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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

PROFESSIONAL LABELING PUBLIC MEETING

Monday, October 30, 1995

9:10 a.m.

Gaithersburg Hilton
Grand Ballroom
620 Perry Parkway
Gaithersburg, Maryland

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P R O C E E D I N G S

O P E N I N G R E M A R K S

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3 DR. LUMPKIN: Good morning, ladies and gentlemen.
4 I first want to thank each and every one of you for coming
5 out on this hearing Monday morning to spend some time with
6 us today to talk about product labeling and particularly
7 product labeling for the health-care practitioner.

8 I know this is a topic that many of you have a
9 great deal of interest in and it is a topic that we have
10 spent a great deal of time and interest here and it is one
11 that many of us at the Agency have been working on over the
12 last several years to try to come up with ways of seeing if,
13 perhaps, we can communicate the information that we know
14 about our products more effectively to people who are going
15 to be using our products.

16 But, before we get started on that, I want to take
17 just a couple of minutes with a couple of housekeeping
18 things. I hope all of you got a copy of the agenda when you
19 came in and a copy of the prototype physician health-care-
20 practitioner label that we are going to be talking about
21 today.

22 As you can tell from the agenda, we plan to have a
23 break about 10:15. At that point in time, there will be
24 refreshments outside. Until then, there is coffee out
25 there. Please feel free to go out and make yourself at home

1 as far as the coffee is concerned. They will keep that out
2 there throughout the program today.

3 Around 12:30, we will be taking a break for lunch.
4 This is a buffet here in the hotel for those of you who are
5 not familiar with the Gaithersburg area. That give you just
6 kind of an overlay of some of the breaks and lunch that we
7 are planning on having today.

8 Again, let me say welcome to all of you for coming
9 out today. What I want to do during the next couple of
10 minutes is give you a little bit of a background on some of
11 the thoughts that went into this particular initiative, some
12 of the history of what has happened thus far, where we are
13 planning to go with this and what we plan to do today.

14 [Slide.]

15 I think when many of us have looked at the
16 pharmaceutical product labeling that exists now, one of the
17 real questions that people come up with is is it really
18 accomplishing the purpose for which it was intended or is it
19 broken and, if it is broken, does it need fixing? If it
20 needs fixing, how might we go about that?

21 [Slide.]

22 I think in trying to answer that question, one of
23 the first things and one of the central issues in dealing
24 with pharmaceutical product labeling is trying to figure out
25 what it is and what purpose it is trying to achieve because

1 I think it is many different things to many different people
2 and, perhaps, that is where the root of the problem lies,
3 that in trying to be all things to all people, I think many
4 people feel that perhaps it is becoming less than adequate
5 for all of us.

6 When you look at the various purposes that
7 labeling has had over the years -- I have put up here on the
8 screen four categories that people have looked at in
9 labeling and said, well, clearly it is information for the
10 prescribing professional. That is what it was intended to
11 be at the beginning and that is one of the tasks that it
12 still has.

13 It is clearly also the embodiment of a company's
14 license to market a product in this country. It defines the
15 promotional limits for the company and, clearly, that is a
16 very, very important purpose of labeling as it exists today.

17 Third, obviously, over time, this labeling has
18 become a document that people have associated with legal
19 liability and people have used it and have been very
20 cognizant of its use and what it says in trying to meet
21 those particular purposes.

22 Last, but not least, I think that even though this
23 is a document that was written and was intended to be used
24 primarily by health-care practitioners, it is information
25 that is read and used by consumers. I think we have to

1 recognize that in a world that we live in today where
2 consumerism is becoming more and more the thing, it is
3 something that we have to realize that, indeed, our
4 pharmaceutical labeling is going to be used for that
5 particular purpose.

6 [Slide.]

7 So, in looking at our labeling and seeing if,
8 indeed, there is something that we can do to make it better
9 to try to meet those various purposes and, particularly, to
10 go back to the purpose of being a document that informs the
11 health-care practitioner on how to use the product, what we
12 know about this product and to get him or her a very good
13 set of data that have been independently vetted to try to
14 make their therapeutic decisions based upon.

15 So, approximately two years ago -- you will see
16 the dates in just a few minutes -- it was decided that this
17 was not a issue that was just a CDER issue. This was an
18 issue that crossed three of our major centers as far as
19 human pharmaceutical products are concerned.

20 Obviously, it is something that deals with the
21 Center for Biologics and, also, the Center for Devices and
22 Radiologic Health. So, under the auspice of the Deputy
23 Commissioner for Operations, these three centers were tasked
24 with forming a Steering Committee which then formed a core
25 working group to try to look at the problem, see if they

1 could come up with some data on how people were using these
2 labels, and then come up with some ideas on how we might
3 improve the labels that we have.

4 [Slide.]

5 Just to give you an idea of some of the people
6 that have been involved in this, the individuals whom you
7 see listed up here, many of whom you are going to be hearing
8 from today, are the individuals who formed the core working
9 group. They were also members of the Steering Committee and
10 they were the people who have been working behind the
11 scenes, as it were, on trying to get this particular
12 initiative to where it is today.

13 [Slide.]

14 The other members of the Steering Committee, whom
15 I have listed here, includes some other people that you are
16 going to be hearing from today including Dr. Bruce
17 Burlington who is the Director of the Center for Devices,
18 Dr. Katherine Zoon who is the Director of the Center for
19 Biologics, Dr. Janet Woodcock who is the Director of the
20 Center for Drugs, along with other people who are within
21 their particular staffs.

22 You will be meeting some of these people today and
23 hearing, later in the program, how they believe this
24 particular initiative will affect their particular products.

25 [Slide.]

1 As I said, from a chronology perspective, the
2 Steering Committee began work in late 1993 when the Deputy
3 Commissioner for Operations tasked it with trying to follow
4 through on this particular initiative. It was also at that
5 time that there was another group of people in the Center
6 for Drugs who had been working with several outside
7 individuals on trying to do some research on physician and
8 other health-care-practitioner uses of our labeling.

9 A lot of the work that they were doing was just
10 beginning to come to fruition so it was thought that, as we
11 do enjoy seeing data, that, perhaps, before we started
12 making any rash decisions that we ought to see the data that
13 this particular group had been working on.

14 When I finish this introduction, you will begin to
15 hear some of this data from Nancy Ostrove and her group.
16 Several of the people who are going to be on our Reactor
17 Panel later today were also people that were part of the
18 advisory group for Nancy and Lou and their particular
19 working group within the Center for Drugs who have been
20 doing a series of physician focus groups and a series of
21 questionnaires of health-care practitioners around the
22 country that have formed the basis of a lot of the work that
23 our initiative has been using.

24 [Slide.]

25 Following the data that you are going to be

1 hearing about in a few minutes, the Steering Committee heard
2 from the core working group and we presented to them a
3 series of options that we thought, based on the data that
4 Nancy's group had come up with, would begin to meeting some
5 of the needs that were identified by the health-care
6 practitioners.

7 We presented to the Steering Committee this series
8 of options late last year. The Steering Committee approved
9 those options and said that we needed to take them to
10 another series of physician focus groups to see if, perhaps,
11 those physician focus groups could help us further to refine
12 the various options to come up with a prototype that would,
13 then, form the straw man, as it were, that we and the public
14 could start working on to see where we went from that point
15 in time.

16 So, after the physician focus groups -- again,
17 which you will hear the details in Nancy's talk here in just
18 a few minutes -- early this year, the prototype which you
19 now have a copy of, was ultimately developed from the input
20 from these last physician focus groups.

21 [Slide.]

22 What we did at that point in time was to take this
23 particular prototype to all three Center Directors and their
24 immediate staffs, present it to them to get input no what
25 they thought of it. They, indeed, gave their approval at

1 that point in time and we began rolling it out and
2 introducing the staffs in all three centers to this
3 prototype, to the research that formed the basis of this
4 prototype and to what our plans were during the early summer
5 of this year.

6 It was decided at that point in time that this was
7 now ready for prime time, as it were, and that we needed to
8 have what we are having today, and that is a public workshop
9 to begin to get input and thought on the process that we
10 have gone through and on the particular prototype that you
11 have seen.

12 [Slide.]

13 This is really kind of what the future plans are
14 for this particular initiative. If the outcome from this
15 workshop today and from the comment period which will last
16 until January is positive, then what we plan to do is, in
17 early 1996, go to the formal rulemaking process.

18 We are planning to go to a notice of proposed
19 rulemaking in early '96 and then, once that is set forward
20 and the final prototype, as it were, for the proposed
21 rulemaking is set, we then want to do one further
22 questionnaire with around 500 physicians around the country
23 and other health-care prescribers to see what their thoughts
24 are during the comment period for the notice of proposed
25 rulemaking.

1 [Slide.]

2 The idea, then, would be if, indeed, during the
3 comment period, again, the comments are predominantly
4 positive and feel that we need to forward with this, the
5 hope would be to mid, late '96, that we would have a final
6 rule in place. Obviously, this is something, once the final
7 rule is in place, that we would need to be doing, a series
8 of reassessments to see if, indeed, the changes in the
9 labeling have brought about the kinds of outcomes that we
10 had hoped.

11 One of the things I know that people have a lot of
12 concern about and one of the issues that we are very keen on
13 hearing what you guys think about later during the program
14 today is if, indeed, we go forward with a new labeling
15 format that has the Summary Section in it, how would we
16 implement it.

17 One of the ideas that we have been kicking around
18 is to have this such that it would be applicable to all
19 newly approved products, it would be applicable when there
20 were new effectiveness supplements that came in, and then
21 that we would go back and look at the 200 most prescribed
22 products here in the United States. At least, this is the
23 way we would handle it in drugs.

24 I think, clearly, the representatives from
25 Biologics and Devices would talk about how they would go

1 forward with it. We would then try to bring into the
2 coverage of this kind of labeling the 200 most prescribed
3 products in the United States and kind of work from that as
4 a beginning point.

5 [Slide.]

6 One of the other things that people have asked
7 questions about and I want to make clear today is that what
8 we are talking about, as you will hear when Nancy talks --
9 we are really talking about formatting of the labeling and
10 how one might use a Summary Section at the beginning to try
11 to put into perspective the product and have a way that
12 health-care practitioners could find the essential pieces of
13 information that they need to use the product appropriately
14 in a much more expedited manner.

15 There are also other smaller initiatives that are
16 going on looking at particular parts of the labeling. I
17 think we would be the first to say that our Adverse Reaction
18 Section is probably not the most helpful section in the
19 labeling as it exists now, and there are parts of that that
20 need to be reworked and rethought.

21 There are people that are looking at the Clinical
22 Pharmacology Section to say, how can we use that particular
23 part of labeling better. Those are not the main issues that
24 we are here to talk about today. We really are looking more
25 at the formatting and this idea of a Health-Care

1 Practitioner Summary at the first part of a label following
2 by a more complete encyclopedia knowledge base for those
3 various points that are in the Summary.

4 [Slide.]

5 So, our agenda for today, as you can tell, is the
6 following: once I finish with this introduction, Dr. Nancy
7 Ostrove will be talking about the history behind this
8 initiative and the research performed to date that formed
9 the basis of what we are talking about. She will also be
10 talking about various early prototypes that we dealt with,
11 why things were changed, what some of the thought processes
12 were.

13 After our break, then I will come back and we can
14 go through the prototype. I want to spend just a couple of
15 minutes highlighting some of the special issues in the
16 prototype for you. Hopefully, there is going to be an
17 adequate amount of time for questions and thoughts on those
18 particular parts right after the presentations.

19 [Slide.]

20 Following my second presentation, then Lou Morris
21 will talk about some of the ideas that people have about the
22 possible implications of this kind of labeling for
23 advertising a promotion of products. Then, right before
24 lunch, we will have Drs. Woodcock, Burlington and Devine
25 spend a couple of minutes telling you how they perceive this

1 initiative, as I said, and how it affects their products in
2 their Centers and where they see it going for their
3 particular Center's mission.

4 [Slide.]

5 Following lunch, I think is going to be probably
6 one of the most fun parts of the day today, and that is the
7 Reactor Panel that we are extremely pleased to have with us
8 today. These individuals are here. They have asked not to
9 have to sit at the table here in the morning which is very
10 realistic. So they are sitting here in the audience with
11 you so they can, hopefully, get a better view of what is
12 going on here on the screen.

13 We have with us a group of people some of whom
14 have been part of advisory group to this initiative over the
15 last two years and some of whom are here representing the
16 various health-care-practitioner organizations who would use
17 professional labeling in order to make therapeutic
18 decisions.

19 We have Dr. Donald Bennett who is, today,
20 representing the USP; Dr. Joseph Cranston from the American
21 Medical Association; Dr. Cheryl Graham who is part of BRI at
22 this point in time who, many of you know, used to be the
23 Head of our Division of Drug Advertising, Marketing and
24 Communications in the Center for Drugs at FDA; Dr. Mark Horn
25 who is representing PhRMA today; Dr. Calvin Knowlton from

1 the American Pharmaceutical Association; Mr. Greg Thomas
2 from the American Academy of Physician Assistants; and Dr.
3 Jan Towers from the American Academy of Nurse Practitioners.

