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convenes

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SPONSORED WORKSHOP ON THIMEROSAL VACCINES

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## C O N T E N T S

PARTICIPANTS (by group, in alphabetical order).....	4
VI. REDUCING AND ELIMINATING THIMEROSAL IN VACCINES	
A. Opportunities and Challenges	
1. Manufacturing Issues Chris Adlam.....	14
2. Regulatory Issues Norman Baylor.....	33
3. The European Issues Mary Teeling.....	56
B. Immunization Issues During the Transition to Thimerosal-Free Vaccines	
1. Transitional Public Health Service Immunization Options Roger Bernier.....	82
2. Implementing Transitional Immunization Options	
American Academy of Pediatrics Perspective Jon Abramson.....	99
National Coalition for Adult Immunization Perspective Peggy Webster.....	106
Institute for Vaccine Safety Perspective Neal Halsey.....	111
Infectious Disease Society of America Perspective Bruce Gellen.....	127
Association for State and Territorial Health Officials Perspective Claire Hannon.....	132

## VI. FILLING THE GAPS: DEVELOPING A RESEARCH AGENDA

A. The Gaps	
Regina Rabinovich.....	165
B. Priorities for a Research Agenda	
Tom Clarkson.....	183
Michael Gerber.....	188
Alison Mawle.....	193
Peter Paradiso.....	198
John Risher.....	202
Bernard Schwetz.....	207

## VIII. WORKSHOP SUMMARY

Jerome Klein.....	233
ADJOURN -- END OF WORKSHOP.....	238

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P R O C E E D I N G S

8:33 A.M.

1  
2  
3 **DR. MYERS:** A couple of just quick announcements. We  
4 mentioned yesterday that if there are others who wanted  
5 to give perspectives on the immunization options  
6 through the transitions, we were underwhelmed. So  
7 there's still -- it's not too late. If other people  
8 would like to give a perspective, if they would contact  
9 Dr. Modlin at the break.

10 Dr. Rabinovich has asked that those of you who are in  
11 the panel on the research priorities, if you would  
12 contact her at the -- if you could get together briefly  
13 at the break this morning.

14 Our moderator for today is Dr. John Modlin, who is  
15 Professor of Pediatrics and Medicine, and, more  
16 recently, the Acting Chair of Pediatrics at Dartmouth,  
17 and he's also Chair of the Advisory Committee on  
18 Immunization Practices, and he'll moderate today's  
19 session.

20 **DR. MODLIN:** Thanks, Marty, and good morning. Before  
21 we begin, just one or two quick housekeeping issues.

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

unnecessary for vaccine manufacture.

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

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

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

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

1 we need to modify in any way, that would be very  
2 helpful.

3 Some of the issues that I think were germane to the  
4 discussions that we had you've heard a lot about, and  
5 that is the assumption about ethylmercury being treated  
6 as methylmercury. I think that that's still the  
7 appropriate thing to do. I haven't heard anything at  
8 this workshop that suggests that we don't need to do  
9 that.

10 Another assumption was that the fetal risk, which is  
11 what guidelines are based -- are trying to address, was  
12 equal to infant risk, I think we are hearing that  
13 perhaps infant risk is lower than fetal risk. So  
14 that's a reassuring thing. It's not that we have a lot  
15 more data on this, but it's tending to go in the  
16 direction from what I'm hearing that infant risk post-  
17 natally may be lower than fetal risk. No one is quite  
18 ready to make a new guideline I don't think, but it's  
19 reassuring rather than being more -- becoming more  
20 worrisome.

21 On the issue of the background level of exposure to

1 mercury, the assumption was made that it's negligible,  
2 and I haven't heard anything that makes us believe that  
3 we ought to be more concerned about background levels  
4 of exposure.

5 Another important issue that has permeated these  
6 discussions is that the guidelines are based on chronic  
7 exposures. What we are dealing with is an acute  
8 exposure and the guidelines may not be applicable. I  
9 think, on that score, it still remains unknown. I've  
10 heard data on both sides, or observations, I should  
11 say, or speculation on both sides, and in my mind this  
12 still remains an unknown.

13 In the Department of Health and Human Services, there  
14 were three guidelines. I think it's fair to say that  
15 because of a two-year process that has been going on in  
16 the Department of Health and Human Services, while  
17 there were three existing guidelines in the U.S. more  
18 weight or preference was given to the ATSDR guideline  
19 as the primary guideline to be -- to be guided by, if  
20 you will, than the other two. That was a decision that  
21 was made, as I say, in the Department of Health and

1 Human Services because of a two-year process. I've  
2 heard nothing to make us believe that we ought to have  
3 done that any differently.

4 Also, another point that arose during the whole  
5 discussion was how do you apply these guidelines in  
6 decision-making. I've tried to allude to that by the  
7 schematic that I showed on the safety margins, but this  
8 was a big issue. Again, depending on how you interpret  
9 those guidelines, as either bright lines or as starting  
10 points, can make a big difference in how you react to  
11 all this, and I think -- I haven't heard anything to  
12 change our view, which was to look at these guidelines  
13 as a starting point.

14 In fact, the more I've heard about this, the more I've  
15 become convinced that -- at least in Dr. Raub's session  
16 yesterday, there was a lot of focus on the guidelines  
17 as screening points or screening levels.

18 And, finally, I don't have a slide for this, but I'd  
19 like to talk about some of the issues that have arisen  
20 that I'm aware of in the implementation of the existing  
21 policies.

1 One of them obviously has to do with hepatitis B. I  
2 mean, that's the only vaccine where we expressed a  
3 change in the current status. You heard Dr. Mast's  
4 presentation yesterday, concerns being raised about the  
5 number of infections that may be arising as a result of  
6 the new policy change. Perhaps that's something that  
7 we were not as fully aware of and didn't have all those  
8 calculations at the time the policy was made. The  
9 question is, do we need to revisit that in some way?  
10 The workability of having an age range, we said that  
11 the AAP and the PHS recommend from age two to six  
12 months. What is the workability of this? How much  
13 difficulty is this causing in the field in terms of  
14 confusion among different groups.

15 I think we thought when we issued the recommendation  
16 that it would be workable. My impression is that it is  
17 working, not without bumps in the road, but that it is  
18 a workable recommendation.

19 One other area has to do with communication, and  
20 perhaps we need to look at improving communication with  
21 providers and parents about this change. We heard from



1 a speaker in the audience from Philadelphia about  
2 confusion that is being caused, and even some mothers  
3 of infants of antigen-positive mothers may not be  
4 getting vaccine. That clearly is not a change. There  
5 has been no change for antigen-positive mothers, and  
6 maybe in the communication arena something needs to be  
7 revisited.

8 Vaccine supply issues. Issues have arisen about how to  
9 manage the stocks of thimerosal-containing and non-  
10 thimerosal-containing vaccines. There are issues about  
11 what's in the pipeline and what's going to happen to  
12 the stocks of vaccine. This may be an issue that we  
13 need to visit that we haven't fully addressed.

14 Another one has to do with the supply of vaccines. We  
15 may, in the near future, have greater availability of  
16 thimerosal-free vaccines. If that happens, will we  
17 want to express any preference for thimerosal-free  
18 vaccines as they become available? If they're only  
19 available from one or some manufacturers but not  
20 others, this has implications for the long-term supply  
21 of vaccines. Do we want to address that in any way?

1 And, fourthly, there are issues around flu vaccination.

2 You've heard there have been no recommendations yet.

3 I think that's in the works and, perhaps, not something  
4 that we need to be overly concerned with. That will  
5 take place.

6 And finally, there are issues around research and a lot  
7 of unmet needs in the information area, and that will  
8 be the subject of Dr. Rabinovich's panel following  
9 later in the morning.

10 So I hope my presentation does provoke some additional  
11 discussion about both the issues that were behind the  
12 policy discussions, as well as some of the issues that  
13 have arisen in implementation.

14 Thank you very much.

15 (APPLAUSE)

16 **DR. MODLIN:** Thanks, Roger.

17 In the interest of time, I'm going to ask we not take  
18 questions, and then I'll -- but I'm certainly going to  
19 ask Roger to join the panel up here at the end, and I'm  
20 almost certain that we will have a fair amount of time  
21 for discussion and questions at that time. So we'll

1 ask some of our other -- the other presenters to go  
2 next.

3 And the first presentation will be by Dr. Jon Abramson.

4 Dr. Abramson is Professor and Chair of the Department  
5 of Pediatrics at Bowman Gray School of Medicine. He is  
6 the new -- the brand-new Chair of the Committee on  
7 Infectious Diseases of the American Academy of  
8 Pediatrics, which, of course, has been out front, if  
9 not antagonistic (sic), on this issue.

10 So we're happy to have Jon here. Thanks.

11 **DR. ABRAMSON:** Thank you, John.

12 I think I have to tell a story. It's actually a joke,  
13 but you'll understand the moral at the end.

14 There was a millionaire in Florida who put an ad in the  
15 paper and said, "I'll give a million dollars, a yacht,  
16 or my daughter's hand in marriage to anybody who can  
17 swim one lap in my pool."

18 The next morning there were 50 people out by the pool.

19 Everybody was standing around. The millionaire comes  
20 out, thanks them for coming, and then he says, "The  
21 only thing I haven't told you is there are 12

1 alligators in the pool." And everybody's standing  
2 around buzzing and saying, you know, "This isn't worth  
3 it. It's not worth dying over."

4 All of a sudden there's a splash in the pool, and the  
5 alligators converge, and guy dives down, comes up about  
6 halfway, the alligators converge, he dives down and  
7 comes up. And he's pulling himself out of the pool,  
8 the alligator bites him on the leg, and he's lying on  
9 the pool bleeding, and the millionaire comes up to him  
10 and says, "That's the bravest thing I've ever seen."

11 He said, "I assume you want the million dollars."

12 "No."

13 He says, "I assume you want my yacht."

14 "No."

15 He says, "Then you want my daughter's hand in  
16 marriage?"

17 He says, "No, I don't even know your daughter."

18 So he says, "What do you want?"

19 He says, "I want the person who pushed me in the pool."

20 (LAUGHTER)

21 **DR. ABRAMSON:** Well, it was an interesting conversion

1 over to -- taking over -- from sitting on the committee  
2 to actually being the Chair.

3 (LAUGHTER)

4 **DR. ABRAMSON:** And I'd like to highlight a few of the  
5 issues. I think there was major areas of agreement.  
6 In fact, I think for the Public Health Service and the  
7 American Academy of Pediatrics the vast majority of  
8 issues were agreed upon.  
9 Number one, we all agreed that the risk of not  
10 vaccinating children for every one of the 11 diseases  
11 that we try to prevent with vaccines far outweighed any  
12 potential risk of giving the vaccine containing  
13 mercury.  
14 Two, that we should eliminate or reduce as quickly as  
15 possible the amount of mercury in vaccines.  
16 And three, which hasn't really been pointed out this  
17 morning, is that we agreed that we should delay the use  
18 of the vaccine in the baby who is born at term and not  
19 use it at term. And why is that? And the reason is  
20 that even if you take a full-term baby who weighs 3  
21 kilograms and you take any of the standards, from the

1 EPA standards to the FDA standards, you are exceeding  
2 on that day the amount of mercury that is -- that  
3 guidelines recommend you give, by greater than tenfold.

4 And we don't know what the safety margin is. This was  
5 pointed out today, and I'm sure it was pointed out  
6 yesterday, we don't really know whether it's cumulative  
7 dose or what that really matters. So we both -- Both  
8 the Public Health Service and the American Academy of  
9 Pediatrics agreed that the hepatitis B vaccine should  
10 be delayed in a mom who is hepatitis B surface antigen  
11 negative.

12 So what were the two areas of divergence? And I must  
13 state up front that some of the confusion that has  
14 occurred has been because of the areas of divergence.  
15 We certainly get letters at the Academy asking us why  
16 we diverged, and at some point, we probably need to  
17 write an editorial just talking about the whole process  
18 that went on. Because one of the issues that I'm going  
19 to raise later on is: How do you deal with emergencies  
20 when the approval process for recommendations varies  
21 substantially between the American Academy of

1 Pediatrics? How do we go through the process of  
2 getting our recommendations approved? We, as a  
3 technical committee, the Committee on Infection Disease  
4 goes through the process of getting our recommendations  
5 approves, versus the ACIP or any part of the Public  
6 Health System which has to go through a very different  
7 process.

8 So where did we diverge? We diverged a little bit at  
9 when should you start the hepatitis B vaccine, and it  
10 simply was over a matter of how safe do you want to be.

11 Everything we did with hepatitis B and the hepatitis B  
12 surface-antigen-negative mom related to how safe do you  
13 want to be, what kind of factor do you want to --  
14 safety factor do you want to add? I don't think  
15 there's a right answer to it. I think the issue is the  
16 safety issue.

17 And the second is, the Academy did not comment about a  
18 hepatitis B surface-antigen-negative mom who is in a  
19 high-risk group or the family is in a high-risk group.

20 In other words, someone from Africa, for instance.  
21 And the Public Health Service said vaccinate them,

1 vaccinate them at term. We did not comment on it and  
2 we specifically didn't comment on it. There's really  
3 two things that go into the equation about that.

4 One is that the risk of horizontal transmission during  
5 the first two years of life is very, very small. And  
6 we are both, both the Public Health System and the  
7 American Academy of Pediatrics, strongly recommending  
8 that you finish out your immunization, your three-dose  
9 hepatitis B immunization by 18 months of age.

10 But the Public Health Service had data  
11 that -- at least when we were making the decisions we were  
12 not aware of, that said that if you do not start the  
13 vaccination at birth, that the completion of the three-  
14 dose series goes down from 96 percent to 81 percent.  
15 So if you're talking as the American Academy of  
16 Pediatrics does to its pediatricians, and you're saying  
17 you can make that individual decision based on your  
18 family, what's the chance that they're going to come  
19 back versus not come back, versus you're dealing with  
20 it from a public health perspective and you know that  
21 number, you could understand where the difference comes



1 from.

2 I do think there are remaining issues, and I think  
3 Roger highlighted a number of them very well, but one  
4 that I'll want to get back to is, when you have  
5 emergent situations -- And remember, this was not the  
6 only emergent situation. Rotavirus was happening at  
7 the same time. I'm not kidding you when I tell you I  
8 hung by phone booths for hours at a time, sitting on a  
9 phone in Canada, going around Canada and hanging by the  
10 phone, and we're trying to deal with this on as fast as  
11 possible basis as we can as we're getting the  
12 information.

13 So how do you go through the approval process when the  
14 approval process is very different? The ACIP cannot  
15 come together as a committee without publishing it in  
16 Federal Registry. We need to deal with that because  
17 this may not be the last emergency that we have to deal  
18 with.

