-thought out.

3 We believe that in order for the advisors to get
4 the best advantage from hearing from the public, which
5 includes generalist consumer groups as well as specific
6 patient representatives, that they're best-served if the
7 comment period occurs after the sponsor and the agency have
8 both had a chance to present data and discuss it.

9 We've had tremendous success with certain advisory
10 committees and panels, in putting this into action and in
11 some parts of the agency it happens routinely.

12 Unfortunately, there's still a few committees
13 where they believe that the only narrow role for the public
14 is to present their needs, rather than actually comment on
15 data, and so we're still struggling in some parts of the
16 agency, but those are our views at least. Thanks.

17 MS. HENDERSON: Thank you very much.

18 Next we're going to hear from Ray Bullman. Mr.
19 Bullman represents the National Council on Patient
20 Information Education.

21 MR. BULLMAN: Thank you. The topic I'll be
22 addressing is the specific question: How can CDER assure
23 that health care professionals and consumers get the
24 information they need about drugs? What methods of
25 communication would be the most effective in getting

1 additional information about drugs to health care
2 professionals and to consumers?

3 First of all, thank you for providing me the
4 opportunity to participate in today's meeting and on this
5 panel.

6 The National Council on Patient Information and
7 Education, NCPPIE of which the Food and Drug Administration
8 is a founding member, is pleased that the Center for Drug
9 Evaluation and Research is seeking input into how it can
10 help assure that health care professionals and consumers get
11 the information they need about their medicines.

12 This objective is indeed similar to NCPPIE's
13 mission, which is to stimulate and improve communication of
14 information on the appropriate use of medicines to consumers
15 and health care professionals.

16 NCPPIE is a participant in the development of the
17 1997 "Action Plan for the Provision of Useful Prescription
18 Medicine Information," is concerned about the quantity and
19 quality of information being conveyed as part of DTC ads, at
20 the point of prescribing and dispensing, and with
21 supplemental information provided to patients along with
22 their prescription medicines.

23 In our comments to FDA last October on the topic,
24 "Draft Guidelines for Industry: Consumer-Directed Broadcast
25 Advertisements," we urged manufacturers to experiment with

1 different formats for supplemental written information as
2 described in the "guidelines" section, Chapter 3, of the
3 "Action Plan for the Provision of Useful Prescription
4 Medicine Information."

5 In light of CDER's recent addition of down-
6 loadable, drug-specific information leaflets for consumers
7 on its Web site last week, today, I would repeat several
8 suggestions that we made to the agency last fall.

9 I brought, by way of example, one of the consumer
10 leaflets off of your Web site, and I wasn't surprised to
11 find those, and then I guess my next reaction, or thought
12 was, or question to myself was how specifically were the
13 criteria and the recommendations put forth in the Action
14 Plan adhered to in the development of these drug information
15 leaflets for consumers?

16 First, CDER is encouraged to commission research
17 to determine which formats of supplemental written
18 information are most useful in terms of, a) improving
19 consumers' medicine adherence and health outcomes as
20 determined by a health care professional, and b) improving
21 information exchange between the patient his or her
22 prescribers, or prescriber, pharmacist, and other health
23 care professionals.

24 The study could concentrate on a prescription drug
25 or a class of drugs representing the top drug or drugs used

1 predominantly by women, older adults or children, and that
2 have been targeted for heavy DTC broadcast or print
3 advertising since the agency relaxed the guidelines in
4 August 1997.

5 Findings from this research can provide guidance
6 to those engaged in developing their own versions of useful
7 written information. Although the 1997 Action Plan
8 recommends specific criteria for the content and format of
9 useful written information, these recommendations are
10 untested in the real world.

11 Second, CDER is encouraged to support the
12 development of a collaborative, national Consumer Medicine
13 Safety and Education Program. The goals of the program
14 would be to educate consumers and health providers about
15 changes and improvements in prescription medicine
16 information; promote question asking and information sharing
17 and giving as valuable tools to improve communication,
18 knowledge and usefulness; and to better equip consumers and
19 caregivers to recognize and report medication-related
20 errors.

21 The campaign can be modeled after the Partnership
22 for Food Safety Education, which includes industry, consumer
23 groups, HHS and several other federal agencies, including
24 CDC, USDA, and the Department of Education.

25 The partnership is developing, disseminating and

1 evaluating a single food-safety slogan and several standard
2 educational messages. The partnership is currently funded
3 by nine industry organizations. The FDA and USDA will
4 expend \$4 million of 1998 funds to support this and other
5 education activities. The partnership enlists a national
6 network of public health, nutrition, food science,
7 education, and special constituency groups to support the
8 campaign and to extend its reach.

9 The partnership has launched a nationwide food-
10 safety education campaign targeting the general public with
11 a focus on key concepts tested for maximum consumer
12 understanding. The "FIGHT BAC", B-A-C, campaign includes a
13 slogan, logo, and identifiable character. The campaign
14 utilizes multiple information channels--the mass media,
15 public service announcements, the Internet, point-of-
16 purchase materials, and school and community outreach
17 efforts--to alert consumers about the problem of food-borne
18 illness and to motivate them to take action. It promotes
19 September as National Food Safety Month.

20 CDER is urged to take the lead, among federal
21 agencies, in developing a memorandum of understanding to
22 organize and support a national Consumer Medicine Safety and
23 Education Program modeled after the Partnership for Food
24 Safety Education.

25 NCPIE is willing to work among the private sector

1 stakeholders to garner support for the program among groups
2 representing health care providers, consumers, and the
3 industry.

4 In the idea, initial campaign messages could be
5 disseminated by October 1999 to coincide with the 134th
6 national "Talk About Prescriptions" Month which could be
7 reformulated as "National Medicine Safety and Education
8 Month."

9 Such an educational program was recommended in the
10 "Action Plan for the Provision of Useful Prescription
11 Medicine Information." Consumer organizations, FDA,
12 industry groups, and other stakeholders should all
13 participate by contributing resources towards collaborative
14 message design, testing, implementation and evaluation.

15 Why Americans need such a campaign. Patients die,
16 fail to recover, or their conditions worsen due to improper
17 medicine use. Estimates of medication noncompliance are
18 well over 50 percent for certain medicines or classes of
19 drugs. Poor compliance among chronic disease sufferers can
20 result in uncontrolled disease and progression of disease.

21 For example, increased risk of death after
22 myocardial infarction has been observed in patients with
23 poor adherence to beta-blockers. Noncompliance with
24 infection disease therapy--tuberculosis, for example--can
25 result in treatment failure and transmission of the

1 infection. Consumers also place themselves and others at
2 risk due to the effects of avoidable side effects and
3 adverse reactions. Among older adults, an estimated 32,000
4 people suffer hip fractures due to falls, for example.

5 The Department of Transportation notes that over
6 100,000 automobile crashes, resulting in over 1,500 deaths,
7 are linked to driver drowsiness due to, among other things,
8 the sedating effects of medicines to control high blood
9 pressure, treat various psychological disorders, or in the
10 case of some OTCs, to treat allergy symptoms.

11 Recently, the National Highway Traffic Safety
12 Administration initiated the "Drug Evaluation and
13 Classification Program" in 27 states. Specially trained
14 officers, called Drug Recognition Experts, or DREs, are
15 empowered to evaluate drivers for the influence of legal
16 medications that might interfere with driving ability.

17 Maryland's DRE coordinator, 1st Sergeant Bill
18 Tower, was quoted in May 1998 as saying, "The drug-impaired
19 suspect has escaped detection and prosecution far too often.
20 That has now changed."

21 Clearly, no one wants loved ones driving while
22 impaired with alcohol or illicit drugs. Nor do we want the
23 public placed at risk from sedated rivers.

24 But I would prefer, for example, that my parents,
25 or other members of my family know the risks of taking their

1 medications, and that they know they can check with their
2 doctor or pharmacist about side effects, or the potential
3 for side effects or sedation when they receive a
4 prescription, or are selecting an OTC, so that they won't
5 put themselves and others at risk by getting behind the
6 wheel. That's the importance of education.

7 Finally, in 1997, national pharmacy organizations
8 convened a symposium to develop strategies for overcoming
9 barriers to effective oral counseling about prescription
10 medicines.

11 Lack of consumer awareness of the value of
12 medicines properly used, and their risks, and the potential
13 for harms for medicines used incorrectly were identified as
14 major barriers at that symposium.

15 A recommendation from the symposium is development
16 of a sustained national consumer education campaign. NCPIE
17 is committed to ensuring that consumers receive useful
18 information about their medicines and are participating in
19 the design, development, implementation and evaluation of
20 such a national consumer medicine safety and education
21 program.

22 Thank you very much.

23 MS. HENDERSON: Thank you, Mr. Bullman.

24 The last speaker on this panel is Charles Myers,
25 representing the American Society of Health-System

1 Pharmacists. Mr. Myers?

2 MR. MYERS: Good afternoon, everyone.

3 As many in this room probably know, the American
4 Society of Health-System Pharmacists, or ASHP, is the
5 30,000-member professional society of pharmacists who
6 practice in places like hospitals, home care, long-term
7 care, and staffed health maintenance organizations. These,
8 in other words, are settings in which pharmacists work in
9 close collaboration with prescribers and nurses and other
10 health care givers.

11 Today I would like to offer comments about three
12 of the six questions that CDER asked in a July 21
13 communication to CDER stakeholders. The first deals with
14 drug marketing and advertising.

15 CDER asked, "How can CDER ensure that drug
16 promotion is both balanced and non-misleading?" I'll give
17 you the punch line now. We are not sure that this can be
18 done, given the nature of promotional messages and the
19 nature of prescription drugs.

20 A little more elaboration. ASHP supports consumer
21 access to full information about all medicines. We believe,
22 however, that for best understanding by most patients, this
23 information must be interpreted for them by learned
24 professionals, including physicians and pharmacists.

25 ASHP continues to believe that promotional

1 advertisements for specific drug products ultimately pose
2 significant risk to patients. They also burden the health
3 care delivery process with partially informed patients and
4 often unrealistic patient expectations induced by the
5 advertisements.

6 ASHP supports direct consumer advertising that is
7 educational in nature about the availability of prescription
8 drug therapies for certain medical conditions, but we oppose
9 direct consumer advertising of specific prescription drug
10 products.

11 This policy of ASHP reflects the awareness of
12 health-system pharmacists that direct-to-consumer ads,
13 advertisers, tend to minimize the risks associated with the
14 drug product being advertised, and that of course is in
15 contrast to the more prominent attention given to the
16 benefits attributed to the use of the product. ASHP
17 believes that given their brevity, direct-to-consumer
18 broadcast advertisements cannot provide consumers with
19 adequate risk-benefit information on prescription medicines,
20 and in that sense they are inherently misleading, we
21 believe.

22 Greater opportunity for full information obviously
23 exists with printed advertisements. We believe it is
24 unrealistic, however, to imagine that the mere printing of
25 package insert type information along with a promotional

1 advertisement provides appropriate interpretive information
2 for consumers.

3 Health-system pharmacists have observed a greater
4 tendency toward self-diagnosis by consumers and more
5 frequent patient requests for prescriptions for advertised
6 drug products. We believe there is a real danger that this
7 eventually will lead to the prescribing of inappropriate
8 medications.

9 This country has a class of prescription-only
10 medicines because the public believes that certain medicines
11 require professional expertise in deciding when and how to
12 use them. The concept of enticing the public to seek
13 prescriptions for those medicines we believe simply cannot
14 be reconciled with the concept of restricting the medicines'
15 availability for public safety reasons.

16 So, given the depth of information and
17 interpretation essential to the appropriate use of
18 prescription medicines, we are not convinced that
19 advertisements for specific drug products can ever be
20 anything but somewhat misleading.

21 The second question we will deal with: drug
22 information. CDER states that it is an authoritative and
23 independent source of drug information and asks, "How can we
24 assure that health professionals and consumers get the
25 information they need about drugs?"

1 While FDA's authoritativeness and independence
2 with respect to drug information is acknowledged, it must be
3 observed that this expertise is greatest with respect to,
4 first, the original indications proposed by drug product
5 manufacturers as a part of their applications for marketing
6 approval, and with respect to post-marketing surveillance
7 information.

8 Entities outside the FDA, however, including ASHP,
9 are also authoritative and independent sources of drug
10 information. Importantly, some of these sources, including
11 ASHP, give broader attention to all scientifically and
12 clinically established drug uses, and ultimately health
13 professionals and consumers need information about both the
14 uses that qualified a drug product for initial marketing as
15 well as other legitimate uses.

16 Dealing narrowly, however, with how CDER can best
17 provide the information it does have to professionals and
18 consumers, we can imagine several possible ways.

19 First, continue to make package insert information
20 available by way of the World Wide Web. We are aware of
21 FDA's resolve to make these accessible for new innovator
22 drugs approved since January 1998. This is commendable, but
23 we believe similar access should be devised for drug
24 products approved before that date, as well.

