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THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL AND PREVENTION

convenes

THE NATIONAL VACCINE ADVISORY COMMITTEE
SPONSORED WORKSHOP ON THIMEROSAL VACCINES

DAY TWO - VOLUME I
AUGUST 12th, 1999

The verbatim transcript of the Sponsored Workshop on Thimerosal Vaccines held Wednesday, August 12th, 1999, at the National Institutes of Health, Lister Hill Auditorium, Bethesda, Maryland.

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PARTICIPANTS

(By Group, in Alphabetical Order)

PARTICIPANTS

Allen Albright
Food and Drug Administration

Juan Archiniega
Food and Drug Administration

Deborah A. Ball

Thom Ballsier

Norman Baylor
Food and Drug Administration

Roger Bernier
National Immunization Program

Robert Breiman
National Immunization Program

Carolyn Buxton Bridges
National Center for Infectious Diseases

Druscilla Burns
Food and Drug Administration

Felecia Butler
Merck and Company, Inc.

Gerald Calver
VDBB&R

Lynn Cates
Department of Health and Human Services

Nancy Cherry
VRBPAC

Helen Cicirello
North American Vaccine

Thomas Clarkson

University of Rochester

John Clements
World Health Organization

Richard Clover
Advisory Committee on Immunization Practices

Janice Cordell
National Institutes of Health

José Corderi

George Counts
National Institutes of Health

Dack Dalrymple
Bailey & Dalrymple, LLC

John Daugherty
National Institutes of Health

Robert S. Daum
VRBPAC

Christopher De Rosa
ATSDR

Carolyn Deal
Food and Drug Administration

Paul Dominowski
PFIZER, Inc.

Filip Dubovsky
National Institutes of Health

William Egan
Food and Drug Administration

Theodore Eickhoff
VRBPAC

Renata Engler
Walter Reed Army Medical Center

Jeffery Englhardt
Eli Lilly & Company

Elaine Esber
Food and Drug Administration

Geoffrey Evans
Health Resources and Services Administration

Lydia Falk
Food and Drug Administration

Michael Favorou
Centers for Disease Control

Theresa Finn
Food and Drug Administration

Alan Fix
University of Maryland School of Medicine

Jim Froeschle
Pasteur Mérieux Connaught

Maryann Gallagher
Food and Drug Administration

Antonia Geber
Food and Drug Administration

Michael Gerber
National Institutes of Health

T. W. Glickson

Karen Goldenthal
Food and Drug Administration

Jesse Goodman
Food and Drug Administration

Fernando Guerra
Advisory Committee on Immunization Practices

Ken Guito

Debra Hackett
SmithKline Beecham

Neal Halsey

John Hopkins University

Claire Hannan
Alabama Department of Health

Karen Hendricks
American Academy of Pediatrics

Thomas Hoffman
Food and Drug Administration

Susan Homire

Alan Horowitz
Institute for Safe Medication Practices

Barbara Howe
SmithKline Beecham

Deborah Jansen

Virginia Johnson
Food and Drug Administration

Rohit Katal

Samuel Katz
Infectious Diseases Society of America

Clare Khan
SmithKline Beecham

Edwin Kilbourne
Centers for Disease Control

Robert Kilgore
Marketing and Business Development

Kwang Sik Kim
VRBPAC

Jerome Klein
Boston University School of Medicine

Cynthia Kleppinger
Food and Drug Administration

Linda Lambert

National Institutes of Health

Len Lavenda
Pasteur Mérieux Connaught

Jack Love
Wyeth-Lederle Vaccines

George Lucier
National Institutes of Health

Kathryn Mahaffey
United States EPA

Laura Martin
Wyeth-AQyerts Pharmaceuticals

Dean Mason
National Immunization Program

Eric Mast
Centers for Disease Control

Alison Mawle
Centers for Disease Control

Joan May
Food and Drug Administration

Gerhard Mayer
Marketing and Business Development

Kent McClure
The Animal Health Institute

Pamela McInnes
National Immunization Program

Roberta McKee
Merck and Company, Inc.

Loris McVittie
Food and Drug Administration

Carlton Meschievitz
Pasteur Mérieux Connaught

Walter Orenstein
Centers for Disease Control

Peter Patriarca
Food and Drug Administration

Robert Pless

Stanley Plotkin, M.D.
Pasteur Mérieux Connaught

Alicia Postema
National Vaccine Program Office

Douglas Pratt
Food and Drug Administration

Regina Rabinovich
National Institutes of Health

William Raub
Department of Health and Human Services

Gopa Raychaudhuri
Food and Drug Administration

Martin Reers
Chiron Berhing

Margaret Rennels
ACIP

Barbara Reynolds

Paul Richman
Food and Drug Administration

John Risher

Patricia Rohan
Food and Drug Administration

David Ryan
CSL Research and Development Limited

Ronald Salerno
Merck and Company, Inc.

Edwin Schaart
Pasteur Mérieux Connaught

David H. Schofield
SmithKline Beecham

Ben Schwartz
National Immunization Program

Becky Sheets
Food and Drug Administration

Natalie Smith
CADHS

Rick Smith
Pasteur Mérieux Connaught

Dixie Snider
Centers for Disease Control

Mary Teeling
Ireland Medicines Board

Kirsten Vadheim
Merck and Company, Inc.

Paul Varughese
Health Canada

Peter Vigliarolo
Conney/Waters Group

Fred Vogel
Pasteur Mérieux Connaught

John Vose
Pasteur Mérieux Connaught

Luba Vujcic
Food and Drug Administration

Beth Waters
Cooney/Waters Group

Peggy Webster
National Coalition of Adult Immunization

David Wonnacott
Merck and Company, Inc.

Laura York
Wyeth-Lederle Vaccines

Adelle Young
Infectious Diseases Society of America

Robert Zeldin
Merck and Company, Inc.

Kathryn Zoon
Food and Drug Administration

1 Number one, Nancy Cherry and her staff have very
2 graciously agreed to help us with taxicabs. So those
3 of you who will be taking cabs to the airport directly
4 from the center here, if you would check with either
5 Nancy or one of her staff members out at the table,
6 either at the break or at lunchtime, they will be happy
7 to arrange a cab for you.

8 Secondly, Harry Greenberg clearly set the standard
9 yesterday by finishing up early. Those of you who
10 attend the ACIP meetings know that I also have an
11 obsession for staying on time and sticking to the
12 agenda. So I will warn today's speakers of that in
13 advance, and you all are so warned.

14 Yesterday we heard how this problem with thimerosal in
15 vaccines has developed. We learned more about mercury
16 toxicity from some very excellent background
17 presentations. Today the focus will be on where we go
18 from here. We don't have all the data that we'd like
19 to have. We still need to make some important
20 decisions in the near future, and this is certainly the
21 case for vaccine manufacturers, it's a case for the

1 FDA, it's a case for advisory committees, and we will
2 hear from representatives from all of these groups
3 today. We'll also hear from a representative, one of
4 our European colleagues, on how they have chosen to
5 deal with this issue.

6 So to begin with, I will introduce the first speaker
7 for today, who will be Dr. Chris Adlam. Dr. Adlam is
8 Associate Director of Regulatory Affairs at SmithKline
9 Beecham Biologicals, and he will be presenting the
10 manufacturing issues under the "Opportunities and
11 Challenges" section of this symposium.

12 Dr. Adlam?

13 **DR. ADLAM:** Well, good morning, ladies and gentlemen.
14 Thank you, Mr. Chairman, for that introduction.
15 What I should like to do today is to expand on some of
16 the points made by earlier speakers, with particular
17 reference to the manufacturing issues surrounding the
18 use of thimerosal in vaccines and, as Dr. Modlin
19 pointed out, moving a little bit to the future as to
20 where we might be going. So, as you see, Opportunities
21 and Challenges is the thrust of this part of the

1 meeting.

2 Thimerosal is used in two different areas in the
3 manufacturing process, and the first, which is the main
4 concern of this meeting, is, of course, its use in
5 final containers of vaccine as a preservative.

6 Now, the reason it is used in that situation is, of
7 course, to guard against contamination which might be
8 introduced during the filling process.

9 The second area, though, where it's still used is in
10 vaccine development; for example, where we need to
11 produce pilot batches of product for testing purposes,
12 or we may require to validate equipment, scale up
13 equipment, for example, but also, we still use
14 thimerosal in full-scale manufacturing processes for
15 some vaccines, and particularly where the method of
16 antigen purification, for example, might be complex,
17 and where manufacturing people may consider that there
18 would be potential risk for contamination if a
19 preservative wasn't present.

20 Now, historically, thimerosal has been used as a
21 blanket cover for most liquid-inactivated vaccines, but

1 as techniques have improved in manufacturing and the
2 concept of good manufacturing practices over the years
3 has come to the forefront, companies have reviewed
4 their use of thimerosal and, indeed, have come under
5 pressure from environmental agencies to reduce the
6 quantities of thimerosal that they use in their vaccine
7 manufacturing processes.

8 So why are preservatives still used in vaccines? We've
9 heard some of these points raised yesterday. As we've
10 heard, multi-dose containers, we have to have a
11 preservative there to guard against the potential
12 contamination when multiple punctures of a multi-dose
13 container are made.

14 I won't deal on point two very much because Dr.
15 Clements gave an excellent overview of the particular
16 problems faced by the international agencies. As we
17 have heard, they have particular problems, which, of
18 course, vaccine companies, most of whom these days are
19 international, have to address.

20 It's worth making the point, though, that if we have to
21 remove thimerosal for, if you like, developed country

1 markets, we still will have to make a second product
2 containing the preservative for multi-dose containers
3 in the international markets. So that is, of course,
4 an added cost to the industry.

5 Finally, and to my mind most important, is that
6 although quality of manufacture has greatly improved
7 over the last 20 years -- Good manufacturing practices
8 have, of course, improved out of sight since I first
9 joined the industry -- and the data and figures that
10 were shown in terms of numbers of filling lots that
11 were contaminated yesterday, these would of, course,
12 not be tolerated by today's standards. Nevertheless,
13 it has to be said that good manufacturing practice
14 remains pretty good but not 100 percent perfect.

15 And to expand on that just a little, it should be borne
16 in mind that today's vaccines, in contrast to those of
17 20 years ago, contain highly purified antigens and that
18 these products may go through very many stages in the
19 purification cycle. Sophisticated equipment, column
20 chromatography would be used, where as, of course, 20
21 years ago these techniques were just considered totally

1 unnecessary for vaccine manufacture.

2 As many as nine or ten bulks, different bulk antigens
3 would have to be stored. Aseptically -- They would
4 have to be blended together aseptically to make a
5 modern multi-component combination vaccine.

6 Elimination of preservatives then, even from mono-dose
7 vaccine presentations, is a serious step, and the
8 appropriate tests and validations have to be done to
9 make sure that the resulting vaccine remains safe and
10 efficacious.