19 What is the mercury exposure from other sources? We  
20 still haven't dealt with that. And, I mean, we put the  
21 data in. I might as well say it. A six-ounce can of

1 tuna has 17 micrograms of mercury in it, on average.  
2 There's obviously a range to it. What does that mean  
3 for a pregnant woman? What does it mean to the fetus?  
4 I sit on the ACIP Influenza Working Group, and we  
5 discussed the issue, what are we going to do with the  
6 pregnant mom? Well, the pregnant mom in the second and  
7 third trimester has a substantially higher risk for flu  
8 than does a non-pregnant mom. So based on our  
9 principles, we would recommend giving the flu vaccine,  
10 and that's what the working group is going to advise.  
11 Now, that doesn't mean the Public Health Service has to  
12 agree to it, but that raises the question of "Is that  
13 the right decision?" -- I think so -- but do we need to  
14 put other things in the consent form to inform a parent  
15 or an expectant mom about that.  
16 The education of the public. I will tell you that we  
17 received a number of letters from angry pediatricians  
18 because they don't use computers and the public -- some  
19 of the public does, and the public learned about it  
20 before the pediatrician did.  
21 And I don't know a way of solving it. We actually put

1 out something that's called the Peds Com, which takes  
2 several days to get out and put out, but it is  
3 expensive and it's much better and much faster to do it  
4 by computer, and it's much cheaper to do it by  
5 computer. Those are all issues that come about when  
6 you're dealing with an emergent situation.

7 I personally think that the AAP and the Public Health  
8 System worked well together during these two emergent  
9 situations, and I've actually learned a lot from the  
10 process and enjoyed working with them.

11 That's all.

12 **DR. MODLIN:** Thank you, Jon.

13 Our next speaker is Peggy Webster, who is Director of  
14 the National Coalition on Adult Immunization, and she  
15 will give us the perspective of that group.

16 **DR. WEBSTER:** Thank you, Dr. Modlin.

17 Good morning. I just came to represent the National  
18 Coalition for Adult Immunizations this morning and give  
19 you a statement of where we stand on these issues of  
20 thimerosal in vaccines. What I have here is nothing  
21 earth-shattering -- I'll give you that -- but let me

1 just read to you what we put together here, and I  
2 appreciate any comments that you might have afterward.  
3 While thimerosal has been used as a preservative in  
4 many vaccines for many decades without apparent ill  
5 effect, it is nonetheless imperative that science and  
6 medicine continually seek safer and more effective  
7 medicines and procedures. With this in mind, we must  
8 make reasoned progress in the area of vaccines and  
9 vaccine research. On the one hand, each of us no doubt  
10 feels some level of concern in knowing that a small  
11 amount of a mercurial compound is present in the  
12 vaccines that we give to children, pregnant women,  
13 nursing women, and adults. On the other hand, it is  
14 also the case that it is difficult to find any  
15 definitive data suggesting that the use of such  
16 compounds has resulted in any direct harm to humans.  
17 We must also recognize that changing from one  
18 preservative to another is not without some level of  
19 risk itself, no matter how small, and may lead to other  
20 potentially unknown side effects.  
21 With this understanding, our organization would like to

1 emphasize concerns about the use of thimerosal in two  
2 settings.

3 First, the Advisory Committee on Immunization Practices  
4 has rightly made the national recommendation that women  
5 who will be beyond their first trimester of pregnancy  
6 during the influenza season receive the influenza  
7 vaccination. Those who have medical conditions that  
8 increase their risk for complications from influenza  
9 should be vaccinated before the beginning of the  
10 influenza season regardless of the stage of pregnancy.  
11 It is important to note that all of the licensed  
12 influenza vaccines in the U.S. do contain thimerosal.  
13 There has been no reason to believe that there may be  
14 adverse fetal effects associated with using thimerosal-  
15 containing vaccinations. The NCAI agrees with the ACIP  
16 that more data are needed in this special circumstance.  
17 Second, there is a small population of vaccine  
18 recipients who have an allergic sensitivity to  
19 thimerosal. Even when allergy testing does indicate  
20 hypersensitivity to thimerosal, most patients do not  
21 develop reactions when given thimerosal-containing

1 vaccines. If reactions do develop, they almost always  
2 manifest as local reactions, but, nonetheless, can  
3 discourage both patient and provider from further  
4 immunization.

5 In effect, the use of thimerosal-containing vaccines  
6 means that a small proportion of the population cannot  
7 or will not receive vaccines which protect them against  
8 the morbidity and mortality of many otherwise vaccine-  
9 preventable diseases.

10 The National Coalition for Adult Immunization is an  
11 advocacy group that is committed to decreasing the rate  
12 of vaccine-preventable diseases in adolescents and  
13 adults, and is therefore in support of the  
14 recommendation to continue utilizing vaccines until  
15 further guidelines are established.

16 In the meantime, NCAI calls for and supports the  
17 following steps:

18 First we support the recommendation from the Public  
19 Health Service and FDA that all vaccine manufacturers  
20 submit a plan for the elimination of all mercury-  
21 containing compounds from human vaccines as soon as

1 possible.

2 Second, we support and call for further research into  
3 the benefits and risks of these compounds in  
4 individuals and their potential impact on public  
5 health, particularly in regards to the possibility of  
6 neurodevelopmental effects on the developing fetus.

7 Third, we support and call for the development of  
8 communication materials for health care providers and  
9 patients that clearly and fairly articulate the current  
10 controversy while maintaining public confidence in the  
11 enormous individual and societal benefits of  
12 immunization.

13 Finally, we support the Public Health Service and the  
14 American Association of Pediatrics call for expedited  
15 FDA review of manufacturers' supplements to their  
16 product license applications which eliminate or reduce  
17 the mercury content of their vaccines.

18 Thank you for the opportunity to participate.

19 **DR. MODLIN:** Thank you, Dr. Webster.

20 Our next speaker will be Dr. Neal Halsey. Neal is  
21 representing the Institute for Vaccine Safety at Johns

1 Hopkins University School of Public Health and Hygiene.

2 **DR. HALSEY:** Thank you very much, John.

3 I didn't come prepared with a rebuttal for Jon  
4 Abramson. I should have thought more about it, but I  
5 can't come up with jokes quite that quickly, but I  
6 agree entirely with what Jon said. I also agree with  
7 almost everything that Roger Bernier presented -- I  
8 can't find him in the audience right now -- and we can  
9 talk about areas where we do disagree, but I do think  
10 that the business of providing guidelines to physicians  
11 and parents is unfinished during this transition  
12 period. I'm asked to comment on what the perspective  
13 is of the Institute for Vaccine Safety during the  
14 transition period.

15 Well, the position is fairly simple, and that is that  
16 all children should be protected against vaccine-  
17 preventable diseases using the safest possible  
18 vaccines. Actually, I think that everybody in the room  
19 would agree with that.

20 The objective in the transition period is to minimize  
21 any potential risks that might be there, but, also, as



1 many people have stated, to maintain public confidence  
2 in vaccines, the agencies, the federal agencies  
3 responsible for both vaccine safety and for delivery of  
4 vaccines, but also to the physicians who not only are  
5 responsible for providing those vaccines, but also for  
6 advice and guidance to parents of children who are  
7 going to be receiving these vaccines.

8 We do need to pay attention to what's happened in the  
9 public in recent years over the increased concern about  
10 product safety in general, and I won't spend the time  
11 to go through all of these examples, but we do need to  
12 be aware that there's been concern about environmental  
13 exposures of a variety of types, food contamination,  
14 automobile safety, toys, as well as drugs and vaccines.  
15 Where these have been handled well, it increases the  
16 confidence of the Public Health Service and government  
17 in general, but there are several examples of where  
18 they have not been handled as well as they could have  
19 been, especially in Europe, with loss of public  
20 confidence in our government agencies that are  
21 responsible for protection of safety, and we don't want

1 that to happen in this situation or any similar  
2 situation.

3 My personal belief is that we should follow the  
4 examples of what some of the producers of food,  
5 particularly children's food, baby food, in this case,  
6 from the representative of Gerber Foods, the CEO of  
7 Novartis, the parent company, in removing some  
8 chemicals, which, personally, I don't think carry any  
9 risk for those children. But their philosophy is that  
10 "We want a mother to buy our product and have no  
11 concern about this issue." We should adopt similar  
12 philosophies with regard to vaccines.

13 I'm going to make seven points, and I will come back to  
14 each of these in detail and only mention them at the  
15 beginning.

16 First, that I think the mercury content of vaccines  
17 should be in the package label.

18 Second, that all children are not created equal with  
19 regard to their risk of exposure to mercury.

20 Third, that I think hepatitis B has been unfairly  
21 targeted and assumed to be in some situations the only

1 problem that occurs with regard to thimerosal.

2 I think we need to do better -- a better job of  
3 informing both physicians and parents about the  
4 uncertainties that we've talked about and the options  
5 that are available to them to help deal with the  
6 potential or perceived possible risk. Everyone has  
7 said, and we fully agree, that there should be an  
8 expedited review of products with -- by the FDA with  
9 reduced or no thimerosal, and FDA has committed to  
10 that. So they don't really need us to tell them that.

11  
12 I think manufacturers should look very hard at  
13 providing unit dosing of vaccines whenever possible.

14 I think there is a problem at the FDA that does need to  
15 be addressed and that we need additional resources and  
16 scientists to address vaccine safety.

17 To go back over some of these issues, now, the first is  
18 the product labeling. I had to ask myself why someone  
19 who -- I felt I knew a fair amount about vaccines over  
20 the past 25 years and knew something about  
21 environmental exposures, why I didn't put it together.

1       Why I didn't realize how much mercury was actually in  
2 vaccines. And I think it's because the product label  
3 indicates a concentration of thimerosal of 1 to 10,000,  
4 or a .01 percent.

5       And as Leslie Ball walked us through, you have to go  
6 through a two- or three- or four-step calculation, and  
7 you have to know the molecular weight of thimerosal to  
8 come up with the 25 micrograms for mercury.

9       Since mercury is the biological agent, the biological  
10 product that's there, and we have guidelines for the  
11 amounts of mercury that people should be exposed to,  
12 that should be in the product label.

13       There are many factors that are associated with mercury  
14 toxicity, and that's what I mean by not all children  
15 are created equal with regard to their susceptibility.

16       Many of these were discussed yesterday, so I won't go  
17 back over all of them, but there are differences in  
18 terms of the age of exposure, the weight of children,  
19 other mercury exposures, differences potentially in  
20 metabolism and excretion rates on an individual basis,  
21 not for the products. No one has really addressed the

1 very well the genetic predisposition to increased risk  
2 of potential toxicity.

3 We can look most clearly at the weights of children,  
4 and I've picked girls here. Boys weigh slightly more  
5 than girls, but if we're looking at who may be the  
6 highest-risk population, the children who are the  
7 smallest, are the three standard deviations below the  
8 norm, their birth weight of 1.8 kilos, there's a  
9 difference, a more than two-fold difference, in the  
10 weights of these children, and if exposure to mercury  
11 is a weight-based phenomenon when you get a fixed dose,  
12 then that two-fold -- that is an important concern.  
13 That two-fold difference persists all the way out to  
14 almost six months of age. And we need to realize that  
15 it's the smallest children that I think that we have to  
16 be preparing our guidelines and decisions as to what we  
17 do with them.

18 If we take those weights of children and then apply the  
19 fixed doses and look at the worst-case scenario of  
20 children who may be getting all thimerosal products, or  
21 prior to the most recent change in the recommendations,

1 it plots out like this. And since sending Dr. Clarkson  
2 and Dr. Raub the data on the actual weights, I did  
3 adjust so that these children were getting hepatitis B  
4 when they weighed two kilograms.

5 We have, through the recent guidelines, addressed this  
6 exposure here, but, in fact, the exposure that's  
7 occurring at two months of age is several-fold higher  
8 than that exposure that's occurring at birth. And,  
9 yes, the infant is slightly older and therefore may be  
10 somewhat less, if there is a risk per dose delivered at  
11 that time, then this is something that I think we still  
12 have to be concerned about and decide whether or not  
13 anything further with regard to advice needs to be  
14 given.

15 I do differ with what Roger said and what I think the  
16 Public Health Service has concluded, that we can take  
17 the exposures and cumulate them over a year or over a  
18 six-month period of time. The evidence available about  
19 mercury toxicity doesn't support that. Yes, that's one  
20 aspect, the cumulative exposure, but there is the  
21 problem of an individual exposure at an individual time

1 from the acute toxicity data that exists.

2 An exposure with a fixed dose, 62.5 micrograms at two  
3 months of age, is different than an exposure at six  
4 months of age, or if that was at nine months or twelve  
5 months.

6 So I really question the philosophy that it doesn't  
7 matter when you got it or if you got a significant  
8 portion of that, one-third of it all in one day, that  
9 you really can take and look at that exposure over a  
10 six-month or a twelve-month period. So that's where I  
11 do differ.

12 I do not know that any of the guidelines that have been  
13 written by any of the agencies say that it's okay. Can  
14 you really get all 200 micrograms in the same day? I  
15 don't see that written any place, and I don't hear that  
16 from the people who have been responsible for  
17 developing those guidelines.

18 Which guidelines should be applied? We've been through  
19 this too many times. You've seen this similar slide.  
20 The Public Health Service has chosen the ATSDR, which  
21 is a little more liberal with regard to the allowable

1 exposures in the EPA. The WHO is quite similar to the  
2 EPA, as we have seen, with regard to those exposures.  
3 But over how much time can you take a single exposure  
4 and then say it's okay to get this over a day, a week,  
5 a month, or a year? We don't know. That's an unknown.  
6 The choice of the ATSDR guideline, which is based upon  
7 the Seychelle data, made sense at the time that it was  
8 done. The process was a good process that they used.  
9 But does it mean that we should ignore data that have  
10 been generated since then, and especially the follow-up  
11 in the Faroes Islands? And does it mean that it isn't  
12 going to change? The Faroe Island data were generated  
13 when these children were 5.5 years, and they were  
14 generated looking mostly at global I.Q. And as we  
15 heard from Dr. Lucier, there will be additional follow-  
16 up and there will be harmonization of the methods to  
17 evaluate these children. So they'll do some of the  
18 more domain-specific analyses that were done in the  
19 Faroe Islands that revealed those very subtle defects  
20 that were picked up. So it's an older age in the Faroe  
21 Islands and a more specific analyses that were done.



1 And equally, or, in fact, far more important, as Dr.  
2 Lucier mentioned and as Dr. Clarkson mentioned, there  
3 is the intermittent exposure that took place in the  
4 Faroe Island where it was coming a lot at one time or  
5 at monthly doses. And is that the explanation for  
6 finding problems in children at seven years of age that  
7 were not detected in the Seychelles at 5.5 years?  
8 Nobody knows that, but it certainly is one of the  
9 hypotheses that might explain the differences in the  
10 exposures and we must take it into account.