4 So I think we have got a broad group of people who
5 are very interested in professional labeling, who have been
6 part of this initiative and some of whom will just be
7 hearing about it for the first time over the last couple of
8 weeks, to get their perspectives from their particular
9 organizations on how the kind of prototype we have talked
10 about might be helpful to them and where some problems still
11 lie from their perspective.

12 [Slide.]

13 Then last, and clearly not least, one of things
14 that we are most interested in and it is why we have left as
15 much time in the afternoon as we have, is to get feedback
16 from you guys who have taken your time to come here today.

17 As you could tell from the process that I outlined
18 a little earlier, there is going to be time throughout this
19 process for other kinds of formal feedback. After the
20 Notice of Proposed Rulemaking goes forward, obviously, there
21 will be a time there. There is still time, as I said, for
22 people to send written comments to the docket for this
23 particular meeting.

24 We are very, very interested in what you have to
25 say. We are very, very keen in your perceptions because we

1 know, as I said in the beginning, labeling means a lot of
2 different things to a lot of different people. What we are
3 interested in is that it become, again, a very usable, a
4 very user-friendly, source of information for the health-
5 care practitioner so that he or she can perform their job
6 better with good information.

7 So, with that as the task that we have before us,
8 I am going to turn this meeting over now to Dr. Nancy
9 Ostrove who will give you some of the history behind this
10 and some of the research that led to where we are today.

11 Thank you, again, for coming today, and now,
12 Nancy.

13 **BACKGROUND AND INITIAL RESEARCH**

14 **ON PHYSICIANS' PERCEPTIONS AND USE OF LABELING**

15 DR. OSTROVE: Good morning. I would add my
16 welcome and ask for your indulgence for about a minute here.
17 I am going to try some high-tech presentation which usually
18 means, "Oh, gee; you have got a system error."

19 [Slide.]

20 As Dr. Lumpkin mentioned, I am here to talk today
21 about the background and the initial research of this
22 initiative. In about 1991, the Center procured a contract
23 with an outside research organization for an effort to
24 evaluate physician labeling. It basically was composed of
25 three parts, which was an exploratory part, a national

1 physicians' survey, and a quasi-experimental analysis toward
2 the end. That last piece is still in the future.

3 As Dr. Lumpkin has already spoken with you about,
4 the labeling is fairly important for a lot of different
5 reasons. It communicates the basis of the approval for the
6 product. It defines the limits of marketing. Later on, Dr.
7 Morris is going to talk about how it is involved in
8 marketing and promotion.

9 It is used by physicians and it is used by
10 patients as well. We have some data that indicate that a
11 large number of patients who get information about their
12 prescription drugs after they have been prescribed refer to
13 the PDR. You will see it on sale in all kinds of
14 bookstores, Price Club, everywhere you can possibly think
15 of. It is also used in liability litigation.

16 [Slide.]

17 And it has encountered a number of changes over
18 the years. Since 1979, when the revised labeling
19 regulations went into effect, a number of changes occurred
20 to the labeling which has had effects on its length and its
21 complexity. The addition of a Clinical Pharmaceutical
22 Section which replaced the section which was called Actions
23 increased the focus on the pharmacokinetic and
24 pharmacodynamic properties of the product.

25 There is increased detail given in the Indications

1 Section. And, nowadays, with accelerated approval and the
2 use of surrogate markers rather than the more traditional
3 clinical endpoints, there is a lot more information being
4 included in Indications to give the physician the background
5 to understand the basis of approval and to allow them to
6 make their own judgments about what that means for them and
7 their practice.

8 There is more structured organization that was
9 given for information about pregnancy and childbearing and
10 nursing, specifically teratogenicity, effects of delivery,
11 transference of the drug to breast-fed children.

12 [Slide.]

13 In addition, we have had lots of ADR experience
14 with the drug class -- not necessarily with the drug,
15 itself, but with the drug class as well -- that has been
16 added to labeling. Increased technology, basically,
17 improvement in technology for detecting and testing drug
18 products has also increased the complexity of the products
19 that are being submitted for approval. So you have more
20 complex information being communicated in labeling.

21 There has been an increased emphasis on
22 communicating the details of conditions and the results of
23 pivotal-study findings, as I said before, to let the
24 prescribers know the basis of approval for the product.

25 And there has been an increased manufacturer

1 desire related to liability issues to include all adverse
2 reactions, many times, anecdotal events as well as events
3 that are more clearly related to the use of the drug.

4 As Dr. Lumpkin has mentioned, there are separate
5 initiatives that deal with the contents so we are not really
6 going to talk about that today. But all of these changes
7 have had an effect on the label in terms of making it more
8 complex, longer for the prescriber to have to deal with and
9 to look for particular kinds of information.

10 My understanding is that Medical Economics, the
11 producer of the PDR, has been constantly doing research on
12 how you can thinner and thinner paper so that they can stick
13 with one book because they really don't want to go to a
14 second book, which is understandable.

15 There are costs involved. There are costs
16 involved in reprinting the labeling in the PDR, for
17 instance. In 1992, when we were first doing the background
18 for the research, we found that reprint charges for the PDR
19 ranged from \$185 to \$446 per inch of text depending on lots
20 of circumstances. So there is that.

21 In addition, there was a kind of a back-of-the-
22 envelope that was given to us by one individual from
23 industry who estimated around \$35 million that was being
24 spent annually to reprint the Brief Summary in advertising.
25 I am sure that that did not take into account all of the

1 package inserts that went with all the promotional labeling
2 that went directly to physicians with detailed pieces, with
3 file cards, with brochures and all the rest of it. So we
4 are not talking about small costs here.

5 What we did was we looked to see what kind of
6 research was currently available to tell us how do people
7 use the labeling, is it useful for them, how might it be
8 improved, is it broken, so to speak. What we found is that
9 there is not a whole lot there in the research literature.
10 We did find that labeling is widely used by physicians,
11 especially as reprinted in the PDR.

12 Abate, Jacknowitz and Shumway, in 1989, published
13 a study where they cited that the PDR is the most frequently
14 used information source, especially in private practice.
15 This was based on a survey of physicians.

16 The Center for Communication Dynamics, in 1991,
17 looked at ten sources of information about the risks and
18 benefits of new prescription drugs and found that 75 percent
19 of their respondents who were physicians said that the PDR
20 was either very important or moderately important to them in
21 communicating. Their higher combined ratings were only
22 obtained for articles and professional journals, independent
23 programs and conferences, and from colleagues.

24 McCue, Hansen and Gal, in 1986, again with a
25 physician survey, found that the PDR was considered to be

1 the most accessible and most frequently used source of new
2 information about drugs of the ten sources about which they
3 questioned their study subjects.

4 Medical Economics does regular studies looking at
5 users of the PDR -- not too surprisingly.

6 [Slide.]

7 But there were still some continuing questions.
8 These studies provided little insight into how labeling is
9 used, how frequently the physicians reference particular
10 sections. There was a little bit in the medical-economic
11 stuff, but not quite on point for what we wanted to get at -
12 - what factors prompt use, and whether there are any
13 practice or individual variables that modify the way that it
14 is used and perceptions of it.

15 So the answers to these questions, we felt, would
16 provide good insight on how best we could communicate
17 labeling information to prescribers.

18 [Slide.]

19 So, in search of how to do this, and given the
20 contract that we had procured for this effort, we put
21 together a project advisory group, which I am always
22 confusing people by calling it a PAG, which consisted both
23 of FDA and non-FDA representatives. For non-FDA expertise,
24 we got the cooperation, the representation, from the
25 American Medical Association. At that time, Don Bennett was

1 with the American Medical Association. Today, he is here
2 representing the USP.

3 From PMA, at the time, now PhRMA, we had Mark
4 Deitch and, when Mark couldn't make it, Marty Rose who was,
5 I think, in Genentech at the time and has since moved, who
6 represented PhRMA, and Keith Johnson from the United States
7 Pharmacopeia.

8 [Slide.]

9 From FDA, we had a couple of medical reviewers,
10 specifically Cheryl Graham and Russell Katz. For the
11 social-science background and expertise in survey
12 methodology and health education and public-health issues,
13 myself, Lou Morris and Ellen Tabak from our Marketing,
14 Communications and Practices Branch within Drug Marketing,
15 Advertising and Communications. That is a mouthful to try
16 and communicate.

17 [Slide.]

18 Basically, the group determined kind of the
19 guiding research questions, the questions that were going to
20 guide what we did from that point on. What we were
21 interested in looking at is what is the frequency of overall
22 referral to the package insert, what is the frequency of
23 referral to the different sections, what are perceived
24 usefulness and important of those different sections.

25 How is the package insert or the labeling

1 referenced? What is the primary source? Why do people
2 consult it because that could give us a lot of information
3 as to the kind of information that should be emphasized?
4 What are their reasons for consulting it? Are they using it
5 as a general educational document? Are they using it as a
6 reference document when they have a particular question that
7 they want to have answered?

8 It is hard for one document to be one thing to all
9 people and it seems as if labeling has been in that position
10 for a long time. So we wanted to get a better sense of how
11 many things it is to how many different people.

12 What are some general attitudes about labeling and
13 how can we improve it? Can it be improved?

14 [Slide.]

15 The first thing that we did is hold two
16 exploratory focus groups. Focus groups can be very helpful
17 in terms of getting insight into how people are thinking
18 when they are looking at particular stimuli. Especially, it
19 can be very helpful for helping you put together a more
20 quantitatively rigorous piece of research. So that was,
21 basically, how we used the focus groups.

22 [Slide.]

23 Basically, it is kind of useful as an aid to
24 explore internal cognitive processes that are difficult to
25 quantify in more structured examinations. What we found is

1 that the PDRs appeared to be in the focus groups. The PDR
2 appeared to be the most commonly used source for labeling
3 information.

4 What they did say, though, is it is not their
5 source for getting revised information. One quote was, "It
6 is the last place to look for revised information." That is
7 not too surprising, given the process that needs to be
8 followed to move it along.

9 They did say, however, that the most important
10 information that they would like to have about prescription
11 drugs in contraindication, side effects, drug interactions,
12 warnings and dosage information. They said that basically
13 when they wanted to get new information, they would get that
14 from drug companies, from literature, from meetings and
15 conferences and, occasionally -- and some of them were not
16 very happy about this -- they said that they get it from
17 National Public Radio and CNN broadcasts.

18 There was a certain amount of disgruntlement about
19 that, I might add. Again, remember, this is a focus group.
20 This is not rigorous research. But it is instructive.

21 [Slide.]

22 Other desired information is included here as
23 well. We got comparative efficacy. That was especially
24 important for the specialists, not as important for the
25 primary-care practitioners. They all wanted cost

1 information. This is cost and cost comparisons. This is
2 fairly consistently brought up. The primary-care
3 practitioners were interested in the indications. The
4 specialists were not that interested in indications.

5 The least important information from their
6 perspective was the pharmacology and the NDC code. Some of
7 them said, "Why do you have that in there?"

8 [Slide.]

9 Finally, and I think this is my last slide on
10 focus groups, in terms of their general perceptions of the
11 package insert, they said things like, "It is okay, in
12 general." So they felt it was generally useful. They also
13 complained that it was hard for them to find needed
14 information because of the extensive detailing of risks,
15 that they had to kind of plough through a lot of stuff to
16 find what it is they wanted to get.

17 Some of them said that the small print was a
18 problem. My recollection is someone said something like,
19 "The print size is ludicrous."

20 A couple of them felt that the information might
21 not be impartial because of the company's need to limit
22 liability and that, as a consequence, there is too much
23 detail about warnings and side effects for which there is
24 truly only a minimal risk. One of them gave as an example
25 warnings that a particular drug can cause the condition for

1 which it is indicated. He said, "That is kind of silly,
2 guys."

3 By the way, they did not know they were speaking
4 to the FDA at that point.

5 [Slide.]

6 And we did ask them how could it be improved.
7 These are some of the things that they brought up. They
8 said, "Well, you could highlight the important information a
9 lot better than it is currently." "You could add a bolded
10 abstract of important information." "You could enlarge the
11 type size." "You could reduce or eliminate the anecdotal,
12 low-risk information."

13 There was one who specifically brought up, "For
14 instance, you could leave out 'may cause testicular atrophy
15 in rats.'" He kind of went on about that. And, "You could
16 add cost information;" that was the other thing that they
17 kind of liked.

18 One said, and I am going to leave out the more
19 profane aspects of this, "It contains every damn side effect
20 in the world and it scares the patients."

21 [Slide.]

22 So, what did that do? That enabled us to come up
23 with a questionnaire, a survey questionnaire, that we felt
24 got at some of these issues in a more easily quantifiable
25 fashion.

1 [Slide.]