11 Why thimerosal? Many people have said, as we've heard,
12 it's been around a long time, and the industry is very
13 used to using it. Up to now, the only concern with
14 this material has been down to the occasional
15 hypersensitivity reaction, which is seen, but I think
16 it's worth saying that in contrast to the use of
17 topical pharmaceuticals containing mercury, where, as
18 we've heard yesterday, sensitizations may occur, this
19 is a very rare event in injectable vaccines containing
20 thimerosal.

21 We have numbers within our company of reports of this

1 type of sensitization which run somewhere between 1 and
2 3 million doses administered and 1 in 20 million doses
3 administered. So we're talking of a very rare event,
4 and the majority of those cases are not life-
5 threatening sensitizations.

6 And secondly, of course, as we heard yesterday again,
7 thimerosal is a very potent substance and does its job
8 extremely well. And we heard about the spiking
9 experiments that companies have to do with all new
10 vaccines to prove that the preservative in the
11 container does the job that it's supposed to do in
12 knocking back potential contaminating organisms.

13 So what are the alternatives open to the industry as we
14 move away from the age of thimerosal? Of course, the
15 first option is to eliminate even from mono-dose
16 vaccines -- we can't do it for multi-dose, but we could
17 eliminate from mono-dose vaccines all preservatives and
18 to rely on good manufacturing practices.

19 This is a laudable objective, and it may be, indeed,
20 possible for some products and some processes, and it
21 certainly is a road down which the FDA is pushing the

1 companies. However, as I've stated already, we should
2 maintain caution when we do this, if indeed we're not
3 to replace one set of problems with another.

4 And the second option, which I have to say is the one
5 we as a company have taken so far, is to use an
6 alternative to thimerosal as the preservative in the
7 vaccine. Now, if you talk to manufacturing people,
8 it's clear that they always prefer to maintain a
9 preservative in their vaccine box and vaccine
10 presentations, for obvious reasons.

11 This slide just lists the vaccines produced by
12 SmithKline Beecham Biologicals and which are
13 commercialized in the U.S. together with their
14 preservatives. And as you can see, only the earliest
15 licensed product, which is the hepatitis B vaccine
16 licensed back in -- launched in 1989, contains
17 thimerosal. And since that time, it has been a
18 decision within the company to move away from
19 thimerosal and to use the alternative 2-phenoxyethanol.

20 And as we heard, again, a little bit on this substance
21 yesterday, it has an excellent safety record and is

1 pretty good as a preservative.

2 The second point I'd like to make from this slide is
3 that there has been a conscious effort on behalf of the
4 industry to move to combination products containing
5 many antigens. And, of course, the more we can do
6 that, the fewer injections that will need to be given
7 to the children, and, of course, the less the amount of
8 preservative that will have to be given. So this is, I
9 think, if you like, an opportunity there and also a
10 challenge to develop this kind of product.

11 Now, as far as the vaccines that are commercialized
12 which contain thimerosal, as we heard, companies have
13 been approached by the agencies and are in discussion
14 with agencies, both in the U.S. and in Europe, as to
15 what their plans are for reducing or eliminating
16 thimerosal. And like other companies, I would guess,
17 we have submitted our plans for removing thimerosal as
18 a preservative from this vaccine.

19 So to conclude this brief résumé and by returning a
20 little bit to the title of this part of the talk,
21 "Opportunities and Challenges," as I've said, I think

1 one of the first opportunities and challenges, if you
2 like, lies in the continued development of new multi-
3 component products, which, of course, will result in
4 fewer injections that need to be given, which, as we're
5 all aware, is a good thing.

6 The second challenge, I think -- And this is a
7 challenge for both the industry and the regulators --
8 would be: how can we speed up the production of good
9 solid dossiers to support these changes and how can we
10 get them through the agency review period in as short a
11 time as possible? And I think we're all exercising our
12 minds along those particular areas, as I said, in
13 discussions with various agencies on this particular
14 topic.

15 And thirdly and finally, of course, all of objectives -
16 - our main objective is to continue to improve the
17 efficacy and the safety of all of our vaccines.

18 So I think I'd like just to leave it there, Mr.
19 Chairman, and if there are questions, either take them
20 now or at the end of this section.

21 Thank you.

1 (APPLAUSE)

2 **DR. MODLIN:** We certainly have time for questions for
3 Dr. Adlam. Are there? Yes, Dr. Egan?

4 **DR. EGAN:** You touched on the use --

5 **DR. MODLIN:** If you would just identify yourself for
6 the --

7 **DR. EGAN:** Bill Egan from Office of Vaccines, CBER.
8 You commented on possibly -- about the use of
9 preservative even in a single-dose vials. Could you
10 expand a little bit on what you feel is the need or the
11 advisability of having preservatives in them and what
12 kind of levels? Thank you.

13 **DR. ADLAM:** Thank you. This is, of course, a little
14 bit of a contentious issue. I think we would all like
15 to be able to say that we can remove all preservatives
16 from mono-dose containers, and this is -- as I said,
17 they are laudable objective to try to achieve. My only
18 caveat to that is, as I say, I think we have to very
19 careful that it can be achieved. I mean, as you're
20 well aware, all companies will submit media fill
21 control data to the agency. These -- This information

1 is out there. We can look at it and we can see whether
2 we are yet in a position to totally remove all
3 preservatives from the vaccine. In terms of quantity,
4 we use the standard quantities of 2-phenoxyethanol in
5 these more recent products.

6 It's a point for debate. We could discuss that, I
7 think, the advisability of dropping it out, keeping it
8 in, but it's something which we should be, in my view,
9 careful -- It should be approached carefully on a case-
10 by-case basis.

11 **DR. CLEMENTS:** Thank you. John Clements, WHO, Geneva.
12 I thank you for bringing the issue of combination
13 vaccines up. WHO is firmly in favor of developing
14 strategies which will enable developing countries to
15 use combination vaccines for the sorts of reasons
16 you've identified.

17 My question is: What opportunities do you think
18 developing countries will have for producing
19 combination vaccines, bearing in mind their desire so
20 often to have local production? What are your ideas on
21 the possibility of technology transfer and local

1 filling, for instance?

2 **DR. ADLAM:** Well, what I can say is that we, as a
3 company, are involved already in discussions on
4 technology transfer in certain areas of the world, and
5 I think this is an area that will continue to expand.
6 I mean, there is no question that putting a combination
7 vaccine together is not just a straightforward mixing
8 of antigens and away you go. I mean, as we're well
9 aware, it's a lot more complex than that, and there are
10 interactions between antigens. We have to confirm that
11 the combinations are compatible with each other and
12 that there is no enhancement in the -- no enhancing the
13 problems associated with safety which could result.
14 And so there's a lot of work to be done, which, in a
15 developing country context, is quite a significant
16 task. But as far as technology transfer, I don't think
17 any of the companies are against that kind of
18 arrangement.

19 **DR. MODLIN:** Further questions?

20 **DR. BRIDGES:** Carolyn Bridges, CDC.

21 Are there any special issues for producing

1 preservative-free single-dose vaccines for vaccines
2 produced in eggs or viruses grown in eggs?

3 **DR. ADLAM:** Yeah. That would be one example that I
4 would look at. If you think about it, what you're
5 doing when you make an inactivated influenza vaccine is
6 to process and purify your influenza antigen from eggs,
7 as you say, from embryonated eggs. Now, that is a
8 whole lot of very rich protein that you have around,
9 plus the fact can you be sure that each one of those
10 eggs does not carry a contaminate of one sort or
11 another. We know, for example, that hens' eggs in the
12 outside world -- Of course, we don't use farmyard eggs
13 to make these vaccines, okay?

14 But, nevertheless, the theoretical possibility is still
15 there that you may have the odd egg with the odd
16 contaminate. Okay? And if you have that, then you
17 have to have something in your system to prevent that
18 becoming a real problem in the final vaccine.

19 So I think that's an excellent example along the lines
20 of the ones that I was -- the protein there, and there
21 may be others.

1 **DR. MODLIN:** Dr. Daum?

2 **DR. DAUM:** I'm Robert Daum from the University of
3 Chicago.

4 I'd like to make a comment and hear your response to
5 it. It seems to me that no matter what strategy is
6 involved from these considerations, whether it's better
7 reliance on PMP or identification of an alternative
8 preservative, that we're going to be giving what
9 results from this new policy to millions and millions
10 of people. Therefore, with a hopefully very low rate,
11 problems are going to occur if it's good medical
12 practice. As you pointed out in your slide, it's not
13 100 percent. There's going to be instances of
14 contamination. I'm certain of that. If it's a new
15 preservative and we give it to millions and millions of
16 people, someone somewhere will have a reaction to it,
17 and it will happen and we'll gather at workshops like
18 this to discuss what to do about that.

19 It seems to me that no matter how try to minimize this
20 problem -- nd minimize it we must because it's not
21 acceptable to have an overly reactive (inaudible) --

1 we're never going to get it to zero. I wonder -- We
2 live in an era now of numerator amplification where one
3 side (inaudible), it instantly becomes -- CNN helps do
4 that and some of our support groups help do that. It
5 just becomes instantly news all over the place.

6 I wonder if the proper way to think about this is to
7 just realize that we're not going to ever solve this
8 problem with taking the side effect or toxicity rates
9 to zero. We're going to pick the method to get it as
10 low as we possible can and then also have an education
11 campaign that says, you know, there's no free lunch in
12 this world. We have a wonderful preventative strategy
13 here, we're offering it to all children, and in the
14 end, like any medical intervention, there are rare
15 occasional problems.

16 I don't -- I don't know that we've really come to grips
17 with accepting that there will be residual benefits and
18 really focusing on it as an educational intervention or
19 alternative. I'm not meaning to belittle the
20 importance of toxicity here, but it just seems to me
21 the rate isn't ever going to be zero.

1 **DR. ADLAM:** No. I think we would -- in this room, we
2 would all agree with that. I mean, as you say, there
3 isn't one single medicament that's out there that's
4 going to be completely safe and free. I mean, if you
5 drink 15 liters of water, you're probably going to die,
6 you know? So that's a philosophical discussion. I
7 think what it does raise -- excuse me, Dr. Modlin --
8 What it does raise, though, is the important issues of
9 communication, and I see on the agenda that we have
10 somebody that will be addressing that. But I think
11 that's obviously a key portion so that the right
12 messages are given so that the general public is
13 properly advised and knows, if you like, what the risks
14 and benefits are for all of these procedures.

15 **DR. SNIDER:** Dixie Snider, CDC. Actually, two
16 questions.
17 First, if I understood you correctly, and I'd like to
18 know if I did understand correctly, that combination
19 vaccines present us with both a plus and a minus in
20 terms of a preservative, that is, that you would have
21 to give a smaller amount of -- per antigen that you

1 were using, but because of the complexity of the
2 manufacturing process, it might be more important to
3 include a preservative when making a combination
4 vaccine.