11 So I don't think that the Public Health Service means  
12 we should ignore all of these data, but we do need to  
13 be aware that they're there and take them into account  
14 and realize that more data will be forthcoming. And  
15 what will happen in two years' time if all of the  
16 experts review it and say, you know, we really should  
17 be using the Faroe Island data as the exposure, how  
18 will we be perceived?

19 And again, these defects that are being detected are  
20 very subtle defects, and they're not going to be  
21 detected without these very sophisticated testings that

1 was done.

2 Some interesting observations is that the males are  
3 more susceptible than females. I think that's a whole  
4 area of research that these groups will potentially  
5 look at, and finding. This is the finger-tapping test  
6 that was done, cumulative amount, both hands, easier to  
7 measure differences than one hand. In other words,  
8 again, you won't find these with less sophisticated  
9 testing.

10 If we accept or use the ATSDR guidelines and we  
11 superimpose those on these exposures and we put the  
12 daily, the weekly, or the monthly exposure here, we can  
13 see that at two months of age we're giving at a single  
14 day more than the total monthly allowable exposure for  
15 the ATSDR guidelines. And, in fact, the smallest of  
16 infants represented in the green bars are receiving  
17 almost three times, almost three months' worth of  
18 exposure on a single day. Is that really -- I haven't  
19 heard ATSDR say that that's really okay to do. I'm not  
20 convinced that it really is. And if we were to apply  
21 the EPA guidelines or the WHO more recent guidelines,

1 they are one-third of this. We're giving eight times  
2 the maximum exposure that they would give you for a  
3 month. Can you get six or eight months exposure in a  
4 single day? I don't think that exposure at two months  
5 of age can -- You can't take all of these over six  
6 months or a year and average them.

7 We haven't told physicians more precisely what they can  
8 do to help reduce that exposure. And if we simply  
9 limited it to one thimerosal-containing product that  
10 was given at 2, 4, and 6 months of age, it would be  
11 DTaP or HIB, then you can reduce this to less than --  
12 you can get less than the total monthly exposure for  
13 all but the very smallest of infants.

14 If we actually just gave the hepatitis B vaccine and  
15 said not use the other two products, then you can get  
16 it down below the weekly exposure for almost all  
17 infants.

18 And we do have the option that, in many situations,  
19 where you don't have to give any thimerosal. And  
20 everybody understands that goal, but it actually is an  
21 option that's available today. We really haven't told

1 everybody that that's something that you can do.

2 We've talked about all of the uncertainties. There are  
3 many. And again, there's not time to go through all of  
4 them, but we do need to focus on the other mercury  
5 exposures and which this exposure is added on top of.

6 We haven't really touched on any of the data on the  
7 potential effect on mild subtle things with regard to  
8 the immune system. Those data are going to be  
9 forthcoming in the next two years from various groups.

10 With regard to other mercury exposures, this comes  
11 directly from the EPA report to Congress, the key point  
12 is that the majority of the population is getting  
13 relatively low-to-moderate exposures. But in this  
14 country we have some populations that have very high  
15 levels of fish intake on a regular basis. And as we  
16 heard yesterday, FDA estimates that about 7 percent of  
17 women of childbearing age are already consuming fish  
18 enough that it would give them more than their  
19 guidelines, .1 microgram per kilogram per day. So any  
20 additional exposure we give them from vaccines is on  
21 top of that baseline that they have set with a safety

1 factor included.

2 But they also note in the report that 1 percent are  
3 receiving more than .37 micrograms per kilo per day.  
4 So there's 1 percent of pregnant women out there who  
5 are already getting more than what the ATSDR guideline  
6 is. And again, what we give them is added on top of  
7 that, and these children are being born with that  
8 exposure and some are getting this continued exposure  
9 through breast milk.

10 After all of the flurry of activity took place in late  
11 June and early July, I did take a vacation, went off to  
12 Maine to try to do a little canoeing and a little  
13 fishing and having some fun, only to come across these  
14 signs that says you can't forget about mercury. And,  
15 in fact, for the inland waters in much of the east  
16 coast of Maine, you're advised not to eat the fish at  
17 all if you're a pregnant woman, a nursing woman, or a  
18 child who's less than eight years of age. So there are  
19 advisories out there from the health departments  
20 indicating "limit your exposure to mercury," but  
21 they're not being followed. The general consensus in

1 the local population is that these are largely ignored  
2 by many of the local populations.

3 To change to one of the other topics about thimerosal,  
4 it's not the perfect preservative. It doesn't totally  
5 solve the problem. There are numerous clusters of  
6 cases of group A strep disease and presumably other --  
7 one, I think, of other bacteria that have occurred. So  
8 it doesn't solve the problem.

9 I personally believe that the manufacturers need to  
10 move more toward unit dosing in this country whenever  
11 possible. And not only is the benefit from  
12 preservatives being not needed in most situations, but  
13 there are the reduced errors due to reconstitution that  
14 we heard a bit about earlier today. And again, we  
15 don't need to go through all of those. There will be  
16 another session this fall on some of those issues.  
17 There are drawbacks, and these are major limitations  
18 that -- and that's increased space requirements in the  
19 refrigerator, but I don't think they're quite as bad as  
20 what John Clements was telling us. There are some  
21 technologies that can reduce the amount of space that's

1 going to be required to store unit dosing. There will  
2 be increased costs, and I recognize that as a major  
3 problem for developing countries, but I think that we  
4 do need to help in terms of addressing that issue. We  
5 need to look at it from this country.

6 So to maintain public confidence in vaccines and people  
7 giving advice about vaccines, I think we should put the  
8 mercury content in the label. I think we need to  
9 modify the vaccine information statements. That is our  
10 primary means of communication with families about any  
11 potential or perceived risks. We don't have it in  
12 there now. I realize the process is long to put it in,  
13 but I think that has to be done as soon as possible.  
14 I also think physicians should be given more precise  
15 guidelines over maximum allowable exposures at each  
16 age. Can we really have recommendations for the  
17 highest risk and have physicians looking at fish  
18 consumption and other things? The Academy of  
19 Pediatrics is developing additional guidelines on  
20 reduction of mercury exposure from all sources. Those  
21 won't be available for six to nine months. I don't

1 know what the time will be there, but do we need to  
2 have separate guidelines for immunization for those  
3 children versus others? In general we have said, no,  
4 we can't do that. We must make guidelines for  
5 everybody that will be applicable to all of the  
6 populations.

7 So my personal belief is that we should do what was  
8 done in Europe, that we should give a preference for  
9 thimerosal-free vaccines for immunization of infants in  
10 this country.

11 The last point I'll make is that we need good science  
12 to be used in making these decisions, and that good  
13 science has to come from all of our federal agencies.  
14 As I looked into what was going on at FDA and research  
15 into alternative preservatives, research into other  
16 ways to approach this and who is going to be reviewing  
17 these applications that were all asking for or  
18 demanding rapid review, what is the research budget at  
19 CBER? The research budget has been cut in the last  
20 five years to one-third of what it was before. Instead  
21 of being 20 percent more just to keep up with inflation



1 in that period of time, it's been cut to one-third. I  
2 don't know why. I don't know who's responsible, but I  
3 hope somebody goes to Congress and says that this is  
4 wrong.

5 Thank you very much.

6 (APPLAUSE)

7 **DR. MODLIN:** Thanks very much, Neal.

8 The next presentation will actually be by Dr. Bruce  
9 Gellen, who is representing the Infectious Disease  
10 Society.

11 **DR. GELLEN:** Thank you. I am speaking for the  
12 Infectious Disease Society because, as many of you  
13 know, about a year ago we began a project in  
14 conjunction with the Pediatric Infectious Disease  
15 Society and now joined by the American Academy of  
16 Pediatrics that's really trying to look at this issue  
17 in a broader way of trying to gauge what the current  
18 level of confidence is in our vaccines and immunization  
19 program, and by that, to try to see what we can do to  
20 maintain or build the confidence in those programs.  
21 So, with that, the area of communication and education

1 has really been a focal point.

2 Sitting through here for a couple of days, I'm  
3 impressed that you can never stop learning the lessons,  
4 and I think I'll talk a little bit about those, but one  
5 of the important lessons I learned this morning is that  
6 if you chair these AAP committees, you can never go on  
7 vacation. Poor Jon was strung out at every phone booth  
8 that was in Canada and Neal finds signs in the middle  
9 of Maine that tells him he needs to go back and do  
10 another PowerPoint presentation.

11 And the final lesson I learned is it sounds like CBER  
12 needs to invest in Microsoft to try to help some of  
13 their budget requirements.

14 But I think that Sam outlined some of the highlights I  
15 want to just underscore, and he did that with his last  
16 slide, that the handwriting's on the wall. I think  
17 that that really tells us that it's our responsibility  
18 to see that it's there, to read it, to interpret it,  
19 and then to effectively communicate it to all the  
20 people who really need that. As has been outlined by  
21 several on the previous panel and at various points

1 throughout this session, that's the public health  
2 community, the clinicians, the parents, the media, and  
3 to legislators.

4 I think that we've had an interesting opportunity to  
5 interact with colleagues from the environmental  
6 toxicology world because, as I've been learning the  
7 lessons of risk communications, they're the people who  
8 have been doing this for a lot longer than we have, and  
9 now we have recognized that that's a part of the  
10 business that we need to get into.

11 As the face of the disease has gone away, there is  
12 increasing concern about the risks, both real and  
13 potential and imagined, of the vaccines, and that we  
14 need to address those in the same way the environmental  
15 risks come up all the time, and I'll bet you can't open  
16 any newspaper in this country where there's some  
17 headline about something that you may be exposed to  
18 that's causing some ill health.

19 So I think that we've learned some lessons. We've  
20 learned some lessons about the development and approach  
21 to guidelines and how that can guide not only policy

1 decisions, but should also guide communication about  
2 those decisions.

3 And finally, I think, under the category of lessons  
4 learned, from the very beginning of this session  
5 yesterday, there were questions about whether or not  
6 the decisions that have been made are up for grabs or  
7 are reversible, depending on what we heard.

8 I think that we all had the subtle hope that a meeting  
9 like this that brings together the world experts would  
10 give us the answer to guide us, and I think that if you  
11 had heard what I've heard, that we don't have  
12 absolutely clear answers and the hopes that a meeting  
13 like this would be done in a -- would bring together  
14 all those people that would provide that kind of  
15 guidance wasn't going to happen because uncertainties  
16 remain. And while everybody keeps pointing to Gina to  
17 tell us what those uncertainties are, we've heard them  
18 and a number of people have highlighted them, but I  
19 think that we know that that's what this arena of risk  
20 communication is about, which is communicating making  
21 good decisions in the absence of complete information.

1       And I think that we also understand that when faced  
2       with an issue, not making a decision or ignoring it or  
3       delaying it is, in fact, making a decision.

4       And I think finally what we also need to be more  
5       transparent and communicative about is the process that  
6       we go -- that we undergo when these things come up.

7       Jon highlighted that, and I think that that's really an  
8       issue that we really should be discussing: what do you  
9       in these emergency situations? And there will be some  
10      that will be far more emergent than this, I imagine, in  
11      vaccines and other issues, but I do think that that's  
12      something that we really need to address, of how you  
13      can, when faced with an emergency, deal with that in a  
14      responsible fashion and make moves in a way -- make  
15      moves and communicate those moves despite uncertain  
16      information.

17      So I think that we've learned that there are health  
18      risks of mercury-containing compounds. We have the  
19      desire, all of us, to reduce those risks from all  
20      sources that we can, and that with a limited data, we  
21      are going to be forced to make assumptions and

1       extrapolations, and there may be differences in how  
2       people handle each of those, but that we then need to  
3       continue to do our best to be as transparent about all  
4       the -- about the process, and to let people know that  
5       there actually is a process in place that's looking at  
6       these things. I think we have heard that from a number  
7       of speakers as well, that it's not as though there are  
8       not systems in place that recognize this. And I think  
9       that, as Jon highlighted, the fact that this went on,  
10      essentially concurrent with the issue of rotavirus,  
11      highlighted that to all of us.

12     We have had a number of these, as we've discussed in  
13     the past, quote, "case studies," and I think that we  
14     really need to take a hard look at the case studies  
15     that we've been presented to see what lessons we can  
16     learn for the next time and how we can go about making  
17     good decisions based on the best available science and  
18     communicate those decisions though there's still  
19     uncertainty.

20     Thank you.

21     **DR. MODLIN:** Thank you, Bruce.

1 The final presentation will be from the Association for  
2 State and Territorial Health Officials. The  
3 presentation will be made by Claire Hannon, who is  
4 Director of Immunization Policy for that organization.

5 **MS. HANNON:** Thanks. The Association of State and  
6 Territorial Health Officials is the association that  
7 represents the state health official or the comparative  
8 senior executive in each state health department in the  
9 territories, just so you know who we are.

10 John Williamson was scheduled to be here today, but  
11 unfortunately he couldn't make it. He's from Alabama,  
12 and they had a legislative issue, as we all know.

13 ASTHO doesn't have a specific policy at this time on  
14 thimerosal, so I just wanted to give you some  
15 background, how we reacted, and a sense of what state  
16 health officials feel about the issue.

17 Vaccine policies are decided on a state level, and for  
18 that reason, ASTHO still maintains clear support for  
19 state flexibility.

20 The ASTHO organization works to make sure that states  
21 have the best information available, and we provide an

1 opportunity for health officials to work with partners  
2 and each other to build consensus. We did work quickly  
3 on the thimerosal issue and gave state health  
4 departments to discuss the issues amongst themselves  
5 and with CDC.

6 As I said, we don't have existing policy. And amongst  
7 all these discussions with the state health officials,  
8 we were not able to reach consensus on specific new  
9 policies in such a limited amount of time in reaction  
10 to thimerosal.

11 So for that reason, states are using the available  
12 science, as well as the CDC and AAP recommendations, to  
13 formulate their own policy on a state-by-state basis.

14 At this point, my discussions with state health  
15 officials I think would indicate that they don't see a  
16 serious cause for concern at the current level of  
17 thimerosal but believe it is prudent to reduce or  
18 eliminate thimerosal, given that new vaccines with  
19 varying manufacturing needs can be expected in the  
20 future.

21 We are very concerned with maintaining immunization



1 coverage, protecting infants from disease, and  
2 maintaining public trust. And again, we, as the  
3 organization of ASTHO, support consensus building based  
4 on science, information sharing, communication among  
5 states and all the other parties involved.