25 Second, provide a fax-on-demand service for access

1 to package inserts, post-marketing surveillance data, and
2 special alerts. We are aware that some fax-on-demand
3 activity already exists.

4 Third, provide a widely publicized hot line for
5 telephone access to information by professionals and
6 consumers.

7 We are also aware of FDA's new consumer
8 information section in the Web site which promises to
9 provide consumers with information for all newly approved
10 drug products. However, unless this information can be
11 expanded and kept up-to-date with respect to unlabeled uses,
12 we question its long-term utility in meeting patients'
13 needs.

14 Having mentioned the Web and fax-on-demand, we
15 wish to acknowledge that FDA has made great strides in
16 providing information by way of these means. The timely
17 posting of special alerts on the Web has improved noticeably
18 in the past couple of years, and these notices have been
19 gratefully received by pharmacists. Automatic e-mailing of
20 such information to various organizations that can then
21 multiply transmission to their constituents has also been
22 very helpful. Links between the FDA Web site and others
23 also has been very appreciated.

24 And the third question, dealing with surveillance
25 and adverse event reporting. CDER asks, "What else needs to

1 be done to detect, analyze, communicate and respond to the
2 causes of death and injury from medicines?"

3 First, we encourage FDA to consider ways to allow
4 anonymous reporting to the MedWatch program. We fully
5 recognize FDA's current commitment to confidentiality with
6 respect to reported data and the value of being able to
7 contact reporters for more information, but we believe the
8 promise of confidentiality is not sufficient to erase the
9 fear of legal discoverability of reported information.
10 Hospitals, as of July, can now report errors anonymously by
11 way of the Internet through the MedMarch program operated by
12 the USP.

13 From time to time FDA has issued MedWatch
14 communications about specific problems. These are very
15 helpful to health professionals. If there is not a standard
16 schedule for release of these communications, we suggest
17 that there be a scheduled distribution of these several
18 times per year, and special alert notices might still be
19 needed in urgent circumstances.

20 ASHP is aware of the efforts of the National
21 Coordinating Council on Medication Error Reporting and
22 Prevention, with FDA's good input, to develop a standardized
23 taxonomy of reportable events. We applaud FDA's efforts to
24 foster this, and we encourage FDA's formal adoption of such
25 a standardized taxonomy if it evolves.

1 In addition to health-system pharmacies' long-
2 standing attention to the prevention of medication
3 misadventures, substantial increased attention to this is
4 recently occurring through various groups. I mentioned the
5 National Coordinating Council on Medication Error Reporting
6 and Prevention. There is also the National Patient Safety
7 Foundation, the Institute for Health Care Improvement, the
8 Department of Veterans' Affairs, the Joint Commission on
9 Accreditation of Health Care Organizations, the Institute
10 for Safe Medication Practices, and the American Association
11 for the Advancement of Science.

12 We now have a lot of parties involved in this, and
13 very interested, and we have the promise of some good
14 progress. We anticipate that many constructive
15 recommendations and initiatives will emerge through these
16 efforts. Among them may be an effort to standardize
17 definitions for terms such as "medication errors," "adverse
18 drug reactions," and "adverse drug events. We encourage FDA
19 to remain open to the possibility of refining its own
20 definitions if this evolves.

21 In the cumulative reports of medication errors
22 there is abundant evidence that poor product design is a
23 contributing factor in many medication errors. Poor label
24 readability, poor nomenclature, look-alike and sound-alike
25 product names, confusing abbreviations, and a lack of

1 machine-readable coding, for example, bar coding, all are
2 examples of product designs that contribute to errors.

3 We are aware that FDA has increased its
4 prospective review of such product design elements with
5 practicing pharmacists, physicians, and nurses before
6 approving drug products for marketing. If this and the
7 formal application of failure mode and effects analysis is
8 not yet a requirement for all drug product approvals, we
9 strongly encourage that it be made a rigid requirement.
10 Ideally, retrospective review of existing approved products
11 would also be valuable.

12 Lastly, to support the research of others, we
13 encourage the continued access by others to the MedWatch
14 database, with appropriate shielding, of course, of
15 confidential aspects of the data. The MedWatch database
16 represents a growing mine of information that researchers
17 might use in analyzing medication error problems and then
18 constructing appropriate solutions. Analysis, by FDA or
19 others, in fact should be a priority if we are to learn as
20 much as possible from the reports received.

21 ASHP appreciates the opportunity to provide
22 comments, and we will be submitting written comments before
23 the deadline. Thanks.

24 MS. HENDERSON: Thank you. I am now going to open
25 the floor up to our panel of FDA participants to clarify or

1 to ask questions of our stakeholders' panel.

2 Questions?

3 DR. TEMPLE: This is for Cindy Pearson or anyone
4 else. With respect to direct-to-consumer advertising, you
5 mentioned particularly you thought at least some of them
6 clearly you see are unbalanced. If it were better balanced,
7 and I guess that might mean it would have to go 45 seconds
8 or something outrageous like that, would it still be a
9 negative from your point of view? Is it the lack of balance
10 or is it the thing itself that is most troublesome to you?

11 MS. PEARSON: I think you have gotten right to the
12 point that we grapple with ourselves, that like the person
13 who was commenting from the Health-System Pharmacists, we
14 support patients and consumers having as much access to as
15 much information as possible. It's the premise on which our
16 organization was founded, so a large part of our
17 philosophical approach to our work would say, if we can get
18 balanced information to women, that's a good in and of
19 itself.

20 And yet we find ourselves starting to doubt
21 whether even the best balanced information provided in the
22 clearest manner can adequately match up against an ad which
23 has visual imagery in it, and so I think we are at this
24 point starting to believe that the thing itself may be an
25 insoluble problem.

1 DR. TEMPLE: Have you sent us comments on any
2 particular ones? If you haven't, it would be helpful.
3 Obviously, we worry about balance, but I think it needs
4 other people to help us know whether we have achieved it or
5 not.

6 MS. PEARSON: We have, including some of the
7 examples I gave in the testimony, but we have more examples
8 and we would be happy to send you more about that.

9 DR. TEMPLE: I guess just one more follow-up. Mr.
10 Myers suggested that institutional ads, that is, "Get your
11 cholesterol checked," that kind of thing, are of benefit for
12 everybody and don't raise the same issues about product-
13 specific, aggressive promotion. Would that be your view,
14 too? Would you like to see more of those, or do you think
15 the whole thing ought to be just discouraged?

16 MS. PEARSON: Well, responding off-the-cuff, it
17 certainly is tempting to think that, and has some logic
18 behind it, to think that an ad that just promotes health-
19 seeking behavior gives another, different kind of
20 opportunity for balanced discussion of information, so in
21 that sense I guess we would agree that that is a better
22 approach to direct-to-consumer advertising than the brand
23 name ads which I used as examples in our testimony.

24 But it still has the issues of advertising
25 associated with it, that it's a very sophisticated way of

1 communicating an impression that by its design doesn't have
2 a detailed or even, balanced approach to risks and
3 benefits. You know, something can get approved on pretty
4 slim evidence of benefit, and then if a large marketing
5 campaign comes out to promote health-seeking for that
6 condition, it can drive a lot more people into using
7 something that really maybe only that slim benefit is worth
8 it in the most serious cases.

9 For example, Accutaine is--you know, I would hate
10 to see health--whatever you call that. I've suddenly lost
11 the name of the ad. But there is more use of Accutaine than
12 there needs to be right now, and if someone started a "Yes,
13 there's treatment for cystic acne, call your doctor," and it
14 was promoted by the people who were selling Accutaine, I
15 would think that would be worse for women than better.

16 So there is a sort of vague answer for you.

17 MS. BAYLOR-HENRY: I also have a question about
18 direct-to-consumer promotion. I had some concerns, we had
19 some concerns about the consumer-direct-to promotional
20 campaigns that appeared on television prior to August 1997,
21 where it would be a suggestion about a treatment and it
22 would sort of walk right up to the line, provide all of the
23 visual imagery that you were talking about, and then--but
24 not give you the name. They may give you the name, but then
25 not the indication, so there was all this confusion that

1 surrounded these particular advertisements.

2 So I guess I am curious as to, from your
3 perspective, whether you believe it is better to somehow
4 link the name of the product with the indication, if there
5 is additional balancing information, or would you advocate
6 returning to pre-August 1997 days? Ms. Pearson?

7 MS. PEARSON: Again, an off-the-cuff answer is, I
8 think the confusion that can come with an ad that is
9 explicitly saying the condition but not mention the name of
10 the drug, or on the other hand mention the name of the drug
11 but just hinting at the condition, it's more obviously an
12 ad. And I think the problems that can come from that are
13 less pervasive than the problems that come from naming the
14 drug, naming the condition, and creating very effectively
15 through advertising techniques an impression that sort of
16 lasts and isn't balanced by carefully weighed information.

17 MR. MYERS: I agree with Mary that specific drug
18 products, the mention of specific drug products is a
19 problem. Imagine back when we were just discovering,
20 though, that peptic ulcers had a cause that was different
21 from what people had imagined for years and years before.
22 You know, it was discovered that there was a bacterial
23 origin for a lot of peptic ulcers.

24 It would be a very useful thing, then, even if it
25 is the manufacturer of the product, in my mind, to have an

1 ad then that says, "By the way, there's a new therapy for
2 peptic ulcer disease. See your physician." It would not
3 necessarily have to mention the name of the drug, but I
4 think that that would still be a public service. It would
5 be wise for the public to know about this.

6 We recognize that there is a really fine line, and
7 that someone would have to be a constant judge, ad after ad,
8 as to whether or not the line had been crossed. I can tell
9 you that ads that don't seem to say--ads that are too vague,
10 we think are just counterproductive. We think they simply
11 confuse the public.

12 So there really is a fine line, and we admit to
13 that, and we appreciate that if the agency is really going
14 to monitor this, it is going to be an intensive activity.
15 We already have heard some comments this afternoon about how
16 the rate of ads has increased, so extrapolate that and
17 imagine that you have got to have FDA staff really
18 monitoring all the details, then, of these ads and making
19 that judgment. That's tough, we recognize.

20 DR. WOODCOCK: Did you want to comment to that?

21 MR. BULLMAN: Yes, just a brief comment, and this
22 is a personal comment. I personally believe that
23 essentially the genie is out of the bottle with information
24 about specific drug products, and I think it would be even
25 not only counter-productive but more confusing if ads rolled

1 back, messages rolled back to just information-seeking kinds
2 of spots.

3 But with that said, I think there is an
4 opportunity to educate as well as to promote with the ads,
5 in particular the print ads. I would personally like to see
6 as a consumer those print ads, after I turn the slick and
7 glossy two- or three-page spread over, I would like to see
8 an educational message in lieu of that microscopic, brief
9 summary.

10 And so one of the recommendations that I would
11 make is that that specific criteria be looked at and be
12 determined and consumer tested and evaluated for what
13 constitutes useful accompanying patient educational or
14 patient information in conjunction with those
15 advertisements. Thank you.

16 DR. WOODCOCK: Now I would like to ask Mary, who
17 commented on Office of Drug Safety, but you didn't--is that
18 right?

19 MS. ROULEAU: Yes.

20 DR. WOODCOCK: But you didn't expand on that very
21 much. Could you give us some more information about--

22 MS. ROULEAU: Well, as I said, my colleague is
23 going to talk about it with more specificity later, so I
24 would just as soon, if that's okay, hold the comments.

25 DR. WOODCOCK: Okay. All right.

1 MS. ROULEAU: Yes.

2 DR. GOLDMAN: I have two questions. Actually some
3 of this was even in the first panel.

4 It was mentioned--these comments would be
5 particularly to Mr. Bullman and Mr. Myers or in general--it
6 was mentioned, information, having information available and
7 information being utilized, and it seems like there is a
8 mixed message here. In a sense we are hearing about where
9 people are very pleased with the information being put up,
10 yet when we take a look at the statistics on our Web sites,
11 they can be somewhat discouraging.

12 An example I can give you is, with the full
13 cooperation of CDER for the last two years MedWatch has been
14 generating summaries of all the safety-related drug changes
15 that have been made, and they are posted within a month or
16 five weeks after they are done. Yet the last time I looked
17 at our Web site, it was discouragingly small. So I am
18 soliciting, the panel and certainly anyone else, what kind
19 of ideas would you have to let people know those things are
20 up, both for consumers and health professionals?

21 MR. MYERS: ASHP has its own Web site, and
22 sometimes find that our own members don't know it's URL and
23 don't know where to find it. And I drive down the highway
24 and I see billboards with people doing nothing but
25 advertising their Web site.

1 And the connection I'm making here is, I think
2 that we for our own Web site, and probably you for yours,
3 are going to have to engage in some promotion, some
4 advertising, if you will, about the fact that the Web site
5 even exists. To expect people to simply discover it or pass
6 the word to their friends apparently is not enough. At
7 least it's not enough in our own case, and I suspect the
8 same is true in your case. So I think you're going to have
9 to promote it.