5 And secondly, assuming at least from SmithKline
6 Beecham's standpoint, that preservative is 2-
7 phenoxyethanol. Are there any concerns about that?
8 Since your company has started to move in that
9 direction, have there been any concerns about reactions
10 or long-term toxicity and so forth from any
11 toxicologists or others you might have consulted?

12 **DR. ADLAM:** The first question was regarding the
13 combinations, and I think you're right there.

14 Obviously, the more complex the manufacturing process
15 is, the more pressure there would be, I would say, to
16 include some kind of preservative in the vaccine. So I
17 think that analysis that you made there is correct.

18 In terms of 2-phenoxyethanol, it is fairly widely used,
19 not just by us, but by others and in the pharmaceutical
20 arena. It has a pretty clean tox profile as a
21 material, and it's fairly effective at doing its job.

1 Of course, we don't yet have 60 years experience with
2 it -- That's a given -- but it's -- it looks to be very
3 effective, and it is accepted by the agencies involved
4 with preservatives.

5 **DR. SCHWARTZ:** John Schwartz from CDC.

6 I also wanted to focus on your use of 2-phenoxyethanol.

7 Yesterday we heard from a couple of the speakers, when
8 looking at the in vitro tests with the USP agents that
9 it performed less well than thimerosal. So I was
10 wondering what type of testing has been done
11 specifically that suggests that it's adequate as a
12 preservative, and your company clearly has made a
13 decision that it, indeed, is adequate to accomplish
14 that particular function.

15 With respect to the adverse -- the potential adverse
16 reactions, you spoke in very general terms about what's
17 known, but I think one of the things that we've learned
18 from thimerosal is that even in a product that has been
19 used for 60 years that there hasn't been a lot of
20 research about its use. So I would expand on Dixie's
21 question and say, well, if the safety profile, quote,

1 "looks good," what research has actually been done and
2 are there areas? Are there gaps where we need to look
3 further to get a better understanding of potential
4 toxicity?

5 **DR. ADLAM:** Okay. An answer to the first point, the 2-
6 phenoxyethanol as all other preservatives, in fact, it
7 seems does satisfy the -- for example, the USP
8 regulations surrounding the use of preservatives in
9 vaccines.

10 It's true that as I said we don't have 60 years'
11 experience with this material. There have been studies
12 done. There is a literature on 2-phenoxyethanol. It's
13 probably outside the -- you know, without having
14 another symposium on 2-phenoxyethanol. Nevertheless,
15 there's a significant body of information. But you're
16 quite right, we don't have 60 years experience with
17 this material.

18 As far a thimerosal is concerned, I think that the fact
19 that 60 years has gone by with it being used as a -- as
20 a useful product has probably meant that people haven't
21 spent a great deal of time going back over the old

1 data, which is what we heard yesterday.

2 Now, this meeting and recent -- recent interest --
3 resurgence of interest in the topic may stimulate some
4 of this research, and I guess that's going to be a
5 situation to be discussed in this afternoon's session
6 as to where we go with thimerosal, 2-phenoxyethanol,
7 and maybe future alternative preservatives.

8 **DR. MODLIN:** Last question. Dr. Klein?

9 **DR. KLEIN:** Jerry Klein, Boston University.

10 The statements of the Academy of Pediatrics and the CDC
11 about thimerosal are to eliminate or reduce use, and
12 I'd like to focus on the second part of that phrase.
13 By reduce, my interpretation is that the number of
14 products that are thimerosal-containing will be
15 diminished. But is it feasible to take some of the
16 products that have thimerosal and reduce the
17 concentration such that it might be more acceptable in
18 terms of the theoretical toxicity?

19 **DR. ADLAM:** That is one option that could be taken.

20 You could say, well, we have X amount of thimerosal in
21 this product, can we reduce it by half and still have a

1 safe effective product? I mean, I think those -- or
2 couldn't we eliminate it completely? Can we
3 substitute? These are the kinds of debates that are
4 being held now with the agency in this particular area
5 for particular products, and, you know, the discussions
6 continue, and there will be, you know, discussions
7 along what will be needed to show that your product is
8 still efficacious if we remove or we reduce thimerosal,
9 and goes -- Those questions have to be addressed on a
10 case-by-case basis and data has -- will have to be
11 supplied.

12 **DR. MODLIN:** Thank you, Dr. Adlam.

13 And that's nice headway to the introduction of our next
14 speaker who is Dr. Norman Baylor. Dr. Baylor is the
15 Associate Director for Regulatory Policy for CBER at
16 the Food and Drug Administration.

17 Dr. Baylor?

18 **DR. BAYLOR:** Good morning. Today I'm going to discuss
19 some of the regulatory issues involved in reducing and
20 eliminating thimerosal in vaccines.

21 Before I begin, I would like to emphasize a few points.

1 As stated yesterday by Dr. Egan, the FDA has not
2 banned the use of thimerosal as a preservative in
3 vaccines. Secondly, there's no evidence -- no evidence
4 has been presented that would suggest that the amount
5 of thimerosal in individual vaccines is unsafe.

6 Lastly, our goal or objective is to assist in
7 decreasing the exposure of humans to mercury-containing
8 compounds by reducing or eliminating, where feasible,
9 thimerosal from vaccines, and this is also stated or an
10 objective of the Food and Drug Administration
11 Modernization Act of 1997.

12 Basically, the regulatory issues involved in reducing
13 and eliminating thimerosal from vaccines is no
14 different than the regulatory concerns of making any
15 other manufacturing change to a vaccine. I think the
16 issue here is, what are the implications involved in
17 removing thimerosal at this time and also for reducing
18 the amount of thimerosal.

19 The options that we have, there are basically three
20 that we can choose from. I think Dr. Adlam touched on
21 these.

1 The first is to eliminate the use of thimerosal as a
2 preservative in vaccines -- That gets into the issue of
3 single-dose vials versus multiple-dose vials, and I'll
4 touch on that a little bit further in a minute -- or we
5 can substitute alternative preservatives for
6 thimerosal, and the third option is to reduce the
7 amount of thimerosal in vaccines. This option, the
8 last option, will involve using criteria other than
9 those outlined in the U.S. Pharmacopeia.

10 However, there's another option which I did not list on
11 my slide -- on the slide, and that option is to
12 continue to use the current concentration of thimerosal
13 in vaccines, albeit, at this time, this would require a
14 justification from the manufacturers to the Agency as
15 to why they felt it's necessary to continue the use of
16 thimerosal in its present concentration in a given
17 vaccine.

18 For all of these options, the regulatory requirements
19 will differ slightly for each of these. As Dr. Egan
20 mentioned in his talk yesterday, there are no
21 regulatory requirements to include a preservative in a

1 vaccine contained within a single dose or a single-dose
2 vial. However, vaccines that are filled in multiple-
3 dose vials do require, by regulation, the use of a
4 preservative with the exception of some live viral
5 vaccines. The elimination of thimerosal from multiple-
6 dose vials will require the exclusive use of single-
7 dose vials or the replacement of thimerosal with an
8 alternative preservative.

9 If we begin with the assumption that manufacturers will
10 continue to use multiple-dose vials for vaccines, then
11 we must assume that thimerosal will either be replaced
12 or the amount used will be reduced as I stated in my
13 outline earlier in the options. Let us begin with the
14 substitution of an alternative compound for thimerosal.
15 One must first determine where in the manufacturing
16 process the thimerosal is used, and I think Dr. Adlam
17 also touched on this. thimerosal may be used as a
18 bacteriostatic agent in the production process. So in
19 processing the various steps involved in manufacturing
20 may require the use of some type of preservative, and
21 in this case, perhaps thimerosal as a bacteriostatic

1 agent. This is the case with some of the influenza
2 vaccines. The use of thimerosal may also be used as an
3 inactivating agent, and an example of that would be
4 whole cell pertussis vaccine.

5 Then thimerosal is also, as we all know and why we're
6 here, is used as a preservative and that preservative
7 may be in bulk/final containment or it be in the
8 diluent.

9 In other words, the replacement of thimerosal with an
10 alternative compound will depend on how and where the
11 thimerosal is used in the manufacturing process. In
12 turn, the regulatory requirements for substituting an
13 alternative compound for thimerosal will depend upon
14 whether the compound is used solely as a preservative
15 or as a bacteriostatic agent for in-process
16 manufacturing or as an inactivating agent.

17 Now, looking at the regulatory -- further into the
18 regulatory requirements, I think it's necessary to
19 explain a little bit about how the regulatory process
20 works. The regulatory reporting category for a
21 manufacturing change will depend upon whether the

1 substitution of thimerosal results in a complete
2 formulation change in the final product or whether the
3 removal or substitution of thimerosal is, for example,
4 only for a buffer used to reconstitute a vaccine. So
5 the reporting categories will be different. We have
6 what is known as a prior approval supplement. The
7 prior approval manufacturing supplement has a maximum
8 review time, and emphasizing the review time, of six
9 months, although we have a target of reviewing a
10 percentage of those in four months. Then the other
11 extreme is a minor manufacturing change where you could
12 have distribution of that product containing that
13 change within thirty days or after a thirty-day period
14 if the Agency -- if the manufacturer does not hear from
15 the Agency that there are problems.

16 So what I'm getting at here is depending on the type of
17 change, that removing this thimerosal from the product,
18 depending on where you remove it, it will dictate how
19 much or how long the review time will be. In other
20 words, if it's a new formulation, that's a full prior
21 approval supplement. Whereas, if your formulation does

1 not contain thimerosal and you are only adding the
2 thimerosal to a buffer that's to be used to
3 reconstitute the vaccine, that may be a lesser change
4 that will require less time.

5 So prior approval supplement versus changes being
6 effected in thirty days, the timing on

7 the -- depending on where and how the thimerosal is used
8 will dictate the review time.

9 Preclinical data may be necessary for some of these
10 changes, including reproductive and toxicological
11 studies on new compounds, compounds that we have no
12 experience with, may require repro/tox studies. Data
13 on the compatibility of the new compound with other
14 components in the vaccine will definitely be required,
15 but depending on where in the process, the amount of
16 data, again, will be dictated by that.

17 Of course, validation of the bacteriostatic and
18 bacteriocidal type of properties of the new compound,
19 as well as inhibition of yeast and fungi will have to
20 be -- data will have to be submitted to support the use
21 of the new or alternative preservative.

1 In addition, batch analysis of consistency lots will be
2 required to be submitted to support a change of
3 removing thimerosal. Stability data will also be
4 required and, preferably, we require real-time
5 stability data for those submissions. Again, all of
6 this we're going to try to work with the companies to
7 work out the amount of data that's needed and what's
8 available from the manufacturers. Stability data would
9 also be required when you're changing from a multi-dose
10 vial to a single-dose vial or syringe.