6 Just to add a little bit of state perspective, I spoke  
7 with Dr. Natalie Smith, who is here today from the  
8 California State Health Department. She's a member of  
9 the Association of Immunization Managers, and they've  
10 also been holding discussions over the last two weeks  
11 or so about thimerosal and vaccine safety issues.

12 It does appear that states are taking a variety of  
13 approaches in the transition to thimerosal-free  
14 vaccine, approaches which are sometimes very different.

15 I think both of our associations are eager to hear the  
16 most up-to-date information, including reports from  
17 this conference, and share those with the states. The  
18 states benefit from clear direction and lead time to  
19 implement policy changes.

20 Thanks.

21 **DR. MODLIN:** Thanks, Ms. Hannon.

1 I'm going to ask Roger to come down and join the panel,  
2 if you would. And at this point in time, I would like  
3 to open this up for questions, for comments. I think  
4 members of the audience are certainly welcome to offer  
5 their own comments or to direct questions directly to  
6 individual members of the panel, and we'll start back  
7 here.

8 Bud Anthony? Again, when you do speak, please  
9 introduce yourselves prior to your question or comment.  
10 Bud?

11 **DR. ANTHONY:** My name is Bud Anthony. I'm with the  
12 Biologics Consulting Group in Alexandria.

13 **DR. MODLIN:** Bud, excuse me. I think you may need to  
14 turn on the mic there. There's probably a switch right  
15 below -- probably up above -- keep going. There you  
16 go. It may be easier just to speak from your seat if  
17 you have a seat with a microphone.

18 **DR. ANTHONY:** My name is Bud Anthony. I'm with the  
19 Biologics Consulting Group in Alexandria. And although  
20 Neal has cautioned that hepatitis B has been singled  
21 out, and it's certainly not the only vaccine that we're

1 concerned about, but it's my greatest concern, and  
2 those concerns were heightened yesterday by the  
3 presentation from Dr. Mast, so I have a couple of  
4 questions.

5 One has to do with the recommendations for deferring  
6 the hepatitis B vaccine in hepatitis B surface-antigen-  
7 negative mothers, and that is this: Isn't this policy  
8 of selective immunization of infants based upon  
9 maternal antibody screening, one that we abandoned  
10 almost a decade ago because it did not work?

11 I know the new policy is different. In a perfect  
12 world, I'd have no disagreement with it, but it seems  
13 to me we're going back to something that did not work  
14 very well.

15 My second question is, perhaps, more of a moot  
16 question, but as I understand -- as I understood  
17 Roger's presentation of the AAP position, it is that  
18 when a thimerosal-free hepatitis B vaccine is available  
19 that it will be given at two months. Why not give it  
20 then to newborns?

21 Thank you.

1       **DR. MODLIN:** Bud, I'm not certain that this is a policy  
2       that we have abandoned. I think it's a policy -- for  
3       screening pregnant women. I think it's a policy that  
4       we have added to. Maybe I'll let Neal -- and,  
5       certainly, Neal has been intimately involved with this  
6       in the past. Both let Neal and Roger respond.

7       **DR. HALSEY:** Jon is current chair, but --  
8       Well, the Academy policy to give the vaccine at birth  
9       was based upon a number of issues, and the Academy  
10      policy was published in '92, but the Public Health  
11      Service was published in '91, and I don't sense from  
12      anybody that I've had any contact with that there's any  
13      abandonment of that policy. I believe the Joint  
14      Statement still has the language in it, although it was  
15      modified, that once the thimerosal-free preparations  
16      were available, the preferred age will be at birth.  
17      The Academy's policy has been that you can initiate it  
18      between birth and two months of age, so there was  
19      flexibility within the schedule. That's the  
20      terminology that was used. But my belief is it makes  
21      sense to go back to birth immunization whenever

1 possible as soon as we have a thimerosal-free, but Jon  
2 is really the chair and should respond.

3 **DR. ABRAMSON:** Oh, I agree. Let's make it clear why we  
4 picked on hepatitis B. It is the one disease in the  
5 hepatitis B surface-antigen-negative mom that the  
6 infant is at very low risk for. The infant is at risk  
7 for pertussis. The infant is at risk for HIB disease.

8 So that is why we picked on hepatitis B, not for any  
9 other reason. And we've stated clearly in numerous  
10 places that once we have thimerosal-free vaccines, we  
11 will go back to recommendations for giving it at birth.

12 **DR. ANTHONY:** Let me respond quickly. My concern is  
13 that babies who we all agree need the vaccine will fall  
14 through the cracks, and we heard examples of that  
15 yesterday. And the selective policy -- I was not privy  
16 to the decision, but it's my strong impression that we  
17 got away from selective immunization because it did not  
18 work.

19 **DR. ABRAMSON:** I don't see us as selectively  
20 immunizing. I see us as immunizing at just a delayed  
21 period of time. The recommendation is still to get

1 three doses in by 18 months of age.

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

3 **DR. DAUM:** Bob Daum from University of Chicago. I've  
4 also been impressed -- I think Bruce made the comment  
5 of how much out there there is to learn (inaudible) is  
6 that there is a big mercury vacuum in your brain and we  
7 don't know much about it and (inaudible) learn a lot in  
8 a couple of days. And there's obviously a long way to  
9 go in terms of understanding what the effects are on  
10 the brain and whether this ethylmercury has any effect  
11 at all, much less what the effect of methylmercury is.  
12 But I'm wondering how this got so quickly translated  
13 into a public and private immunization policy. And I  
14 read when the Beatles were doing public performance and  
15 they actually gave up performing before they broke up,  
16 and the reason they gave up performing is because they  
17 were having to perform in larger and larger stadiums.  
18 And what they found was they couldn't do anything  
19 subtle on stage, because if they tried to, no one would  
20 see it and no one would understand it. They were  
21 performing in 100,000-seat stadiums.

1 And in a way we are performing in a similar stadium,  
2 because we make very fine and sweet vaccine  
3 implementation policy here in rooms like this, or much  
4 smaller ones, and expect pediatricians and public  
5 health people around the country, and we've heard also  
6 around the world, to go forward with these utterances  
7 and carry it out in a crisp, precise clinical activity.

8  
9 Well, that's not what happens. I've learned from my  
10 activities in inner city Chicago that there are -- it's  
11 like playing the telephone game, that people whisper  
12 and people read these recommendations and then come  
13 away with vastly different interpretations of them and  
14 vastly different concepts of them and, therefore, the  
15 translation of this is going to have errors and  
16 consequences along the lines of what Dr. Watson talked  
17 about here yesterday.

18 In addition to that, John, I don't know if you were  
19 here yesterday, but we know from our inner city  
20 population in Chicago that if you look at kids that  
21 received their first dose of hepatitis B vaccine at

1 more than three months of age, only 10.6 percent of  
2 those kids have finished the three-dose series by 19  
3 months. We also know that if you delayed -- whatever  
4 that first intervention is doing, if you delay it and  
5 take a (inaudible) in receipt of 4, 3, 1 by two years  
6 of age.

7 The bottom line of these two kinds of things is the  
8 translation of a sudden change of policy interaction  
9 and with, in my view, a relatively minimal amount of  
10 information that demands this kind of emergency is that  
11 we're going to throw a lot of vaccine programs into  
12 confusion.

13 It certainly sounds as if mercury is an issue that we  
14 all ought to think about. It certainly sounds as if we  
15 all ought to be thinking about how to get a mercury-  
16 free vaccine. I'm the first one to stand up and want  
17 safer vaccines -- I think that's a crucial part of our  
18 program -- but I just don't understand why it was so  
19 urgent to shift this immunization policy so quickly.  
20 It creates a confusion that you're hearing only distant  
21 echoes in this room, because a very few of us are out



1 on the front line doing vaccine implementation. But,  
2 nevertheless, I can tell you, it's beginning to sound  
3 like a louder and louder noise among the people that I  
4 take phone calls from and interact with every day.  
5 So I guess that's my comment, and I'd certainly like to  
6 hear anybody's response to that.

7 **DR. MODLIN:** Roger?

8 **DR. BERNIER:** I was thinking you probably expected Neal  
9 to answer that question, but I'll probably surprise you  
10 by trying to tackle it myself.

11 I think what's happened is that -- I've told this to  
12 some people -- we've had a paradigm shift in how we  
13 think about this preservative. And when I went to  
14 leadership classes, I was told paradigm shifts take  
15 years. I think we experienced a paradigm shift in  
16 days, or maybe weeks at the most.

17 And it has to do with our consciousness being raised  
18 about the potential, potential, effects of mercury.  
19 Once we had that realization -- And I think in some way  
20 there was a new realization for all of us, and some of  
21 us came to it for different reasons in different ways.

1  
2 I think Neal likes to talk about how, you know, the  
3 concentration and the dilution were not an easy way to  
4 realize this, but all of us in some way have had a sort  
5 of heightened awareness now, and we can't do business  
6 as usual. I mean,  
7 that's -- While there's not a lot of evidence about harm,  
8 and it's a potential thing, it does become a matter of  
9 choice and goal and direction that you want to go into.  
10 That's how I would tackle it.

11 **DR. MODLIN:** Yes?

12 **DR. RICHARD:** I'm John Richard from the Agency for  
13 Toxic Substances and Disease Registry. For Dr. Halsey,  
14 you brought up some very good and very germane points  
15 that's consideration --

16 **DR. MODLIN:** Apparently, you don't have your microphone  
17 on. I'm sorry. Let's try this again.

18 **DR. RICHARD:** Yeah, for Dr. Halsey. I'm John Richard  
19 from the Agency for Toxic Substances and Disease  
20 Registry.

21 You raised some very good points, and I was just

1 pointing out that those are things that the government  
2 health agencies that are involved in this and involved  
3 with the analysis for assessment of health effects of  
4 mercury have been concerned about and have considered.

5 And I think this afternoon, in the research needs  
6 portion of the program, some of those will be  
7 addressed.

8 You also raised some questions or asked questions of  
9 ATSDR, and real quickly I'd just like to point out  
10 three things.

11 One is that in a series of three injections, three  
12 vaccinations, the total dose, as I understand it, is  
13 62.5 micrograms per child. While that's to the child  
14 in the Seychelles study, we looked at the dose that the  
15 mothers received every day on the average throughout  
16 pregnancy, and that was 78 micrograms per day. Well,  
17 that's to the mother, of course, and on a milligram-  
18 per-kilogram basis, that's different. But if you take  
19 that 78, then that every week they're receiving almost  
20 600 micrograms of mercury, and this goes on throughout  
21 pregnancy. Not only that, but the methylmercury is --

1 all mercury, or most mercury is accumulated in the  
2 fetus at higher levels in the fetal circulation than it  
3 is in the maternal circulation.

4 So these were infants or neo -- excuse me, not neonates  
5 -- fetuses being exposed throughout critical times in  
6 their development, and we're not saying one point of  
7 development is more important than the other, or  
8 whether it's the beginning of (inaudible) migration  
9 early in the third week, or whether it's further into  
10 cerebella or cerebral organization, but throughout all  
11 those critical points of fetal development, they were  
12 exposed to mercury, methylmercury, through high levels  
13 of maternal ingestion relative to the levels that we're  
14 talking.

15 For what it's worth, methylmercury is believed to be  
16 absorbed close to 100 percent, 95 to 100 percent,  
17 through the gastrointestinal tract. So those 78  
18 micrograms a day is actually an absorbed dose.

19 Two other quick things, then I'd be happy to hear your  
20 response, sir.

21 In the Seychelles, by and large, the tests were of

1 global cognitive function. However, the McCarthy  
2 scales tests were conducted, and back in November when  
3 the workshop was conducted in Raleigh, one of the  
4 panels actually examined the data from the McCarthy  
5 subscales and they concluded -- And it's in that report  
6 that George Lucier said he had available -- that the  
7 data from that on a limited -- not limited, they didn't  
8 use the term -- but domain-specific effects indicated  
9 no domain-specific change in alteration and function as  
10 a result of methylmercury.

11 One thing that I think is a misunderstanding, I think  
12 there's the impression that EPA used the Iraqi data and  
13 that we used the Seychelles data, and that's, in part,  
14 correct. We looked at all the data, but from ASTDR's  
15 perspective, we actually used the Faroes -- the results  
16 of the Faroes study as the basis as the basis of an  
17 additional uncertainty factor. So we did look at that  
18 and did consider that in our evaluation.

19 That's all I had to say.

20 **DR. HALSEY:** The one thing you haven't done is answered  
21 the key question that the physician and the parent have

1 to face on the day of immunization. That is, how much  
2 of that exposure can they get on a single day? You  
3 haven't given us the answer to that. I would hope that  
4 your agency goes back and tries to address that  
5 question. Would you really accept getting three months  
6 worth of exposure at one time?

7 **DR. MODLIN:** Stan, is it on this issue?

8 **DR. PLOTKIN:** Well, no.

9 **DR. MODLIN:** Okay. Well, we'll come back, then. Dr.  
10 Mahaffey?

11 **DR. MAHAFFEY:** Some comments and a couple of points.  
12 First of all, while on average the amount of mercury  
13 exposure through food is under the EPA .1 microgram per  
14 kilogram per day for adult women, it's certainly not an  
15 even distribution and, as Dr. Halsey pointed out, there  
16 are groups who are far higher with one percent above  
17 the ASTDR level. There are also groups within  
18 subpopulations who go a great deal higher, and we have  
19 some idea of who these subpopulations are. We know  
20 that there are people in this country, probably two or  
21 three percent, who eat fish just about every day. So

1 while, on average, yes, it's true, the exposures are  
2 lower, they're certainly equal.

3 As far as the safety factors go, our safety factor of  
4 ten really is aimed at dealing with person-to-person  
5 variability and kinetics and differences in  
6 susceptibility to the effects of mercury. We started  
7 with a dose of mercury in maternal hair is about 11  
8 parts per million, which is really up there in the  
9 range that WHO indicates there are questions about with  
10 respect to vulnerability of the fetus. So that safety  
11 factor of ten is designed to deal with differences in  
12 susceptibility and kinetics.

13 Finally, the question -- I understood from the comment  
14 that the American Academy of Pediatrics is planning to  
15 look more broadly at mercury exposures and I would  
16 certainly be interested in a description of what those  
17 plans are.

18 **DR. MODLIN:** Jon, did you respond to --

19 **DR. ABRAMSON:** Did I understand the question to be,  
20 what else we're looking at making recommendations  
21 about? It's really outside of the Committee on

1 Infectious Disease. It's a question of should there be  
2 other guidelines as far as fish exposure, other sources  
3 of mercury exposure. So I'm really not in a position  
4 to comment about it.