2 What we did was design a national probability-
3 based survey of physicians to examine these issues more
4 rigorously. It was conceived of -- it was a telephone
5 survey. It was meant to be about 15 minutes long. It ended
6 up being more like 20 or 25 minutes long. We built in
7 certain aspects to try and enhance what can be a problematic
8 response rate with physicians. We built in a \$50
9 honorarium. We had a letter sent out prior to the first
10 telephone contact with the physician from the then-Director
11 of CDER, Carl Peck, asking them for their participation and
12 telling them how important it was.

13 [Slide.]

14 Basically, our study population -- and so I am
15 going to get into the details of the survey at this point --
16 was that it was based on office-based positions. We were
17 interested in people who were using the label on a fairly
18 regular basis in their clinical practice.

19 So we used a sampling frame from the American
20 Medical Association. They have a physician master file
21 which is nice because it tracks all physicians from their
22 medical-school entry regardless of whether or not they
23 become members of the AMA. It uses a self-identified
24 practice classification.

25 So, for instance, if the physician perceives

1 himself or herself as a specialist, they indicate that
2 themselves in the updated questionnaire. It is consistentl
3 updated. It is problematic in some sense in that the
4 telephone numbers are not the best, so there are tradeoffs
5 in using this particular master file.

6 [Slide.]

7 The sample was designed so that it would be
8 representative of nine geographic census regions. It was
9 stratified from the beginning by primary-care versus
10 specialty so that we would have an equal number of primary-
11 care practitioners and specialist practitioners so that we
12 could control the precision with which we could make
13 estimates of the population parameters based on the sample
14 statistics.

15 We considered the primary-care practitioners were
16 those who were in family practice, general practice,
17 internal medicine, those who didn't have a self-identified
18 subspecialty, and pediatricians. I realize, and this has
19 been brought up, that pediatricians are not primary-care in
20 the same sense as family and general practitioners. They
21 are specialists, but they do a lot of primary-care work and
22 see people on that basis. So we felt that they would fit
23 nicely in that particular categorization.

24 In addition to that, we wanted to make sure that -
25 - again, these were people involved in clinical practice, so

1 they had to have at least half-time involvement in patient
2 care.

3 [Slide.]

4 The final sample that we achieved was 204 primary-
5 care practitioners and 200 specialists. The response rates
6 were not as high as we would have hoped, but I think it was
7 around Thanksgiving and Christmas time that we did this. It
8 was probably a bad time to start it but that is when we got
9 OMB clearance. When you get OMB clearance and you have been
10 waiting for a while, you go ahead.

11 The subsamples were similar; that is, the primary-
12 care practitioners and the specialists were similar with
13 regard to the year of medical-school graduation and hours
14 per week that they spent in direct patient care. The
15 primary-care practitioners spent an average of 50 hours a
16 week in direct-patient care plus or minus 15. This was
17 similar to the 49 hours a week cited by the specialists, and
18 they were plus or minus 17; again, fairly similar.

19 They differed with regard to the type of practice
20 setting that they had their clinical practice in. The
21 primary-care practitioners were more likely to see patients
22 in an organized-care or HMO setting than the specialists.
23 It was like 10 percent of the primary-care practitioners
24 versus 5 percent of the specialists.

25 The specialists were likely to see their patients

1 in a hospital setting, 14 percent of them versus 4 percent
2 of the primary-care practitioners who saw their patients in
3 a hospital setting. Most of the patients were seen in
4 either solo or group practices.

5 [Slide.]

6 They also differed with regard to the number of
7 prescriptions written per week. The primary-care
8 practitioners wrote more prescriptions in an average week.
9 They averaged 141 whereas the specialists only averaged 74.
10 Those prescriptions included hospital and institutional
11 orders.

12 [Slide.]

13 What was a primary source that they used when they
14 were looking for labeled information? Basically, they used
15 the PDR. 88 percent of them said they used the PDR.
16 5 percent of them said that they actually used package
17 inserts. The rest kind of used various different reference
18 works.

19 [Slide.]

20 In terms of how often they referred to the label
21 in an average week of practice, this is how it breaks down
22 in terms of the percentages. About two-fifths of them said
23 that they refer to labeling at least once a day. Almost
24 one-third of them refer to labeling between once a day and
25 once a week and the remaining quarter refer to it less than

1 once a week.

2 There were some differences between the primary-
3 care practitioners and the specialists. The PCPs, please
4 let me say that because otherwise my mouth is going to go,
5 refer to labeling significantly more often than specialists.
6 55 percent of them refer to labeling once a day or more
7 compared with only 20 percent of the specialists who do so.

8 So we see it is used on a fairly regular basis and
9 that is consistent with the research that had been done
10 previously.

11 [Slide.]

12 Now, the other thing, what we did after that, is
13 we asked them to rate each of ten different sections on a
14 four-point rating scale for both referral and importance.
15 For instance, with regard to referral, they were asked,
16 "When you consult drug labels, how often do you read each of
17 these sections? Do you always read them, usually read them,
18 sometimes read or rarely or never?" It is 4, 3, 2, 1, a
19 four-point scale. The higher the number, the more often
20 they referred to that particular section about which they
21 were being asked.

22 For importance, we basically asked them how
23 important is having this information in the label for you,
24 personally. They were asked, again, the ten different
25 sections. Basically, these are rank ordered. The numbers

1 probably don't mean very much to you, but I put them up here
2 just in case.

3 [Slide.]

4 Basically, what it comes down to is that the most
5 important sections -- they are all rank-ordered here -- are
6 Dosage and Administration, Contraindications, Warnings,
7 Adverse Reactions, Precautions -- you can see that after
8 Dosage and Administration, it is all the bad stuff -- then
9 Indications and Usage, then How Supplied.

10 [Slide.]

11 There were certain differences, and the next slide
12 has the last three, the ones that they referred to least
13 often, which included Clinical Pharmacology, Abuse and
14 Dependence and Overdose, I believe. We will go to that
15 next.

16 There were certain differences that appeared
17 between the PCPs and the specialists in these measures,
18 specifically the primary-care practitioners refer more often
19 than the specialists to the Dosage and Administration
20 Section, the Product Abuse and Dependence Potential, which
21 is on the next slide, and the How Supplied Section.

22 The primary-care practitioners also gave higher
23 importance ratings to Product Contraindications, to the
24 product's potential for abuse and dependence and how it is
25 supplied. The only place where the specialists gave higher

1 ratings than the primary-care practitioners was for the
2 importance of the Clinical Pharmacology Section. The
3 specialists felt that that was significantly more important
4 for the specialists than it was for the primary-care
5 practitioners. That is how the other three went.

6 We asked them what information, if any, they felt
7 could be omitted from the labeling. The base for these
8 percentages is the 26 percent of respondents -- I thought it
9 was 27 percent; that may be a typo -- who answered yes to an
10 open-ended question asking whether there were any sections
11 or categories of information they think could be omitted
12 from drug labeling.

13 [Slide.]

14 We coded their responses after the fact into
15 certain categories which is why you have the second one as
16 chemical "composition/formula, slash,slash". It was kind of
17 put a whole bunch together there that seemed to be fairly
18 similar. Basically, what we find here is that Clinical
19 Pharmacology was the section that was most often mentioned.
20 It is 44 percent of the base; that is about 12 percent of
21 the total sample who said that that section could be
22 omitted.

23 The chemical composition -- a lot of it is
24 chemical information -- was 10 percent of the base, about
25 3 percent of the total sample. The common side effects;

1 9 percent of this base felt they could be omitted which is
2 only about 2 percent of the total. Although this wasn't a
3 direct answer to this particular question, 15 percent of
4 these people said that the information and labeling should
5 be condensed. They just volunteered that in response to
6 these questions. That is about 4 percent of the total.

7 [Slide.]

8 They were also asked what information should be
9 added. We wanted to make sure we got both sides of this.
10 In other words, "Are there any categories or types of
11 information that you think need to be added to drug labels
12 that currently are not included?" We got some interesting
13 results here.

14 About 190 said yes to this question. So that is
15 the base here for these percentages. Again, similar to what
16 we heard in the focus groups, 23 percent of this base, which
17 is about 11 percent of the total, said that cost and cost
18 comparisons would be very useful for them, that you could
19 add that information.

20 15 percent said drug interactions. That is 7
21 percent of the total. 9 percent of them said side-effect
22 occurrence rates. That is about 4 percent of the total.
23 8 percent said whether there was a generic available for
24 this particular product would be useful information to have.
25 This is something we also heard in the focus groups.

1 6 percent said pediatric information, use in pediatrics.

2 And 5 percent said information concerning use of the product
3 in pregnancy and for breast-feeding women.

4 It is interesting in that some of this information
5 is in the labeling.

6 [Slide.]

7 We gave them a listing of factors, of kinds of
8 circumstances, that might cause them to refer to the label.
9 Basically, what I put up here are the factors that were most
10 likely -- that people said that it was highly likely that it
11 would cause them to do this. Again, this was a four-point
12 scale that we used with one saying it is not at all likely
13 that this circumstance would cause them to refer to the
14 labeling, two being slightly likely, three being moderately
15 likely, four being very likely.

16 The factors most often cited as very likely to
17 lead to labeling referral are right here; that is, for a new
18 drug, 87 percent said that that would be very likely to
19 cause them to refer to the label. If the patient overdoses
20 or has a severe adverse reaction; again, 87 percent. If a
21 patient experiences side effects, 73 percent said that it
22 would be very likely for them to, then, refer to the label.

23 [Slide.]

24 In general, the factors that were most likely to
25 trigger referral were related to immediate patient

1 experiences or circumstances as opposed to the factors that
2 were least likely to trigger referral, things like seeing a
3 advertisement for the drug, hearing a manufacturer
4 representative mention the drug, the drug appearing
5 ineffective. These ranged from about 11 percent to
6 22 percent.

7 Also, even a colleague mentioning use of the drug;
8 only 22 percent said that that would be very likely to lead
9 them to refer to the product. The drug mentioned in a
10 journal article or a conference; only 23 percent said that
11 that would lead them to a referral, that it would be very
12 likely to lead them to a referral.

13 [Slide.]

14 From the focus-group results, we had put together
15 four potential alterations that could be made, just format
16 alterations, that could be made to labeling that we heard
17 from the focus-group participants might make it more useful
18 to them. These are things that we actually felt could be
19 done as opposed to some things that we offered that we
20 really didn't feel were possible; increase the type size
21 used, highlight the most important information, add an
22 abstract of the most important information and use more
23 tables, graphs and lists as opposed to narratives.

24 What we did is we paired each one with each of the
25 other ones so we had a set of paired comparisons. We said,

1 which one of these two that we have got paired here would
2 you prefer to see as an alternative as a change to labeling
3 that would make it more useful to you?

4 [Slide.]

5 What we found, basically, is that highlighting was
6 preferred, highlighting the important information. It was
7 preferred over adding an abstract by 62 percent. It was
8 preferred over increasing the type size by 77 percent. It
9 was preferred over adding more tables, graphs and lists by
10 83 percent.

11 Secondly, adding an abstract of the most
12 important information was preferred over increased type size
13 by 65 percent over adding more tables, graphs and lists by
14 72 percent. Then, of what was left, basically, increasing
15 the type size was preferred by 62 percent over using more
16 tables, graphs and lists. So tables, graphs and lists were
17 definitely at the bottom of these four potential
18 alternatives to labeling.

19 [Slide.]

20 So there were a number of specific conclusions
21 that I don't have a slide for that we reached. Physicians,
22 especially those in primary care, refer to the label on a
23 regular basis most commonly in its reprinted form in the
24 PDR. For the physicians, the most often read sections are
25 Dosage and Administration, Contraindications, Warnings,

1 Adverse Reactions, Precautions, basically Dosage and
2 Administration and the bad stuff, as we will hear more about
3 later from other focus groups.

4 The importance ratings basically parallel the
5 frequency of referral ratings. Some differences in ratings
6 appear between primary-care practitioners and specialists
7 with the specialists being more likely, for instance, to
8 appreciate the Clinical Pharmacology Section but being less
9 likely to appreciate certain others.

10 Physicians seem to be prompted to refer to
11 labeling most by negative product experiences, specific
12 adverse reactions and newness of the product. Labels overly
13 stress the occurrence of extremely rare events. I didn't
14 put the data up for that but that was one of the general
15 attitudes that we asked about. Basically, they agreed
16 fairly consistently with that statement that labels
17 overstress the occurrence of extremely rare events.

18 Although the respondents said that they could
19 fairly easily find the information they need in the label --
20 that was another one of the things we asked about -- the
21 credibility of that particular assertion is kind of
22 challenged by requests from at least some people, a small
23 number, admittedly, to include information that already is
24 in there; drug interactions, pregnancy information and
25 pediatric information, although pediatric information has

1 been less consistent until recently.

2 The usefulness of labeling can best be improved by
3 highlighting the most important information and,
4 secondarily, by providing an abstract of the most important
5 information. These are kind of the general conclusions.
6 They use it. The specialists find detailed information more
7 important than the primary-care practitioners. And there is
8 a perceived need for more effective communication. Certain
9 formatting alterations are preferred over others.