11 Also, human clinical data may be necessary if the
12 result of the substitution of a new compound for
13 thimerosal results in a new formulation or a new
14 product. In some of our old products, we can see where
15 that product may change significantly. We may require
16 human clinical data. Now, the amount of the human
17 clinical data, again, we would have to work with the
18 manufacturers in designing protocols to decide how much
19 of this would be necessary.

20 Now, in some cases, thimerosal may not be easily
21 replaced by an alternative preservative. An option

1 would be to reduce the amount of thimerosal in a
2 vaccine, especially if exclusive production of single-
3 dose vials is not an option.

4 But, basically, the regulatory requirements for
5 reducing the amount of thimerosal are the same as those
6 for substituting an alternative preservative. However,
7 most important here is the validation of the inhibition
8 of microorganisms using the reduced concentration of
9 thimerosal, as well as stability data supporting the
10 desired shelf life of the final product. Now, some of
11 the options we could take here is by -- Well, let me
12 back up.

13 Most importantly, as I stated, the manufacturers would
14 have to validate the reduced amount of thimerosal has a
15 given effect, i.e., bacteriostatic/bacteriocidal, on --
16 with the given preservative. Now, those would not meet
17 the USP requirements, but as stated yesterday, we're
18 not really bound by the USP requirements. The USP
19 requirements are accepted, but we would work with the
20 manufacturer to -- and look at the validation data, and
21 what we may come -- we may come to a point where we

1 would reduce the shelf life on that product. So if you
2 had a thirty-month dating period and you could validate
3 -- you could substitute or reduce the amount of
4 thimerosal and shorten that dating period, that would
5 be an option also.

6 So, in summary, the regulatory requirements for the
7 elimination, substitution, or reduction of thimerosal
8 in vaccines must be determined for each individual
9 vaccine on a case-by-case basis. The FDA has
10 recommended that each manufacturer discuss with the
11 Agency how they intend to address the issue of
12 thimerosal used in all of their vaccines prior to
13 submitting supplements to the Agency for review and the
14 FDA is committed to expediting the review of these
15 submissions.

16 Thank you.

17 (APPLAUSE)

18 **DR. MODLIN:** Questions for Dr. Baylor?

19 **DR. ABRAMSON:** Jon Abramson from the American Academy
20 of Pediatrics. It would seem to me that scientifically
21 what had to happen prior to all of this is that as for

1 each vaccine you were figuring out how much thimerosal
2 was needed that there is data on the lower side of what
3 was finally put in there that would tell us that. I
4 mean, I can't believe that people would pick a number
5 and did the studies just with that concentration and
6 didn't do (inaudible) factors.

7 **DR. BAYLOR:** I think you have to estimate -- I think
8 what we're -- When we receive the data, we're looking
9 at -- we've going to evaluate that data on the safety
10 and efficacy of that vaccine. So looking at the amount
11 of thimerosal and -- Again, some of these products were
12 licensed decades ago and the review was somewhat
13 different, but, even then, there was concern about the
14 toxicity of these compounds. So we did look at that in
15 the whole package, but I think also that you have to --
16 the point that was made yesterday about the
17 requirements in the United States versus Europe, some
18 of those requirements, some of the Pharmacopeia
19 requirements in Europe are higher. And looking at what
20 the manufacturers are going through, producing multiple
21 formulations for the world or taking the option of

1 producing one formulation and that formulation happens
2 to have a slightly higher amount of thimerosal than
3 needed for the U.S. or to be the beat the USP, as long
4 as it's safe and effective, we're going to -- we're not
5 going to disapprove that vaccine, but, you know, we are
6 going to look at the toxicity. I think the bar is much
7 higher now than it was when some of these old vaccines
8 were approved.

9 **DR. MODLIN:** Dr. Gellen?

10 **DR. GELLEN:** I have two questions. The first one --

11 **DR. MODLIN:** Could you just introduce yourself?

12 **DR. GELLEN:** I'm Bruce Gellen from the Infectious
13 Disease Society.

14 There may not be a blanket answer to this, but when you
15 have -- when you use thimerosal in the process, does it
16 necessarily stay in the end product?

17 **DR. BAYLOR:** No. So it can be removed.

18 **DR. GELLEN:** Okay. And my second question, you were
19 quite careful in your introductory remarks about -- I
20 may have not quoted this perfectly, but you said
21 there's no evidence presented that thimerosal in

1 individual vaccines is unsafe. You were cautious to
2 talk about individual vaccines. Do you -- Is there a
3 stance about the vaccination process, that there's a
4 feeling that as given currently that there's evidence
5 presented that thimerosal content overall in infants is
6 unsafe?

7 **DR. BAYLOR:** No. And what I was trying -- The point I
8 was trying to get out there is that this issue that
9 we're dealing with today and that we've been dealing
10 with revolves around the cumulative amount of
11 thimerosal, a mercury-containing compound, to
12 individuals receiving several vaccines, but if you look
13 at the vaccines individually, there are no -- whether
14 you look at EPA or FDA, there are no levels that are
15 exceeded on those vaccines. The issue comes about when
16 you administer a number of the vaccines, for instance,
17 when a child receives all the recommended vaccines on
18 time within the first six months. That's really the
19 issue we're dealing with. We're not really dealing
20 with -- I don't know if there's -- We, as an agency,
21 don't have concerns that there's something -- there's

1 an amount of a compound in these products that are
2 unsafe. It's the cumulative receipt.

3 **DR. MODLIN:** Dr. Myers?

4 **DR. MYERS:** Martin Myers, NVPO. I'd like to ask a
5 question about the regulation to require a preservative
6 in multi-dose vials. Dr. Egan made the point yesterday
7 and you made it again today that we have multi-dose
8 vials of vaccines that do not contain preservative,
9 measles/mumps/rubella being perhaps the most obvious
10 example that a preservative would inactivate the
11 vaccine, but we do license that as a multi-dose vial
12 with no preservatives in it.

13 So is it another alternative for the manufacturer to
14 consider the multi-dose vial without a preservative
15 that has a very short shelf life after being entered
16 the first time?

17 **DR. BAYLOR:** Okay. Basically, the answer is, since we
18 have the current regulations, no. However, that is a
19 possibility if the manufacturers can validate that they
20 can actually make or produce a multi-dose vial without
21 a preservative and validate that that product would not

1 -- or would maintain its integrity as far as absence of
2 contamination. We could consider that. However, the
3 only way to consider that at this time is to eliminate
4 that regulation. As long as the regulation is on the
5 books, we have to have -- we have to require that, but
6 that's not something that can't be done. We've
7 eliminated regulations before. So . . .

8 **DR. MODLIN:** Yes, Dr. Horowitz?

9 **DR. HOROWITZ:** Yes, Alan Horowitz from the Institute
10 for Safe Medication Practices.

11 As an entity that works in collaboration with USP
12 receiving medication errors, which, of course, we
13 forward to FDA as a med watch partner, over the years
14 we've received numerous incidences of adverse drug
15 events related to multi-dose vaccines, confusion with
16 (inaudible), cross-contamination up to, in one
17 incident, 468 patients. You had mentioned four
18 different alternatives that the Agency may do if I
19 understood your presentation. It seems to me that with
20 the sole exception of moving into a single-dose,
21 essentially a unit dose, those same problems that are

1 reported to us and that have been reported to us are
2 likely to occur.

3 Having said that, do you foresee any agency activity in
4 terms of mandating the single-dose vials?

5 **DR. BAYLOR:** Mandating the single-dose vials --

6 **DR. HOROWITZ:** As opposed to reducing the amount of
7 thimerosal or seeking an alternative?

8 **DR. BAYLOR:** At this time, we are not considering
9 mandating single-dose vials. To do that has a number
10 of implications and we feel that basically the -- with
11 the multi-dose vials in their current state, they're
12 safe. I mean, the manufacturers have validated that
13 with using the current preservatives in those products.

14 They maintain their integrity.

15 See, the complicated part here is we have no question
16 that the manufacturer can produce a vaccine in a multi-
17 dose vial or single-dose vial or any kind of vial
18 that's going to be sterile. The issue is when you get
19 out in the field. And we don't know if everyone is
20 practicing aseptic techniques. That's something we
21 can't control as an agency, but by requiring -- I mean,

1 that's part of the rationale for requiring
2 preservatives in multi-dose vials. We're trying to
3 address that issue, but we'll never be able to address
4 that issue across the board because we just can't -- we
5 cannot police aseptic techniques in the field.

6 **DR. HOROWITZ:** Thank you.

7 **DR. ENGLER:** I was just wondering, in the options that
8 have been discussed -- Dr. Engler from Walter Reed. I
9 was just wondering in the options why there's no
10 consideration of leaving the concentration of
11 thimerosal the same, but increasing the concentration
12 of the active antigen and giving a smaller dose, which
13 would also reduce the pain of the injection, facilitate
14 jet injector technology development, and would
15 potentially be a win/win. The half cc comes from the
16 era when syringes did not have small enough markings
17 and you couldn't readily measure more than a half cc.
18 From a clinical perspective, it seems we might move to
19 a new era considering we have tuberculin syringes.

20 **DR. BAYLOR:** I think that's a viable option. I mean,
21 again, it would have to be validated and if the data

1 supports it, I don't see why that -- you know, we would
2 definitely consider it.

3 **DR. MODLIN:** Dr. Daum?

4 **DR. DAUM:** Bob Daum from the University of Chicago. I
5 may have missed something in the logic here and I just
6 need to clear --

7 **DR. MODLIN:** Bob, I think your mic may not be on. Do
8 you want to just press the button that says "Request to
9 Speak." That may help.

10 **DR. DAUM:** How's that? Sorry about that.

11 I may have missed something, but I think you said at
12 the beginning that the FDA is committed to decreasing
13 or eliminating thimerosal from vaccines, and I'm just
14 sort of wondering, having listened to the discussion
15 now, whether the FDA has considered not doing that,
16 leaving the thimerosal situation as it is. And if the
17 answer is "no," exactly which piece of evidence are you
18 relying on to come to the conclusion that something
19 must be done?

20 **DR. BAYLOR:** Well, I did present a fourth option. I
21 did not rule that option out.

1 **DR. DAUM:** But is the Agency committed to asking
2 manufacturers to do something about thimerosal or is
3 the Agency just having discussion at this point?

4 **DR. BAYLOR:** The Agency is committed in asking the
5 manufacturers what are they doing to address thimerosal
6 in vaccines. We sent out a letter this summer to all
7 vaccine manufacturers asking them to address this
8 issue. Again, our objective is to -- It's just like
9 anything. Our objective is to remove or to decrease
10 the exposure of humans to mercury. Thimerosal is a
11 mercury-containing compound.

12 So if that's feasible, and I did use that word in my
13 discussion, then we want to -- we want a dialogue with
14 the manufacturers to find out if that can be done.