5 I would like to address for a second just Bob's  
6 comment. For at least many of the people on the  
7 Committee on Infectious Disease, the crucial deciding  
8 factor for us to make a -- to go forth with a  
9 recommendation that differed than saying "Leave  
10 everything the same" is, at birth, we were giving many-  
11 fold higher than recommended by whoever guidelines you  
12 want to use. FDA or EPA or ATSDR, it was more than  
13 tenfold. And from everything we could hear, it was  
14 unclear that there was that kind of safety factor built  
15 into the equation. That's the answer from my  
16 standpoint.

17 **DR. MODLIN:** Yes?

18 **DR. ROGAN:** I'm Walter Rogan from the National  
19 Institute of Environmental Health Sciences and I'll  
20 briefly put my hat on as liaison to the Academy  
21 Committee on Environmental Health and say we are



1 writing a new mercury statement. We think, but we  
2 haven't been cleared, the intention for the statement  
3 is in and we haven't been cleared to write it yet, but  
4 we will write a new mercury statement. All that other  
5 mercury stuff that isn't infectious diseases is ours,  
6 so we will do that. That's the only thing I have to  
7 say about that. So we'll do that.

8 Take that hat off, I wrote the sentence about the  
9 McCarthy scale stuff. I think it's a little unfair to  
10 take that one sentence out of the context. I think  
11 that, broadly speaking, if you use the Faroe data as  
12 opposed to the Seychelle data, you would come up with a  
13 lower number because the Faroe data are positive and  
14 the Seychelle data are negative. So we, in that  
15 committee -- I was the Chair of the Psychometric  
16 Endpoint Committee for that meeting -- were  
17 uncomfortable dismissing the Faroe data on the basis of  
18 those objections that had been brought about on  
19 confounding domain-specific scores and things like  
20 that. So I don't want the impression left that we  
21 thought that because of some decomposition of the

1       McCarthy scales, the Seychelle data were somehow  
2       preferable. We ended up saying these are both good  
3       studies and you have to take both into account when you  
4       look at them.

5       Finally, back to -- It's hard to keep more than two  
6       things in my mind at once. Finally, back to risk  
7       management and something Dr. Gellen said, I think the -  
8       - I think the choice back in June was not between the  
9       Public Health Service and the Academy of Pediatrics  
10      saying something and, perhaps, producing a change that  
11      didn't benefit everybody, but, rather, between -- and  
12      saying nothing which would have resulted in everything  
13      going along just fine. I think at least the perceived  
14      idea was that to say nothing and to have the  
15      information that the FDA, during the process of  
16      implementing the Modernization Act, had uncovered or  
17      analyzed or calculated that these numbers were higher  
18      than we had expected would have gone out. There would  
19      have been inquiries of physicians, of state health  
20      officers, of vaccine programs, of everybody, and that  
21      would have gone into a void from -- with no statement

1 from the Public Health Service or the Academy. So it  
2 wasn't a question of this could just sort of go along  
3 with nobody saying anything. We won't know what the  
4 effect of that kind of uncontrolled and unprepared sort  
5 of thing would be because it was circumvented by having  
6 something in place, however imperfect and done in  
7 whatever haste, but I think that the emergency was not  
8 a toxicological emergency. It was the fear that the  
9 professional people responsible for answering the  
10 questions would be unarmed unless something went out  
11 from the Academy of Public Health Services.

12 I'm sorry I took so long.

13 **DR. MODLIN:** Thank you. Stan?

14 **DR. PLOTKIN:** At the risk of seeming to pick on Neal,  
15 who is partly paranoid by now -- Well, actually, it's a  
16 clarification. Neal suggested that the European  
17 attitude is to switch to thimerosal-containing vaccines  
18 immediately, and I'd like really a clarification from  
19 Dr. Teeling because it's my understanding, as I read  
20 the CPMP statements, that the ideal is to switch to  
21 thimerosal-containing vaccines as soon as possible in

1 terms of working with manufacturers to eliminate the  
2 material from the vaccines. I am not aware, and I'd  
3 like Dr. Teeling to clarify, that any national or  
4 European authorities have instructed physicians to stop  
5 using vaccines containing thimerosal.

6 **DR. HALSEY:** Can I clarify what I said, Stan, and then  
7 let Dr. Teeling respond? Okay?

8 What I said is I interpret the wording of that  
9 statement is that for infants and children there is a  
10 preference -- I didn't say stop -- there is a  
11 preference for the use of thimerosal. And I have it  
12 written in front of me, but, perhaps, Dr. Teeling could  
13 deal with that sentence that I was referring to. I  
14 didn't say stop and there isn't any order, it's a  
15 preference.

16 **DR. PLOTKIN:** I have to say that I think it's clear  
17 that we rule our preferring vaccines without it. The  
18 issue is, is it an emergency or not?

19 **DR. MODLIN:** I think we better let Dr. Teeling settle  
20 the issue. There is a black button there.

21 **DR. TEELING:** I'm quite happy to let everybody else to

1 answer my question. There's no problem.

2 I mean, I think what you're referring to is the  
3 sentence, "For vaccination in infants and toddler, the  
4 CPMP concluded that although there is no evidence of  
5 harm caused by the level of exposure from vaccines, it  
6 would be prudent to promote the general use of vaccines  
7 without thimerosal and other mercurial-containing  
8 preservatives, particularly for single-dose vaccines."

9 So I think you're both right and I think the statement  
10 that you're talking about is that this should be done  
11 within the shortest possible time frame, but in order  
12 to achieve this, we must work in cooperation with the  
13 WHO and the European Pharmacopeia as vaccine  
14 manufacturers, FDA, et cetera.

15 So I think the prudence is to move to that. We are not  
16 recommending stopping vaccinations in the meantime.

17 Now, it does state here that vaccinations should  
18 continue according to national legislation. And in  
19 reply to the second part of your question, this  
20 statement went out on the 8th of July. And certainly,  
21 my visit to the CPMP at the end of July, I had not been

1 informed that any national authorities had made a  
2 change. However, we did look at -- And I think this is  
3 an issue that has been looked at not particularly in an  
4 hurry, but is an ongoing issue at the national level,  
5 and there is the instance of one particular country,  
6 Austria, which had a tick-borne encephalitis, which is  
7 a particular type of disease which is very specific to  
8 the Austrian population. They use a vaccine for that.

9 And the addition of the tick-borne encephalitis  
10 vaccine added an additional burden of thimerosal to  
11 their vaccination programs, and I am aware that they  
12 have now withdrawn that vaccine and are using a  
13 thimerosal-free vaccine which has recently been  
14 authorized.

15 So I think it's an ongoing issue in Europe, much more  
16 so than it would appear to be here. I think we've been  
17 living with this for the last year and a half or so,  
18 with this move, and I think we have had communications.

19 Indeed, we have had some vaccines where the companies  
20 have already started to put in variations to reduce or  
21 eliminate thimerosal from the vaccines. So it's

1 probably a more ongoing issue. I think this statement  
2 is from the 8th of the July and, as to hard facts as a  
3 result of that, we haven't had anything else yet.

4 **DR. MODLIN:** There you go, a bit of Irish diplomacy.  
5 Roger?

6 **DR. BERNIER:** I would just like to one comment to try  
7 to give a sense of deliberations of the Public Health  
8 Service and the Academy of Pediatrics.

9 One of the big issues, in a situation where you're  
10 trying to take something that you believe is safe to  
11 make it safer, you are introducing a change, but for  
12 the sake of the credibility of the program, there was a  
13 big concern about not creating a perception of good  
14 vaccines and bad vaccines. And I think that this issue  
15 of preference gets into that category, that as we  
16 transition, we're trying to avoid the perception that a  
17 label of bad vaccine that would be put on a vaccine  
18 that contains thimerosal because it was considered to  
19 be a safe product. So there was a lot of discussion  
20 about this issue. So I think when we talk about  
21 preferences, we have to be careful. We all do prefer,

1 but I don't think it's a preference in the sense that  
2 we're willing to call things good vaccines, bad  
3 vaccines. Now, that was a very important driver for a  
4 lot of the deliberations.

5 **DR. MODLIN:** Yes?

6 **DR. HAUSDORF:** I'm Bill Hausdorf with Wyeth-Lederle. I  
7 have a question.

8 Yesterday, I was very impressed by the rapidity of the  
9 CDC surveying the hepatitis B screening practices, et  
10 cetera, in the wake of this change. That was really  
11 very impressive to have data like that. I wondered,  
12 given Dr. Daum's comments and also anecdotal things  
13 that I've heard about physicians misinterpreting the  
14 recommendations to assume that thimerosal-free vaccines  
15 are indeed evil and they don't use them, whether  
16 there's any attempt or plan by CDC to look at the  
17 effect of these recommendations on immunization timing  
18 or the rates of immunization outside of hepatitis B?  
19 Yesterday, Dr. Schwartz presented, I think, a pretty  
20 persuasive case, that if you delay DTP or HIB or  
21 whatever, you can clearly have a potential problem. I



1 wonder, is the CDC going to be looking at that?

2 **DR. BERNIER:** One of the recommendations in the Joint  
3 Statement -- I believe there were six of them. One of  
4 them is to carry out surveillance activities for these  
5 changes, and that is something that I think CDC is  
6 thinking about. Dr. Mast had told me yesterday about  
7 planned investigations to look specifically at  
8 hepatitis B issues, but at the moment, there's not a  
9 detailed action plan. In fact, we're stretched pretty  
10 thin doing a lot of these rotavirus investigations and  
11 doing a case-control study related to rotavirus, but it  
12 was foreseen in the Joint Statement, that there would  
13 be surveillance to monitor the implementation to see if  
14 any adjustments needed to be made.

15 **DR. MODLIN:** Back of the room? Yes?

16 **DR. GOODMAN:** Yeah, Jessie Goodman from CBER.  
17 Just to follow up on a couple of the comments, I think  
18 one of the things that may have occurred, and I guess  
19 luckily I was out of the country when all this  
20 happened, but if I was here I could speak more from  
21 firsthand knowledge, is that there is this spectrum of

1        what our public health emergencies are, true public  
2        health emergencies, epidemics of pneumococcal disease  
3        or exposures to toxic or infectious substances, and  
4        then there are potential public health threats. I  
5        think this very clearly is a potential public health  
6        threat that warrants very careful consideration and,  
7        because of the kind of consequences people have talked  
8        about, very careful consideration of the response. But  
9        under the microscope of the media and public concern  
10       and all that, what has tended to happen is that whether  
11       something is a potential public health threat or a  
12       public health emergency, they're all being handled as  
13       public health emergencies. I think although I'm  
14       hearing that the agencies all work together well under  
15       the circumstances, I would second Bruce's comments,  
16       that I think, one, I'd think through carefully if there  
17       are any ones we can improve our responses to these  
18       kinds of issues, not necessarily critiquing the  
19       response to this issue in its particulars, but not  
20       falling into that particular trap of everything being a  
21       crisis and everything being an emergency. That's

1 really all I wanted to say.

2 **DR. MODLIN:** Thank you. Further comments? Yes, Stan?

3 **DR. MUSIC:** Stan Music, working with Merck at the  
4 moment.

5 (LAUGHTER)

6 **DR. MUSIC:** I want to express some concerns about the  
7 epidemic of disease that I think we're beginning to see  
8 as a result of the controversy. When I hear John  
9 Abramson talk about a 3 kilogram normal infant and say  
10 on that day we exceed the guide by tenfold or when I  
11 heard Roger Bernier say "I haven't heard anybody say  
12 differently," I mean, I understand that the complexity  
13 is enormous and I think that that's an underestimate.  
14 I also want to make it clear that I am speaking  
15 professionally, as an epidemiologist with thirty-plus  
16 years now, and though I work for Merck, I'm not  
17 speaking for Merck. This has not been cleared.  
18 I spent twenty-eight years at CDC, mostly infectious  
19 disease, mostly outbreaks, mostly training  
20 epidemiologists, but in '96, I became the Chief of  
21 Environmental Epidemiology from North Carolina and I

1 learned a lot of NOELs and LOELs and mercury in fish  
2 and I was responsible for wording of the signs on the  
3 creeks that gave the warnings and was very unhappy with  
4 the way we had to interact with the regulators and the  
5 sort of emphasis on regulation without the true public  
6 health effectiveness of making those warnings heedable  
7 (sic). It's all over the east coast. It's not just up  
8 in Maine. It's in Maryland, it's in North Carolina,  
9 it's all the way down to the Gulf Coast.

10 When a MRL, a minimum risk level, or other guideline is  
11 applied here, it's -- I think it's being misapplied and  
12 I think it's being misapplied because of the way we  
13 label slides and because of the shorthand way we have  
14 to speak, but we have no data for ethylmercury. So in  
15 addition to what has been said, and I respect the  
16 rights and the integrity of everybody that said it, I  
17 think it's also legitimate to say that when a MRL,  
18 which is for chronic exposure for ingestion or  
19 inhalation and for methylmercury, is applied to what we  
20 are injecting with vaccines, will we get it all on the  
21 same day and we, at the same time, ignore any excretion

1 or we assume that it is all totally instantly  
2 bioavailable, I think that's an abuse of the MRL and I  
3 think we need to make slides say those things and say  
4 it the right way so that everybody understands that the  
5 shorthand doesn't confuse them.

6 That's the concern, and I want to state it clearly  
7 because I am concerned about the epidemic of disease  
8 that this controversy is causing. That is, delayed  
9 vaccinations are not good.

10 **DR. MODLIN:** Thank you. Dr. Clarkson?

11 **DR. CLARKSON:** I strongly agree with the previous  
12 speaker. I think there has been a misuse of these MRLs  
13 and guidelines. They are, as the speaker pointed out,  
14 intended for chronic long-term exposures. So the  
15 number you get for long-term exposure is a daily  
16 exposure that goes on continuously, six months, a year,  
17 and so on. You can't take that number and apply it to  
18 a single day, as apparently has happened by the  
19 statement that in a single day they'll get ten times  
20 what the guidelines says. The guideline is intended  
21 for day after day after day exposures. Let me give you

1 an example.

2 A comment was made about eating six ounces of tuna fish  
3 which contains 17 micrograms of mercury. Now, if you  
4 take that once, as a pregnant female weighing 60  
5 kilograms, the increase in mercury level in blood or  
6 tissues would be so small you couldn't measure it. If  
7 you took that six ounces day after day for six months  
8 to a year, her blood levels would slow rise until they  
9 reach the level consistent with these guidelines, about  
10 20 parts per day.

11 So there seems to be a tremendous misunderstanding as  
12 to what these guidelines mean, and with the benefit of  
13 hindsight, we should write a talk on the kinetics of  
14 mercury so that we have some understanding of what the  
15 meaning of a day dosage in terms of tissue levels  
16 versus the meaning of a six-month dose. And this is --  
17 I mean, in this learned audience, it worries me that  
18 there's such a misunderstanding of the guidelines.  
19 Lord only knows what the general public views these as.