10 Briefly, recently, the Center for Biologics
11 Evaluation and Research sponsored a study of physicians to
12 look at vaccine package inserts, what they call the DPIs.
13 They looked at family practitioners and internists who had
14 prescribed a vaccine within the previous six months and
15 pediatricians who had prescribed a vaccine within the last
16 month.

17 They queried them regarding their use and
18 perceptions of vaccine package inserts and other decision-
19 making sources that they might use. These are just kind of
20 preliminary data that I have gotten access to. The nice
21 thing about it, though, is that they are consistent with the
22 data that we got.

23 Basically, what they found is the most highly
24 rated sections, and this is the percentage indicating that
25 the section is very useful -- and, again, since they used

1 different metrics, things are likely to be a little bit
2 different, but the general outcomes are pretty consistent;
3 Dosage and Administration, Contraindications -- and you can
4 see Warnings, Adverse Drug Reactions and Precautions are up
5 there.

6 Indications and Usage had a slightly higher ranking
7 for theirs than they did for ours because if you recall,
8 with our study, Indications and Usage came after all the bad
9 things that might happen.

10 So this was very encouraging to see that there was
11 consistency in these studies.

12 [Slide.]

13 They also looked at some alterations that might
14 increase the usefulness of the vaccine package inserts for
15 their study population but asked different kinds of
16 questions, gave different kinds of alterations than we did.
17 What they found is that they would like to see a list of
18 rare but serious reactions. They would like to see headings
19 and subheadings bolded which is similar conceptually to our
20 "highlight to important information."

21 They also would like to see risks stated
22 numerically, would like to have information added on the
23 simultaneous use of different vaccines which is similar to
24 drug-interactions information which, as I will point out
25 later with something that came up in the latter focus groups

1 in looking at the draft prototypes that we put together.

2 And they would like to see a list of expected non-serious
3 reactions.

4 [Slide.]

5 What I thought I would do at this point is just
6 kind of take a break and see if you have any questions about
7 the survey or any of the work up to this point. If you
8 don't, I can go on. But if you do, we can take a break now
9 and then I will go on to the initial draft and the focus
10 groups that we did to look at reactions to the initial
11 drafts of the prototype.

12 DR. MARK HORN: I am Mark Horn from Pfizer and,
13 today, also from PhRMA. I would like a little bit more
14 detail, if you have it, on the ranking of the changes in the
15 package insert and what people were actually responding to.
16 I was a little surprised to see that highlighting ranked
17 No. 1. In reviewing your documents, it looks like you chose
18 to go a little bit different route than simply highlight.

19 When people were ranking highlighting No. 1, were
20 they basically saying that what they wanted, or what they
21 felt would be best, would be to take the package insert as
22 it currently exists and simply highlight those areas that
23 they had specified were most interesting to them or was it
24 more than that? If it was more than that, in terms of a
25 highlighting, could you explain exactly what they were

1 voting for?

2 DR. OSTROVE: This is basically the wording that
3 they were given in the questionnaire. They were told that
4 they would be faced with two possible alternatives that
5 could be made, and they were to choose the one they felt
6 would be more useful than the other for them. And they were
7 basically given this; increase the type size used, highlight
8 the most important information.

9 I would like to give you more detail but,
10 unfortunately, this is what it was. I wish we had more
11 detail but, unfortunately, there is only a certain amount
12 you can do in a telephone survey.

13 The thing that I was encouraged by is the fact
14 that the CBER-sponsored survey had that -- they didn't do it
15 this way, unfortunately. They just asked people whether,
16 for each of the alterations that was offered, would it make
17 it more useful for them, less useful or make no difference.
18 Bolding headings and subheadings for them was fairly high up
19 there in terms of the ones that they felt would make it more
20 useful for them.

21 It was, I think, one of the top three or four.
22 But I am afraid I can't give any more detail about the
23 highlighting issue. Sorry. Wasn't there.

24 Any other questions?

25 If not, I am going to move on.

1 **PROTOTYPE DEVELOPMENT: FIRST DRAFTS AND FOCUS-GROUP TESTING**

2 [Slide.]

3 DR. OSTROVE: The initial draft prototypes -- it
4 is difficult to know what to call them -- this is going to
5 be a little difficult for those of you in the back to see.
6 We developed two versions of a Summary of Prescribing
7 Information based on the focus group results and the survey
8 results. We wanted to make sure that we put the information
9 that the survey respondents said was important in there.

10 The question was how much detail was necessary.
11 So we played with levels of detail. We had one that we call
12 the Short Summary where all the kind of substantive
13 information fit on one page here. It started with any
14 warnings. It went to indications and usage,
15 contraindications -- we were thinking about it in terms of
16 the flow of information in decision-making that you would
17 first look and see something is used for what.

18 Then, when is it not used, because you might want
19 to know that right away. Then, how do I use it and then
20 what are things that I need to take into account. So back
21 here, for instance, we played with putting together all of
22 the warning and precaution information under a title Special
23 Considerations. Sometimes we called it Special
24 Considerations, sometimes just Warnings/Precautions.

25 We asked focus groups what they felt about the use

1 of that term and kind of broke it down into different
2 categories; hypersensitivity reactions, major toxicities --
3 and that is where the warnings go, generally -- general
4 precautions and drug interactions.

5 [Slide.]

6 Then we broke out use in specific populations
7 since a number of them had asked about that, about wanting
8 to be able to find information that currently they were
9 having trouble finding because it is buried in a lot of what
10 they felt was extraneous information. So we broke out
11 pregnancy, nursing women, pediatric use, any other special
12 populations.

13 We put in a fair amount of detail here of patient-
14 counseling information. Right now, there is a section in
15 the labeling with that. It is used in very varied ways from
16 product to product -- some have a lot of information, some
17 have practically none -- in concert with other Agency
18 initiatives to encourage information and to get to patients
19 about the drugs that are being prescribed as well as to
20 encourage prescriber counseling of patients. We kind of put
21 it up front there.

22 And we put in a separate section of Most Common
23 Side Effects and left How Supplied pretty much where it is
24 in the label now at the bottom.

25 [Slide.]

1 We also added a Table of Contents, so to speak,
2 with numbers that refer to the comprehensive document. You
3 see down here at the bottom that each one of the different
4 kinds of major paragraphs has a number associated with it.
5 Those numbers refer back -- the Table of Contents takes you
6 directly to those because, since they are set off at the
7 side, it makes the important information that you may be
8 looking for easier to locate.

9 You say, "I want to look for impaired renal
10 function." That is 18, so you go and you find No. 18.

11 [Slide.]

12 In addition, if we can go back to the first page,
13 in this Summary, the numbers are included. So, for
14 instance, if you want more information about treatment of
15 diabetic nephropathy, you see the 04 there tells you that
16 you can go to the more detailed part of the labeling, to the
17 comprehensive document, and look under 04 and you will get
18 more detailed information about that.

19 [Slide.]

20 Let's go to the moderate version. It is pretty
21 much the same except there is a lot more detail. You see
22 under here, the treatment of hypertension, rather than being
23 a couple of lines, has a couple of dot points. There is a
24 lot more detail here under major toxicity under neutropenia.
25 There is more detail on drug interactions. There is

1 basically more substantive information.

2 [Slide.]

3 As a result, the substantive information went on
4 to a second page and then the complete Prescribing
5 Information, Table of Contents, is at the bottom and it
6 would be followed by everything else.

7 [Slide.]

8 We focussed on highlighting important information
9 both through using the numbering system and also, in terms
10 of the Comprehensive Section that we put out, we tried to
11 use a little bit more white space and make the major
12 headings a little larger.

13 We ordered it in terms of the decision flow. We
14 linked Warnings and Precautions. We split out
15 considerations related to specific populations and we put in
16 detailed patient information. Then we took these and we
17 conducted four focus groups to try and get some reactions,
18 initial reactions, to these.

19 Two focus groups were primary-care practitioners,
20 two specialists. We started the focus groups out by having
21 them kind of talk about what information is important for
22 them to get out of labeling and then asking them to
23 construct a synopsis of drug-product labeling. We used a
24 magnetic board with all the different kinds of information
25 that you could use in kind of big headings and said, "Okay;

1 how would you construct a synopsis to kind of get them in
2 the mood for doing this kind of thing?"

3 Then we had them critique both of the labeling
4 variations that we put together, the initial "short version"
5 and the initial "moderate version." I am putting quotes
6 around this because these are all relative. We
7 counterbalanced the order; that is, some groups got the
8 short version first and half the groups got the moderate
9 version first.

10 [Slide.]

11 This is what we found. They basically told us
12 that they refer to labeling after the prescribing decision
13 has been made. For example, they say things like, "It is
14 more of a reference. Usually you learn about new medicines
15 either through journals or meetings."

16 Another one said, "I look at it second-line, after
17 I prescribe it for those unusual side effects if I am not
18 familiar with the drug." "When I open the PDR, nine times
19 out of ten, it is to look for one piece of information."

20 The shorter synopsis was clearly preferred. Many
21 of them said that they should shorten it further. In fact,
22 what we found -- and, again, it is difficult to separate
23 this out; this is only four groups -- showing the medium
24 synopsis first, we got kind of hostility from them when we
25 called it a Summary. They really didn't like that. They

1 said, "This is not a Summary. How can you call this a
2 Summary?"

3 Basically, what they said is, "Look; a Short
4 Summary is something you refer to when you don't want to
5 read the whole text so it should be short." Another said,
6 "A lot of these problems we are talking about would be
7 eliminated if every effort were made to fit the Summary on
8 one page rather than having the Summary spread over the
9 second page."

10 Another said, "The right format should be one
11 sheet. The top half is the Summary and the bottom half the
12 Table of Contents."

13 [Slide.]

14 They also said that the Summary would not stop
15 them from reading the comprehensive document. They said,
16 for instance, "I wouldn't just look here. It would help you
17 to use the rest of the text a lot more efficiently."

18 They said that the Index, the Contents listing,
19 was very helpful. They said, for instance, "The rest of the
20 text being indexed is really helpful. You can find out what
21 you are looking for rather than trying the peruse three or
22 four pages. You can go right to the sources and take out
23 what you need."

24 They said that the Contents list is almost like a
25 Summary in a sense. I think that is very effective.

1 This third bullet, here, came from, basically, the
2 original exercise that they did in putting together what
3 they wanted in a synopsis. They wanted prominent inclusion
4 of Indications and Usage, Dosage and Administration, and How
5 Supplied.

6 [Slide.]

7 They also wanted to know the limitations important
8 for them to know about, what they called the "bad things."
9 In fact, a number of them, independently in different
10 groups, came up with that. One said, "The bad news should
11 be all together. How about combining a number of them
12 together. You can throw those together and call them 'bad
13 things.'" Seriously. Most of us think of these as bad
14 things that can happen. You put them in one section and you
15 list them accordingly; 1, 2, 3, 4, 5. Put the bad stuff
16 altogether.

17 By the way, I have to thank Karen Lechter, who is
18 here today, for picking out these quotes for me because she
19 did a great job.

20 And, they said it doesn't have to be complete.
21 Specifically, they said, "It does not have to be complete.
22 You just have to hit the highlights." Bullets are much
23 easier to find. So we have, basically, only highlights are
24 wanted.

25 Many of them wanted Drug Interactions as a

1 separate heading, or heading, which is what I alluded to
2 earlier. One said, "I would have a separate category for
3 Drug Interactions." Another said, "I believe Drug
4 Interactions should be a special page. The Drug
5 Interactions should be made more prominent."

6 So, where are we going from here? What we are
7 doing at this point, now, of course -- well, we are here.
8 Dr. Lumpkin is going to be presenting the Revised Summary
9 Section that came out of this whole process to date. We are
10 going to be going into the field and testing this with some
11 more physicians in an experimental design. That is coming
12 up very soon. That needs to be done very soon so that we
13 can look at this and get some more data to help guide where
14 the Agency is going to be going.

15 Are there any questions?

16 If not, I thank you for your attention.

17 DR. LUMPKIN: Thank you, Nancy. Thank you all for
18 your attention this morning. I hope you have found this
19 interesting. It is 10:15. According to the Agenda, we will
20 have about a 30-minute break.

21 [Break.]

22 DR. LUMPKIN: I had a question. Several of us
23 were just curious. How many people here -- we are just
24 curious as to what different disciplines people represent
25 who have chosen to come. How many people are here are from

1 either the drug or the device industry. Could you just
2 raise your hands?

3 [Show of hands.]

4 How many of you are regulatory affairs?

5 [Show of hands.]

6 How many are medical?

7 [Show of hands.]

8 How many are advertising and marketing?

9 [Show of hands.]

10 A couple. How many are from one of the FDA
11 Centers?

12 [Show of hands.]

13 Little patches here and there. How many are from
14 the health-care-practitioner community, not associated with
15 industry or FDA?

16 [Show of hands.]

17 Good. Great. How many are from press?

18 [Show of hands.]

19 A couple up here. Anybody that we have left out?

20 Are there other groups? Good. It sounds like it is a nice
21 cross section of people who are concerned with this topic.