15 **DR. DAUM:** But what comes with that statement, doesn't
16 it, an implication that that exposure is -- the
17 exposure to this kind of mercury compound is harmful?

18 **DR. BAYLOR:** No, it doesn't. But it says that -- I
19 mean, any -- If we lived in a perfect world, none of us
20 would want to be exposed to mercury. So if we have an
21 opportunity to decrease our exposure to mercury or any

1 other harmful chemical, we would do it. So we would
2 like to know from the manufacturers what are they doing
3 to address this issue. Can they address this issue?
4 We have not issued any mandates at this time and this
5 was not the purpose of (inaudible) in Section 413. It
6 was not to issue any kind of mandate. It was
7 exploratory.

8 **DR. KIM:** Kwang Sik Kim, Los Angeles. You indicated
9 that preservatives must have about bacteriostatic and
10 bacteriocidal activities, and the question to you is
11 that: Does FDA have any specific guidelines how to do
12 those assays? For example, if the compounds are being
13 tested with let's say bacteria of 10^3 instead of
14 traditional 10^5 , is this sort of acceptable? That may
15 be the way to reduce the concentration of
16 preservatives.

17 **DR. BAYLOR:** Again, as I stated, that's going to have
18 to be validated. If the manufacturers want to go that
19 route, they will have to validate -- I think the
20 guidance is in the USP. You can start with that and
21 then go back, but you have to validate the amount of

1 preservative that you're going to use. In that
2 validation, what are the inhibitory properties
3 resulting from a reduced amount of preservative? And
4 then we, as an Agency, will decide whether that's
5 acceptable or not. In that decision, we may say, well,
6 we need to cut your -- based on the data that you've
7 accumulated, we need to cut your shelf life in half, or
8 whatever.

9 **DR. MODLIN:** Dr. Plotkin?

10 **DR. PLOTKIN:** My question is not philosophical, but,
11 specifically --

12 **DR. MODLIN:** Stan, I'm sorry. Please --

13 **DR. PLOTKIN:** Plotkin, consultant, PMC.

14 My question specifically is, if thimerosal is taken out
15 of a vaccine, I believe what you said is that stability
16 studies would be required because you've taken out the
17 preservative, although I'm not sure that affects the
18 stability, but you would require stability studies --

19 **DR. BAYLOR:** But -- I'm sorry. Go ahead.

20 **DR. PLOTKIN:** -- and my question is, would you require
21 clinical studies as well, in other words, to show that

1 the material is still immunogenic and safe?

2 **DR. BAYLOR:** Again, depending on where that
3 preservative is used will dictate whether we will --

4 **DR. PLOTKIN:** As a preservative?

5 **DR. BAYLOR:** As a preservative. As a -- Your question
6 is, as a preservative?

7 **DR. PLOTKIN:** Yes.

8 **DR. BAYLOR:** Well, if your preservative is in the final
9 formulation versus, say, you've made your final
10 formulation and you have in your diluent, we may not
11 require clinical data, but if it's in your final
12 formulation, we may require clinical data because your
13 final formulation has changed. But, again, that
14 statement does not go across the board about products.

15 We have to look at the individual product that you're
16 speaking of and determine it from there, determine how
17 you're adding -- or where the thimerosal is and the
18 parameters that are involved in incorporating that into
19 your final product. I mean, another example is you may
20 have the -- you may have a preservative in your bulk
21 and decide to leave that in, but as you're doing your

1 final fill, you may remove that from your bulk at the
2 time of final fill and demonstrate that it's at a level
3 of -- or below the level of detection.

4 **DR. MODLIN:** Yes, Dr. Clements?

5 **DR. CLEMENTS:** Thank you. I'd like to come back to a
6 question that Dr. Myers has just made about multiple-
7 dose MMR vaccines, and I really offer this as a
8 comment.

9 I'm concerned that the meeting may be under a
10 misapprehension about such vaccine vials. At WHO, we
11 encourage countries to use the measles vaccine, which
12 is a multi-dose, ten-dose vial, but once the vaccine is
13 reconstituted, then it has -- we give strict training
14 that this vaccine must be discarded up to six hours
15 from the start of reconstitution and failure to do that
16 has, in many, many instances, resulted in
17 contamination, overgrowth of staph, and what is known
18 as the toxic shock syndrome. The tragedies that result
19 from that are the deaths of multiple -- two, three, or
20 six children at a time from overgrowth of staph in the
21 vaccine.

1 So I would caution the enthusiastic procedure of multi-
2 dose MMR vaccines.

3 **DR. MODLIN:** As well as lost potency, which is a little
4 bit different issue than it is with perhaps some other
5 vaccines.

6 **DR. BAYLOR:** Right.

7 **DR. MODLIN:** This is an important line of questioning.
8 Are there others? Dr. Egan?

9 **DR. EGAN:** I would just like to make a very quick
10 comment on the MMR vaccine itself.

11 First of all, it's a freeze-dried preparation. It does
12 contain some neomycin, a preservative, and perhaps the
13 representative from Merck can correct me, I believe the
14 package insert says that it must be utilized within
15 eight hours of reconstitution. So it's similar to the
16 WHO. I think it's eight and not six.

17 **MR. GUITO:** Ken Guito from Pasteur Merieux Connaught.
18 I appreciate your attempts to try and shed some light
19 on this challenging situation. If I can go back to
20 your option four, if I might, and expand on your
21 comments and Dr. Daum's comments.

1 You see a potential for, I guess, a hybrid of that
2 situation where you could have a product such as flu
3 where you would produce single-dose vials for a very
4 specific population, women of childbearing potential,
5 pregnant mothers, and the occasional infant. You had a
6 multi-dose presentation that kept the existing level of
7 thimerosal.

8 **DR. BAYLOR:** I'm not going to rule that out. I think
9 what we're going to be faced with in the short run is
10 that situation anyhow, because as we move -- as
11 manufacturers move toward removing thimerosal from some
12 of their products, we're going to be in a situation
13 where there are going to be thimerosal-containing and
14 thimerosal-free products, the same products, same
15 manufacturer on the market at the same time. So we're
16 going to have a period where that's going to happen
17 anyhow. Now, whether we're going to prolong that
18 period, that's up for discussion.

19 **DR. MODLIN:** Okay. Thanks very much.

20 Our next speaker is going to give us a perspective on
21 how our European colleagues have dealt with this issue

1 very recently. She is Mary Teeling, who is Medical
2 Director of the Ireland Medical Boards.

3 Dr. Teeling, welcome.

4 **DR. TEELING:** First of all, just to say that we have in
5 Europe been looking at the issue of thimerosal for --
6 We've been doing this, in fact, for a year and a half.

7 So it's a great honor and privilege for me to come
8 here to share with you our deliberations and, more
9 importantly, how we are coping and what we are doing on
10 an ongoing basis with thimerosal.

11 And thank you to Dr. Myers. And I did say to him that
12 I do have the facility, being a good Irish woman, to
13 use many words rather than a few, but I really didn't
14 think that my introduction was going to be as long as
15 this.

16 (LAUGHTER)

17 **DR. TEELING:** So to put into perspective exactly what
18 we do in Europe -- Because I think this is very
19 important and it's an important issue when we're
20 looking at thimerosal -- we have in Europe two methods
21 of licensing. Now, there are 15 member states in the

1 European Union and each member state has its own
2 national agency. So you can imagine 15 FDAs, albeit
3 all different sizes and shapes. And that's important
4 because that means that it is possible to have a
5 national license for medicines, including vaccines.
6 We also have a European Agency for Evaluation of
7 Medicinal Products called the EMEA, and that is
8 responsible for community authorization. So that means
9 it's a one-stop shop. If you go the agency with a
10 particular type of medicine, you can get a license
11 that's valid in the 15 member states.

12 Now, it is important to note that the European system
13 of licensing, community licensing, is not available to
14 everything. For instance, it's not available to
15 existing authorized medicines unless they can show a
16 totally new indication. It's not available for
17 generics. It's obligatory for biotech products. And,
18 of course, with the combination vaccines containing
19 hepatitis B, that's important, because they will have
20 to use this system because they are biotechnology-
21 derived.

1 Now, the European agency has two main arms. The first
2 is the Secretariat -- Quite an extensive secretary is
3 taken from all over the European Union, and these are
4 mostly people who will have worked in agencies within
5 the 15 member states -- and a scientific committee
6 called the Committee for Proprietary Medicinal
7 Products, the CPMP. Now, as I said, the CPMP is a
8 scientific committee. It's made up of two members per
9 member from each member state, but you leave your
10 national hat outside the door when you come into the
11 CPMP. It is a truly scientific committee where science
12 is evaluated. So national issues are not discussed at
13 the CPMP.

14 Now, if you were to ask me what the role of this
15 scientific committee is, I think you can get many, many
16 different views, but I think, in general, it's to
17 ensure the provision of safe and efficacious medicines
18 to the market place in a timely fashion.

19 Now, that's very important. I know the FDA have time
20 limits. In fact, Norman Baylor mentioned some time
21 limits before, and we have implemented time limits, 210

1 days from time of -- beginning of the authorization to
2 approval, positive opinion, or otherwise, from the
3 CPMP. And that's for the community licenses, for the
4 ones that get the European license.

5 Does the CPMP have any other role? Of course, it
6 does. It's a public health body, and so we look at
7 ongoing safety of marketed medicines. Now, these are
8 medicines that will around at national level, as well,
9 and if they're judged to be community interest issues,
10 then they are discussed by the CPMP.

11 And, of course, a very important point in today's world
12 is to ensure that the provision of adequate information
13 takes place to both health care professionals and to
14 the public.

15 And we have in Europe -- I think it's a totally
16 different system, but certainly over the last years we
17 have become far more transparent. We have a standard
18 method of provision of what's called a summary of
19 product characteristics, which is the health care
20 professional document, and also patient information
21 leaflets in user-friendly language. These are new --

1 certainly new procedures for many of the member states.
2 Okay. Now, this is -- The CPMP has a number of
3 permanent expert groups and, again, these are important
4 because they've all been involved in the thimerosal.
5 There is a Biotechnology Working Party looking at the
6 pharmaceutical aspects of biotech products, a Efficacy
7 Working Party looking at the effectiveness of drugs, a
8 Quality Working Party looking at the chemistry and
9 pharmacy of chemicals, a Pharmacovigilance Working
10 Party that's clinical safety of medicine, a Safety
11 Working Party, pre-clinical issues are discussed there,
12 and we can also have ad hoc expert groups as
13 appropriate. But the other working parties are
14 permanent working parties and they work very closely
15 with the CPMP.