10 DR. GOLDMAN: Well, as one of our MedWatch
11 partners you have been supposedly helping us promote.

12 MR. MYERS: Right, yes. And we do do that, and we
13 do do that by our newsletter, so we hope that a few people
14 are noticing. But yes, you're right, and we will certainly
15 continue doing it.

16 DR. GOLDMAN: The second part of that was the
17 intriguing idea about the Consumer Medicine Safety and
18 Education Program. Again, the information is out. We do
19 try. We don't want to get lulled into the idea that
20 everyone is on the Internet and utilizes the Internet. We
21 get phone calls, we fax, we have fax-on-demand.

22 One question that--one comment was made about the
23 MedWatch notifications not being done regularly. Could you
24 just clarify what you meant by the notifications? I just
25 want to be sure about that.

1 MR. MYERS: I wish I could remember the names of
2 the documents that we have received. I'm sorry, I can't
3 right now. But from time to time obviously FDA issues
4 alerts about various things. It may be that not all those
5 are coming from the MedWatch program, so I apologize if
6 that's not the case.

7 But what we are saying is that there needs to be
8 some regular scheduled appearance of these things for people
9 to begin to anticipate them and appreciate the information
10 that is coming. If it is regularized, we believe that
11 people will start to build in their minds a better
12 impression that, "Oh, the agency is a group that we can
13 count on. They're going to be giving us stuff on a
14 scheduled basis." I think there is a power in a schedule.

15 DR. GOLDMAN: Just again to clarify, we want to
16 make sure we're on the same wave length, notifications like
17 "Dear Health Professional" letters, safety alerts,
18 notifications come out as they are released with all the
19 centers, CDER obviously being one. We also have the
20 Continuing Education Program, which you may be referring to,
21 comes out once a year. There is the FDA Medical Bulletin.
22 There is the FDA Consumer.

23 Those things are scheduled. But safety-related
24 notifications such as public health advisories and others
25 are done as things are done.

1 MR. MYERS: We understand that safety alerts need
2 to be done as the occasion requires, but would it not also
3 work to have periodic summaries of those?

4 DR. GOLDMAN: That's what I was wondering if you
5 were getting at.

6 DR. SMITH: I have a question, also for Mr.
7 Bullman. You were talking about the new Web site and other
8 ways of getting information to consumers. We are very
9 interested in--you know, what we put up last week is an
10 initial method. We are very interested in improving that in
11 any way possible, and would appreciate feedback from
12 everyone.

13 I was intrigued, though, with your comment about
14 our keeping it up-to-date, especially with respect to off-
15 label use and so forth, because while we can--I think we
16 will make every effort to keep it up-to-date with labeling
17 changes, with supplemental indications and so forth, I don't
18 think there is any way that we as an agency will be able to
19 put up any information about off-label use. And I was
20 wondering if you felt that other organizations should be
21 putting up that information, or what?

22 MR. BULLMAN: Well, the 1997--the action plan that
23 I referred to, the voluntary private sector guidelines for
24 useful written information, in the acceptance of those, of
25 that plan in '97 by HHS, there was a specific comment made

1 in terms of providing off-label use information and the idea
2 that that--the basis for the recommendation is that that
3 information be customized and that it not be for broad
4 classes of medicines, but that it be patient-by-patient
5 specific in terms of its generation and provision at the
6 point of--essentially at the point of dispensing.

7 But it is--if I could--it is a--technologically it
8 is, if nothing else, it's a huge challenge to keep
9 information up-to-date and current even on approved uses for
10 the private sector drug information vendors, or database
11 developers as well, but of course then we as consumers are
12 placed at risk because of that lag time or--knock on wood--
13 but inefficiencies as well in the current system.

14 DR. SMITH: My concern is the problems we are
15 having, I guess, which FDAMA addresses in some ways, about
16 the dissemination of off-label use will require a certain--
17 you know, that they be in refereed journals and other
18 requirements for the information before it could be put out.
19 Would you--I would hope that any information that would go
20 out on a consumer Web site would also require those same
21 restrictions.

22 MR. MYERS: Well, I for one would certainly agree.
23 If one is going to hold out information to the public or to
24 professionals as being reliable, then indeed it must be
25 based upon good science and good clinical experience, well-

1 documented and, as you suggest, peer refereed journals would
2 be an ideal place for that kind of information to have
3 appeared.

4 The comment that I was making earlier about the
5 importance of keeping that information up-to-date and
6 addressing unlabeled uses really deals with the reality that
7 if we don't do that, if the agency doesn't do that, then
8 after a period of time, if for example the majority of uses
9 for a particular product happen to be unlabeled uses, how
10 useful then will this monograph, I'll call it, be?

11 One can understand, though, when a drug product is
12 new that it might have some real merit, because
13 theoretically when the drug product is new, maybe the uses
14 are going to be more limited to those that were originally
15 the basis of the drug product's approval for marketing.

16 I appreciate the agency's dilemma here, because on
17 the one hand we can see that the agency would want to create
18 consumer-oriented information about a newly approved
19 product. That actually would be very appreciated by
20 consumers. I'm just worried about the longer term. I don't
21 have an answer for you about how to do that, but I can
22 appreciate that it would be very resource-intensive. It
23 certainly is for us, as we try to maintain our own
24 information.

25 DR. TEMPLE: This is for Mr. Bullman. I'm not

1 sure I wrote the name down, but you were talking about the
2 National Consumer Medication and Drug Safety Program or
3 something like that. And you had some interesting examples
4 of what one might want to communicate. One was that non-
5 adherence is rampant and that if you're trying to treat
6 something and you don't take your drug, you probably will
7 get sick from what you were trying to prevent.

8 You mentioned large numbers of hip fractures due
9 to falls, presumably relating to sedating drugs in older
10 people, and automobile crashes. Those aren't the sorts of
11 things one ordinarily thinks about. When one thinks about
12 drug misadventures, it's usually something more glamorous
13 like a valvulopathy that was unexpected.

14 I wonder if you--I have a couple of questions.
15 One, do you think there are more things like that? And how
16 far would you push this? For example, the remedy to
17 automobile crashes due to drowsiness is to pick a drug with
18 the same effect that isn't that sedating.

19 So would this organization remind people that
20 there are non-sedating anti-anxiety drugs and non-sedating
21 antihistamines? And how does one work that out? That's
22 getting perilously close to promoting one drug over another.
23 Do you think it can be managed, or would the number of
24 things one could talk about be relatively limited to avoid
25 seeming to promote things?

1 MR. BULLMAN: I don't think there--I don't think
2 what could be talked about could be, would be limited in any
3 way. I think there's more than enough to talk about in
4 terms of some basic information-sharing and educational
5 ground-laying across the general populace, and that
6 obviously becomes compounded with issues of low reading
7 level and illiteracy, the need for different languages, as
8 well.

9 I certainly would not advocate for any kind of a
10 national educational initiative that would end up being even
11 perceived as promotional for one type or class of medication
12 over another. That was not the intent of my use by example
13 of, for example, sedation and driving. Because there is
14 also a concomitant problem or a similar type problem, for
15 example, inadvertently taking medications, for example, with
16 an afternoon cocktail, or mixing alcohol and medications;
17 issues related to food and drug interactions.

18 I think there's a whole gamut of educational areas
19 that are ripe for the opportunity of increasing the reach
20 and frequency of the educational message. That is really I
21 think personally what has been lacking in terms of a
22 national educational initiative. There are lots of points
23 of light and roman candle messages that go up and flare
24 wonderfully, and then they glitter down and then there is
25 this long gap between the next wave of public service

1 announcements. I think we are really interested in reach
2 and frequency.

3 DR. TEMPLE: But just let me press that. If you
4 wanted to remind people that some of their drugs might
5 sedate them, you would limit it to a very general message.
6 You would say, "Some drugs sedate you. Ask your doctor if
7 this is one of them. Sometimes there's another drug." That
8 kind of thing.

9 MR. BULLMAN: That's correct. For example, we
10 advocate, our group and our member groups have advocated
11 core questions about medications. One is, "Are there any
12 side effects, and what should I do if they occur? Will this
13 new medicine work safely and effectively with the other
14 medicines I am taking?"

15 By asking that question, you automatically as a
16 health professional cannot answer it unless you say, "What
17 medicines are you currently taking?" So we hope that that
18 will--these will be initiating questions and kind of
19 stimulate the dialogue.

20 MR. MYERS: I can't escape the observation, just
21 tell patients to also ask their pharmacist.

22 [Laughter.]

23 MS. BAYLOR-HENRY: We have heard arguments on both
24 sides of the debate regarding direct-to-consumer promotion,
25 and certainly appreciate getting information from all

1 interested parties. But one of the arguments that is
2 frequently raised is that the health care environment is
3 changing, and as we move more into a managed health care
4 environment, that patients have to be their own advocates.
5 And there is less time on the part of the health care
6 professional to spend time with patients discussing
7 particular treatment regimens, and so therefore the patient
8 must come in with the information that is needed in order to
9 actively participate in these decisions.

10 So I was curious about how--maybe, Ms. Rouleau,
11 you could answer this--about your comments about this
12 changing health care environment and how this impacts on
13 direct-to-consumer promotion.

14 MS. ROULEAU: Well, I'm hardly an expert, but I
15 think there's a distinction here between--and, hell, I've
16 been out saying people need to be better, you know,
17 consumers of health care--but I think there's a distinction
18 between consumers and patients needing to understand how the
19 system operates versus diagnosing and treating their own
20 problems. That's kind of where I draw the line.

21 In a managed care environment they need to
22 understand, for example, that their plans probably have a
23 formulary and what is on that plan, and if they are on a
24 chronic--if they have a chronic condition, that their
25 prescription drug be part of that formulary before they

1 switch. They need to understand they may need to do
2 referrals before they can see specialists, and a whole
3 litany of questions that I think people have to be able to
4 ask.

5 Some of the questions that you all have put
6 together, about if you are going to take a drug, what are
7 the side effects, those are very good. That is, I think,
8 what I mean when I say consumers need to be better--you
9 know, consumers need to be better consumers of the system
10 and to take responsibility for their health care.

11 But that's a big jump between saying that and
12 saying, "Well, hell, I think I need Allegra" or something
13 like that, and this is only my own anecdotal observation. I
14 really think--well, I have seen doctors stand up and say
15 this, too--that we are creating a system, if we are going to
16 ask consumers to, you know, spend too much time with this
17 information, where I think it's--and I don't know if the
18 word "conflict" is appropriate here, but I think we're going
19 to put doctors and patients in many situations at odds with
20 each other.

21 If the message we're giving to consumers is, not
22 only do you need to understand what is deductible in your
23 health plan, but you should have enough information to go in
24 and essentially discuss with your doctor the proper course
25 of a drug therapy treatment, I draw the line there.

1 I mean, I think it's important for a patient to
2 understand that they're being given a drug, what the side
3 effects are, you know, making sure they understand that if
4 they're on something else, there could be an interaction,
5 certainly arming consumers with enough questions to get at
6 those issues, but that's to me different than asking them to
7 essentially become their own physicians. I'm not ready to
8 go there yet, and I think I read more than most people.

9 DR. WOODCOCK: Many thing we have been discussing
10 are health policy issues where there are various opinions on
11 different sides of the issue. One of the problems I think
12 that FDA has had in navigating especially these
13 communication issues is that there is little research that I
14 know about, about the various options.

15 We have not ourselves conducted the communications
16 research or other research that would enable us--we do some.
17 We have a small research program where we utilize surveys
18 and focus groups to learn the impact of various changes or
19 proposed changes, but do you know, are there other sources
20 of research that we could utilize to resolve some of these
21 issues?

22 Otherwise we end up relying on people's opinions
23 about what is the impact of various changes. And it is a
24 very difficult environment, I think, in which to make policy
25 decisions.

1 MR. MYERS: I confess to not being totally
2 informed, but it occurs to me to wonder whether the Agency
3 for Health Care Policy and Research might find this of
4 sufficient interest. At least to the extent that this issue
5 may relate to patient safety, there are groups like the
6 National Patient Safety Foundation that might be a body to
7 turn to. That group is just getting to the point where it
8 is ready to start making its choices about things that it
9 wants to invest in for research, so that is a possibility.
10 And I suppose there might be some independent foundations
11 that would have sufficient interest in this as a topic.

12 MS. ROULEAU: There is a project, and you're
13 probably aware of it, I think it's called the Health
14 Literacy Project. I went to a day-long seminar about a year
15 ago. I have all the information back in my office. And my
16 memory is, although it's fuzzy, that it was cosponsored by
17 both the Foundation and one of the--I think Pfizer--one of
18 the drug companies.