22 Fine. Thanks very much.

23 **PRESENTATION OF FINAL PROTOTYPE LABEL:**

24 **SUMMARY AND REORDERING**

25 DR. LUMPKIN: What I wanted to do was just spend a

1 little bit of time with you now.

2 [Slide.]

3 Don't worry. I am actually going to do some
4 blowups of this that are much bigger as far as font is
5 concerned. As Nancy told you in her presentation, we went
6 through several iterations of possible prototypes looking at
7 what we call the "initial short version," the "initial
8 moderate version." You heard the kinds of reactions that we
9 got from the physician focus groups when we put those out
10 for initial consumption.

11 Based on what we heard from them, this prototype,
12 the prototype that you received over the FDA fax on demand
13 or that you received at the table when you checked in this
14 morning is kind of the next iteration and where our mind is
15 right now.

16 This is, clearly, not a final done-deed. There is
17 a lot of talk and there is a lot of thought that needs to go
18 into this kind of a prototype.

19 [Slide.]

20 What I wanted to do was just highlight a couple of
21 that Nancy talked about and how we tried to address them and
22 then highlight some areas just marching through different
23 parts of this prototype where we still have questions, and I
24 would be very interested to hear what you have to say about
25 it.

1 As you can tell from the kind of prototype that we
2 are putting forward now, this is one that, indeed, looks at
3 highlights. It is one that continues to maintain the
4 Summary of Prescribing Information, the abstract at the top,
5 and gives you the Table of Contents down here.

6 At the end of my talk, one thing that I will show
7 you a little bit about the Table of Contents that we tried
8 to do here is keep the numbers in some kind of a normal
9 consistency between products, that each of the sections that
10 we have up here on the top -- Indications would always be
11 Section No. 3; Dosage and Administration, No. 4; How
12 Supplied, No. 5; and so forth all the way down, so you would
13 have a way to consistently reference from Product A to
14 Product B to Product C.

15 If you are going to the more encyclopedic, the
16 more complete text, of the labeling, if you are looking at
17 Indications, you would always be looking in sections that
18 were numbered 3.1, 3.2, 3.3, whatever.

19 The other thing that this lends itself to, and as
20 I said we will show you in just a few minutes, is in the
21 electronic world having kind of the hypertext between the
22 Summary at the beginning and the Encyclopedic part, without
23 even having to go through the kind of a Table of Contents
24 that are there.

25 But, before we get to that, let's just start at

1 the beginning and highlight a couple of the things that you
2 see up here. As I say, the font is not great and I
3 apologize, but this is the best we could do right now. I
4 know you have got this at your seat.

5 Some of the things that came up; the first one was
6 there was this issue and interest in putting at the very
7 beginning whether the product has to have a prescription or
8 whether it was an OTC product. That would be the symbol
9 that would be up in that particular part.

10 Another thing that came up in our discussions is
11 that for a person who is looking at this and they would see
12 the trade name and the generic name, many people, perhaps,
13 would not know what class of drugs it falls into. There is
14 a suggestion that underneath it, here, that the class of
15 drugs be listed underneath it so that, for example, if you
16 had an antimicrobial, you could put underneath the generic
17 name, cephalosporin antibiotic, quinalone antibiotic,
18 whatever the class happened to be. That was one of the
19 thoughts that had been sent to us as an addition there.

20 Obviously, I think many of us felt strongly that
21 any kind of a boxed warning that was required in the product
22 label should be the very first thing that came in the
23 Summary.

24 This particular section here, this New
25 Information, was a section that we were all very interested

1 in and, in talking to focus groups, as Nancy showed you, was
2 an area that they were interested in. The way we envisioned
3 this was our answer to the situation that you are all
4 familiar with and I am familiar with that when there is a
5 change in the label, there is no way to know that a label
6 has been changed.

7 You can't easily tell that something has been
8 added, something has been deleted, whether it was important,
9 whether it was not particularly important. What we wanted
10 to do was within the Summary Section have an area for New
11 Information. This would kind of a bulletin board, as it
12 were, of information that was new to the label over the past
13 six months, with what we were talking about, just as an
14 initial way of looking at this.

15 If there were new indications, if there was new
16 safety information, anything that was important new
17 information about the drug, would clearly be put in the
18 label where it belonged, both in the Encyclopedic Section
19 and in the Summary, but that it would also be put here in
20 the New Information Section and could stay there for up to
21 six months.

22 When you got down to the next group here, to
23 Indications and Usage, and the Dosage and Administration,
24 one of the big issues, and I think we are very, very
25 interested to hear what you guys have to say about it later

1 today, is whether it is appropriate and helpful to have the
2 Indications and Usage and the Dosage and Administration
3 Sections done in the format that you see up here of having
4 the bulleted information, kind of a tabular information
5 here, but it doesn't have the complete, verbatim text out of
6 the I&U Section or the Dosage and Administration Section.

7 An alternative proposal that we have had given to
8 us is that, at least for these two sections, Indications and
9 Usage and the Dosage and Administration, is that they should
10 be the verbatim that is in the Comprehensive Encyclopedic
11 Section and they should not be highlight, that the
12 information is important, that it defines areas of the
13 Indications and Usage Section and limitations in certain
14 diseases, that the information might not be communicated as
15 well if it were just highlighted here.

16 At this point in time, based on the kind of
17 feedback that we got out of the physicians group, we have
18 done it in the way that they suggested to us by bulleting it
19 and then having a reference to the various comprehensive
20 areas where more information could be found.

21 [Slide.]

22 The next area that was one that was, clearly, of
23 interest, as you heard, was the How Supplied. It is
24 interesting that in the focus groups when people talked
25 about How Supplied, it was one of the things about present-

1 day labeling that they really know. They all knew, go to
2 the end. You are going to find How Supplied at the end.

3 So I think that kind of made us realize that,
4 indeed, they were interested in this because most of the
5 people knew where to find this. It also underscored the
6 necessity of having things placed on a repetitive basis in
7 the same area so that people know where to go.

8 Just for your information, this is a misprint.
9 This should be a 5 here, not a 3.

10 When we get down to the Contraindications, the
11 Warnings and Precautions, what we have tried to do here is,
12 in the Contraindications, indeed, put down in the best and
13 as shortened language as we can what the real
14 contraindications are using the definition that we presently
15 have in our regulations; when should you not use this
16 particular product.

17 Under Warnings and Precautions, we tried, under
18 the major toxicities here, to bullet the various ones that
19 would normally be included predominantly in the Warnings
20 Section of our present labeling. One of the big issues is
21 how one deals with this terminology of Most Common Side
22 Effects. It is interesting, as those of you who have dealt
23 with drug-safety reporting and drug-safety terminology, it
24 is funny that people here in these focus groups didn't like
25 the term "adverse reaction," "adverse event," that "side

1 effect" was kind of the colloquial term.

2 Yet, when you start talking in the international
3 world and dealing with the international world of safety
4 reporting, they really hate the term "side effect." It has
5 a very negative connotation and really not the colloquial
6 connotation, internationally, that, apparently, it has here
7 in this country.

8 One of the issues that we tried to come up with
9 was how in the world would we take our present Adverse
10 Reaction Section of the labeling and try to say, "Which ones
11 of those are really the most common? Which are the ones
12 that are important? What would we put forward?"

13 What we are, at this point, proposing would be
14 that, indeed, in most products, kind of the norm would be
15 that you would include here anything that has, in the
16 clinical trials, an incidence of greater than 1 percent
17 that, indeed, was considered to be possibly causally related
18 to the product, that we would not list every event that
19 occurred in the clinical trial, that we would only list
20 those that had this kind of a clinical-trial incidence rate
21 and ones that had been thought to be possibly related to the
22 use of the drug.

23 When you get to drug interactions, one of the big
24 issues here was, again, whether you just list those products
25 that have drug interactions, or of which there are suspected

1 drug interactions with this particular product, or do you
2 give more information?

3 Again, talking to the focus group, what they
4 wanted was an ability to look down the list and see, "This
5 is my patient. He or she is on this group of products. Do
6 I need to worry if I add this product to their particular
7 group of products that they are on?" If, indeed, there does
8 seem to be a problem, then go to the more complete
9 information to find out about that.

10 Finally, the specific populations was a grouping
11 that we would put pregnancy information, that we would put
12 the use of the product in women who are breast feeding. We
13 would put use of the product in pediatric populations, use
14 of the product in geriatric populations, and then, even
15 though it is hard to see underneath here, if there are
16 medical populations; for example, renally impaired or
17 hepatically impaired. In any group of people that one needs
18 to take special care in trying to use this particular
19 product, it could be highlighted here.

20 Now, again, the issue and, finally, the last thing
21 I wanted to point out here was the use of the Patient
22 Counseling Information. In trying to figure out how to
23 shorten this, how to get the information in that is needed
24 to be included, and yet also highlight the kind of
25 information that was thought to be important in using the

1 product and in counseling patients on the use of the
2 product, we would put this at the very back, taking the clue
3 from what we learned up here in How Supplied, that is either
4 usually -- if it is at the beginning of the label or at the
5 end of the label, people can remember where it is and can
6 find it.

7 So the suggestion was if we were going to take it
8 out of this front part that we highlight it by consistently
9 putting it at the very end of the Encyclopedic Information
10 and we would see it there.

11 Just in finishing, what I would like to do is to
12 ask Dr. Ostrove to come down and show you some kind of
13 medium high-tech. I realize that what you are going to be
14 seeing here is kind of a poor man's hypertext. It is using
15 the WordPerfect way of doing it. But just to show you some
16 of the other ideas that are of concern to us knowing the
17 reality that, as we go into the 21st Century, a lot of this
18 is going to be on electronic servers and not so much sitting
19 on paper, and that one of the things that we were interested
20 in, as I showed you at the beginning, is somehow ordering
21 this, that people who are going to be using this on an
22 electronic server could use hypertexts or other ways of
23 finding out the more comprehensive information.

24 So, Nancy, I will turn it over to you.

25 DR. OSTROVE: Thank you.

1 [Slide.]

2 Basically, this is done -- this is using the
3 hypertext function within WordPerfect which then actually,
4 you could -- I don't know how much detail to go into here --
5 probably not a lot. HTML is the language, the hypertext
6 markup language that is used in the Internet that allows you
7 to kind of doubleclick on a word or an icon and then have
8 other information brought right up.

9 This is kind of a very elementary way of doing it
10 within WordPerfect, just to kind of give you a sense of how
11 it might work. For instance, if you set it up so that if
12 someone goes to the Warning, and they want additional
13 information, they just click on that. In normal hypertext
14 use, they would simply doubleclick. Here, you have got to
15 perform.

16 It is set up so that it is linked with the
17 comprehensive document and then it would bring up the
18 information from the comprehensive document. And then you
19 can go through and read more of the detail that is there.
20 Now, in WordPerfect, you have to go back again. I am not
21 sure exactly how it is done within hypertext, but you would
22 do the same thing as long as you set up these linkages, for
23 instance -- go to Use in Nursing Women, say, and then you
24 would doubleclick on that if it was in normal hypertext, and
25 it would bring up the additional information about Use in

1 Nursing Mothers. It would give you the detailed information
2 from the comprehensive document.

3 So that is just kind of a couple of examples of
4 how that can be done. Then there are, of course -- I'm sure
5 you can all think about the implications for how it might be
6 used in advertising with the Brief Summary. I am not going
7 to go into any more detail about that because there will be
8 further talk about it later.

9 So I think that is kind of it.

10 DR. LUMPKIN: That gives you an idea of kind of
11 where we are at this point in time, how we see the
12 prototype, the ideas that we have on it, some of the
13 questions that we still have about it.

14 Before we get into kind of a general discussion on
15 it, as we said this morning, there are a couple of other
16 issues that I think we need to highlight. One is the issue
17 of the effect, if we were to go to this, that this might
18 have on the promotional use of labeling. What I am going to
19 do now is ask Dr. Lou Morris from the Center for Drugs,
20 Division of Drug Marketing, Advertising and Communications,
21 to talk to you about that, and then we will go to hear from
22 the Center Directors about their perceptions on this
23 particular initiative and how it might or might not affect
24 the products in their Center.

25 Lou?

1 **IMPLICATIONS FOR LABELING CHANGES**

2 **FOR ADVERTISING AND PROMOTION**

3 DR. MORRIS: Thank you.

4 [Slide.]

5 My role here today is really to raise issues. We
6 have not had a lot of discussions within our Center and,
7 certainly, not even in the working groups about advertising
8 implications. So my job today is to just raise some issues
9 and throw them out for feedback. I would also like to
10 acknowledge the help of Leslie Frank and Melissa Moncavage
11 in pulling together some of the information that I will be
12 presenting here.

13 [Slide.]

14 When I saw the Summary, my first response was, "It
15 sure looks like a Brief Summary to me." In the hearings
16 that we held a couple of weeks ago on direct-to-consumer
17 advertising, one of the things we heard again and again is
18 that the Brief Summary is neither brief nor a summary. Here
19 is one that is brief and is a summary and, on its face, it
20 sure looks potentially to have some obvious implications.