16 And my final introduction slide, if you like, this puts
17 very much into context what we are discussing. Before
18 1995, life did exist in the European Union, before the
19 implementation of the European agency, and prior to
20 that we had purely national authorizations. The
21 further you go back, the more national the

1 authorizations were. And it is very likely that for
2 the older medicines, particularly vaccines, in Europe,
3 that you would have 15 different licenses for the same
4 vaccine. I know that sounds crazy, but that's the way
5 it worked. So you are setting -- The playing field is
6 not a level one when you're looking at these issues,
7 particularly for products prior to 1995.
8 And, of course, in the same vein, although the CPMP is
9 not involved with the National Immunization Programs,
10 it is important to note that the National Immunization
11 Programs vary between the member states. I'm not even
12 sure that you would have two identical immunization
13 programs in the 15 member states. So you are dealing
14 with a very uneven surface to start off with.
15 Many of these issues have been covered already and
16 that's very good, because, you see, we're all thinking
17 the same way. I mean, thimerosal is a widely used
18 preservative and it has been used in biologicals and
19 multi-dose preparations for chemicals, as well as
20 biologicals. Of course, this big issue and the reason
21 why we're all here is that it's a mercury-containing

1 compound.

2 Now, how we actually got involved with this at the
3 European level was that in January of 1998, the
4 biotechnology working party, who has ongoing dialog
5 with the vaccine manufacturers and reviews vaccines on
6 a regular basis brought up a possible -- the
7 possibility of a safety hazard using thimerosal and, in
8 fact, other organomercurial compounds, although to my
9 knowledge there are very few of those left and only in
10 the very old products.

11 This was referred to the Safety Working Party to look
12 at the preclinical evidence associated with use of such
13 compounds in products in general, in medicines in
14 general, and they reported to the CPMP.

15 Now, the CPMP decided to set up a multi-disciplinary
16 group, and this was to view the benefits versus the
17 risk of thimerosal in medicinal products. And many of
18 the speakers -- Even this morning, many of the
19 discussions from the audience are bringing this issue
20 of benefits versus risk of using this. And this was
21 very much in our mind when we undertook this.

1 Now, the most multi-disciplinary group posed three
2 questions on behalf of the CPMP to the various working
3 parties: that was the rationale for inclusion of
4 thimerosal; Are there suitable alternatives available;
5 And the implications of removal of thimerosal from
6 medicinal products. So they were the three issues that
7 the individual working parties had the review from
8 their perspective.

9 The other points that came up was a questionnaire on
10 the immunization schedules in the first two years of
11 life for all member states was also undertaken.

12 Now, what we asked the member states to do was not only
13 to tell us what vaccines were recommended, but the
14 actual vaccine types if that was possible. It's
15 certainly possible in Ireland because of the 3 1/2
16 million population. The Department of Health in
17 Ireland buys all of the vaccines for any particular
18 year. So although we may have licensed seven or eight
19 DPTs and two or three DTaPs, it is likely that one, or
20 at most two, of those only will be in use in the
21 country at any particular time. And so it's quite

1 similar in the other member states, so it was possible
2 to actually get actual usage information from this
3 particular immunization questionnaire.

4 Now, the safety issues have been extensively discussed
5 yesterday by people far more appropriate to discuss
6 this than me, but, of course, the issues that we did
7 focus on were the neurotoxicity. Again, we're talking
8 about a potential here, a potential neurotoxicity.

9 Hard data are certainly absent with regards to use in
10 vaccines or, indeed, other medicinal products, but it's
11 the potential because of the mercury content.

12 And we especially focused on certain at-risk groups,
13 pregnant women, to the risk for the fetus, and also
14 infants and -- infants and toddlers.

15 Sensitization was also looked at. Here we do have some
16 pharmacovigilance data. And as you know, the type of
17 sensitization is delayed hypersensitivity. I think it
18 was particularly important because, remember, we were
19 looking at all medicinal products and not just vaccines
20 and we had information on the eye preparations. We
21 also had some very minor information from the

1 intramuscular immunoglobulin multi-doses which require
2 a preservative, and some of which contain thimerosal.
3 And I think with regards to the vaccinations, we looked
4 at the issue of the type of injection that was to be
5 used, and basically the deeper you go, the less likely
6 you are to get the reaction, and I think that's
7 something that is generally accepted.

8 Yesterday many people discussed nephrotoxicity and, in
9 fact, nephrotoxicity was pursued, particularly by the
10 Pharmacovigilance Working Party, but we really didn't
11 have -- I mean, ever how little data we have with the
12 other two, we certainly had no firm data to draw any
13 conclusions with regards to nephrotoxicity with use of
14 thimerosal in medicines.

15 Now, again, all of these were discussed yesterday. I
16 think with regard to the distribution, we were very
17 much aware of the fact that the -- this crosses the
18 blood/brain barrier. Again, I think -- I have to draw
19 your attention to the fact that we're talking about
20 methylmercury data here, so we're extrapolating. And
21 the brain and placental transfer was obviously

1 something that was very important for the possibility
2 of neurotoxicity.

3 And we also, based on WHO data and their technical
4 reports, noted that the hair concentration was a very
5 good indicator because a very high concentration of
6 mercury occurred in hair after administration, and so
7 that hair levels could be used as perhaps as a
8 reasonably valid marker and, of course, a non-invasive
9 marker.

10 Metabolism, we did look into the issue of organic
11 versus inorganic. I think we used a working half-life
12 of 50 days, sort of a range 39 to 70. And of course
13 this issue of accumulation, and this was very
14 important, because I think what you're hearing is, it's
15 probably not the single stab, it's the many sources and
16 the multiple administrations. In fact, we did look at
17 this issue of the sources of organic mercury. And, of
18 course, food, especially fish, is a big source. Now,
19 this is oral intake, obviously. And we did look at the
20 possibility that the medicinal intake would also
21 increase your level, your critical level.

1 Now, the allowable levels that we worked
2 on -- So I was interested to hear the speakers yesterday.
3 We worked on 200 micrograms per week in adults. This
4 is the total permissible weekly intake from WHO figures
5 of, I think, 1989-1990. And, again, these figures are
6 based on methylmercury. All of this information is
7 based on methylmercury.
8 So this is a very rough calculation of how and why we
9 took that, and I think we were looking at the initial -
10 - the initial symptoms of mercury poisoning, and these
11 would -- paresthesia would be very much the early
12 symptom that something was wrong. This was seen in the
13 Iraqi outbreak after a certain number of weeks. It was
14 estimated by the WHO that 50 micrograms per day would
15 give an 0.3 risk of developing paresthesia, which is a
16 fairly low risk. I think if you take a higher level of
17 200 micrograms per week, based on a 70 kilogram man,
18 that's 0.4 micrograms per kilogram per day. That gives
19 you a safety margin of 1.7 against developing an 0.3
20 percent risk of paresthesia. So, again, you're
21 widening your safety margins all the time. So we

1 accepted the WHO level of 200 micrograms per week as
2 the working level for adults for oral intake of
3 methylmercury.

4 Now, when we came to pregnant women and infants -- And
5 remember, we're looking at all medicinal products in
6 Europe, and this is why we included both categories,
7 pregnant women and infants. The pregnant women, we
8 calculated that the level of 200 micrograms per week
9 for adults should be cut by -- to one-fifth, and this
10 is based on hair concentrations reported in the WHO for
11 the Iraqi women where they had the children and the
12 mother pairs. So our working level for women would be
13 one-fifth the adult dose, above which we would have
14 safety concerns for the fetus.

15 Infants was even more difficult. And as you can see
16 yesterday, there is -- this issue is, is the newborn as
17 sensitive as the unborn? We did a calculation based on
18 the fact that if you take the worst possible case
19 scenario, we came up with a working figure of 200
20 micrograms in the first year of life. However, and I
21 must say the issue of the spiking or the episodic

1 versus the chronic administration was something that we
2 couldn't actually come to grips with, because I don't
3 think anybody can give advice on that because we
4 actually don't know.

5 So very much, it's very much a part of the version of
6 our safety aspects. All of the safety data that were
7 presented yesterday were reviewed by us and nobody can
8 argue with the facts. It's basically how you deal with
9 the facts and how you interpret them and bring them
10 forward.

11 So if we go back to the three questions that the group
12 posed to the experts working on behalf of the CPMP, the
13 first is the rationale for inclusion of thimerosal, and
14 you've heard all of this before, particularly from this
15 morning's speakers. Vaccines consisting of protein and
16 polysaccharide in a solution or a suspension may
17 potentially support bacterial or fungal growth. Fact.

18
19 So if you add a preservative, this will hopefully
20 prevent contamination, and this can be done either
21 during the manufacture or in the end product, in the

1 case of multi-dose preparations, and this prevents
2 contamination which could be harmful for the recipient.

3 We heard of the fatal contamination cases yesterday.
4 So if you add a preservative, is it just to prevent
5 contamination? I think we also looked at this idea of
6 maintaining the integrity of the vaccine and to
7 maintain the desired biochemical properties or
8 functions of the active component. Obviously, if you
9 look at -- the whole cell pertussis is an example here.

10
11 Also, we did look at this issue of its use in single-
12 dose vials, and we felt that it could even have a role
13 in single-dose in certain cases. For example, in the
14 influenza vaccine, where you're using the eggs as
15 starting materials.

16 So we felt there is a rationale for including a
17 preservative in some circumstances. Okay. So does it
18 have to be thimerosal. Well, what are the alternatives
19 to thimerosal? And we have some listed here.

20 Phenol, we heard yesterday that that's no longer
21 acceptable by the WHO. Cresol, I'm not sure that I'm

1 too impressed with cresol. 2-phenoxyethanol, I --
2 Perhaps I'm getting old and a bit cynical, but I'm
3 really not sure that we have the full safety picture on
4 2-phenoxyethanol. It certainly does look to be a safe
5 and efficacious vaccine -- preservative, but we're
6 actually not 100 percent sure about either of these at
7 this point in time. Formaldehyde has also been used.
8 Now, there are other preservatives that have been used
9 in other medicinal products, like benzochromium
10 chloride. I think the important thing is that for a
11 preservative to be used, they must fulfill the European
12 Pharmacopeia specifications. That's a requirement in
13 order to get a license either nationally or at
14 community level in the European Union. So they do have
15 -- So they will, more or less, fulfill the PH Euro
16 requirements.

17 But we're not really -- Ever how much information we
18 have on thimerosal, I think we have less on the others.

19 So you're into a situation, or are you -- You know the
20 phrase, "The devil you know is better than the devil
21 you don't know." And I think that's a very important

1 aspect of this whole review.

2 So, well, of course, the real alternative is to get rid
3 of the need for preservatives, and that's why using a
4 good manufacturing practice and get a preservative-free
5 product.

6 Now, again, I think we've heard that that's not always
7 possible. So from that point of view, it's something
8 that has to be debated, but it is an alternative that
9 should be looked at.

10 Right. The final question that the group posed to the
11 experts was the implication of the removal of
12 thimerosal from medicinal products. Well, the group
13 still maintained its position that GMP adherence should
14 reduce the need for preservatives, certainly reduce the
15 need for preservatives. And there will be a need in
16 certain cases, and this is particularly in the multi-
17 dose preparations where the seal is repeatedly
18 breached. I think we did hear some examples of where
19 the multi-dose preparations might be used from Dr.
20 Clements yesterday, and I think we in the European
21 Union are certainly very much aware of the WHO need in

1 this regard.