19 But, you know, it was very enlightening to me
20 because, you know, let's face it, a lot of these ads that
21 we're arguing over, even if we all agree about these ads,
22 what segment of the population really is going to read that
23 and understand it at any level? And it was a very eye-
24 opening experience for me to realize how much I take for
25 granted my ability to access the system at a more--at a

1 fairly detailed level, as it turns out, even though I feel
2 pretty stupid.

3 But some of the very basic instructions about
4 medicines are just totally not understood by large segments
5 of the population, even people who don't necessarily have a
6 functional reading problem, and we know there are a lot of
7 people out there who have that. So I don't know how far
8 their work has progressed, but it's out there. And, again,
9 if you don't have the information, I have it back at the
10 office.

11 DR. WOODCOCK: We did research on the physician
12 insert, and that was an extremely eye-opening experience to
13 go out and ask physicians exactly how useful the format and
14 content of the physician package insert was to them in their
15 decision.

16 Of course, I have opinions on this already, but,
17 if changes are to be made, it is very, very useful, I think,
18 for a Government agency to have access to information on the
19 impact of those changes and the current level of functioning
20 and whatever we have at the moment, so thank you.

21 MR. BULLMAN: I think it would be helpful for
22 non-governmental organizations--I cannot speak for all,
23 obviously, but, personally, I think it would be helpful if
24 information and data that you obtain in the consumer focus
25 groups and their research surveys that you do of health care

1 professionals is made available to private sector
2 organizations, with, for example, an encouragement to use
3 those data and information to build and to develop their own
4 research base, for example, or to extent the research
5 effort.

6 There are some groups like the U.S. Pharmacopeia,
7 for example. This month, I think their schedule is to
8 release results of a study that they have commissioned on
9 the useful of written drug information and consumers'
10 preferences for drug information.

11 It was a contract with the University of North
12 Carolina, Duke University, for example. There are some of
13 those kinds of research efforts underway that, knock on
14 wood, will be shared very broadly, and people can use those
15 to build on.

16 DR. GOLDMAN: As a follow-up to this, to what Dr.
17 Woodcock is mentioning, one of the things that we try and
18 get across and something that hopefully we can work
19 collaboratively is the fact that post-marketing surveillance
20 is a loop, that medication is approved. We monitor it for
21 the wear, significant event, through the passive system, if
22 you will.

23 And then when a labeling change is made or a
24 public health advisory comes out, it shows the loop that
25 something was done, regulatory action was taken. It impacts

1 consumers, health professionals in that way. So that loop
2 is there, and we rely on the partners.

3 One thing I do want to clarify before I ask the
4 question directly. When we post something on the web site,
5 we do not just let post it and let it sit. We have two list
6 serves that we utilize. One is the partners list serve,
7 134, 135 maybe by now, organizations. We have a second list
8 serve which has now opened up. They can go into the web
9 site and sign on for, including the drug centers and
10 individuals, to let people know something has been posted,
11 and we have that. We are trying very hard to do that
12 through advertising ways.

13 The second part of that is, as Dr. Woodcock is
14 mentioned, trying to figure out is that the best way to do
15 it, the formats we are using, the kind of information we do.
16 I can say anecdotally that we have gotten very positive
17 feedback on Q's and A's that we have put out along with
18 "Dear Health Professional" notifications.

19 I see heads nodding. Obviously, that is something
20 that has come across.

21 That is very useful to us in terms of what we can
22 utilize, and one of the other things we might mention, as we
23 are kind of scribbling down here, are things like that,
24 about how to best get the information out.

25 MS. BAYLOR-HENRY: Also, in follow-up to Dr.

1 Woodcock's comment about research, in the Federal Register
2 Notice in August of 1997, the Federal Register Notice about
3 broadcast, direct-to-consumer advertising, the agency said
4 that at the end of a 2-year period, 2 years after the
5 publication of a final guidance, that the agency would
6 revisit this issue and look at the public health impact.

7 The agency at that time also stated that we would
8 encourage those in the private sector to conduct research,
9 to look at the public health impact, including the impact on
10 the relationship between the health care professional and
11 the consumer as a result of these types of advertisements.

12 So I would just like to reiterate the importance
13 of going back to your organization, perhaps, and considering
14 doing some kind of research.

15 I know the American Pharmaceutical Association in
16 conjunction with Prevention magazine did some survey
17 research a couple of years ago, and they shared that data
18 with us.

19 Prevention magazine has recently done an
20 additional study that looked at broadcasts as well as Time
21 magazine. We are always encouraged when we continue to get
22 the results from these research projects in. So I would
23 just like to reiterate this.

24 Thank you.

25 MS. HENDERSON: Great. I want to thank all of our

1 panelists very much for your time.

2 We will now take a 15-minute break. Actually, we
3 will make that a 20-minute break. So we will start back on
4 the hour at 3 o'clock. Be back in the room for Panel No. 3.

5 [Recess.]

6 DR. WILLIAMS: All right. I would like to welcome
7 you back for the third and last panel for today's session.
8 I will start by introducing the two panelists who are new to
9 the panel from the agency. One is Dr. Bernard Schwetz from
10 the Office of Science and NCTR, sitting next to Dr.
11 Woodcock.

12 The other new panelist to you is Mr. Doug
13 Ellsworth, who is director of the New Jersey District
14 Office, Office of Regulatory Affairs.

15 We have three speakers in this next panel session.
16 The order will be changed slightly. We are going to hear
17 first from Scott Sanders of the Patients' Coalition.

18 MR. SANDERS: Good afternoon. Can everyone hear
19 me? My name is Scott Sanders. I work with the American
20 Foundation for AIDS Research, and I have been asked today by
21 the Patients' Coalition to deliver these comments on behalf
22 of the Coalition. There is a list of supporting
23 organizations on the front of the testimony if you picked
24 that up.

25 The Patients' Coalition came together several

1 years ago because of concerns that the needs of patients
2 with serious and life-threatening illnesses were being
3 ignored, or in some cases misrepresented, during the early
4 discussions about possible changes to the Food, Drug, and
5 Cosmetic Act.

6 These groups then joined together with other
7 consumer organizations, united in the common desire to see
8 that new products are thoroughly tested and developed, pre-
9 and post-approval, and that the FDA's authority as a
10 regulatory agency not be diminished.

11 It was our belief then and it remains our belief
12 today that the changes necessary at the FDA do not need to
13 take place through legislation, especially through
14 legislation that lowered the standards and authority of the
15 FDA, as was done in FDAMA.

16 Our task today and the task of the agency in the
17 coming years is to define the FDA strategy for meeting its
18 legislative mandates, all of its legislative mandates in the
19 FD&C Act and the coming years.

20 First, as you have heard before, and I think you
21 will continue to hear from us, the FDA must make an
22 assertive effort to get more resources. The Center
23 directors must carry the message to the acting commissioner
24 and the new commissioner, when she is confirmed, that she
25 must be a vocal advocate within the administration, in the

1 Congress, and to the American people, an advocate for the
2 resources that the FDA must have to meet its legislative
3 responsibilities.

4 There is simply one way for the FDA to do its job
5 with the resources it has now. I think we all saw the
6 references to that in your message to the stakeholders. We
7 have all experienced it in our work with the agency.

8 Certainly, one strategy that deserves your
9 consideration is for the agency to work more constructively
10 with its stakeholders, as is done by many other Federal
11 agencies, to build support for adequate funding levels.

12 One concrete step that the FDA must take in this
13 planning process is to generate a realistic budget for
14 meeting its legislative mandate. By enacting Section 406,
15 the Congress gave the FDA the perfect venue for developing a
16 budget estimate that reflects the professional judgment of
17 the FDA leadership. Indeed, the FDA would be seriously
18 remiss if it developed this plan and did not attach a budget
19 to it.

20 If there is one message that you take away today,
21 it should be to work within the agency to ensure that the
22 FDA leadership seizes the opportunity that it has been given
23 by the Congress to document what resources the agency needs
24 to do its job.

25 Second, the FDA must forcefully reassert its role

1 as a regulator. The skewed debate over the past 3 years has
2 shifted the perception of what the FDA's role is in our
3 society and in our economy, and we fear that it has also
4 shifted the FDA's own perception of what its role is.

5 The FDA is, first and foremost, a regulatory
6 agency with the primary responsibility to protect and
7 promote the public health. The mission should never be open
8 to opinion polls.

9 While the agency should never unnecessarily act in
10 ways that are harmful to industry, it is not appropriate for
11 FDA to compromise its mission in order to support through
12 its decisions the financial well-being of a particular
13 company or type of company.

14 The FDA's job is to make sure that the regulated
15 industry follows the rules that are designed to protect the
16 public health. For the process to work, there must be two
17 separate roles, one for the regulator and the other for the
18 regulated.

19 These parties can and should communicate
20 frequently and work cooperatively, but their missions and
21 their roles are distinct. To be credible and respected, the
22 FDA's regulatory process must maintain its clear
23 independence from the regulated industry.

24 As the FDA moves forward with developing the
25 congressionally mandated plan, it must keep this perspective

1 at the forefront.

2 One pointed example of the impact of the prolonged
3 lack of adequate resources and the skewed perspective at the
4 FDA is Question No. 5 in the list provided by CEDER, "How
5 should CEDER balance the need for strong and timely pre-
6 market review programs with the need for effective post-
7 market inspection, surveillance and enforcement programs?"
8 That is like asking the American people to find a balance
9 between building safe aircraft and providing adequate
10 maintenance over the course of a plane's life, or it is like
11 asking a parent to choose between adequate food and shelter
12 for their child. It is simply not appropriate to balance
13 pre- and post-market responsibilities against one another.

14 If the FDA is to fulfill its mission, it must do
15 both fully and energetically. The solution to the problem
16 is not to cut back on either, but to find the will and the
17 resources to do both. Certainly, the death and injury
18 figures cited in the FDA's own Message to FDA Stakeholders
19 tells us very clearly the price that the American people are
20 paying as a result of trying to find a balance between these
21 two important responsibilities. Certainly, the current
22 facts dictate the need for a great commitment to drug
23 safety.

24 A significant step that CDER could take to begin
25 to make meaningful progress toward fulfilling its

1 surveillance and adverse event reporting responsibilities is
2 to create an Office of Drug Safety with the resources and
3 authority to do its job.

4 The current situation is alarming. The FDA has
5 fewer than 60 employees and a budget of \$6 million to
6 monitor the safety of 3,200 different approved drugs in the
7 marketplace. A staff of less than 60 is unequal to the
8 challenge of reducing deaths and serious injuries from
9 approved drugs.

10 A study recently published in JAMA showed that
11 106,000 Americans died and another 1.3 million injured as a
12 result of adverse reactions to properly prescribed
13 medications. This study has been attached, as well as
14 several other studies that show similar results.

15 The extremely limited staff that the FDA has to
16 deal with this tremendous problem is in sharp contrast to
17 the 4,000 inspectors the FAA has to monitor the safety of 11
18 major and 12 smaller air carriers and private pilots, an
19 industry which in 1996 had accidents resulting in a total of
20 945 deaths.

21 The time has long since come for CDER to establish
22 a strong Office of Drug Safety with its own advisory
23 committee to consider safety questions about already-
24 approved drugs. The office should have the funds and
25 capacity to use all major tools of public health prevention,

1 including case control studies, patient surveys, data from
2 existing health care information systems, and the MedWatch
3 system.

4 The office should be required to assess and
5 publish and annual detailed analysis of drug-related
6 injuries and deaths to monitor progress towards improved
7 drug safety, and to measure any problems with newly approved
8 drugs.

9 As a part of the planning process required by
10 FDAMA, the FDA should determine what resources and staffing
11 would be needed for this office to do its job, and the FDA's
12 leadership should be on Capitol Hill making the case. We
13 can assure you that patient and consumer groups would be
14 right behind you making that case as well, and we would hope
15 that the regulated industry would do the same. Certainly,
16 they would agree with us and with you that drug safety is in
17 everyone's best interest.

18 Another area where CDER must strengthen its
19 authority and effectiveness is in compelling drug sponsors
20 to conduct the post-approval trials that are agreed upon at
21 the time of approval. This is especially important for
22 priority drugs intended for the treatment of serious and
23 life-threatening diseases, many of which have seen a marked
24 reduction in pre-approval regulatory requirements for data
25 to demonstrate safety and efficacy.

1 Many of these drugs are approved quickly under
2 "accelerated" NDAs. Many of the members of the Patients'
3 group advocated forcefully for this mechanism and have seen
4 the impact it has had on moving drugs through quickly. It
5 was never our goal to see those drugs approved without
6 continued research after approval. Patients desperately
7 need post-approval data to confirm the early indications of
8 effectiveness and address ongoing safety concerns and
9 issues, such as dosing and regimens.

10 CDER must develop a stronger system for compelling
11 sponsors to conduct controlled studies, to confirm clinical
12 efficacy, and expand upon the limited knowledge base which
13 formed the basis for approval. Post-marketing research must
14 get done... A medical officer should be responsible for
15 monitoring the conduct and completion of all agreed-upon
16 post-marketing research for each approved drug.