20 (APPLAUSE)

21 **DR. MODLIN:** Yes?

1       **DR. ENGLER:** Dr. Engler. I just want to speak from a  
2       clinician's perspective and from an educator, both for  
3       physicians and nursing staff.

4       This event -- And I just want to emphasis the last two  
5       speakers; I agree a hundred percent -- has really  
6       stressed the front lines, once again, in ways that are  
7       hard to imagine until you sit in a clinic with a rapid  
8       rate of health care delivery challenges you where there  
9       is no adequate recognition of the complexity of  
10      immunization health care delivery and you very rapidly  
11      have thirty-minute visits that are not being counted or  
12      are not paid for in any of our systems, trying to  
13      answer questions that this illustrious group can't  
14      answer. I think that the whole issue of how we  
15      translate what the questions are and the words we use  
16      have a huge impact, and I want to take a lesson from  
17      the latex allergy issue.

18      We've moved away from saying we need to create latex-  
19      free environments because it's unrealistic. We talk  
20      about latex-safe environments which acknowledge that  
21      there is some latex exposure.

1 So just the language of saying thimerosal-free does  
2 convict in the layperson's mind and most providers who  
3 already don't think much of the vaccines. Some of the  
4 worst people who don't want to be immunized are  
5 physicians and nurses as a group.

6 Why aren't we talking about thimerosal-safe and  
7 recognizing that there is a balancing of issues in that  
8 arena? If we're going to make edict, then what about  
9 information fact sheets for providers and for the  
10 public that are readily available and palatable and  
11 let's call them "Draft version 1," so that the edicts  
12 that come down are translatable and usable in a quick  
13 user-friendly fashion. I think we should enhance the  
14 funding for the CDC section that helps write in a  
15 language that people understand.

16 If AAP, ACIP, et al. -- And it is very hard to teach  
17 people about all these organizations and what they do.

18 I'd love you to give me a teaching slide set on it  
19 that's user-friendly for our use. Why not use those  
20 people as you're working these rapid-response edicts to  
21 create those interim or early VIS version 1 so that as



1 you're evolving these issues, you take the rest of the  
2 world with you? When I've been to the Armed Forces  
3 Epidemiologic Board, I've said to them, "Do you all  
4 care that almost no one knows you exist or what you do  
5 and you're twixes never get to anybody who's doing the  
6 work?" And that is not just a problem in the military  
7 health care system. That is a problem throughout the  
8 health care system. Just speaking for, as I say, the  
9 nurses and physicians on the front lines, you know, we  
10 want to work with you, but it's awfully hard and also  
11 challenging.

12 **DR. MODLIN:** Thanks, Dr. Engler? Further comments?  
13 Dr. Klein?

14 **DR. KLEIN:** I think one of the positive aspects that  
15 we've learned from this experience is that introducing  
16 immunization in the nursery is a very positive feature  
17 of vaccine utilization and that that lesson should be  
18 carried through with hepatitis returning to the nursery  
19 at the earliest possible time, but the opportunity to  
20 introduce during that period where there is so much  
21 positive educational opportunity, I think, is one of

1 the most important things we've learned in the last  
2 couple of days.

3 **DR. MODLIN:** Thanks, Jerry. I think on that very  
4 positive note, I'll ask that we wind things up and  
5 certainly thank our speakers, our panel, and all the  
6 participants for their comments. It, indeed, has been  
7 a terrific morning and we look forward to a terrific  
8 afternoon.

9 We will start back again at 1:30 on the dot.

10 (LUNCH RECESS FROM 12:25 P.M. TO 1:34 P.M.)

11 **DR. MODLIN:** We are, this afternoon, being asked to  
12 look even further beyond the issues that we discussed  
13 earlier this morning and to begin to develop -- to  
14 identify, define, and develop the important issues for  
15 research regarding preservatives in vaccines and,  
16 specifically, thimerosal. The person that we've asked  
17 to lead the discussion this afternoon is Dr. Regina  
18 Rabinovich from the National Institutes of Health.  
19 Regina actually will take over and moderate the rest of  
20 the session for this afternoon. Regina?

21 **DR. RABINOVICH:** Thank you. Can people hear me? I

1 wish Sam Katz was here so I could thank him for the big  
2 buildup, but you know what he was really trying to do  
3 was set the stage so that you were trying to both  
4 listen to the meeting, as well as begin deriving your  
5 own conclusions as to what the next steps were. And  
6 you've all come here awake from lunch ready to work  
7 because I'm going to attempt to define the landscape as  
8 I understand it right now. I am not going to attempt  
9 to devise or force consensus because I don't think it's  
10 doable. Then I'm going to define some of the questions  
11 that remained in my mind as I listened to the  
12 presentations of pre-clinical, clinical, and public  
13 health and industry perspectives.

14 The panel members will each -- Dr. Clarkson, if you  
15 could join us up front, so that as each panel member  
16 speaks, they'll be up at the front. The panel members  
17 will each -- have been asked to speak for several  
18 minutes, no more than five or I will cut it off. I  
19 have Bill Egan's watch, good interagency collaboration  
20 here, and then the real work starts and all of you have  
21 to make sure that we have covered what it is we should

1 be considering in terms of research priorities,  
2 important questions, what's doable, and what's  
3 answerable.

4 I chose to spell "thimerosal" the way I finally learned  
5 to spell it, which is the U.S. way, and let me -- Okay.  
6 This is just a little part of the vaccine R and D  
7 component that I happened to have a slide ready for,  
8 but it's to remind me to remind us that when we talk  
9 about individual vaccines and when we worry about the  
10 vaccine schedule that each of the vaccines has gone  
11 through an intensive process of evaluation from Phase I  
12 through Phase IV where safety is a consideration as the  
13 number of subjects goes up and the questions that  
14 you're answering, be it immunogenicity, efficacy, or  
15 effectiveness, alter. There's, in reality, a huge  
16 oversight process to this part of it, and I think it's  
17 true for preclinical and what manufacturers need to do  
18 with potency and establishment licensure applications,  
19 which you guys don't have to follow anymore, that kind  
20 of thing. But it includes people overlooking the  
21 trials, people looking at ethics, the safety monitoring

1 boards, and as you go into Phase IV, which is kind of  
2 where we are now with the immunization schedule, the  
3 post-licensure period -- This is fifty years or sixty  
4 years post-licensure -- including the company, the  
5 federal agencies, the parents, interests groups, and we  
6 all have some interest or another, as well as those  
7 people from the National Vaccine Injury Compensation  
8 Program.

9 I have to state some principles which I hope, but don't  
10 presume, that everyone will agree with. Although some  
11 of them are truisms, I think that it's really important  
12 to keep those in the context of: What is the next step  
13 and what is it important to do?

14 First of all, vaccines are not perfect. Everyone  
15 agrees with that, I would hope. Yet, we understand the  
16 enormous value of the role of vaccines in preventing  
17 disease. That was beautifully stated yesterday.

18 I think what people don't realize unless they've been  
19 involved in some process development or evaluation of  
20 that process is that GMP, those standards defined by  
21 the field of good manufacturing process, are not

1 perfect. Actually, I've seen some studies where you  
2 can quantify the rate at which you will have  
3 contamination of a vial given different GMP practices,  
4 but that it's not zero. It's a quantifiable risk. At  
5 the same time, there are both regulatory and field  
6 requirements for a preservative in multi-dose vials.  
7 There are some questions that we'll come up and things  
8 that I still haven't learned after two days of  
9 discussion regarding use of multi-dose vials in the  
10 public sector, both domestically and globally.  
11 I have learned that the ideal preservative does not  
12 exist. I was trying to elucidate the characteristics  
13 of an ideal preservative. I've got that list for  
14 vaccines and antimicrobials, and I decided I really  
15 didn't know enough to do that, but, perhaps, it would  
16 be helpful to have someone help us by doing that. But  
17 the ideal preservative probably does not exist.  
18 I think another principle that you should all  
19 acknowledge as we are attempting to come up with the  
20 required research agenda is that the data that you have  
21 heard and the data that we're having to deal with and

1 listen to from the environmental community and the  
2 infectious disease community are qualitatively  
3 different. As you heard in the afternoon yesterday,  
4 you're talking vaccine efficacy. You've got relatively  
5 clear endpoints. You've got measurable health effects.

6 And when you're talking to the environmental  
7 epidemiologists and environmental health people,  
8 they're talking a language which makes sense to them  
9 and for us, it's like parts per million and it's  
10 modeling with uncertainty factors. Yet, to them, and  
11 in the field of environmental epidemiology, many of  
12 those approaches, although not driven to consensus,  
13 have a validity and a validity that we, in the  
14 infectious disease community in evaluating the  
15 randomized clinical trials, the gold standard, have  
16 difficulty attributing them. It's probably just better  
17 to acknowledge that you've got two communities talking  
18 across each other.

19 Now, there are some principles that I think I've  
20 learned from thimerosal, and if I haven't, please feel  
21 free to speak up because this is what I learned and it

1 should be correct. The first is that we have to look  
2 at thimerosal in context, and the context is that  
3 children do not grow up in a mercury-free bubble. They  
4 don't grow up in a mercury-free bubble prenatally and  
5 they certainly don't do it postnatally. This is  
6 probably my third day-long or -- Well, I don't know if  
7 you can group all the conference calls we had in that  
8 two-week period into a two-day period, listening to a  
9 number of different people talk about thimerosal and  
10 realizing that the efforts to decrease mercury exposure  
11 in childhood is not something new, that twenty years  
12 ago -- I don't remember the date exactly -- there were  
13 diaper powders that had mercury in it, in which it  
14 wasn't until people recognized that those were deleted  
15 from there. So this is not a -- This is not new. We  
16 haven't dealt with it in vaccines.

17 I think the principle is that the health goal is to  
18 decrease exposure to mercury overall before you get  
19 into the issue ethyl versus methyl or inorganic, et  
20 cetera.

21 The other principle is that -- Someone asked me on the



1 way in, they said, "Is this thing about coffee not in  
2 the room, is that a regulation or a guideline?" I  
3 went, "It's a regulation. They'll throw you out of  
4 here." That's a regulation. This is not. This is a  
5 guideline. I think that I want -- Where's Roger? I  
6 want that slide that shows the gray zone, the white  
7 zone, because we got it from whoever presented that at  
8 the influenza meeting, and I think that's the best  
9 graphic to really present. It doesn't matter, .1  
10 versus .3, until you start talking in smallest children  
11 and then I'm not sure how it matters, but the .1 versus  
12 .3 versus .4 are built into how the non-methyl people  
13 think about guidelines and what kind of question  
14 they're trying to answer when they create guidelines.  
15 The environmental community, having listened to three  
16 different sets of them -- Or maybe at least three  
17 different sets of them -- are not unified in their  
18 assessment of ethylmercury. They may be a lot more in  
19 consensus about methylmercury, but they've done that on  
20 the basis of detailed review, and I don't think we have  
21 the data to look at that. This is the scientific

1 issues relevant to have effects from exposure to  
2 methylmercury.

3 Two-day meeting full of preclinical primate/human  
4 epidemiologic -- we haven't done that for ethylmercury  
5 and we won't have the data to do it at this point. I  
6 think the last thimerosal principle that the vaccine  
7 community -- we're faced to deal with is different from  
8 what the environmental folks have to deal with. It's  
9 what I call the Caesar's wife principle. And some of  
10 those things my dad taught me, but you sort of  
11 remember, is that not only did Caesar's wife have to be  
12 pure, she had to appear pure. This issue of appearance  
13 being everything, that we have to not only be doing  
14 what we think we're doing, but to appear and to be able  
15 to inform and to be open and transparent about it. I  
16 think it's something we need to keep in mind as we go  
17 on and define the research.

18 So gaps? Now, gaps are in the context of what I  
19 thought were the general principles, and they're not  
20 necessarily in the most logical sequence. I sort of  
21 started pasting together my thoughts over the past day

1 and a half and the past two hours. Let me just go  
2 through them and I promise to distribute them to anyone  
3 who wants something a little bit more logical here.  
4 None of the mostly methyl exposure epidemiologic  
5 studies took into effect -- into measurement of effect,  
6 although they have clinical hair samples, et cetera, an  
7 understanding of the potential role of immunization of  
8 the child of an additional bolus during the time of  
9 infancy. This all relates to mercury, in general, and  
10 not just necessarily just thimerosal. I'll try to  
11 speak with some more relevance specifically to  
12 thimerosal on the next slide.

13 The whole issue of the sensitivity of the human in the  
14 postnatal period versus the prenatal period, I think  
15 there are still a lot of questions unanswered about  
16 that. What was clear in the group that evaluated the  
17 effects of methylmercury is you have to look not only  
18 at the route of exposure and the method of exposure,  
19 but with particular relevance to where in the  
20 neurocognitive development you think the sensitivity to  
21 exposure exists.

1       There were questions made and I think the pediatric  
2       community has learned a lot about lead. We're used to  
3       thinking about that substance and how to decrease  
4       exposure and how to deal with the parts-per-million  
5       issue there. That's something I think we know probably  
6       more about. Apparently, from a statement made  
7       yesterday, the effect of lead is a continuous variable  
8       over time. Is that a relevant sort of framework for  
9       thinking about mercury? The issue which we have to  
10      acknowledge I think remains unanswered: Is toxicity  
11      related to peak or chronic exposure? Because the  
12      guidelines are based on chronic oral and the exposure  
13      that we're talking about is different. It leads to  
14      bolus and peak and intermittent.

15      Now, we spent several conference calls arguing about  
16      ethyl/methyl and, you know, I was going, "Is there a  
17      difference of carbon group? Is that organic  
18      concentrate ethyl/methyl?" A colleague of mine, Dr.  
19      DeBosky, said, "Yes, but think about it. It makes a  
20      really big difference. You're talking ethyl alcohol  
21      versus methyl alcohol." Okay. I will admit that I

1 don't know. While it may be perfectly reasonable, in  
2 an effort to assure that we're doing is the safest  
3 possible, to take the data that we have for  
4 methylmercury and to extend the conclusions and the  
5 considerations to ethylmercury. I don't know. It's --  
6 In thinking of methylmercury in the kinds of settings  
7 that are referenced here, the primate data printed on  
8 methylmercury exposure which has been associated with  
9 motor and sensory changes, alterations in primates, and  
10 much less with cognitive effects, led to their  
11 conclusion that they needed data on specific domains.  
12 Not being

13 a -- What's it called? -- not environmental, but a  
14 development specialist, I'm not quite sure what  
15 specific domains are. I just know it means more than  
16 global assessment of cognitive or any single parameter  
17 of development.  
18 We need to evaluate potential health impact of prenatal  
19 exposure and, if we're going to do that and figure out  
20 ways to answer those kinds of questions, it has to be  
21 in the context of timing of exposure as it's related to

1       those critical windows of susceptibility during  
2       development. That was recommended by the methyl group  
3       and I think the ethyl group, and ethyl considerations  
4       need to include that.