2 One particular issue regarding vaccines is the turbid
3 vaccines. So if there's microbial contamination, the
4 turbidity may actually mask this contamination. That
5 was felt to be a particular specific issue that we
6 needed to address.

7 But, finally and most importantly, the implications of
8 the removal of thimerosal from medicinal products,
9 really the group was very concerned that this would
10 pose risks to the continuity of the immunization
11 programs.

12 So the group recommended that we would have adequate
13 labeling for the sensitization on all thimerosal-
14 containing medicines. Now, this is not something that
15 was universally applied in the European Union. There
16 is a requirement that thimerosal or other preservatives
17 are included routinely on the label, but a warning
18 statement has not been mandatory. So it was agreed
19 that this should be drawn up in the interest of
20 informing patients and health care professionals.
21 For vaccination in infants and toddlers, the use of

1 vaccines without thimerosal or other mercurial-
2 containing preservatives was to be encouraged.
3 However, we were very concerned that the continuing
4 supplies and vaccination programs would be jeopardized,
5 and so it was agreed that we would have a workshop with
6 interested parties. That took place in April of this
7 year with representatives from the WHO. We had Norman
8 Baylor from the FDA. We had representatives from the
9 European Pharmacopeia because, as you can see, the
10 European Pharmacopeia requirements are mandatory to get
11 a license in the European Union, either at --
12 nationally or community level, and so we need to have
13 the European Pharmacopeia on board if we're
14 recommending changes.
15 We also had the vaccine manufacturers and the other
16 manufacturers, the eye manufacturers, the plasma
17 protein fractionaters (sic), and we also had the
18 representatives from the CPMP and our experts.
19 In the working party, this interested parties meeting,
20 we did reach agreement in principle to labeling,
21 obviously a standardized wording, and we addressed this

1 issue of whether it's used as a preservative so it's
2 added in a known amount at the end of the procedure or
3 whether it's used in the manufacturing procedure where
4 it's still present in trace amounts, but this, of
5 course, may be important for sensitization purposes.
6 And we also had an agreement in principle to work
7 towards reducing or eliminating thimerosal and, indeed,
8 other mercurial-containing preservatives in the
9 production of vaccines. So we've now moved forward,
10 and we are in the process working to achieve those
11 issues.

12 Now, I would like to draw your attention to the public
13 statement that we issued in July regarding this. As I
14 say, we're very much -- this is very much a working
15 procedure. We haven't come to the end -- We have a lot
16 more work to do -- but it's ongoing.

17 Now, the background points to our public statement
18 were, again, thimerosal has been used for many years.
19 The level of ethylmercury in any single medicinal
20 product is not considered a risk. I think that's
21 something that Norman Baylor said, that the last

1 speaker said, and I think we would agree. However,
2 it's the cumulative exposure from a range of sources,
3 not just from medicines, but from food, and, indeed, if
4 you read the WHO reports, intake from the air and from
5 water. So there are many sources of mercury. So,
6 therefore, we could -- we could have a situation where
7 this would lead to a potential cause for concern.
8 I don't have the bullet point that Dr. Klein so rightly
9 mentioned yesterday, and I think it is an important
10 one, and I'll actually read it out to you because I
11 have the document here.
12 "Data on methylmercury has been used in the assessment
13 of risks associated with ethylmercury as the toxicity
14 profile of the two compounds would appear to be
15 similar."
16 I think that's a great use of the English language, but
17 I think it's as far as we can go because we don't have
18 the information on ethylmercury and we're doing the
19 best we can with the information that we have, and I
20 think it's probably the same for all of the workers who
21 are doing this at the moment.

1 Now, the remainder of this, I'm actually going to read
2 for you what we said because each line is very
3 important.

4 "For vaccination in infants and toddlers, the CPMP
5 concluded that although there is no evidence of harm
6 caused by the level of exposure from vaccines, it would
7 be prudent to promote the general use of vaccines
8 without thimerosal and other mercurial-containing
9 preservatives, particularly for single-dose vaccines.
10 This should be done within the shortest possible time
11 frame."

12 Next point. "In the interests of public health and in
13 order not to jeopardize vaccine supplies and
14 immunization programs, the EMEA will continue to work
15 with the WHO, the European Pharmacopeia, the Food and
16 Drug Administration, and vaccine manufacturers with the
17 objective to eliminate organomercurial preservatives in
18 vaccines in the follow-up to the joint workshop which
19 was held in April 1999."

20 Now, this is, I think, very important. "The CPMP would
21 like to stress that this is only a precautionary

1 measure. There is no evidence of harm from the use of
2 such thimerosal-containing medicinal products. While
3 reformulation work on vaccines proceeds, it is
4 imperative that vaccination continues in accordance
5 with national vaccination schedules to prevent disease
6 outbreaks." That was a very important message that we
7 wish to get across.

8 And finally, just for the sake of completeness, we did
9 look at immunoglobulins and eye and nasal preparations,
10 and basically, apart from the labeling issues, no
11 further action was deemed necessary. I think that's an
12 important issue.

13 Where are we now -- Okay? -- August, 1999? Well, our
14 Pharmacovigilance Working Party has drawn up standard
15 warnings on sensitization for all thimerosal-containing
16 medicines. Now, we need an agreed implementation
17 procedure here, and remember the vast majority of these
18 medicines are licensed at national level, and we all
19 have different time limits and time levels, and that's
20 what makes the European Union so wonderful. It's so
21 varied. But the problem is, we have to agree an agreed

1 time frame for implementation here.

2 The second is that the Biotechnology Working Party is
3 working on a guidance document relating to the
4 reduction or elimination of thimerosal and, indeed,
5 other preservatives in vaccines. And I would love if
6 Dr. Baylor would come and work with us because many of
7 the issues that he raised are issues that we are
8 raising in our discussion document. Because it's very
9 difficult, each individual case will be a case-by-case
10 basis.

11 I think the other most important -- and I would like to
12 give you this commitment, that we will continue to work
13 with all relevant parties to ensure the continuity of
14 supply of safe and efficacious vaccines.

15 Thank you very much for your attention.

16 (APPLAUSE)

17 **DR. MODLIN:** Thank you, Dr. Teeling. There is time for
18 just one or two questions. Yes, Rob?

19 **DR. BRIEMAN:** Rob Brieman, the National Vaccine Program
20 Office.

21 Now, I'm impressed with how oftentimes we tend to be

1 very vertical and look at and consider issues that are
2 only related to our area, and I'm not thinking about
3 what happens in Europe. I'm thinking about what we
4 might do here in the U.S.

5 But when you were considering the issue of cumulative
6 exposure, was there any discussion about issuing any
7 sort of strict guidelines or information to pregnant
8 women regarding ingestion of, let's say, you know,
9 mercury-containing fish? Is that something that is --

10 **DR. TEELING:** No, no. And it's not a particular issue
11 for us, obviously, because we're not a food and drug
12 administration. We are primarily -- and I think that's
13 -- we're not -- The agency is not a European FDA. I
14 think we deal specifically with medicines. From a
15 public health point of view, that is important. I
16 think we didn't want to add to the burden. And the
17 reason why pregnant women were particularly
18 investigated was not just from the point of view of the
19 vaccines and any vaccinations that they may get, but
20 because of the possibility that they could be getting
21 anti-D immunoglobulin prior to delivery, which would

1 affect the fetus. So we specifically honed in on
2 those.

3 I think with regard to your general point, we did not
4 make any recommendations for people to go back and view
5 their national programs. In fact, we said that, you
6 know, in accordance with national decisions. However,
7 some of the national agencies could have gone back to
8 their departments of health who are responsible for the
9 vaccination programs and taken on -- or, indeed, taken
10 on anything with regards to the foods levels as well.
11 It's not something that we would get involved in, but
12 it might be a knock-on effect from the CPMP.

13 **DR. MODLIN:** One more question. Dr. Geller?

14 **DR. GELLER:** Bruce Geller from the Infectious Disease
15 Society.

16 You read many quotes from your group, and I wonder
17 whether these are ready available, if there's a website
18 where some of this information may be --

19 **DR. TEELING:** Yes, yes, yes. And I even have the
20 website for you. I am computer illiterate, as you may
21 have gathered. It's a disease, I can't help it, but I

1 actually have the website. I have a copy here, if
2 anybody would like a copy from the photocopy machine,
3 but it is available on the EMEA website. Interestingly
4 enough, we got very few comments, in fact, from this.
5 We have a website. We have a publication every month
6 from the CPMP. So everything that we do is put on.
7 This was a specific -- a specific public statement that
8 was put out. We actually got very little requests. In
9 fact, we got more requests from the MMWR statement than
10 we did from European statement, which I don't know what
11 that says about European doctors. Certainly, you can -
12 - I'll give you this later on.

13 **DR. MODLIN:** One final. Neal?

14 **DR. HALSEY:** Neal Halsey from John Hopkins again.
15 I notice that you have gone a little further than our
16 Public Health Service and the Academy of Pediatrics
17 have and that you have encouraged the use of
18 thimerosal-free products in the use of infants and
19 toddlers. Was there any discussion about those
20 particular populations in Europe which do have a fairly
21 high background of fish consumption and a presumed

1 higher background of mercury exposure with regard to
2 even going beyond that?

3 **DR. TEELING:** No, actually there wasn't. I mean -- and
4 I think the issue was identified for the national
5 agencies to do it as they wish with it. But I think --
6 The one issue that I didn't raise, because it wasn't a
7 part of the final deliberation, is that we did the
8 immunization schedule, the questionnaire. In fact, two
9 member states had greater than 200 micrograms in the
10 first year of life. Now, one of those, in fact, has
11 since introduced a thimerosal-free version of the
12 vaccine, but I think -- and so they have come down. I
13 think what it did show us is that the vaccination
14 programs are greatly different. Hepatitis B is not
15 mandatory in all member states. It's nearly all DTaP,
16 and the vast majority of DTaP supplied appears to be
17 thimerosal-free. So the two main problems that you
18 might have here in the U.S. don't appear necessarily in
19 our vaccination program for infants, but there was no
20 specific discussion on the additive nature of fish,
21 other than it was highlighted as a point as part of the

1 accumulation.

2 **DR. MODLIN:** Dr. Teeling, thank you.

3 We'll break for coffee and other things, and start
4 precisely at 10:30. Thanks.

5 (RECESS FROM 10:10 A.M. TO 10:35 A.M.)

6 **DR. MODLIN:** We're now going to move on to the next
7 phase, which is entitled "Immunization Issues During
8 Transition to Thimerosal-free Vaccines." Our first
9 speaker will be Dr. Roger Bernier. Roger is at the
10 CDC, has been the point person for the CDC for
11 thimerosal issues the past couple of months, and he is
12 going to present to us the public health service
13 immunization options.