21 [Slide.]

22 Could this document, or this piece of the label,
23 serve as a Brief Summary? A couple of things that we looked
24 at; first, we looked at what the existing Act and
25 Regulations say about it. In the Act, it says it is

1 required to have, in advertising, other information in Brief
2 Summary relating to side effects, contraindications,
3 effectiveness, et cetera.

4 So there is a requirement in the Act for a Brief
5 Summary. By Regulation, FDA has said, however, that this
6 Brief Summary needs to disclose each of the specific side
7 effects and contraindications. Use of a single term for
8 summarization is permitted if it is in the labeling. So
9 this document would be able to summarize information that
10 could be lifted from the labeling for a Brief Summary.

11 However, this doesn't answer the question of does
12 it serve the purpose of the Brief Summary.

13 [Slide.]

14 To look at that, we went back and tried to pull
15 some historical perspective on what the purpose of the Brief
16 Summary was intended to be from some of the early reports
17 and early thinking. And we found a Congressional Conference
18 Report that talked about the Brief Summary and we pulled
19 some of the quotes and some of the things that try to
20 implicate what the idea behind the Brief Summary was in the
21 first place.

22 What that report said was its purpose is to show
23 the effectiveness of the drug and its contraindications.
24 While brief, it should not be false and misleading. It also
25 said that there should be some reasonable variation. The

1 reason for the variation was to keep the costs for small
2 manufacturers from being too large.

3 So there was the concept that there should be some
4 type of brief, but not misleading, summarization in the
5 advertising.

6 [Slide.]

7 The reason for that comes from -- this is from the
8 Congressional Record, Senator Kefauver, who was one of the
9 authors of the '62 Amendments, said, obviously, the Brief
10 Summary is a fair condensation of the full-disclosure
11 information that exists in labeling. He also said that a
12 summary that was also approved by the Secretary can be
13 substituted if the length of the existing Brief Summary
14 appears excessive.

15 He also talked about why he felt that a Brief
16 Summary should be there. Back in that time, he reported
17 basically a flood of complaints from physicians about the
18 unsupported advertising claims. He felt there needed to be
19 a statement in the advertising that a physician could look
20 at and that would show, in a fair and nonmisleading way,
21 what the drug did and didn't do in terms of its
22 effectiveness.

23 [Slide.]

24 One more piece of history. Harry Chadduck was the
25 first Director of the Division of Drug Marketing,

1 Advertising and Communication back before, actually, it was
2 Marketing, when it was just Advertising. He had his own
3 perspective that he published in a 1972 paper. He said
4 that, from his perspective, the Brief Summary is prescribed
5 regardless of whether the audience is misled by its absence.

6 So he felt that one of the things that had to be
7 there, regardless of whether a case could be made on whether
8 people were being misled or not. The purpose was, from
9 Chaddock's perspective, to avoid any misleading impression
10 that the drug is more effective than otherwise indicated.
11 So even if the advertisement, in any way, exaggerated
12 effectiveness, again, there would be a Brief Summary.

13 One other benefit that he said; while it is there,
14 we can just look to see that it is there -- we, as FDA --
15 and we wouldn't have to make any subjective judgment as to
16 whether the ad is misleading or not, but we can just look to
17 make sure it is there. So he had this objective criterion
18 that he felt was beneficial.

19 So, with that as rationale, we can see that there
20 are actually some reasons why a Brief Summary would actually
21 be more consistent with the original intent but, also, some
22 issues that we have to work through.

23 [Slide.]

24 Another question is why is there this concern
25 about a Brief Summary. One of the things that we did was we

1 went back and we wanted to look at how the Brief Summary has
2 changed over time. So we pulled the first issue of the year
3 of JAMA in 1972, every five years; '77, '82, '87, '92 and
4 then '95 as well. We took a couple of measures to see how
5 the Brief Summary has changed over time.

6 A full page is about 44,000 square millimeters.
7 What we find is that the Brief Summary went from about a
8 half a page to about three-quarters of a page if we want to
9 include this one in early '95. But it really hasn't changed
10 as dramatically. It went up about 50 percent in terms of
11 sheer physical size.

12 Now, of course, there is a lot of variation that
13 occur. We only took one issue of one journal.

14 [Slide.]

15 The other thing we did, we counted the number of
16 words. And while the size may not have changed, what we see
17 is the brief summaries went from about 500 words to about
18 25,000 words. So, even though there has been, like, a 50
19 percent increase in size, there has been a 500 percent
20 increase in words.

21 [Slide.]

22 Clearly, what we find -- it is not so much the
23 barrier entry that has been a problem, it is sheer density.
24 This is what we have. The density has gone up consistently
25 and dramatically over time.

1 [Slide.]

2 Let me show what this means in terms of what a
3 Brief Summary looks like. Here is one from 1972. It is
4 very interesting to see what drugs were being used in 1972.
5 Valium -- the psychotropics were hot. I don't know if you
6 can read it, but I can. I can actually read this stuff
7 here. It is about a half a page and you can make sense out
8 of it next to the ad.

9 [Slide.]

10 Compare that to one of the ones we pulled from the
11 January issue of JAMA. I can't read it. Actually, with
12 this light, I can. We tried to take some measures in terms
13 of point size. As far as we can tell, this is about seven
14 point. This is about four point. So what has happened to
15 brief summaries over the years is that they have gotten
16 dense, not necessarily in terms of the content. But this is
17 a lot of material in a shorter space.

18 It is not so much that it has caused this excess
19 burden on the industry in terms of the amount that they have
20 to pay for more space, although it has gone up. The
21 question is is this actually useful in its present form? We
22 have to ask that question, is it useful today in the way
23 physicians learn about drugs, or consumers learn about
24 drugs.

25 [Slide.]

1 So we can ask the question why should we adopt
2 this new form as a Brief Summary. I think there are some
3 good reasons. First, we can criticize existing brief
4 summaries. They are just too long. They are difficult to
5 read. They are unnecessarily expensive. And this other
6 access the physicians have to labeling information, what is
7 the value of it?

8 Plus, we also know that the new Summary -- we
9 don't know it, but we think -- has some benefits. The new
10 Information Section in the ad could be a very good way of
11 making sure that physicians are aware of new information in
12 the labeling because they know where to look in the
13 advertisements for this new information.

14 We also find that -- and this is evident in the
15 focus groups -- that one of the benefits is that physicians
16 can very easily skim down a formatting Brief Summary and,
17 actually, pick up stuff that they may not have known
18 otherwise. They actually could learn something from it, and
19 that is maybe more in concert with the way physicians
20 actually read ads or look to read this kind of information.

21 The third issue is it has implications for
22 adapting to evolving media, as Nancy has shown, with
23 hypertext.

24 [Slide.]

25 Of course, there are reasons not to adopt the

1 Brief Summary and we should bring those up as well. The
2 first issue is one of physician access. Will a physician
3 have access to the full prescribing information, especially
4 during the initial period with which a drug is launched when
5 it may not be readily available in other sources.

6 Could the Brief Summary serve the function of not
7 being misleading unless people can't have access to the
8 longer information.

9 The second issue is some kind of symbolic or
10 reminder function. I know in advertising research these
11 days, it is one of the big issues in the ad is what is kind
12 of a symbolic meaning of products and purposes. Just the
13 fact that it is there, the longer Brief Summary is there.
14 Does that have some kind of reminder function to physicians
15 that yes, these are serious products. You have to think
16 about it carefully.

17 We don't know the answer to that. I am just
18 raising that as one of the things to consider.

19 The next two issues are kind of subtext issues.
20 Another issue that raises that frequently, as a regulatory
21 agency, we hear is the issue of equity. If we lower the
22 burden for one form of media, will the other people who
23 produce other media complain to us that we are not being
24 fair. So is there an equity issue? I am just raising that
25 as another issue.

1 The last issue is really a drug-company issue more
2 than it is an FDA issue, and that is the product-liability
3 implications. I'm sure you will hear about that. Are we
4 messing up the learned-intermediary defense? Are there any
5 problems with liability? I'm sure the attorneys within each
6 of the companies will want to consider that issue.

7 [Slide.]

8 We talked this new document, the Summary, as a
9 Brief Summary. What about it as a basis for promotional
10 claims? One thing we can think of is that we now have, in
11 theory, an FDA-approved summarization. It may actually
12 allow companies to simply lift those claims out of the
13 summarization, that the FDA will have approved what is a
14 more condensed version, perhaps, of a claim, and use that in
15 advertising and that would make -- it would certainly reduce
16 uncertainty on behalf of people in marketing to say what
17 they can and can't permissibly say in advertising.

18 On the other hand, one of the things we know is
19 that meanings change when the context of information
20 changes. In a promotional context, how is that going to
21 change the meaning of claims in promotion? On the good
22 side, at least from FDA's perspective, it may actually have
23 a clearer communication of what is acceptable.

24 On the other hand, one of the questions that we
25 will, I'm sure, be wanting to ask is when you change the

1 context, is there a sufficient claim qualification in
2 promotion so it is not false and misleading. This may set
3 up a concern that we have now when people use certain
4 concepts extracted from labeling in advertising, does that
5 change the meaning? This issue will continue and it may
6 continue with this summarization.

7 [Slide.]

8 Another implication for advertising is that the
9 Brief Summary, or the summarization, may actually serve as
10 an aid to help people learn what is helpful for fair
11 balance. The Act talks about information being misleading.
12 This is a failure to reveal facts that are material in
13 claims of the representations that are made.

14 What are these material facts? Here are some
15 clues. Our summarization actually helps people figure out
16 what may be important for them to disclose in advertising so
17 that may actually help people in determining what should
18 serve as the basis for fair balance.

19 [Slide.]

20 I would like to end with a few other implications
21 for other forms of promotion. We had a recent hearing on
22 direct-to-consumer advertising. It was fairly consistently
23 heard that the Brief Summary is useless. Actually, that was
24 euphemistic. That was being kind, I think. When Dr. Temple
25 talked about it in terms of a fish floating face up with not

1 too much water running through its gills, I thought was the
2 summarization of the status of the Brief Summary for
3 consumer advertising.

4 We could ask a question. Even if we took a
5 shortened version of a Brief Summary, would that be at all
6 useful for direct-to-consumer advertising? We have options.
7 One option is to try to translate what is a Brief Summary
8 for health professionals perhaps into something useful for
9 patients.

10 Another is to just say we need different
11 approaches for different audiences. There are other options
12 as well. The dockets are open on both the DTC hearing and
13 this hearing and we would certainly want to hear
14 implications or ways we might want to consider going in that
15 direction.

16 [Slide.]

17 What about the implications for broadcast media?
18 Right now, the current requirement is that someone who is
19 engaged in broadcast advertising needs to either have a
20 Brief Summary as part of the ad or have a combination of
21 what is called a major statement and the dissemination of
22 labeling information. The major statement is simply even a
23 more condensed and more extracted version.

24 Could this Brief Summary serve as the basis for
25 disclosure in television advertising and, if so, you don't

1 have to worry about dissemination of labeling. We have to
2 think through what that means. That means you could
3 actually have a t.v. ad with a billboard up of what this
4 Brief Summary is, and that would be an acceptable ad. That
5 would be the implication of that.

6 However, would that billboard be sufficient? We
7 don't know. What about audio disclosure? This is just
8 something you would see. But what about radio? Would a
9 major statement be more useful? Again, these are just
10 questions. These are things that would helpful for us to
11 have your views on them and things that we would want to
12 think through.

13 [Slide.]

14 The implications for labeling. Much of what is
15 promotion these days is not advertising but, rather, it is
16 labeling; the patient education material, the reprints, the
17 books, et cetera, the reports. Right now, these materials
18 require full disclosure which is that accordion of paper
19 that people have already found to show us. They take it and
20 say, "Why is this accordion necessary?"

21 We should think through those issues as well.
22 Having said that, there are huge legal implications that
23 have to be thought about and thought through, putting
24 material in interstate commerce with or without a label. I
25 think that this needs a very careful legal analysis.

1 But I do want to raise it as an option that people
2 should think about.

3 [Slide.]

4 Finally, just to mention implications for new
5 media, as Nancy showed, there is, I think, enormous
6 application and flexibility that is now permissible in text-
7 based computer media through hypertext. There also is an
8 ability to "chunk" the information in ways that people can
9 process the information more reasonably. It really can line
10 up what is a promotional claim along with a fair-balance
11 claim, and that could be done in a very flexible way without
12 taking any more space on the screen through either hypertext
13 or through a box of some sort.

14 Even with graphics; we can consider having a
15 little box and using some kind of disclosure in graphics.
16 So I think it has enormous implications for permitting
17 advertising to be more flexible and, also, make it more
18 useful for the reader.

19 And, with that, I will thank you.

20 DR. LUMPKIN: Thank you, Lou. What I would like
21 to do now is go ahead and hear from the three Center
22 Directors. Then we will have a fair amount of time at the
23 end that if any of you have questions for any of us up here
24 regarding what you have heard this morning, we would all be
25 happy to try to answer as kind of a panel up here.