5       Now, when I start talking about ethylmercury and  
6       especially ethylmercury presented intramuscularly, the  
7       question really is, how different is it from  
8       methylmercury? The potential differences, and I've  
9       heard everything from "mercury is mercury" to "it may  
10      be 20 percent less toxic" or "really, you need to use  
11      it as the model" to "we don't know." And the  
12      differences could relate to the potential health  
13      effects and the pharmacokinetics, the biological  
14      activity, the clinical endpoints one must worry about,  
15      the effect of a route of administration, and the dose  
16      schedule. And even something as relatively simple to  
17      answer -- And we hope to have data not too long from  
18      now, Dr. Clarkson -- is, is it excreted and how in  
19      infancy? We can't answer that today and we should be  
20      able to do that if we're doing our jobs very shortly  
21      from now.

1       What levels are reached intramuscular -- after  
2       intramuscular doses of childhood vaccines? We can't  
3       answer that today. And Dr. Clarkson presented what I'm  
4       now calling the Clarkson model, and I think it's  
5       something that can be tested and it can be tested with  
6       some observational data and we hope to hear more about  
7       that.

8       The potential health effects have been learned from  
9       either high dose or poisonings. And the one that's  
10      acknowledged is the sensitization which is an effect  
11      regardless of how ethylmercury is presented, but at low  
12      doses, how one can correlate what's known at toxic  
13      doses to low doses, to me, is unclear and remains a  
14      question.

15     The issue of cumulative levels, it's clear that -- I  
16     was worried that after listening to all this, I still  
17     don't know what's new to vaccines versus background  
18     exposure and what is the most appropriate useful,  
19     accurate, truthful time frame for evaluating childhood  
20     exposure. You know, in statistics, you can take a dose  
21     level and divide it to an average daily dose over six

1 months or over seven months and -- Let's figure out  
2 before we start doing the math what the appropriate  
3 window is that we're worried about and do it in  
4 consultation with the environmental folks who -- and  
5 then compare the different strategies to decrease  
6 mercury exposure, regardless of source, to that  
7 measure.

8 I guess I did ask some questions yesterday trying to  
9 understand the impact of some things that we thought we  
10 knew, and when statements were made about as to how  
11 ethylmercury and methylmercury came apart a little  
12 differently, I asked, is this good or bad? Well, it  
13 could be good and it could be bad. So the theoretical  
14 concerns of nephrotoxicity and neurotoxicity, the brief  
15 review of the literature we did showed nephrotoxicity  
16 could be more of a concern, but I haven't heard anyone  
17 talking about the potential of nephrotoxicity. So  
18 these are both theoretical and I think we need more  
19 information.

20 At the same time, there are gaps in our knowledge of  
21 vaccines and the vaccine field, and that has to do with



1 alternative preservatives. I'm glad to hear that some  
2 of the manufacturers have a lot more information than  
3 we appear to have on specific pharmacokinetics of  
4 methylmercury for -- What is it? -- 2-phenoxy,  
5 whatever. I'm not sure it's published. If it isn't,  
6 it should be published and we should evaluate it  
7 because we have a sixty-year track record with these  
8 vaccines. And before we go around running to replace  
9 them with another preservative, I think we have lots of  
10 questions to be answered. Do that very carefully. It  
11 doesn't mean that the data can't be collected or at  
12 least wait to hear from our colleagues in the industry  
13 that the feasible goal and that this data, the safety  
14 data that we're interested in, can be collected.  
15 Although we heard a lot about the cost of eliminating  
16 and the lack of feasibility of eliminating multi-dose  
17 vials, I didn't hear any data and I think it would be  
18 useful to know -- Maybe we heard a little bit from WHO,  
19 but for the U.S. -- what is the real cost of  
20 eliminating the multi-dose vials and going to single-  
21 dose vials and what's the real cost in terms of space

1       that's needed to maintain the cold chains for these  
2       vaccines? I think you need that for decision-making  
3       for the U.S. and I think there's other factors  
4       globally. In a country where we  
5       are -- I have to quote Dr. Orenstein -- paying three million  
6       dollars per dose -- per case of wild-type poliomyelitis  
7       to provide -- to avert poliomyelitis due to vaccine, we  
8       obviously value vaccine safety and we have the  
9       resources to support that kind of approach. So if it's  
10      an issue of eliminating multi-dose vials, what are the  
11      costs?

12      Can there be novel approaches to limiting mercury  
13      content? By this, I meant -- The "novel" word is one  
14      that we use at NIH when we want to sort of reach in and  
15      have people come up with things that we haven't thought  
16      of. By "novel," I mean some suggestions made around  
17      how to play with formulation and a way to limit  
18      thimerosal, but different kinds of delivery vehicles,  
19      total delivery vehicles, which may not need it. Dry  
20      powders, DNA vaccines, whatever, novel formulations and  
21      approaches to limiting mercury content. Notice that

1 say "limiting" without presumption of value to that of  
2 absolute elimination.

3 I think it is possible to get a little bit more data on  
4 when in the first two years of life are infants exposed  
5 to hepatitis B, because we keep having to come back and  
6 discuss that when it comes to the hepatitis B issues.

7 There will be -- There will be -- This is not a  
8 question. There will be an ongoing need to conduct an  
9 assessment of the cumulative effect of the immunization  
10 schedule. And Bruce talked about lessons learned, and  
11 I think a lesson learned is as we add and recommend  
12 vaccines that we need to look not only at individual  
13 vaccines but at the schedule that we're recommending  
14 from every perspective. I'm sure we'll continue to be  
15 surprised, but we won't be caught with this one again.  
16 Data, people have raised "Who's going to do this?" and  
17 "Are you going to talk about it?" So let me ask: Do  
18 we have data -- I don't think we do -- on which to  
19 comment upon the long-term effects on vaccine-level  
20 exposure to ethylmercury? I think the first place to  
21 look, and I'd ask those communities that have -- the

1 scientific communities that have these databases, can  
2 some sort of assessment be made from analysis or  
3 evaluation of existing data sources? In other fields  
4 like the diabetes issue, we were able to provide, I  
5 think, useful analysis from an existing database  
6 resulting from a randomized clinical trial in a country  
7 in which there was a very detailed and validated  
8 diabetes registry to answer a specific question. Are  
9 there places we could be looking for information  
10 pertaining to this or do we need to go look for novel  
11 sources and at what point do we need to go? Do we have  
12 enough knowledge about what's going on from animal  
13 models or fairly simply measurement of levels in  
14 children to have a high enough level of concern that we  
15 need to worry about bad health effects as opposed to  
16 recognizing the levels that are being administered  
17 potentially through vaccines? And I think Roger  
18 presented the diversity of the vaccine schedules to say  
19 we need to limit exposure.  
20 There are different presumptions that lead you to  
21 different conclusions.

1 Finally, how to communicate controversial and  
2 inconclusive data and at the same time maintain  
3 confidence in vaccines. I think we began to hear today  
4 what becomes sort of second-guessing what was a very  
5 difficult time of a vaccine group trying to understand  
6 data that, as you heard over the past two days, was not  
7 conclusive, but what was quite worrisome, and to decide  
8 when it's compelling enough for some action and at what  
9 point and what timing information is distributed.

10 There are lessons learned about systems we need to put  
11 in place and how to access our advisory committees  
12 rapidly and how to maintain -- Where's Dr. Plotkin?  
13 What's the word? -- sang-froid.

14 The charge to the panel -- And I'll ask each speaker to  
15 talk for three to five minutes and I have my FDA watch  
16 on -- is, number one:

17 What are priorities for research from your perspective?

18 Number two, even if you don't include that in whatever  
19 you had thought you were going to present up to now,  
20 can you comment on the feasibility and the urgency to  
21 do so?

1 I ask you to do this in the constant context of a  
2 comment that George Kirwan would make if he was here  
3 and he would say, "You know, the most expensive words  
4 in the English language are, I wonder if." So you have  
5 to put some value on if the "if" that you're trying to  
6 answer is, indeed, important for science, for public  
7 health, or public policy.

8 The first speaker will be Dr. Clarkson. I think you  
9 just need lights on. Do you need to turn this off?

10 **DR. CLARKSON:** With regard to human studies, some  
11 suggestions that the group might want to consider,  
12 first of all, is this calculation that I did which I  
13 think it -- the calculations like this have to be done  
14 to assess risk from ethyl and methylmercury. You have  
15 to base them on blood levels because all of these  
16 guidelines from these various government agencies and  
17 so forth all start with toxic blood levels and minimum  
18 toxic blood levels and so forth, and they work from  
19 them. So what I've given here, for example, is the  
20 blood levels that might develop in an infant given  
21 these schedules of vaccines. For example, the first

1 shot only raises the blood level to about four parts  
2 per billion which is actually about the equivalent of  
3 the EPA guideline.

4 So I heard this morning a single dose will be ten times  
5 or something the EPA guideline. It's certainly not.  
6 It might approach about the EPA guidelines, but as you  
7 can see, as it builds up with subsequent doses from the  
8 vaccines, it does certainly exceed the EPA guideline by  
9 a factor of four or five.

10 But all this is based on all kinds of assumptions. One  
11 is that methyl is the same ethyl, which it probably  
12 isn't. It's based on the assumption that there's no  
13 excretion, and as the Chairperson pointed out, that's  
14 something that we should definitely check and I  
15 promised to do that, be a good boy.

16 We also should validate hair as a marker for exposure  
17 to ethylmercury. That would allow us to do some more  
18 population studies to see what hair levels are like in  
19 infants, but we have to validate it first. I think  
20 that can be done with the infants already available.  
21 Hair monitors methylmercury and not inorganic. The

1 hair then could be very useful. It might just monitor  
2 the intact ethylmercury in the infant which is probably  
3 responsible for the neurological effects, and we'd have  
4 to have some other measure for inorganic mercury like a  
5 blood sample.

6 As I say, I learned an important thing -- many things  
7 from this meeting, but one was that we didn't take into  
8 account vaccines in the Seychelles study. I think it's  
9 possible now -- Thank you, Dr. Myers -- that it's  
10 possible that we may now be able to go back and look at  
11 that. We have an enormous amount of behavioral data,  
12 clinical data, development data on these kids who are  
13 now nine years of age. So we have a huge database. So  
14 we might be able to now take a look and see who got  
15 vaccines and how much and whether this has an impact on  
16 our data, and we might therefore get some -- I hope  
17 some useful human data out of this. Of course, this  
18 will be a vaccine on top of a substantial dose of  
19 methylmercury. So this could be useful, too. When we  
20 heard about all other kinds of mercury exposures that  
21 kids are exposed to, here you've got a population that



1 really is getting an exposure, on the average, ten  
2 times higher than the U.S. population. If we  
3 superimpose vaccines on top of that, if we're going to  
4 get any effect, we'll get it in the Seychelles as I  
5 mentioned. If we don't get an effect, I think it will  
6 be very reassuring for this situation.

7 As far as animal experiments are concerned, I  
8 understand that it's really not going to be practical  
9 to do a major Seychelles type study in this country  
10 with regard to vaccines, but I think that animal  
11 experiments are feasible. I mean, one can do a lot of  
12 neurobehavioral tests and kidney function tests on  
13 animals. There are three or four papers in the  
14 literature on ethylmercury, so we've got good  
15 guidelines to start with for ranging effects. So I  
16 would suggest we could do that or somebody could do  
17 that. We'd be happy to make them an offer. I'm in my  
18 elements this afternoon. I'm after research money.  
19 The other point is that -- especially with regard to  
20 this figure here, the salicylic acid may be playing a  
21 role here. I've talked to some of my colleagues here

1        today and yesterday. We don't know how rapidly it may  
2        go from the intramuscular side. I've assumed in this  
3        figure here that it's a very rapid, almost  
4        instantaneous distribution, but it may not be and  
5        that's something we could test in animals, too. All  
6        our previous animal work has been done with  
7        ethylmercury chloride, which is a very lipid soluble  
8        commodity that diffuses readily from tissues. It will  
9        be interesting to see if the salicylate compound  
10       behaves the same way. For example, if you're looking  
11       at the transport of methylmercury into the brain,  
12       methylmercury-L sistine gets in the brain rapidly. The  
13       disomer, the optical isomer, the only difference is the  
14       optical activity. The disomer does not go into the  
15       brain. So the chemical compound, not just the mercury  
16       itself, but the chemical compound when mercury is  
17       present may play a very important role in its  
18       distribution and kinetics. This may -- If it was a  
19       slower release, for example, these peaks may not be as  
20       high as they are in this figure. So I think it's worth  
21       considering.

1       So with that, Madam Chairman, I hope I've earned myself  
2       a little grant of some sort. I don't know.

3                       (LAUGHTER)

4       **DR. RABINOVICH:** Can I understand from your  
5       presentation that you think all of the -- answering all  
6       of these are doable?

7       **DR. CLARKSON:** Yes.

8       **DR. RABINOVICH:** Yes, thank you. Next, Dr. Michael  
9       Gerber.

10      **DR. GERBER:** Thank you. Well, as we've heard several  
11      times yesterday, as well as today, we can speculate on  
12      what the mercury levels may be in infants who've  
13      received immunizations with thimerosal-containing  
14      vaccines, but as far as the actual data demonstrating  
15      what those levels are, there really is very little. In  
16      fact, the only data that we have comes from stages of  
17      study at the nursery at Emory. We heard yesterday  
18      about the limitations of that study, the fact that it  
19      hasn't been published except in abstract form, the fact  
20      that there are only five term infants and fifteen  
21      premature infants, that the fifteen premature infants

1 had a mean weight of only 750 milligrams, concerns  
2 about the methodology of that study. So, needless to  
3 say, with that being the only data that we have, we  
4 really have very little.

5 As little as we have about the levels, we have even  
6 less about the distribution, about the kinetics, about  
7 the metabolism, about the excretion of ethylmercury.  
8 In fact, we know essentially nothing about those things  
9 in ethylmercury.

10 So what we at the NIH are proposing to do, and we're  
11 proposing to do this in conjunction with our  
12 colleagues, Dr. Ball and Dr. Pratt at the FDA, and  
13 we're proposing to do this through our vaccine and  
14 treatment evaluation units at Maryland and at  
15 Rochester, working with Dr. Clarkson at that same  
16 institution. What we're proposing to do is to attempt  
17 to obtain this data and we attempt to do this by  
18 getting together a cohort, first of all, of premature  
19 infants who have been vaccinated with the hepatitis B  
20 vaccine sometime within the last week to several  
21 months. These would be infants whose mothers were

1 hepatitis B surface-antigen positive, infants whose  
2 mothers hepatitis surface-antigen status was unknown,  
3 or infants who were born at hospitals that were not  
4 following the current recommendations of withholding  
5 the hepatitis B vaccine until a later time and those  
6 infants born to hepatitis B surface-antigen negative  
7 mothers.