14 Roger?

15 **DR. BERNIER:** I had some questions about whether this
16 topic or title would still be appropriate this late in
17 the workshop because I thought that this might be
18 fairly clear by now. But I think that it's still
19 valuable. I think Bob Daum's question during the last
20 session, and as well, the last presentation by Mary
21 Teeling, I think indicates that it would still be

1 helpful to have a presentation about -- from the public
2 health service point of view, or in the U.S. what is
3 the position that we have evolved to on this thimerosal
4 question.

5 Well, I think it can be expressed by the goals that we
6 have articulated. The first is to reduce or eliminate
7 thimerosal from vaccines as soon as possible. And
8 second, to reduce exposure to thimerosal from vaccines
9 during the transition period to thimerosal-free
10 vaccines.

11 And I think one of the points I want to make is that in
12 some ways something is different, that there is not a
13 business-as-usual view of this matter, and I think that
14 that's one of the things that we're trying to hold
15 together in our minds, the idea that somehow it's not
16 business as usual, yet, in another way, we are trying
17 to do our usual business during the transition period.
18 And how can we keep together these two difficult
19 concepts, if you will, or, the concepts are not
20 difficult, but holding them together is difficult, that
21 we're in a non-business-as-usual mode and we are trying

1 to do some of our business as usual?

2 Well, I want to try to explain how we got here, and
3 that means, I think, trying to answer the question
4 about why it's worthwhile to try to reduce or eliminate
5 thimerosal. I think one of the important concepts is
6 one that Leslie Ball presented, I think perhaps
7 borrowing from the work of the European Union in trying
8 to calculate what might be the exposure from the
9 vaccines. As you may recall from her presentation
10 yesterday, when you look at DPT, HIB an hepatitis B
11 using three doses, the potential exposure to mercury
12 from vaccines in the United States over approximately
13 the first six months is this 187.5 micrograms, assuming
14 there's not flu.

15 Now, in the U.S. there are -- Again, people caution me
16 not to use the word "standards," and half the time I
17 remember and half the time I forget. These guidelines,
18 I think is the best term that people seem to feel is
19 the best term to describe them.

20 In the U.S. we have three different sets of guidelines.

21 Again these were mentioned yesterday, as well, from

1 EPA, ATSDR, and FDA, and there are also some from WHO.

2 They are different, from .1 in the U.S. for the EPA,
3 which is the lowest, to .4 with the FDA.

4 Now, one of the concepts that -- And, again, I knew
5 very little about this before and I still am learning
6 about this every week, but this represents my
7 understanding of what we mean by safety margin in
8 relation to these guidelines.

9 This represents the level of zero exposure. And I'm
10 using here as an example the ATSDR guideline, but,
11 apparently, there are safety margins, large safety
12 margins, associated with all of the three guidelines in
13 the U.S. If you take this level as the zero exposure
14 level, the current ATSDR guideline is .3 micrograms.
15 In fact, in the data that the ATSDR relied in the
16 Seychelles, the average exposure in the high-risk
17 group, where no effect was observed in the moms, where
18 I believe it was 15 parts per million, approximately.
19 That translates to 1.3 micrograms, which is four times
20 above the ATSDR guideline level. So this much safety
21 margin exists on this ATSDR guideline.

1 In addition, if you'll at the highest exposure group in
2 the Seychelle, again, this is the highest exposure in
3 the high-risk group, where again no effect was
4 observed, that equals to approximately 2.5 micrograms,
5 which is eight times over the base line ATSDR
6 guideline.

7 In terms of total exposure that might be permissible
8 under that, if this translates to approximately 250
9 micrograms over the first seven months of life, this is
10 about 1000 and this would be about 2000.

11 After the highest exposure group with a no- effect
12 level, then you get into this grey area because,
13 presumably, between this exposure level where there's
14 no effect and the first level where you begin to see a
15 mild effect, that is a grey zone. We don't know how
16 wide that grey zone is. It might be very narrow or it
17 might be very wide, but there is a grey zone when you
18 begin to see a mild effect. Then at an exposure level
19 that produces very serious effects, obviously, that's
20 represented by this black area in the bar, but this
21 represents the safety margin that we've heard so much

1 about and that why we've heard that these guidelines,
2 .3 in the case of ATSDR, or .1 or .4, why interpreting
3 them as bright-line types of thresholds is probably not
4 an appropriate way to interpret them, but rather to
5 think more about them as starting points -- starting
6 points or screening levels or whatever most appropriate
7 adjective, but not as a threshold, a bright-line-type
8 of value.

9 Now, again, if 187.5 represents the potential exposure,
10 what are the potential limits that might be allowable?

11 And if you use the different standards, the different
12 guidelines from EPA, ATSDR, and FDA, the -- Dr. Ball's
13 group has calculated -- And we have somewhat slightly
14 different assumptions, so I'm going to show the results
15 that Dr. Ball's group did as well as the one at CDC.
16 They're very similar, but they are slightly different.
17 These are the results from Dr. Ball's calculations.
18 From the calculations that we did at CDC, they are just
19 a little bit higher. The major difference is that we
20 calculated out to 30 weeks, again, thinking that what
21 you wanted in coming up with your suggested limits was

1 the limits during the period of time that children are
2 most likely to be exposed. For most children, they're
3 not going to be vaccinated exactly at six months. I
4 think this is the question that Stan Plotkin raised
5 yesterday: Why don't you calculate it at seven months?

6 I told Dr. Ball I didn't really plant that question.
7 But if, in fact, you do that, you'd come up with
8 slightly different limits.

9 Now, comparing these two, then, here's the potential
10 exposure as calculated by Dr. Ball from the vaccines on
11 the routine schedule. And if you look at the three
12 guidelines that we have in the U.S., you can see that
13 the total exposure that some children might receive
14 would be in excess of the guidelines suggested by the
15 EPA but would be within the limits of the guidelines
16 suggested by ATSDR and FDA. This is for children at
17 the fifth percentile.

18 Well, that's the potential exposure for some children.

19 What do we know about what children are actually being
20 exposed to? Well, we don't have a lot of information
21 on that at this time, but what we did do is look at the

1 potential number of combinations of vaccines in the
2 United States for DPT, HIB, and hepatitis B, and look
3 at, of all the possible combinations of ways that
4 infants could be vaccinated, what are all the potential
5 total endpoints in terms mercury exposure that these
6 combinations might lead to. And what it shows is that
7 there's approximately -- I think it's 100 different
8 ways that infants can be vaccinated, but about, say, 15
9 or 20 total mercury exposure endpoints that they can
10 end up with.

11 If you'll look at the vaccine combinations, most of the
12 vaccine combinations that are available in the United
13 States, about a quarter of the combinations produced
14 would produce mercury exposures of about 100 micrograms
15 over the first seven months, or 112. And I've put on
16 here the guidelines where you can see that for some of
17 the combinations, if children got these, they would
18 exceed this EPA guideline but would for all the
19 combinations available in the U.S., children, if they
20 got any of these, would still be below the guidelines.
21 Well, we do have one set of data from the California

1 Kaiser that is part of our vaccine safety data link,
2 and, basically, what this shows is what mercury
3 exposures 85,000 children received at this HMO, and
4 what you can see is very similar to what you would have
5 predicted based on the existing number of combinations,
6 namely that approximately 90 percent of the children
7 got 112 micrograms or less, 91 percent, 125. Again,
8 for some of these, they were in excess of the EPA
9 guideline, but below the ATSDR and the FDA.

10 And to summarize, I guess, what I've just said for
11 these guidelines, as far as potential exposure, the
12 values were below FDA and ATSDR, above EPA, and on
13 actual, they were well below, if you look at 100 as the
14 actual -- or approximately 100 micrograms as close to
15 an average exposure, this is well below the ATSDR but
16 still above EPA.

17 So it was based on those kinds of considerations that
18 public health service groups and others deliberating
19 about these matters recently basically came to the
20 conclusion that it would be worthwhile to reduce or
21 eliminate thimerosal in vaccines. While we did not

1 exceed the guidelines from ATSDR and FDA, there was
2 some excess relative to the EPA guidelines, and given
3 that uncertainty and the possibility of a potential
4 risk, I think there was this agreement that it would be
5 prudent to reduce or eliminate thimerosal in vaccines.
6

7 We then would face a transition period where, again, we
8 had now made a commitment to change, but we would still
9 have a supply situation that was similar to the one we
10 had -- There hadn't been any change in supply -- and,
11 therefore, we would have to manage the transition. And
12 one of the major principles guiding this transition was
13 that the benefits of vaccination were believed to far
14 outweigh the risk, if any, of exposure to thimerosal,
15 and this guided many of the choices and decisions that
16 were made.

17 And here, then, captures in policy terms -- Because we
18 can talk all about this, and bottom line is, at some
19 point we have to make a recommendation that makes
20 everything very

21 specific -- you capture -- You have to deal with the

1 uncertainty and make it specific. And what it boiled
2 down to was the following.

3 That the U.S. has recommended that there be no change
4 during this transition period in the use of DTaP, HIB,
5 or hepatitis B for antigen positive mothers, or for
6 hepatitis -- no change in hepatitis for mothers whose
7 antigen status is unknown, or for infants who come from
8 high-risk populations. However, again, in light of
9 this potential risk and concerns raised by that, there
10 was a feeling that some action need -- should be taken
11 at this time, and the decision was made, or
12 recommendation made, to postpone the initiation of
13 hepatitis B in mothers whose antigen status is negative
14 and for whom that status is proven or documented to be
15 negative. In those mothers, the infant vaccination
16 could be postponed until two to six months.

17 This statement was issued jointly by the American
18 Academy of Pediatrics and the Public Health Service.
19 In subsequent guidance, the Public Health Service
20 expressed a preference for initiating this postponed
21 immunization at the lower end of this agreed-upon

1 range, and the American Academy of Pediatrics expressed
2 a preference for starting at the upper end of this
3 range. The Academy did recommend that if you had a
4 thimerosal-free vaccine available, then you could begin
5 at the lower end of the range with that product.

6 Now, in the remaining time, I'd like to talk a little
7 bit about what are some of the issues that were raised
8 in reaching these conclusions about where we are, and
9 I'd like to allude to a couple of problems or issues
10 that have arisen in the implementation of these. One
11 of the things that we hope to get out of this workshop
12 is a discussion of the issues around these decisions
13 and help us to evaluate whether or not there are any
14 refinements or adjustments that we need to make to the
15 decisions that were taken.

16 So I'd like to just point out some of the issues that
17 I'm aware of. I think the speakers in the rest of this
18 session will really focus on some of these other
19 issues, and maybe new ones will arrive, but if the
20 workshop could be helpful in getting people's views
21 about these matters as to where we are now and whether