1 We will start with Dr. Janet Woodcock who is the
2 Center Director at the Center for Drug Evaluation and
3 Research.

4 **IMPLICATIONS FOR THE CENTER**

5 **JANET WOODCOCK, M.D.**

6 DR. WOODCOCK: Thank you, Mac. I am really
7 pleased to be here today and the hear about the progress we
8 have made on this initiative. Within the Center for Drugs,
9 I think we recognize that any changes that might be made in
10 labeling in the package insert will have a lot of workload
11 implications and a lot of other implications that will have
12 to be worked through, as Lou has just presented.

13 However, I believe this is one of the most
14 important things we are going to be doing over the next
15 year. In the Drug Center, we realize that in addition to
16 our role in protecting the public health and so on, and our
17 role in reviewing new drugs, one of the parts of our mission
18 is really to make sure that the information that is gained
19 in drug development and in our review is relayed effectively
20 to the people who need that information.

21 I think what we heard from our focus groups and
22 what we know from other sources is that we need to relay
23 drug information more effectively both the prescribers and
24 to consumers, to patients. We need to evaluate as many ways
25 as possible to get this information out and make sure that

1 drug prescribing is done on the basis of as much information
2 as possible.

3 The computer and electronic technology is going to
4 provide a new paradigm, I think, for getting information to
5 people. We need to be, along with, I think, the
6 pharmaceutical industry, aware of this. We need to be out
7 in front of this. We need to get ready for information
8 being conveyed in a manner in which we haven't been able to
9 do in the past.

10 In addition, there are more drugs out there.
11 Every year more drugs are prescribed. We have more
12 knowledge about drugs. It is our mutual obligation, I
13 think, to make sure this information is arrayed and packaged
14 and conveyed in a way that people have access to it and can
15 use it effectively.

16 I really heard what the prescribers said in our
17 surveys, for example, about drug interactions; long lists of
18 side effects, long lists of drug interactions are not
19 helpful to people. All this other information,
20 contraindications, warnings, having it summarized and having
21 it strewn through the label, I can say, as a prescribing
22 physician, myself, is not a modern or helpful way to present
23 information to people.

24 I don't know whether or prototypes that we have
25 put forward are the actual best way. I think, given

1 upcoming computer technologies, they may be a very good
2 start but I think we need input from the pharmaceutical
3 industry on the implications of this as well as from the
4 biomedical company and the consumer company on how we can
5 best present information to them that they can use it
6 because there are prescribing errors made.

7 Some of these errors are made because people don't
8 have the information. Any way that we can improve the
9 presentation access of physicians to the information they
10 need is going to improve the outcomes of prescribing in this
11 country. So I feel very strongly about this and I really
12 support this effort. We will be moving on this in the next
13 year.

14 DR. LUMPKIN: Thank you, Janet. As all of you,
15 I'm sure, are aware, what you have heard this morning has
16 primarily been a label from a drugs and therapeutic
17 biologics perspective. But very, very active players in
18 this entire initiative have been our colleagues at the
19 Center for Devices and Radiologic Health. Because their
20 labeling implications are so different from what we have in
21 drugs and therapeutic biologics, you are actually going to
22 hear from two people from the Center for Devices and
23 Radiologic Health.

24 First, you will be hearing from Dr. Susan Alpert
25 who is the Director of the Office of Device Evaluation at

1 CDRH. Following her presentation, we will go direction to
2 Dr. Bruce Burlington who is the Director of that Center.

3 Susan?

4 **SUSAN ALPERT, Ph.D., M.D.**

5 DR. ALPERT: Before I begin, Mac asked a question
6 or a couple of questions a little while back and I would
7 like to start with the same question. First of all, for
8 those of you in the audience that would help me to know, how
9 many of you are now or have ever been health-care providers,
10 health-care practitioners?

11 [Show of hands: many.]

12 How many have ever seen a device label?

13 [Show of hands: few.]

14 That's what I thought. That is sort of why I
15 wanted to begin with talking a little bit about how the
16 world of medical devices and labeling in medical devices is
17 quite different from the situation with drugs and
18 therapeutic biologics. I think it is important to
19 understand the impact of this multi-Center initiative by
20 understanding a little bit about that background.

21 I think, first of all, we serve the same clinical
22 communities and the same patient communities. We just serve
23 a different part of that community in the sense of what we
24 provide or what devices provide in health-care.

25 One of the things we found out in doing our focus

1 groups, and I am going to keep talking -- I am going to
2 bounce between what we do now and what we found out from ou
3 focus groups because we also did some focus-group
4 questioning and analyses.

5 [Slide.]

6 The first thing was to understand what was the
7 scope of medical devices. It was interesting for those who
8 conducted the focus group to find out that many people in
9 the health-care community didn't know what things they used
10 were actually considered medical devices. That is a problem
11 because medical devices covers a very broad area. It is not
12 surprising in the sense that people don't know all of the
13 things that we actually regulate at CDRH.

14 It ranges from all of the diagnostics. All in
15 vitro diagnostics, all lab tests, are regulated as medical
16 devices. In addition, all of the tools that have
17 implication for direct patient care from hospital beds, X-
18 ray machines, bandages, as well as the more common things
19 that you think of as being medical devices; surgical
20 instruments, implantables like pacemakers and artificial
21 joints. But all of those are medical devices.

22 As you can see from their scope, the kinds of
23 access to information about them and as seen by the reaction
24 in this group is very limited. We don't have a PDR for
25 medical devices. And, in addition, since most of medical

1 devices are, in fact, equipment of some sort that is bought
2 by the central supply in hospitals, that is where most
3 device labeling resides. It doesn't reside in the hands of
4 the user.

5 So this initiative to provide a health-care
6 professional labeling is really an important one for us.

7 What I would like to do now is just run you
8 through quickly another comparison between the issue for
9 labeling in medical devices versus drugs and biological
10 therapeutics, and that has to do with sort of the structure
11 and the regulations around the way labeling is provided for
12 these kinds of products.

13 I am just going to briefly go through it. The
14 first thing is that we have three different ways that
15 medical devices can get into the marketplace. The most
16 common way that medical devices get in, about 6,000 a year,
17 is through a process called the 510(k) or premarket
18 notification process where devices go to market as being
19 similar to, or substantially equivalent to, something
20 already in the market.

21 In the environment in which medical-device
22 regulation was involved in these statutes, there are no
23 regulations about how these products need to be labeled.
24 The only requirement is that the submission to the FDA and
25 the labeling contain information about the intended use of

1 the device; what is the device supposed to provide? What is
2 it supposed to do? Again, that is 6,000 new products a yea
3 going into the marketplace.

4 The second path to market is the one I talked to
5 about in vitro diagnostics, all of the laboratory tests,
6 most of which are also in this 510(k) arena. But in the
7 area of in vitro diagnostics, there is a labeling regulation
8 and so we have consistency in terms of how laboratory
9 products are labeled.

10 There is a reg that goes through what has to be
11 listed in the labeling, most of it centering around what is
12 in the actual package, what are the reagents, what are the
13 concentrations and then directions for how to use them.

14 [Slide.]

15 Lastly, the third major avenue to market is
16 through the premarket approval application, the PMA, the
17 brand-new product not substantially equivalent, not like
18 what is in the marketplace. And there, also, there are no
19 regulations comparable to 201 in devices.

20 But what we have done over the years at the Center
21 is to develop the first approach to the consistency of
22 providing information to health-care providers and that is
23 that by standard operating procedure, in internal memoranda
24 which we have shared with the industry, we incorporated the
25 definitions and the basic way in which drug labeling is

1 written and applied that to those aspects of device labeling
2 where it fits.

3 Clearly, there is additional information in device
4 labeling that doesn't appear in drug labeling. The
5 instructions for use are much more extensive, and then there
6 is an entire manual sometimes filling entire shelves of the
7 hospital's central supply that talk about how to actually
8 use and trouble-shoot the product.

9 The next thing we did when we went back to our
10 focus group -- as I said, that it sort of the background.
11 We don't have regulations that cover most of the products
12 going into the marketplace and many people don't even know
13 what medical devices are. So after we instructed or
14 educated the focus group as to what devices were, we asked
15 them what they would like to see in device labeling.

16 Actually, I take that back. The second question
17 was where did they get their information. If, like this
18 audience, they didn't see device labels, where did they get
19 their information? Since there is no PDR, the answers were
20 sort of second-order answers; from teaching, from
21 experience, from colleagues, from meetings and from
22 manufacturers was where they got most of their information.

23 When asked what information they would like to see
24 provided to them in the hands of the health-care provider,
25 basically, they wanted to see what it cost, how the new

1 product compared or how this product compared to other
2 products for similar uses, and basic instructions.
3 Everything else was clearly second or third order.

4 The message is that, like with other devices in
5 the world in which we live, the users of medical devices
6 would like to see them labeled in the same way, very basic.
7 What is the information I need to know to operate the
8 system? Then provide me all the rest as some trouble-
9 shooting information, a manual where I can go when I have a
10 problem.

11 But, up front, give me cost, give me comparison to
12 what it will do or what other things will do for the same
13 uses that I want to make of this product, and give me very
14 basic instructions. I want to turn it on. I want to use
15 it. And that is about it.

16 I think this is a very important issue for us
17 because, as I said earlier, we are trying to provide very
18 similar patterns of information. We serve the same
19 community and we think there would be a lot to gain in
20 providing it in the same or similar format as we do
21 information on other medical products to the same community.

22 **D. BRUCE BURLINGTON, M.D.**

23 DR. BURLINGTON: I would like to add a few things
24 to what Janet and Susan have already addressed as far as
25 medical devices. I agree with Janet Woodcock's contention

1 that basically, at FDA, we think of ourselves as being in
2 the information business. Congress has clearly told us that
3 we have a job to keep bad and defective products off the
4 market. We intend to do that and we do that seriously.

5 But, more than that, there is also, in the
6 efficacy standard, in the safety standard, a sense that we
7 should be obtaining or fostering a climate in which there is
8 the development of information about how to use products so
9 that they can achieve the benefit that the manufacturer
10 hopes for and that information on how to use them as
11 evaluated by FDA, as transmitted, or hopefully transmitted,
12 to the person who is making the decision about the use of
13 the product in labeling, in promotion and advertising, is
14 one of the major functions that we do at FDA. It is one of
15 the major justifications for having an FDA interpose between
16 the manufacturer and the medical community or the using
17 community.

18 As Susan said, for medical devices, we may do a
19 fair amount of work in terms of looking at the information
20 on how to use products, but the idea that that exists in
21 some well recognized label which is then available to the
22 decision maker just doesn't play out in practice.

23 In fact, if you go to your local medical library
24 and you look for compilations or compendia of labeling on
25 drugs, you find a bookshelf five or six feet long which has

1 got a whole bunch of different volumes on there. It has got
2 the PDR. It has got a four-volume set of the USP Drug
3 Information. It has the Merck Manual, et cetera, et cetera.

4 When you go and look and say, "Well, what is there
5 on device labels?" you find that some of the device labels
6 are in the PDR for ophthalmic products but only a few of
7 them. It is mostly about drugs. There is almost nothing
8 else there. You can't find it.

9 As a practitioner, when you go to the hospital and
10 you want to find labels on devices, you have a really
11 challenging time to even find them if you want them. That
12 is in part because a great many devices are durable, medical
13 equipment. They are anything from a piece of imaging
14 equipment which may have a trouble-shooting manual but it
15 doesn't really have anything like a label as we are
16 accustomed to for a pharmaceutical that says, "Here ^{are} ~~at~~ the
17 indications. Here are the contraindications. Here are the
18 adverse events," et cetera.

19 With the in vitro diagnostics where there are
20 labels that are reasonably standard in format, you have to
21 know where to find them. And where you go to find them is
22 you have got to go to the laboratory and you have got to
23 look in the kits there. If you are a practitioner ordering
24 a test, your chance of finding that is very slim, indeed.

25 The one place that, as practitioners, you may have

1 encountered device labels is in single-patient use items. I
2 recently had a chance to open a lumbar-puncture kit and
3 there was a little package insert that was inside the
4 sterile wrapper. Obviously, the decision to use the product
5 had already been taken at that point and it really wasn't
6 amenable to sitting there and reading through a several-page
7 document right at that point in the procedure.

8 But it shows that we have a way to go to achieve
9 what our intent is. What are the implications for devices?
10 We regulate advertising and promotion for devices
11 differently than for pharmaceuticals. Basically, promotion
12 is pretty much the same -- that is, the direct contact sort
13 of information. But advertising is quite a bit different.

14 The Agency regulates advertising for devices when
15 devices are restricted. That means that they either entered
16 the market through a premarket application, a small minority
17 of devices, or that we have a restricted-device regulation
18 for them. To date, that means they are a hearing aid
19 because that is the only restricted-device regulation we
20 have.