17 Monitoring and completing of this research must be
18 a top priority. As more and more drugs are approved on less
19 and less data, the manufacturers must be held accountable
20 for the research they commit to doing as a condition of that
21 approval.

22 We acknowledge that the FDA's ability to
23 successfully compel manufacturers is hampered by the lack of
24 appropriate enforcement mechanisms, such as civil monetary
25 penalties. The unwillingness of Congress to include such

1 authority in FDAMA is a major failing of that legislation,
2 but the FDA must still move forward to implement a system
3 that will ensure this critical research gets done.

4 In a small victory for patients, the status of
5 individual, post-approval studies is now the subject of a
6 public reporting requirement. The statute states that these
7 public reports must include "information...to establish the
8 status of a study described...and reasons, if any, for
9 failure to carry out the study." To be useful and to meet
10 the requirements of the statute, the information provided
11 must be of sufficient detail to be meaningful.

12 If a study has been halted, the report should say
13 why it was halted. If it was stopped because of adverse
14 reactions, for example, that should be stated, along with a
15 listing of those reactions and their numbers.

16 If a study is in progress, but not meeting
17 projected milestones because of poor enrollment, that should
18 be reported. Congress included this provision so that
19 patients and consumers could effectively monitor the
20 progress of Phase IV studies that are committed to by the
21 manufacturer. The FDA must not allow this provision to be
22 crippled by unnecessarily limiting the information that is
23 publicly reported.

24 As I stated, there has been a significant shift
25 toward approving new products on less data, and that will

1 certainly continue with the implementation of the fast-track
2 provisions of FDAMA.

3 These regulations include some important
4 safeguards, such as a fast-track withdrawal mechanism. All
5 drugs approved under the new fast-track mechanism should be
6 subject to all provisions of the section. The proposal that
7 some fast-track products be exempt from requirements of this
8 provision, as has been suggested by some, is inappropriate
9 and clearly in conflict with the statute.

10 Finally, Dr. Woodcock stated earlier that we
11 needed informed stakeholders, and that is certainly
12 something that we agree with and are working for. I would
13 just say that in order to be informed stakeholders, we need
14 information, and, unfortunately, patient and consumer groups
15 have a very difficult time often getting access to the
16 information that they need.

17 We have numerous stories of trying to get basic
18 non-proprietary information from the FDA, only to meet with
19 roadblocks, and I will give you a brief recent example from
20 my office.

21 We were trying to gather very basic information on
22 drugs approved through the Treatment NID process, which is
23 being reviewed right now by the agency, and we want to give
24 comments about how that process should be changed. So we
25 are trying to look back at AIDS drugs that have gone through

1 the process to see what has worked and has not worked.

2 At the suggestion of FDA employees, we prepared a
3 FOIA request for the information we needed. One thing that
4 several people had told us to ask for, which should be
5 easily available, was the summary basis of approval. We
6 hope that information would answer a question regarding the
7 type of information that was submitted when these drugs were
8 approved.

9 In return, we received a terse letter from the FDA
10 stating, "The Food and Drug administration has not prepared
11 Summary Basis of Approval for any approvals in the past
12 several years. These documents are no longer prepared and,
13 therefore, are no longer available." But some of the
14 information we requested was on drugs that were approved 10
15 years ago. Is that several years?

16 Upon talking to someone else, we learned that the
17 FDA now prepares an alternative to the Summary Basis of
18 Approval, and that we should now request that information
19 separately. We have done that.

20 It would have been far more helpful if the agency
21 had provided the alternative information when we originally
22 asked. It seemed very clear what type of information we
23 were looking for.

24 Most groups like ours and the other consumer and
25 patient groups you have seen have very limited resources,

1 and when we are trying to make a contribution to the
2 process, it is very difficult when we have to keep going
3 back just to get basic information about a drug that has
4 already been approved and is on the market.

5 This example is representative of difficulty that
6 many patient and consumer groups have. Other examples are
7 far more serious, I think.

8 We have all heard cases about patients who are
9 told that the FDA would not move forward with a drug. They
10 turned down an application. They are not moving quickly
11 enough, and the agency can make no comment on that. We find
12 out maybe years later that, in fact, the company submitted
13 an incomplete application.

14 We know this is frustrating for the agency, too,
15 but something has got to be done in your planning process to
16 talk about how you are going to be able to speak more
17 forcefully with the public about these issues because we
18 want to be your allies in certain issues. We want to be
19 able to advocate appropriately on Capitol Hill, and we
20 cannot do that when we do not have the information we need.

21 The FDA is at a crossroads, and we hope that CDER
22 and the agency as a whole will seize the opportunity that
23 this FDAMA-required plan presents to put forth a complete
24 picture of the programs and resources that will be required
25 for the FDA to fulfill all of its legislative

1 responsibilities to the American people.

2 Thanks.

3 DR. WILLIAMS: Thank you, Scott.

4 Our next speaker is Arthur A. Levin from the
5 Center for Medical Consumers.

6 MR. LEVIN: It is the hour of low blood sugar. So
7 I will try to be stimulating.

8 First of all, I just want to endorse everything
9 that my advocate colleagues have said during today's
10 meeting. I view many of the provisions of FDAMA as a
11 retreat from the historic mission of the agency to protect
12 the public health and certainly find a lot of them
13 troubling.

14 I am going to talk mostly about Medguides, but I
15 thought at the risk of boring you, I would continue the
16 discussion about direct-to-consumer advertising.

17 As troublesome as sort of the relaxation of
18 broadcast ads are, I do not think print ads do the job
19 either.

20 I do not know how many of you were unfortunate
21 enough to see this full-page ad which ran in June in the
22 Wall Street Journal and the New York Times for a new drug to
23 treat type II diabetes, Rezuin. This is an example of why
24 direct-to-consumer ads are not educational, not informative,
25 not in the consumer's best interest, and despite what PHRMA

1 had to say this morning, certainly not empowering.

2 The ad plays down the potentially fatal risk of
3 liver toxicity. That is something "generally reversible,"
4 but in "very rare instances, fatal."

5 As of June 1998, there were 14 confirmed deaths in
6 the U.S. attributable to liver toxicity of this drug,
7 reports of another dozen or so deaths under investigation,
8 and deaths reported outside the U.S. That is not what this
9 ad suggests is the experience with this drug.

10 The message here is very clear. We have three
11 alive, happy people, who feel this drug has improved their
12 life, and down here, way down, is a very limited statement
13 as to risk. It misrepresents what we know about this drug.
14 It is a new drug. We do not really know if the incidence of
15 liver toxicity is very rare or fatality is very rare.

16 In fact, during the clinical trials, there was
17 almost no evidence of a problem. The evidence came after
18 the drug was widely diffused.

19 In November of '97, when there was enough evidence
20 to cause concern in Great Britain, the drug was withdrawn in
21 the U.K., and the manufacturer began to suggest an urge that
22 liver monitoring be done of patients receiving this drug,
23 but that was not true before November of '97.

24 This is a hard sell for a drug which is expensive.
25 It is made more expensive now by the need to monitor liver

1 function, to treat a disease, type II diabetes, which is a
2 serious disease affecting a lot of Americans, but for which
3 other treatments exist about which we know a lot more as to
4 benefit and risk.

5 The ad pretends to know a lot more about the risk
6 profile of this drug than we really know. It pretends to
7 have knowledge that serious liver toxicity is only very
8 rare, and we simply do not know that is true yet.

9 I believe that permitting the distribution of this
10 kind of misinformation, especially when considered against
11 the background of studies, both old and recent, that tell us
12 that death and injury due to adverse reactions to drugs,
13 excluding errors, may be the fourth or fifth largest cause
14 of death in the United States. 100,000 people dying a year
15 puts reactions, adverse reactions to drug as the No. 4 or 5
16 cause of death, some of which is preventable.

17 We have in harm related to prescription drugs a
18 public health emergency on our hands. I would suggest, we
19 seem to be willing to rely on Madison Avenue rather than
20 public health professionals to address it.

21 Now I would like to turn to the issue of how
22 consumers can get better information, or more information
23 about prescription drugs.

24 In an environment in which Government regulation
25 and oversight is the enemy and the marketplace are false

1 idol, the last line of public protection is the public
2 themselves. A well-informed properly warned consumer may be
3 the only public health intervention that makes sense in this
4 political climate.

5 The FDA made an effort to enhance that protection
6 when it proposed Medguides in 1995. What was Medguides? It
7 was an effort to establish some standards for the written
8 information that is distributed to consumers when they are
9 dispensed to prescription drug and to require that such
10 information be given out rather than rely on the kindness of
11 pharmacies.

12 Medguide was a reaction to the 20-plus years of
13 failed private sector initiatives that have begun when the
14 Reagan administration halted the FDA's attempt to mandate
15 PPIs, patient package inserts, be provided with--I think
16 there were 10 classes of drugs, which were going to be
17 required to have PPIs.

18 In '96, I think, after the proposed reg, maybe it
19 was still '95, the FDA held a 2-day meeting in the
20 Washington area to discuss the proposal, and every speaker
21 representing manufacturers, information publishers and
22 vendors, drug compendia, and health professionals opposed
23 the FDA initiative. They all lauded the notion of
24 information for consumers, but they thought Medguides was
25 Government overkill and was going to stifle innovation, and

1 that the FDA should not be getting into this business.

2 Every consumer and patient advocate at that
3 meeting spoke in favor of Medguides, and in fact, in favor
4 of even stronger oversight of written information.

5 Industry ultimately was able to prevail and a
6 Congress friendly to the notion that Government regulation
7 was an unnecessary burden in the marketplace, and the result
8 was a mandate in Public Law 104.180, to set up a
9 collaborative process to develop a long-range comprehensive
10 action plan consistent with the goals of the proposed rule
11 of the FDA administration on prescription drug product
12 labeling, medication guide requirements, or Medguide.

13 The process became known as the keystone process.
14 I and other people who are here today were part of the
15 steering committee that guided that process, which was a
16 very long contentious and difficult one, in an attempt to
17 reach consensus, and actually reach some consensus, but not
18 consensus on every issue.

19 From the beginning, again, aside from all the
20 consumer and patient--not all, but most of the consumer and
21 patient representatives, all the other members of the
22 steering committee oppose the notion that there needed to be
23 an independent expert oversight effort, preferably conducted
24 by the FDA of whatever private, public process would go
25 forward to meet the congressional mandate.

1 We pointed out that more than 20 years of the
2 previous private sector effort was deemed by advocates and
3 by then-Commissioner Kessler and then Assistant Secretary
4 Phil Lee as a dismal failure. When the steering committee
5 concluded its efforts, several consumer groups, including
6 the Center and others, urged the Secretary not to approve
7 the plan as submitted or request one unheeded.

8 Now, the purposes of my comments today is not to
9 provide a history of the frustrating decades of efforts to
10 provide consumers and patients with the information about
11 prescription drugs they need to protect themselves from
12 harm, to make informed decisions about their health care, to
13 optimize their opportunities to get well and return to the
14 highest level of function possible. My purpose is to call
15 on the FDA to revisit the congressional mandate for a
16 private sector solution, and to immediately begin a process
17 of review of the quality of written prescription drug
18 information being provided consumers and patients in
19 preparation for the year 2000 evaluation mandated by P.L.
20 104180.

21 We should not forget that as long ago as 1979, the
22 FDA stated that, "Oral communication about prescription drug
23 products by health professionals cannot be relied upon to
24 provide patients with the information they need to use
25 prescription drug products properly," and when proposing the

1 Medguide regulations, the agency went on record saying,
2 "Inadequate access to appropriate patient information is a
3 major cause of inappropriate use of prescription
4 medications, resulting in serious personal injury and
5 related cost to the health care system."

6 Now, not everyone here today may be aware that
7 Public Citizen has petitioned the FDA to "...immediately
8 stop the distribution of dangerous misleading prescription
9 drug information to the public." Joining them in this
10 petition are the parents of a young boy whose death was
11 likely caused, according to a medical examiner, by an
12 overdose of imipramine prescribed to treat attention deficit
13 disorder.

14 The written information accompanying the
15 prescription, published by a major commercial information
16 vendor, failed to provide information that would have warned
17 the boy's parents that their son was receiving three to four
18 times the pediatric dose, and that his reactions, his
19 symptoms were indicative of a potentially lethal overdose.

20 Now, Public Citizen also has conducted its own
21 surveys of written drug information provided for consumers
22 by pharmacies for 15 non-steroidal anti-inflammatory drugs
23 and for 5 floroquinolone antibiotics.

24 In surveying the NSAID information, Public Citizen
25 established four criteria. One, the GI toxicity was

1 identified as a potentially serious adverse effect. Two,
2 the GI toxicity is identified as potentially life-
3 threatening. Three, there is a listing of symptoms
4 associated with GI toxicity, and, four, there are
5 instructions to stop taking the drug if symptoms of GI
6 toxicity occur. It seems appropriate.