21 The vast majority of devices, as Dr. Alpert
22 alluded to, entered through the abbreviated application
23 process, the 510(k) process, and the advertising for them is
24 regulated by the FTC unless that advertising seems to create
25 a new intended use and go so far beyond the balances to

1 for a summary for the package inserts. In fact, at our
2 Office of Vaccines, we have had a mandate to look into the
3 package inserts from Section 314 of the National Childhood
4 Vaccine Injury Act of 1986. Our focus was on making sure
5 that the Warnings Sections were adequate.

6 As Dr. Ostrove mentioned earlier in her talk, we
7 also conducted a survey. That survey was driven to try to
8 find out what we needed to do to improve the uses of package
9 inserts. We also found out that if we had something of a
10 summary, as we have been discussing here, that important
11 information would be readily accessible and read rather
12 quickly from the health-care providers.

13 We are also glad to know that the information in
14 our survey coincided with the information in the survey done
15 by drugs. We also believe that there is some concern in
16 CBER for some of our unique products like vaccines and how
17 the labeling of those products will fit into the summary
18 information and provide usefulness for not only the
19 physicians but also the end users of those products.

20 But, again, we are participating in this activity
21 and we support it fully.

22 DR. LUMPKIN: Thank you, Norman.

23 **AUDIENCE FEEDBACK**

24 We have approximately 35 minutes before we had a
25 planned break for lunch. I would like to open the floor now

1 for any questions that any of you might have regarding what
2 you have heard this morning. Please, as I say, just
3 identify yourself and your affiliation and to whom you would
4 like to direct your question, whether to one of the Center
5 Directors or to the other of us up here about any of the
6 issues that we have talked about this morning.

7 [No response.]

8 Surely, we weren't this clear.

9 DR. WOODCOCK: Mac, could I start it off, maybe
10 break the ice?

11 DR. LUMPKIN: Sure. Go right ahead, Janet.

12 DR. WOODCOCK: One of the things you alluded to,
13 Mac, and I was talking to Bob Temple while we were looking
14 at the prototypes, was that the issue -- I think what Nancy
15 said very early in this -- is that the label has many uses.
16 That has probably caused some of the problems with the
17 current label is we are trying to do many things.

18 We are trying to establish formal claims, what you
19 have actually succeeded in showing in clinical trials. We
20 are trying to have all this legal liability information and,
21 somehow, I think communication with the prescribers go to
22 the end of the list, the bottom of the list, in the current
23 format of the insert.

24 What we were talking about in the prototypes was
25 the Indications and Usage Section. Right now, the way it is

1 written, it seems to be more of a usage than an indication.
2 It doesn't really reflect a formal claim, if you follow me -
3 - what have you shown in your trials -- and that may require
4 saying more and it was left out for brevity purposes.

5 What kinds of thoughts went through your mind,
6 Nancy, and the other people in the group about that
7 particular area?

8 DR. OSTROVE: Basically, I think we were
9 responding to a lot of what we had heard in the focus groups
10 from the physicians which is that -- you get the impression
11 from the groups that they do not pay as much attention to
12 the kinds of detail that we feel is very important in
13 including in the labeling to kind of communicate the basis
14 for approval.

15 They really simply want to know, what do you use
16 it for. So you are right. It really gets more at the use
17 than at the indications because basically that is what they
18 had communicated to us which is that is what they want to
19 know about.

20 They don't want to read through a whole paragraph,
21 necessarily, of the minutia of what was found in the trials.
22 They really want to know in general what do we use this for,
23 what is it recommended for. And then, what are the things
24 we have to look out for and how do we use it?

25 DR. LUMPKIN: I do think one of the important

1 parts that has come up on that is that there still are,
2 though, the situations where you read the indications, there
3 is a lot to be learned from the verbiage that is in the
4 Approved Indications Sections. There are limits on its use
5 in certain indications. There are special populations where
6 it is supposed to be used.

7 I think one of our fears is that if only the title
8 of the use is put there that it gives the impression that it
9 is for the broad use and that you have to be sure to go to
10 some other part of the label to find out really that it is
11 only part of that broad use that really the efficacy and
12 safety have been established for.

13 That was the basis behind my comments when I was
14 talking about whether it makes better sense to bring the
15 Indications and Usage Section verbatim into the summary to
16 make sure that the physician, when he or she reads that,
17 indeed understands the full implications of the indication.

18 DR. WOODCOCK: That's true, but it may be that
19 bringing it all in means they don't read any of it. That is
20 the tension we are talking about here. I believe we have
21 sort of a construct in our minds about what physicians do.
22 We need to find what they actually do and what they actually
23 want to know.

24 That is why I would be interested to hear the
25 audience's ideas on this.

1 DR. LUMPKIN: Audience?

2 MR. JONATHAN PARKER: Actually, it wasn't on that
3 issue, but it was -- I'm sorry; Jonathan Parker with Rhone,
4 Poulenc, Roher. I did have a question about your section on
5 New Information. I found it a very interesting concept. I
6 guess the question I have is where were you planning on
7 going with that new information because, obviously, you can
8 do that in many different ways. And there are many
9 different ways that new information presents itself that is
10 possibly rewriting a paragraph to make it clearer because
11 you have heard from prescribers that it is a little unclear
12 and you want it clarified.

13 It could be something like a new indication. And
14 how exactly were you presenting them, in bullet form, in
15 "See this section only," or how were you planning on doing
16 that?

17 DR. OSTROVE: I think those are excellent
18 questions. I am not sure if we have really gotten to the
19 point where we have gotten to that level of consideration.
20 I think that what we had in mind, and this may not be in
21 total agreement with everyone else -- but I think what we
22 had in mind, though, was important information that needed
23 to be communicated so that we are not talking about minor
24 changes. We are talking about something that physicians
25 would want to know, the prescribers would need to know in

1 terms of adding information, for instance, about important
2 new warnings or adding new information about new indication.
3 or limitations that have come up since the last -- in the
4 past six months or whatever it happened to be.

5 DR. LUMPKIN: I think what we had in mind when we
6 have just kicked it around is just as you say. If there is
7 important information, no matter what it is, whether it is a
8 clarification, a new indication, new safety information, the
9 idea of having a bullet point that would say, "New
10 Indication:" and then write out what the new indication is.

11 "New Safety Information:" write it out.
12 "Clarification of Information:" write it out. There are
13 different ways that you could put it in, but it really is
14 kind of a bulletin-board type of approach with the basic
15 summary within the reference to what part of the label you
16 would need to go.

17 MR. PARKER: If I can follow up on that, too. The
18 original statement I heard was for six months. Some drugs
19 are very dynamic and they have inserts that change multiple
20 times in a year, especially new drugs. Some are quite
21 static and can take two or three years before labeling
22 changes.

23 When you said a new change was six months, would
24 you then expect six months following that to have that
25 removed?

1 DR. LUMPKIN: What we had thought was that it
2 could stay within the New Information Section for a period
3 of six months and then it would go out at the next printing
4 because it would already be in the appropriate part of the
5 label from the initial information being placed in the
6 label.

7 So it is just that it would stay there for six
8 months and then it would come off. It would be kind of like
9 when you do an Rx-OTC switch and, for six months, you say,
10 "New," or something along those lines and then it drops out
11 after that concept.

12 MR. PARKER: Thank you.

13 DR. BOB TEMPLE: Temple, FDA. It is always
14 dangerous to say the same thing twice. One of my
15 nervousnesses about the labeling, about having the
16 Indications Section in two slightly different forms and
17 slightly different words is that a lot of things become
18 ambiguous. What is the real claim?

19
20 The other thing is that we have historically put
21 important limitations of use in that section. In the
22 captopril, for example, the advice on using the drug in
23 hypertension is that you are supposed to be especially
24 careful with people with impaired renal function which, for
25 better or worse -- I mean, it is a somewhat historical

1 matter. Maybe people know it, but it is one of the major
2 factors that you have to face in using captopril in
3 hypertension.

4 You cannot pull that out of the Summary. There is
5 a reference to "Caution in people with renal failure," but
6 because this was in the Indications Section which was one of
7 the sections being truncated, you really miss one of the
8 major factors of use of the drug.

9 That is not the only one. The claim, "Use in LV
10 dysfunction" is almost silly if you don't know why you are
11 doing it. You are doing it because it improves survival and
12 decreases the chance that you will have overt heart failure
13 which does not appear in the truncated version.

14 So there are some significant disadvantages to
15 trying to be too truncated there. I guess it strikes me as
16 a better use of space to put a little more from the
17 Indications Section and put the Table of Contents or Index
18 or whatever, that whole thing, in a little later. Anyway,
19 that strikes me as a good use of space.

20 The other thing is, the other section that seems a
21 candidate for expansion, is Dosage and Administration. We
22 are increasingly putting information about individualization
23 in there, one of the most important things we think that is
24 going on in recent drug development, and you will lose that
25 if you try to strip it down too much. The use of tables

1 seems a very good idea, and all that.

2 I guess the last thought I have is that we pay a
3 price for some of the ways we have behaved in including
4 things in labeling. Among the leading adverse reactions for
5 captopril is chest pain. That surely isn't something that
6 captopril causes. For all we know, it treats it. It is
7 because we haven't been very successful at leaving out the
8 things that are probably not related so we are sort of
9 paying a price for our inability to have done that.

10 DR. WOODCOCK: When we started this effort, I
11 predicted that the Adverse Reactions Section would be the
12 hardest one for us to deal with. It really wouldn't be
13 right, in my mind, to try and explicitly inform physicians
14 about side effects that actually don't occur with the drug.
15 That would really be a very bad outcome of this.

16
17 If they occurred in 10 percent of the patients in
18 the trials, you might have to go back and see did they occur
19 with greater frequency in the placebo group. Bob and I were
20 talking about that. It would be a really bad thing to
21 highlight in a summary label events that actually just occur
22 in the population and do not occur with that drug because
23 then they will be attributed to the drug when they occur,
24 and they will occur.

25 But we don't have a good way of dealing with this,

1 frankly.

2 DR. BURLINGTON: Bob, I would like to respond to
3 this. You basically said you think more information on two
4 of the sections that FDA has traditionally put a lot of
5 emphasis on ought to be included -- that is, the Indications
6 and the Adverse Events -- that you thought tables were a
7 good way to represent data.

8 That is an antithetical trend to what we heard
9 from the focus groups of physicians. It asks us to deal
10 squarely with who are we writing the labels for. Are we
11 writing the labels for those who are day-to-day using them
12 and who need to have them tooled, tailored, to their needs
13 or are we writing them for the pharmaceutical-device legal
14 manufacturing establishment whose needs are quite different,
15 or may be quite different?

16 DR. TEMPLE: That is a fair question, but I don't
17 think you get complete answers from focus groups. They are
18 like any polls. A lot has to do with what you put into it.
19 I guess I would say that what they want most is not the sole
20 determinant of what they should get. It is a major
21 determinant, but it is not the only one.

22 For example, I thought the part where it listed
23 interactions and then you could follow up if you wanted to
24 know more about the interaction with a particular drug was
25 perfectly satisfactory from everybody's point of view. It

1 told them what to watch for and, if the person was on that
2 drug, then they could worry about it more and follow it up
3 in hypertext or read the label.

4 On the other hand, a physician who has pretty much
5 decided he or she wants to use captopril really ought to be
6 reminded fairly often that there are some limitations that
7 go with this. Even though they don't think they need that,
8 I think it is good to remind people of those things because
9 they are important.

10 Now, if we are putting dumb stuff in that is not
11 important, we should take it out. But assuming that it
12 really is important, it is good to remind people of that
13 because -- I am in the drug business. I don't remember
14 everything you are supposed to worry about even for the
15 things I use on my family, and I doubt anybody else does
16 either.

17 So, partly, we should be telling people things
18 that they need even if they are not -- now, that doesn't
19 mean we can't highlight hypertension and then put some words
20 in less obvious print so they know it is for hypertension,
21 they know it is for heart failure and they can see that, and
22 they can decide whether they want to read the detail in the
23 paragraph.

24 But I guess there are some things you should be
25 told even if it wasn't the thing you thought you needed

1 most.

2 MS. TAMMY MARTIN: I am Tammy Martin. I am with
3 Otsuka America here in Rockville. I am very interested in
4 the legal-liability aspects of the document. I think we can
5 all agree that that is probably one of the reasons why the
6 document is as long as it is. Have you had any legal
7 analysis done on the document? Do you plan to do that?
8 Have you conferred with your general counsel?

9 DR. LUMPKIN: We have actually had a member of our
10 general counsel as part of the Steering Committee and part
11 of the core team. Seth Ray is that individual and has been
12 working with us on it. Obviously, that particular issue
13 doesn't come to the forefront from our perspective when we
14 put it through. We know it is a very, very important issue
15 and one that has to be put into this equation.

16 I think it is one of the areas that we need
17 particular advice and thought from the pharmaceutical
18 industry because you are the ones that have the expertise on
19 that particular issue all the way through. So if you guys
20 have thoughts on that, I'm sure you do and I am sure we will
21 hear from you, we really do need to have that part of it.

22

23 But I think Janet made a very good point. There
24 is a point where you have got to make a decision. Do we
25 want to put everything in a summary document even though you