7 None of the written information, 59 examples
8 surveyed, met all four criteria, and only one in four warned
9 about stopping the drug if symptoms of toxicity occurred.

10 The FDA itself has compared the written
11 information published by eight commercial vendors for three
12 commonly prescribed drugs for consistency with the approved
13 product labeling. The FDA has found substantial differences
14 between the quality of information provided by each of the
15 vendors.

16 Is that red light mine? It is. I will hurry.

17 I believe we cannot wait for the year 2000 before
18 the FDA acts on P.L. 104180 to assess the quality of written
19 prescription information provided the public.

20 I would like to suggest what some of us suggested
21 in the final report to the Secretary in 1996 that the FDA
22 immediately establish an independent ongoing evaluation to
23 review the written prescription drug information being given
24 to consumers and patients. The evaluation should determine
25 if the published written drug information currently

1 distributed to consumers and patents meets the criteria
2 established in the action plan, specifically that it is
3 scientifically accurate, unbiased in content and tone,
4 sufficiently specific and comprehensive, presented in an
5 understandable and legible format that is comprehensible to
6 consumers, is timely and up to date, and is useful.

7 In regard to the first criteria, the action plan
8 specifically states that the information should be
9 consistent with or derived from FDA-approved labeling.

10 I said at the outset that providing consumers and
11 patients with the information necessary to make informed
12 decisions about their health provides a safety net to
13 protect against harm. I believe the information has to
14 first and foremost warn of risk: first, do no harm.

15 As more and more drugs come onto the market and
16 they are approved more quickly with less pre-market
17 experience, consumers and patients bear the brunt of the
18 increase in the risk. While I strongly agree the FDA needs
19 to take steps to strengthen the process by which we assure
20 drug safety, both in the pre-marketing clinical trial
21 experience and post-market, I am not sanguine that such
22 action will occur any time soon, at least until we have a
23 catastrophic drug-related event that will force the issue
24 politically.

25 The FDA, with a mission to protect the public

1 health, must take immediate steps to ensure the integrity of
2 this safety net, not to act in the face of the evidence that
3 the safety net is badly frayed, would be, in my mind an
4 abdication of its responsibility.

5 Thank you.

6 DR. WILLIAMS: Our next and final speaker in this
7 panel is Dr. Craig Brater, speaking on behalf of the
8 American Society for Clinical Pharmacology and Therapeutics.

9 DR. BRATER: Thanks.

10 First, let me thank CDER and the agency for the
11 opportunity for ASCPT to comment, and let me say I am
12 flattered that our society would ask me to be the
13 spokesperson.

14 Now I am going to prove that I am an academician
15 by the fact that, number one, I flew here and, number two, I
16 am going to use slides and, number three, I have got a laser
17 pointer. So I have got to get contorted here a little bit.

18 That is me. So I am from Indiana University, and
19 I have been very active in our society that is commenting to
20 you today, and this is what our society is all about.

21 We were established in 1900. I was not around
22 then, but sometimes I feel like it. We have about 2,100
23 members, and I think our society is characterized by being
24 very broad-based. It is really a bridging society, just
25 like clinical pharmacology is a bridging discipline. So we

1 are comprised of M.D.'s, Ph.D.'s, and Pharm.D.'s, all of
2 whom are engaged in research and education and therapeutics,
3 needless to say right at the heart of the FDA's
4 responsibilities.

5 In addition, we are multifaceted in that our
6 membership encompasses FDA, so the Government, academia, and
7 the pharmaceutical industry.

8 These are the three aspects that we would like to
9 comment upon today; firstly, the safety of marketed
10 products; secondly, maximum information for consumers; and
11 then the issue of scientific expertise and infrastructure
12 for FDA. All of these necessarily overlap, and they should.

13 That also means that you cannot just tease out one
14 of these things and throw the other two away or slice it and
15 dice it. I think all of this stuff fits into a continuum.

16 What about safety of marketed products? First,
17 the lead-in to this should be that the FDA is a strong and
18 efficient organization, but despite that fact, we are having
19 reports that adverse drug reactions may cause 100,000-plus
20 deaths per year and may be the sixth-leading cause of death
21 in the U.S. You have heard other speakers refer to this.

22 So what are we going to do about this? Well,
23 believe that there needs to be education, education,
24 education, and that needs to be not only for consumers, but
25 it needs to be for prescribers, and it needs to be for other

1 members of the health care team, including pharmacists,
2 nurses, et cetera, et cetera.

3 The problem that one has here is that there are a
4 paucity of resources for this education, and these resources
5 are not only fiscal, but they are also human in terms of
6 people who have the kind of training that is necessary to
7 fulfill this education admission, and this is a major issue
8 that hopefully the agency can help us address.

9 Now, to properly educate people, you also have to
10 do research into this area, and in particular, into the
11 causes of adverse drug reactions. And there is much
12 improvement that could occur into this area, and we will
13 expand upon that in a bit.

14 One of the problems that you have, of course, is
15 substantial amounts of resources are invested in the
16 research, getting a drug onto the market, but once it is on
17 the market, then who is going to pursue research issues
18 after that? Some will be pursued by the sponsor, but there
19 are many important questions that the sponsor is not
20 interested in pursuing, and who is our traditional source of
21 funding for research? Well, it is the NIH.

22 The NIH has had an abysmal track record in terms
23 of supporting patient-oriented research, and those of us in
24 this area have screamed and yelled about that for years.
25 They are starting to show more attention now, but,

1 basically, the bottom line is that there is a major problem
2 in terms of getting the resources to do these kinds of
3 studies.

4 So how do we fix that? Well, one early attempt to
5 do that is in this current legislation where there is a
6 component for Centers for Education and Research on
7 Therapeutics, and we think that this should be an important
8 collaboration with FDA to improve prescriber education and
9 to improve research.

10 I would like to emphasize that what has been
11 approved in the legislation, I would hope would be viewed as
12 a starting point, and certainly not an end point. And it is
13 a good start, but it is certainly not sufficient for
14 addressing the magnitude of the problems that we have now
15 and that are going to increase as we have more and more
16 drugs coming to the market and more innovative science in
17 this area.

18 We would also advocate an increase in the drug
19 safety staff at FDA, and that has also been touched on
20 today. One also might think of ways to -- innovative ways
21 to potentially leverage access to other sources of
22 information. So, for example -- and this may be a bit
23 controversial -- the PBMs have vast databases.

24 Right now it appears that the agency and PBMs are
25 sort of in a grenade-throwing contest, but if you think

1 about it, they have access to databases that could be
2 enormously valuable in terms of looking at concomitant drug
3 prescriptions and identifying just how big a problem some of
4 these things are. So it would help define the entire ice
5 berg, rather than simply working from the tip of what might
6 be an ice berg, but you don't really know.

7 We would also advocate that post-marketing safety
8 decisions be independent from the medical review process.
9 What is meant by that, let's say if a drug is approved and
10 then something bad goes on, it is just a natural human
11 reaction that the person who was responsible for approving
12 that drug is going to worry that maybe their judgment has
13 come into question, and it should not be personalized that
14 way. And if there was some way to make this more
15 independent, you would avoid that risk.

16 In addition, we advocate expanding regulatory
17 research on safety factors. So this is a continuation of
18 that theme.

19 Lastly, to reassess the risk-benefit analysis of
20 lifestyle-modifying drugs, there are a variety of those, and
21 maybe they should be subject to a different type of
22 scrutiny.

23 What about maximum information for consumers?
24 Well, my comments are a bit redundant of what others have
25 said, but the problem, of course, is that there is a

1 critical gap in provision of quality objective drug
2 information. This gap is widening at an ever-increasing
3 rate, and at a time when drug prescribing and usage
4 increasingly is documented to be suboptimal.

5 I mean, the advances in science and in drug
6 development are occurring at an astonishing rate. That is
7 the good news. The bad news is that we do not have an
8 infrastructure to communicate that information to the public
9 or to prescribers.

10 What could be done to help this? Well, one
11 potential thing could be that the FDA could specifically act
12 to fill the gap left by AMA drug evaluations and USPDI. AMA
13 drug evaluations was essentially surrendered by the AMA to
14 USPDI and merged with that. USPDI is basically a money
15 loser, and there are questions about whether or not that
16 should be jettisoned. This would be a catastrophe.

17 Parenthetically, these issues about off-label
18 uses, my own bias is that the USPDI is a very good
19 clearinghouse for those kinds of issues because of the way
20 that they gather information and make decisions, and I think
21 this is an enormous resource that needs to be protected and
22 embellished. If there is any way the agency could help with
23 that, I think that would help staunch some of this problem.
24 It would not be a total solution.

25 Another thing that could be done is a frequently

1 updated Internet-based drug label database that could be
2 queried by any user. So it could have various levels in
3 which people could drill down to different levels of detail,
4 depending upon their expertise and just how much information
5 that they want.

6 What about the question of scientific expertise
7 and infrastructure? A couple of things in here might be a
8 bit controversial, but I guess that is what we are here for.

9 Firstly, staff and the agency need to understand
10 modern science and they need to speak that language because
11 the people they are going to regulate understand that and
12 they speak that, and there is just not going to be any way
13 that proper regulation can occur without people being able
14 to communicate at the same level about this science.

15 In turn, science is, again, advancing at an
16 astonishing rate. So there has to be some mechanism by
17 which people can be recruited and kept up to date. So that
18 means, again, not just recruitment, but also mentoring,
19 mentoring of young people that are recruited into the
20 agency, but also retooling of people who have been there for
21 a while.

22 There needs to be maintenance and renewal of the
23 state-of-the-art scientific leadership. It has to start
24 from the top.

25 What are some things that could be done to fulfill

1 these goal? One, maybe you could have some novel programs
2 where you bring academic types into the agency for periods
3 of time to kind of benefit from their expertise and
4 perspective, and, obviously, these academic scientists would
5 also benefit from the experience of working closely with the
6 agency.

7 This will cause some people's impulses to
8 increase, but what about a program of time-limited tenure of
9 division and office director should be instituted? Take
10 that in a little bit different perspective. For example, in
11 academia these days, I run a department that is about half
12 the size of the FDA in terms of the number of staff people,
13 and everybody in our department has an annual review.
14 Objectives and values are delineated, and we see how every
15 person lives up to those each year. Those are not simply
16 quantitative. They are also qualitative, and this becomes a
17 way of people having their own measuring stick because
18 people have a natural tendency as to always want to do
19 better.

20 Our natural tendency is to want to know what
21 people expect of us. So things are very well defined, and
22 then that translates into things like promotion, continued
23 holding of positions of leadership, and, hey, if we can do
24 that in academia, certainly that can be done in an
25 institution like the FDA.

1 We would advocate considering things like national
2 search committees for important positions so that you get
3 insight and input from scientists not just internal to FDA,
4 but also external, and cross-center FDA staff, and cross-
5 center means not just within the FDA, but also interfacing
6 with academia.

7 One might also consider a sabbatical program where
8 FDA scientists can go and spend varying amounts of time,
9 minimum perhaps being a month, but maximum being 2 years,
10 going into a formal fellowship essentially in a specialty
11 area to really get up to speed in terms of what is new, in
12 terms of that scientific domain.

13 It would be nice if internal FDA and contract
14 scientific research could be augmented, again, to enhance
15 the level of science within the agency and access people
16 from the outside.

17 Lastly, we would propose that advisory committees
18 -- there be particular attention to their skill level. I
19 served on one of these advisory committees, and I thought
20 that it was an enormously valuable experience, and I hope
21 that I contribute as much as I gleaned from it. So it is
22 something that people in academia see as being worthwhile to
23 do, but you need to pay particular attention to the skill
24 level in addition to the independence of these people.

25 We would suggest that there be a clinical

1 pharmacologist on every one of these committees, again,
2 because of the bridging nature of this discipline and its
3 broad perspective. You could view the clinical
4 pharmacologist as somebody who could look at the forest and
5 not get lost in the trees. We would also suggest a
6 biopharmaceutical scientists as perhaps nominated by AAPS,
7 and pardon the misspelling there.

8 That concludes my remarks, and, again, I
9 appreciate the opportunity to have our society comment. We
10 do have a more detailed commentary that is in a stack of
11 killed trees back there on the back table.

12 Thanks.

13 DR. WILLIAMS: Okay, thank you, Dr. Brater.

14 Now I will turn to the panel to ask questions of
15 the presenters.

16 DR. SCHWETZ: I would be happy to start with one.

17 I thank all of you for your insight.

18 I have a question that relates to two of you. Dr.
19 Brater is suggesting mechanisms whereby the science and the
20 scientists within the agency could interact more effectively
21 with scientists in academic, and because many academicians
22 are also working closely with industry, then that is a
23 connection to industry.

24 On the other hand, Mr. Sanders is suggesting there
25 should be independence between the science of the agency and

1 the science of the regulated industry. How do we reconcile
2 these two, so that we as an agency are more aware of the
3 science that we will be seeing 4 or 5 years down the road?

4 DR. BRATER: Maybe I misunderstood Mr. Sanders,
5 but I did not think I heard him say that.

6 I thought he said that the regulated and the
7 regulator have to clearly keep a separation in terms of that
8 regulatory process, but I think it seems to me that
9 profiting from one another in terms of maintaining a level
10 of science does not need to interfere with that.

11 For example, if you sent an FDA staff person off
12 to do a sabbatical at our place and in so doing they
13 interacted with some of the scientists of Eli Lilly because
14 they are just down the street and we have some collaborative
15 relationships with them, it is hard for me to see that once
16 they get back into the regulatory mode that that is going to
17 contaminate them.

18 I think they should be able to keep their same
19 level of objectivity, and I would think that the people in
20 the industry with whom they interact would expect that to
21 also be the case.

22 MR. SANDERS: Exactly.

23 Yes. I think we as the community have always
24 thought it was important that there is collaboration both
25 between us and the agency and the industries and the agency.

1 I think working with each other in terms of sharing ideas,
2 sharing experiences, possible suggestions for how to do
3 things better is always appropriate.

4 Our concern really grows when we talk about
5 lowering of a standard based on the needs of a particular
6 company or a particular group. The agency has clear
7 legislated, mandated standards that they need to follow, and
8 we think they can do that while still collaborating with all
9 concerned stakeholders. I think it is a model that we have
10 used in working with the agency, and we think that is
11 appropriate.

12 DR. BRATER: Let me just say that I think that the
13 advances in science are so fast these days, and those are
14 translating readily into drug development, that the
15 imperative is compelling, and in terms of maintaining this
16 level of scientific expertise in people in the agency. So I
17 just don't think there is any way to get around that.

18 It seems to me that if that is bumping up against
19 the regulatory responsibilities, wise people and properly
20 motivated people can sort that out and figure it out.

21 DR. SCHWETZ: We would benefit from input from all
22 of you on how we can continue that so that we can learn more
23 extensively what industry and what academicians are thinking
24 about that we will be seeing in the future, so that we will
25 have the right expertise at a time when we need it, without

1 getting into some kind of a conflict or working too closely
2 with the regulated industry. We would benefit from some
3 input on how we can do that most effectively.

4 MR. SANDERS: Let me give a specific example. I
5 mean, in the AIDS community, an issue that we have been
6 grappling with a number of years are what are effective
7 surrogate markers for drugs. What tells us that a drug is
8 likely to work for an accelerated approval? And I think it
9 is very appropriate for the agency and the industry and the
10 community to sit down, as has been done, to talk about what
11 those surrogate markers are, what do we know about them,
12 what more research do we need to do on what markers are
13 effective, but then, ultimately, the decision has to be with
14 the agency about what markers they are going to use.

15 If the industry sees a surrogate marker that they
16 think 2 years from how it is going to be an effective
17 surrogate marker, it is appropriate for them to have a
18 conversation with that about the industry, and the community
19 and the agency together, so that the agency is ready for
20 that when those applications start to come in.

21 DR. WOODCOCK: I would like to thank all the
22 panelists for their thoughts on assuring drug safety. It is
23 a very important issue for us, but I do have a question.

24 For the past 4 years, the agency has heard
25 numerous comments about how requirements have ballooned over

1 the past 10 years and how drug development overwhelming
2 requirements, forgetting drugs approved in this country, and
3 excessive requirements. I heard today a number of the
4 panelists say that they feel the safety requirements have
5 diminished over the past few years.

6 I know when I spoke this morning, it probably
7 seems like a long time ago at this point, but one of our
8 problems is we do not have those statistics easily at hand
9 on actually what is drug development and what are the
10 statistics on drug development, what is the size of the
11 trials.

12 Our idea and impression at the agency is that,
13 however, over the past 10 to 15 years, the size of drug
14 development programs have increased a fair amount, and the
15 number of patients exposed is larger than was in the past.
16 In fact, I would say the quality of reviews have improved
17 fairly significantly over that time.

18 Although drug development programs for AIDS and
19 some other serious diseases may be very small and truncated,
20 and they may seem that way in comparison to the extremely
21 large development programs we see for chronic disease,
22 actually that might have been very typical in the past for
23 many drug development programs, a decade or two ago.

24 Do you have a factual basis for your impression
25 that the safety standards have been lowered, and could you

1 all explain that?

2 DR. BRATER: Well, I did not say that, but I am
3 happy to comment on almost anything.

4 [Laughter.]

5 DR. BRATER: First, let me say that my bet--and,
6 of course, this is a hypothesis that is likely untestable,
7 so I can say it with authority--is that the increase in the
8 size of NDAs and things like that and patient exposure and
9 stuff, my sense is that is not driven by regulatory
10 requirements, but more by the change in the health care
11 environment, and the fact that if you have got a compound
12 that is coming out, you have got to do more than just show
13 that it works and it is safe to go out and sell it. And you
14 have got to convince formularies and HMOs that this thing is
15 cost effective. So you have to generate a whole different
16 kind of data to successfully market your drug, and I think
17 that is probably driving a lot of it.

18 DR. WOODCOCK: That still increases the safety
19 database available.

20 DR. BRATER: That is good.

21 I would also say, and my co-panelists might
22 disagree with me, but it would seem to me that I think the
23 "safety issues" that are occurring are the ones that are
24 happening when the drug starts getting exposed to large,
25 large numbers of patients. These are not issues that are

1 going to be solved by looking at the NDA process and that
2 approval process.

3 So it is all at the back end and what can be done
4 to monitor at that level and how can we bring scientific
5 principles to looking at those issues.

6 DR. WOODCOCK: Thank you.

7 This morning, I commented sometimes there would be
8 events that could be picked up by a much larger
9 investigational program, but there are rare events and there
10 are events that relate to the use of the drug in the
11 population that is not the same as the use in the clinical
12 development program that result in lack of safety of that
13 drug.

14 So, yes, there are certain issues that you cannot
15 discover, practically speaking, during the drug development
16 program possibly, but go ahead.

17 MR. LEVIN: I was just going to say that it seems
18 to me, the evidence we do have is that adverse drug
19 reactions or adverse drug events, depending on the
20 researcher, how that gets defined, whether it is error or
21 includes error or not, in the last 10 years we just had a
22 lot more research that indicates that there is a significant
23 public health problem related to both preventable and non-
24 preventable adverse events with prescription drugs. Most of
25 those or all of those occur after the drug is well diffused

1 in the population.

2 So it seems to me, the answer to the question is
3 we may not have evidence that anything is slipping in the
4 up-front process necessarily, and that people in clinical
5 trials are subjected to any more risk than they were before,
6 but I think, first of all, it is common sense that as the
7 number and complexity of drugs increase, that the likelihood
8 of adverse events also increases.

9 I think also as the profitability of bringing new
10 products to market increases, particularly with lifestyle
11 drugs where the benefit-risk equation, as people have
12 suggested, is a very different one, that, again, some of our
13 calculus needs to be different, but I think the evidence
14 that we are finding is really the evidence of adverse drug
15 events and adverse drug reactions that simply were not well
16 studied in decades previous to this. We are getting more
17 and more evidence this is a significant public health
18 problem, and it seems to me that is why we are sort of
19 saying to the FDA, if it is the fourth, fifth, or even sixth
20 leading cause of death, as a public health agency, don't you
21 have a responsibility to be taking a really close look at
22 why this is happening, particularly when a number of these
23 are preventable deaths and preventable morbidities?

24 DR. WOODCOCK: Thank you.

25 Yes, I think we all agreed with that. The issue

1 is, if the emphasis is on what are the standards or is it
2 the drug development process, we may be putting the emphasis
3 or looking potentially at the wrong thing, and that is why I
4 asked the question what evidence do you have where this
5 problem is. Has this problem always existed out there? Is
6 it getting worse, as maybe that is what I am hearing you
7 say, but it has not been really well documented in the past?

8 DR. LUMPKIN: Janet, if I could follow up just a
9 little bit on that, having been closely involved in a lot of
10 the issues over the last several months with drug safety, it
11 has been very interesting in the discussions with various
12 groups involved with this, and a lot of it has to do with
13 perception.

14 I think one of the examples that was used earlier
15 today, people were talking about airplanes and airplane
16 crashes and what we do as a society to monitor that.
17 Obviously, I think we all know, in that situation you have
18 got a product, an airplane, which for all intents and
19 purposes are clones of each other. People get on airplanes,
20 and the laws of physics apply to all of the people and all
21 of the products in the same way, and you expect to go up and
22 you expect to come down. I especially expect to come down.

23 We know how many people get on an airplane, and we
24 know how many people make it safely to their destination.
25 So we have got a metric that quantitates the benefit of

1 airplane travel. When people do not make it safely to their
2 destination, we know that, and we immediately, I think as a
3 society, assume rightly that should not have happened, that
4 was preventable, there should not have been an airplane
5 crash, the way that the laws of physics apply to this.

6 So we have got good metrics on benefit of airplane
7 travel. We have got good matrix on risk of airplane travel,
8 and we can communicate to the consumers of airplane travel
9 what their risks are, but when we start doing that for
10 drugs, it completely begins to unravel because it is not
11 that easy, and I think we all know that. I think we are
12 getting into a completely multifaceted issue here where we
13 have known reactions, new unknown reactions. We have, as
14 people have talked about, preventable reactions, non-
15 preventable ones, things that are inevitable that we assume,
16 as Janet said earlier on, that we as a society have said we
17 will take a certain amount of risk for very, very few
18 numbers of people because of the great benefit of a large
19 number of people.

20 Then, when we do see something, we are tasked with
21 trying to figure out, was this a toxicity of the drug, of
22 the chemical? Was this an inappropriate use of a drug? Was
23 this a medication error? Was this a product quality defect?
24 That is only on the risk side. We will do not have a metric
25 to say what is the quantitative benefit that we as a society

1 have gotten out of this drug as it is being used in the
2 market to really try to come up with a way of saying what is
3 the public health problem here and put it in the kind of
4 perspective we can do with airplanes and airplane crashes.

5 I would be the first to say, I am not sure how to
6 do that, but I think that is one of the challenges. If any
7 of you guys have ideas, I think this is what Craig was
8 beginning to talk about, about education. I agree with
9 education, but it seems to me, it is one step before that.
10 It is figuring out what we are going to educate people and
11 what the data are here on the quantitative benefits and the
12 quantitative risks of these products and actual use to see
13 what the extent of the public health issue here is, and to
14 try to sort all of that out.

15 So, if any of you have good ideas on how to do
16 that, I think that would be really tremendously helpful to
17 all of us.

18 MR. LEVIN: We agree.

19 [Laughter.]

20 MR. SANDERS: I do want to say, I think the
21 airplane analogy is clearly not perfect.

22 DR. LUMPKIN: Right.

23 MR. SANDERS: But I think that the point we tried
24 to make is that in terms of the resources that we as a
25 country have put into this issue of drug safety is alarming.

1 It is even more complex in some ways. The questions are
2 very difficult, and we have a very, very few number of
3 people working for the public health agency who are trying
4 to answer those questions. That, I think, is what is so
5 scary. That is our concern.

6 Certainly, I think one thing that is important is
7 the more we can document the events that are happening, the
8 better sense we will have of what we need to fix the problem
9 and the kind of information people need, the consumers need.
10 Why are we having so many adverse events? Are people not
11 using them correctly? Are they not getting the information
12 they need? Are they missing doses? Are they doing too many
13 doses? There are more we need to know about, the number of
14 adverse reactions and why they are happening, and the more
15 we can study that, the better off we can be, so we can begin
16 to educate people about the things they need to prevent
17 those reactions.

18 DR. BRATER: At the risk of sounding like a broken
19 record, what both of you were doing is making an eloquent
20 plea for research.

21 MS. GRAY: I have a change-up question. All three
22 of you have stated in one way or another that FDAMA has been
23 a retreat or lessening of FDA's traditional stance, as did
24 the panel before you, and all of you on the last panel and
25 this one have made some good suggestions about what we ought

1 to do, where we ought to go.

2 It seems very close in context as compared with
3 what is happening in pharmaceutical science being
4 harmonized, being sort of universal in pharmaceutical
5 industry, particularly in manufacturing, crossing borders
6 more.

7 So, from that point of view -- and that is driving
8 more international activity within FDA and by FDA -- what
9 are your viewpoints or the viewpoints of the organizations
10 that you represent with regard to the international issues?
11 Do you address them? Do you have specific concerns about
12 them? Do you have druthers for FDA?

13 DR. BRATER: I have not been privy to the formal
14 discussions of the people in our society that have been
15 addressing that, but I think my gestalt is a simple one, and
16 that is that we are very supportive of the harmonization
17 effort, in part, driven by the notion that it would seem
18 that if there is more uniformity and less variability in
19 terms of what drives drug approval sand drug use, it seems
20 like that would be better for everybody, and we would all be
21 able to learn a lot more.

22 It is not a whole lot different than variability
23 in physician treatment patterns. Everybody agrees that they
24 are too broad. The Gaussian curve is too broad, and you
25 need to get more uniformity.

1 That does not mean that there are not a host of
2 issues to which you have inferred, but I personally do not
3 know what the hot buttons are in that area. So I could not
4 really comment in more detail.

5 MR. SANDERS: I will say it again. As patient and
6 consumer groups, we have struggled to face the challenge of
7 learning as much as we can about the U.S. drug approval
8 process, and we have not been able to venture into
9 understanding the issues around harmonization. So I cannot
10 answer your question.

11 MS. GRAY: Just one response to that, the U.S.
12 drug approval process may be changed to be more like a world
13 or a universal drug approval process, or the rest of the
14 world may become more like the U.S. Whatever it is, it may
15 be coming together, but not always smoothly.

16 DR. LUMPKIN: Craig, if I could ask, could you
17 clarify a little bit more? I was intrigued by one of your
18 last suggestions where you talked about perhaps a different
19 risk benefit for lifestyle-modifying drugs, what you are
20 talking about there, and maybe you could define "lifestyle-
21 modifying drugs" and what that is.

22 DR. BRATER: Well, you know, it might be something
23 like monoxidil for hair growth as opposed to treatment of
24 resistant hypertension. In the latter case, you are using
25 it in a life-threatening situation where people have not

1 responded to other things. So your risk benefit ratio is
2 certainly very different than when you are using it for hair
3 growth. So I think that would be a reasonable example.

4 DR. LUMPKIN: Are you really advocating a
5 different efficacy standard or a different safety standard
6 for certain drugs, or like having two classes of safety
7 standards?

8 DR. BRATER: I think nit is probably more one of
9 articulating very clearly to the prescriber and to the
10 potential consumer that it may look like it is the same
11 compound, but you are really in two totally different
12 domains.

13 So I think it really is more than anything at the
14 educational level than anything else.

15 MR. LEVIN: I do not know. I mean, I think you
16 could make an argument that maybe it is two different
17 calculus, and that it is not simply an issue of education.

18 I would also argue that there is sort of another
19 categorization, and it is important to me because, very
20 often, for those of us who are sort of concerned about
21 things moving too quickly in terms of approval, what is held
22 up against that is the pleas of patients for more drugs more
23 quickly.

24 I think it is always good to stop a moment and
25 reflect that most drugs that come on the market are not

1 breakthrough drugs. They are not drugs to treat life-
2 threatening conditions. They are drugs that are simply "me,
3 too" drugs for the most part; that simply piggyback
4 endlessly to treat conditions for which there are already a
5 number of drugs marketed. Very often, there is absolutely
6 no real evidence of any increased safety or efficacy in the
7 new product. That is most of what goes on.

8 Maybe that is going to change because of the Human
9 Genome Project. Maybe it won't.

10 So, in my calculus, I think it is always important
11 to make that division because it is hard to argue that it is
12 worth taking a lot of work with a new drug product which in
13 no way adds therapeutic benefit.

14 While if there is no drug available or very few
15 drug choices available to treat life-threatening or chronic-
16 disabling condition, one might argue that the acceptable
17 risk in that analysis goes up, and I would say the same with
18 lifestyle drugs.

19 Monoxidil was first approved to treat the second
20 condition, not hair growth. So that equation was quite
21 different when it went through the advisory committee
22 process and finally was approved by the FDA. Then,
23 subsequently, it gets used for a lifestyle and, by the way,
24 has some toxicity associated with the topical use.

25 So I think there are different ways that we have

1 to consider benefit and risk, and that might be the
2 distinction worth considering.

3 DR. WOODCOCK: I believe it is considered now, but
4 possibly not as overtly, and possibly not for the "me, too"
5 drugs. We always do a risk-benefit calculus, and risks that
6 are quite tolerable in treating cancer or other serious
7 diseases are not tolerable for conditions that have a lot of
8 alternatives or for OTC products, for example. So there is
9 something built in, but I think you are suggesting a more
10 formalized approach in certain categories.

11 MR. ELLSWORTH: The question I have has to do with
12 Mr. Sanders' statement about CDER or the agency must develop
13 a stronger system for compelling sponsors to conduct
14 controlled trials, to confirm clinical efficacy and expand
15 upon the limited knowledge base that formed the basis on
16 which accelerated approval has been granted.

17 You also acknowledge that FDA really lacks a good
18 enforcement mechanism to compel sponsors. What would you
19 suggest the agency do to compel publicity? Notify patients?

20 MR. SANDERS: No, no. This one, we have thought
21 about. Oh, if we could give you the power, we would like to
22 in that case.

23 I think the first thing you can do is the public
24 reporting requirements in FDAMA. I mean, it was one of the
25 few things that we fought for that we actually got in the

1 bill, and it was watered down somewhat. It is clear that
2 the companies now do have to report on every trial that they
3 agree to at the time of approval, and that that report be
4 public.

5 I know that there have been suggestions to the
6 agency from the industry that that information be very
7 limited, that it be, essentially, A, B, C, or D trial
8 started, not started, suspended. I think it has to be much
9 more information than that.

10 The legislation, as I quoted, says if a trial is
11 not progressing, the company needs to say that and to say
12 why. So we would urge that the agency, when writing the
13 regs for that, be very clear that in that report, the
14 company needs to say why the trial is not moving forward,
15 and that that be the first step we take.

16 Everyone kept telling us, oh, you know, public
17 humiliation, that will work, that is the trick. Everyone is
18 doing these trials. If someone is not doing them, we should
19 all know about them, and we should embarrass them.

20 So that is what we are going to have to try. I
21 think that is the first step. Again, I think it is
22 something that the agency internally has to commit to that
23 they are going to follow these drugs; that they are going to
24 look at these reports every year. If a company is not
25 moving forward, they are going to find out why, and they are

1 going to make sure that they move forward with the trial.

2 There was a GAO report that showed that for a
3 number of trials, they had not been done or no one knew why,
4 or they might have been done, or people were not sure if
5 they were done. So the agency, I think, internally has got
6 to make a real commitment to saying this is a top priority.
7 If we are approving a drug, either accelerated approval or
8 regular approval, where there are commitments to future
9 trials, we are going to assign resources and staff to make
10 sure those trials get done. So I think it has to be an
11 internal commitment and the use of these public reports.

12 We want access to that information so we can help
13 in publicizing the bad guys who do not do the trials because
14 that was the only thing we were given.

15 MS. SUYDAM: A number of people have mentioned
16 that the FDA should use this process as a mechanism for
17 getting resources, and that, in fact, the Center directors
18 and the acting commissioner and the soon-to-be new
19 commissioner should use it as a mechanism to lobby for an
20 increased budget.

21 While I was also glad to see that you recognized
22 in the message that we have a problem in terms of resources,
23 and that clearly was what we tried to get across in that
24 message, there is a prohibition, a legal prohibition against
25 Federal employees lobbying on behalf of their agency.

1 So I would like to know what kind of suggestions
2 you might have for us in how we might be able to get our
3 message across in addition to the way we have already gotten
4 it across and having missed these meetings without violating
5 that legal prohibition.

6 MR. SANDERS: The first thing we would suggest is
7 a professional-judgment budget as a part of your plan. The
8 NIH has been doing that for years. It allows their allies
9 and advocates to say this is the amount of money they need
10 to do their job. I think it seems very appropriate that as
11 a part of a planning process, the agency should say here is
12 what we need to do in order to meet our legislative mandate,
13 and here are the resources we need to do it, and at least
14 that is the first step.

15 We have no idea how much money you guys need to
16 really do your job, and if the community outside the agency,
17 the stakeholders, at least had that basic information, it
18 would allow us to begin because we can lobby to try and make
19 that case. I think when the NIH director goes to Congress,
20 they know what his professional-judgment budget is, and so I
21 think if we begin to change the perception that FDA is
22 wasteful or whatever the perception is to say, "Look, they
23 cannot meet the responsibilities, and here is what they need
24 to do it, and there are people out there who would support
25 you in that," that is the first step we would urge you to

1 take.

2 MS. SUYDAM: We appreciate that very much because
3 there is a long history, as you mentioned, of the NIH having
4 a professional judgment budget. That is not the tradition
5 in the FDA. That is a hurdle that we have to get beyond,
6 and we do see the 406(b) plan as an opportunity to lay out
7 what it is that the agency needs to really get the job done
8 and to meet the statutory mandates that the law says we must
9 meet.

10 Thank you.

11 DR. LUMPKIN: At the risk of following up on
12 Linda's question, one of the things that I would be
13 interested in hearing -- and people talked earlier this
14 morning about the success of the user fee program for that
15 part of our mission that it was applicable to -- I think I
16 would be interested in hearing your thoughts on whether that
17 mechanism for funding, for other parts of the agency
18 mission, is a way to go because it is always an interesting
19 debate to hear, particularly on the post-marketing, safety,
20 surveillance side, where we know that in other parts of the
21 world that have rather sophisticated post-marketing systems,
22 there are user fee programs that support those. We do not
23 have that in this country at this point in time.

24 The argument has been is that a societal
25 responsibility that ought to be paid for out of tax dollars

1 or is that a responsibility that could fall within the idea
2 of a user fee augmentation or payment of it.

3 MR. LEVIN: Funny you should mention user fees.
4 During lunch, I began to sort of rethink user fees a little
5 bit. I will tell you why. It is sort of a matter of
6 principle.

7 I realize that for advocates, for people who at
8 least we think we represent the public interest, our call on
9 the agency is the fact that it is supported with our tax
10 dollars.

11 As it increasingly becomes supported by user fees
12 from industry, it strikes me that we run the risk of the
13 call on the agency being by industry, and that those of us
14 representing the public have less and less voice.

15 So I think when it comes to sort of the public
16 health mission, I would hate to see us privatize public
17 health, and I think we run a risk. Obviously, it is a very
18 attractive mechanism in this day and age when the desire is
19 to cut Government budgets, when rightfully or wrongfully,
20 the historic perception is the FDA is this great burden to
21 industry and probably spends a lot of money on foolish
22 things and so forth. I am not saying that is true, by the
23 way, but there is a long history of sort of FDA-bashing.

24 This is a very attractive alternative which sort
25 of says, "Okay, the guys that use the system get to pay the

1 piper," but they also get to pay the piper in terms of
2 policy and sort of that dependency then that the agency has
3 on the industry. I think it is a risky road to go down.

4 So I do not want to say that PDUFA was a mistake,
5 because clearly it achieved a lot of things, but, in
6 principle, private financing of a public agency, I think, is
7 a very disturbing trend to continue to pursue past a certain
8 point.

9 I think it is good that as a country, we accept
10 the fact that the public health good that the agency
11 achieves is worth support of general tax revenues, and that
12 means that I as a citizen can say, hey, guys, you are not
13 doing your job.

14 I was sort of shocked to hear how much of CDER
15 budget comes out of PDUFA. I think that is already sort of
16 a tricky situation. I just think we may have to rethink
17 whether this is a road to go down, as attractive as it is in
18 this era of tight money.

19 DR. WILLIAMS: All right. I am going to thank our
20 panelists on both sides of the aisle and close Section C and
21 turn it over to our prime moderator, Nancy.

22 Thanks.

23 DR. SMITH: Thank you.

24 I would like to ask the CDER and FDA panelists to
25 stay up here for a few minutes, if you could, those of you

1 who can. Perhaps Bob and Ralph and some of the others that
2 are still here could join us at the front.

3 We wanted to open the floor to those of you who
4 are here who would like to make a statement to us or provide
5 comments verbally, and we would like to ask that anyone who
6 speaks, very clearly state your name and your affiliation.
7 Then try to limit your comments to about 3 minutes. If you
8 would, come to the mike in the center aisle. We will be
9 glad to listen to your comments.

10 Do we have anyone who would like to speak?

11 [No response.]

12 DR. SMITH: I guess it is speak now or forever
13 hold your peace or whatever. Speak now or submit it to the
14 docket.

15 I would like to say that there are three ways, as
16 Linda mentioned at the very beginning, to submit information
17 to the docket. You can do it via the web or by e-mail or by
18 the old-fashioned pen-and-ink letter. We will accept it any
19 way.

20 We do appreciate all of you attending today, and
21 would like to thank all of the stakeholders who spoke to us
22 today and thank all of the members of the CDER and FDA
23 community who joined us as panelists.

24 Thank you. [Applause.]

25 [Whereupon, at 4:20 p.m., the meeting concluded.]

C E R T I F I C A T E

I, **THOMAS C. BITSKO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in black ink, appearing to read 'T.C. Bitsko', written over a horizontal line.

THOMAS C. BITSKO