8 And what we've proposed to do after identifying these  
9 premature infants is to obtain blood, stool, and urine  
10 specimens from them, as well as maternal hair samples.

11 The maternal hair samples would be to get a baseline  
12 idea of what the in utero exposure had been. Maybe as  
13 a point of clarification, and we can get it from Dr.  
14 Clarkson later, I understood you to say that we could  
15 not measure inorganic mercury in hair, only organic,  
16 but I was unclear as to whether we could distinguish  
17 ethyl from methyl and maybe you could address that  
18 later.

19 But, in any case, in addition to the premature infants,  
20 we would then want to look at a cohort of term infants  
21 and look at term infants coming from three different

1 kinds of pediatric practices, one practice in which the  
2 routine immunization had been providing the patients  
3 with vaccines that had a relatively high amount of  
4 thimerosal. We would want to look at a second group of  
5 practices where the cumulative exposure from  
6 vaccination of thimerosal would be relatively low, and  
7 then, finally, practices or a group of practices where  
8 only thimerosal-free vaccines had been used. Again, we  
9 would want to look at these infants within one month to  
10 several months following the two-month immunization and  
11 at that point determine what the exposure, what the  
12 combined exposure had been at that two-month visit, as  
13 well as all of the possible previous exposure to  
14 thimerosal from earlier immunizations, and collect  
15 blood, stool, urine from those patients, as well as  
16 maternal hair samples if we could.

17 We would also want to look at a similar group of  
18 infants from those same three types of pediatric  
19 practices after the sixth-month immunization and,  
20 again, make a determination of the total thimerosal  
21 exposure at that six-month immunization, as well as any

1 exposure from previous immunizations and again collect  
2 blood, stool, urine specimens from those infants, as  
3 well as maternal hair samples if we could.

4 Hopefully, with that information, we would be in a  
5 position to make some determinations about what the  
6 expected mercury levels would be after immunization  
7 with thimerosal-containing vaccines, about what the  
8 distribution, what the metabolism, what the excretion  
9 of ethylmercury in these infants would be.

10 Is this feasible? I think it is feasible. One  
11 limitation of the feasibility is trying to do this as  
12 soon as possible while children are still receiving  
13 thimerosal-containing vaccines. Why is this important?

14 If we're moving towards -- hopefully moving towards a  
15 situation where infants in this country would no longer  
16 be receiving thimerosal-containing vaccines, I think  
17 there are three reasons. First of all, I think the  
18 information that would be obtained would be helpful for  
19 those parents whose infants have already or will  
20 continue to receive thimerosal-containing vaccines.  
21 Number two, as we heard from Dr. Clements, although we

1 may be approaching thimerosal-free vaccines in the near  
2 future, for much of the world, this is something that's  
3 not going to happen for several years, at least several  
4 years, so this information would be important for those  
5 populations. Finally, as one of the charges in the  
6 Joint Statement from the American Academy of Pediatrics  
7 and the Public Health Service, this type of research  
8 was one of the things that we had committed ourselves  
9 to performing.

10 Thank you.

11 **DR. RABINOVICH:** Alison Mawle.

12 **MS. MAWLE:** When Gina charged the individual panel  
13 members, she deliberately did not want us to consult.  
14 So if some of the same things came up, you would  
15 presumably take it as a reinforcement of the kind of  
16 things we should be doing.

17 I think speaking -- I work at CDC. I'm part of the  
18 National Centers for Infectious Diseases, and as we  
19 have listened over the past two days, but also over the  
20 last several weeks, to some of the issues that have  
21 been brought up around thimerosal, I have been



1 repeatedly struck by the fact that we really don't know  
2 how this compound breaks down. We heard yesterday from  
3 Jeffrey Englhardt that there's very little kinetic data  
4 on thimerosal, but the one paper that we have seen in  
5 squirrel monkeys suggests that a fair proportion of  
6 this breaks down not into ethylmercury but breaks down  
7 into inorganic mercury. And we've heard the data on  
8 methylmercury. We're now hearing a little bit about  
9 how we want to do the studies on ethylmercury. I think  
10 it's absolutely critical that we know how this compound  
11 breaks down, because if what we're looking at is  
12 inorganic mercury, we're looking at a different thing  
13 again. We've heard very little at all about inorganic  
14 mercury. Dr. Clarkson mentioned that if we want to do  
15 studies in hair that we cannot use inorganic mercury as  
16 a marker. I have learned more about how you do these  
17 studies over the last few weeks than I ever wanted to  
18 know and I still feel very ignorant about many of these  
19 things, but I do see that -- do feel that that is, in  
20 terms of both feasibility and urgency, one of the first  
21 things we should be doing. It's, certainly in animals,

1 a fairly straightforward experiment to do.

2 Other speakers have talked about looking at where it's  
3 compartmentalized, the issue of giving thimerosal  
4 intramuscularly versus orally, which is where most of  
5 the data we have on methylmercury comes from, what is  
6 the half-life, is it excreted in infants -- I was very  
7 surprised to discover that it's thought there is no  
8 excretion, but we don't know -- the role of the bolus  
9 effect. I'm also delighted to hear that you're going  
10 to be going back and looking in the Seychelles at the  
11 possibly effects of immunizations. I don't know --

12 **DR. CLARKSON:** Why don't you come? It's a nice island.

13 **MS. MAWLE:** I'd be delighted to come. I just don't eat  
14 the seafood.

15 But I think that that's a real important study to do,  
16 clearly from the Faroe Island studies and the  
17 Seychelles Island studies. If there are effects of the  
18 mercury from the vaccines, they're going to be subtle.

19 It's going to be very hard to do any kind of study in  
20 current populations that are being immunized,  
21 especially as we have heard from FDA that the

1 commitment is to move towards mercury-free vaccines if  
2 at all possible. I think that -- I've certainly not  
3 heard any argument against that. If we need  
4 preservatives in certain cases, if we need to keep  
5 thimerosal there for a specific reason, FDA will be  
6 willing to discuss that, but, clearly, the move is to  
7 move -- get rid of mercury if we can. That comes in  
8 the context of the environmental mercury load. I think  
9 it's very easy for us to focus on our little issue of  
10 vaccines, but that's not where this is coming from.  
11 This is coming from the fact that we live in a mercury-  
12 contaminated environment and seeing the contribution of  
13 vaccines within that context I think is critical.  
14 From CDC's perspective, I think it's very important and  
15 very urgent that we monitor any changes on immunization  
16 practices. The data that Eric Mast presented yesterday  
17 I found very disturbing, that in such a short time you  
18 can already see an effect of this. We heard from -- I  
19 don't know if they're going to address this, but we've  
20 heard from the manufacturers over the last few weeks  
21 that we could not go to a thimerosal-free schedule

1 right now without introducing dramatic vaccine  
2 shortages, which would totally disrupt the current  
3 schedule.

4 So we clearly want to keep our current immunization  
5 program in place, we want to reassure people, and we  
6 also want to -- in some way, come up with a time line  
7 for reducing or removing thimerosal. I think that that  
8 is something that CDC can contribute to in terms of  
9 doing surveillance on what effect is being had on the  
10 schedule itself.

11 I don't want to talk much about the manufacturing  
12 issue, but I did hear the issue of combination vaccines  
13 raised. I think that -- I mean, there were many other  
14 compelling reasons for going towards combination  
15 vaccines, but I think that that is something that we  
16 should be pushing towards, but if we do need to be  
17 keeping preservatives in, then, obviously, that's a way  
18 of reducing it. Looking at other ways of reducing the  
19 thimerosal load, we heard the idea of reducing the  
20 amount of vaccine that's actually given.

21 Lastly, I just want to leave you with the idea that we

1 really, really need to increase our ability to  
2 communicate with our constituents. I think that we can  
3 certainly be faulted over -- in terms of being  
4 complacent about the efficacy and safety of vaccines,  
5 and it's become clear over the last two or three years  
6 that the public's concern about vaccine safety has  
7 risen. We've seen congressional hearings recently on  
8 that issue, and I think the way that we communicate,  
9 both with the public and also with providers, is  
10 critical in terms of maintaining confidence in our  
11 program and in giving them information to give to their  
12 constituents in order to reassure them, or not, if  
13 that's what we need to be doing as we've seen in the  
14 case of the rotavirus issue, which has been going along  
15 parallel with that.

16 So I hope that's given a few thoughts from our  
17 perspective. Thank you.

18 **DR. RABINOVICH:** Dr. Paradiso, Wyeth-Lederle.

19 **DR. PARADISO:** Thank you, Gina. Gina said I only have  
20 a half-an-hour to talk, so I'll try to go quickly.

21 I have to first apologize for the fact that I was not

1 here yesterday. I couldn't make it, so I missed a lot  
2 of the detailed discussion. I want to tell you that  
3 during the course of the several weeks and also during  
4 the course of this morning, when thinking about  
5 research in this area, particularly as it relates to  
6 thimerosal and what we need to know and what we don't  
7 know, I have a little trouble getting past the fact --  
8 getting past what we're going to do with any data at  
9 this point that we collect with thimerosal. I think  
10 that we have made a judgement -- or a judgement has  
11 been made on the basis of a desire to eliminate  
12 thimerosal because it makes sense not to inject  
13 mercury. And there is not, to my knowledge, a specific  
14 outcome besides that that we're trying to avoid. So in  
15 designing studies to look at thimerosal, it's hard for  
16 me to think specifically about outcomes that I would  
17 have any confidence in or that I would think about to  
18 counterbalance the decisions that have been made so  
19 far. I'm not trying to be flip about this, but I think  
20 -- I think we have to be a little careful about  
21 thinking that data that we collect on thimerosal, while

1 I think it will be useful in our understanding of  
2 thimerosal and its metabolism, it's not clear to me  
3 that it's going to tell us too much about potential  
4 rare adverse events that may occur as a result of  
5 having thimerosal.

6 Now, having said that, at the end of this morning, I  
7 heard Dr. Clarkson, who knows far more about thimerosal  
8 and mercury than I do and also is from Rochester like I  
9 am, so that raises him a little bit higher on the scale  
10 -- Rochester, New York, that is -- it seems clear to me  
11 that we, infectious disease vaccinologists, perhaps  
12 have no idea how to use these numbers that we're using  
13 and using as our guidelines. So if I were to back off  
14 what I said at first and think about things that I  
15 would like to know, it would be: How do we assess  
16 cumulative effect when we talk about vaccination? The  
17 only data, I guess, that would be convincing to me  
18 would be data that actually measured levels in the  
19 blood or in an appropriate bodily fluid that could be  
20 related to the potential toxic effects that we're  
21 worried about. Those are mostly neurological. You

1 know, I think we need to, however, then think, what if  
2 it's undetectable? Would that change what we're  
3 thinking? If it wouldn't, then we have to accept that  
4 the outcome of these studies is going to be for our  
5 understanding and not going to really help us in terms  
6 of future use of thimerosal.

7 So I think we, as manufacturers -- or our company is  
8 looking more towards potential new formulations or new  
9 preservatives that could be used or towards the  
10 elimination of the use of preservatives, and that  
11 obviously gets us to single-dose vials. I think it's  
12 important for us not to underestimate the practices  
13 that was just mentioned in the United States. Multi-  
14 dose vials are greatly favored. I mean, the reason we  
15 use them in the United States is because that's what  
16 the physicians' offices prefer. In Europe, that's not  
17 the case. They, in fact, prefer single-dose vials. So  
18 that is the market there.

19 So this is not an overnight change from a multi-dose  
20 dose presentation to single-dose only because of the  
21 capacities that have been developed in our



1 manufacturing around those needs.

2 In thinking about new preservatives, I think we need to  
3 think hard about what outcomes we'd be looking for from  
4 a safety perspective when we use new preservatives, and  
5 it seems clear to me that tests for toxicity that  
6 thimerosal passed are obviously not enough for the next  
7 preservative. So we need to think about what outcomes  
8 we're specifically looking for. Somebody said this  
9 morning, for the unknown, the new preservatives are  
10 really the unknown and without experience, and we need  
11 to think in our research, when we think about research,  
12 what those outcomes would be.

13 Lastly, I just want to comment, Norman Baylor talked  
14 this morning about the FDA review process and the  
15 desire to expedite review. I need to point out that on  
16 those two slides, the list of potential requirements  
17 for the presentation for a new preservative or the  
18 presentation of any new formulation is potentially not  
19 a small task, and if you're talking about doing  
20 stability studies in real-time, usually that's a two-  
21 year real-time stability study. If you're talking

1 about doing consistency studies and if you're talking  
2 about efficacy trials, you're talking about several  
3 years and fairly major programs for the presentation of  
4 new preservatives. So all of that needs to be put  
5 together before the review process can start,  
6 obviously.

7 So I just wanted to tell you that when we think about  
8 these changes in formulations, we think about the time  
9 lines that are required prior to that submission and  
10 those are fairly long time lines from a manufacturing  
11 perspective.

12 That's all I've got to say. Thanks.

13 **DR. RABINOVICH:** Dr. John Risher?

14 **DR. RISHER:** This will be a little bit of a challenge  
15 for me. I teach biology classes for six hours on  
16 Saturday and I always run out of time before I get the  
17 information through. So five minutes is really going  
18 to be a challenge.

19 Most of what I have to say, and I'm approaching from a  
20 toxicology and human health risk assessment  
21 perspective, has already been said, but I just wanted

1 to put a couple of points of clarification that I don't  
2 know -- This may help. This is just from a general  
3 introductory biology textbook. I don't know how many  
4 people really understand when we're talking about the  
5 main specific effects versus global effects. An  
6 example of the global effect is IQ. The main specific  
7 effects -- This is 1999, so we know a lot more about  
8 the brain than we did a hundred years ago and we know  
9 that specific areas of the brain are associated with  
10 specific cognitive or motor functions. I don't have a  
11 pointer here -- Oh, great, thanks.

12 If you can just look, where it says "language  
13 structure" on the upper left and go down, we know that  
14 certain areas of the brain are associated with that.  
15 So specific neuropsychological tests are designed to  
16 probe specific cognitive functions and the ultimate  
17 intent is to find out if -- even although you may not  
18 have been exposed to enough of a substance to have an  
19 effect on global function cognitively, there still  
20 might be enough effect in a particular area of the  
21 brain associated with a certain function. So when they

1 talk about domain-specific effects versus global  
2 effects, that's, in general, the difference between the  
3 two.

4 Again, the first one on here is just common sense, but  
5 what I did is I tried to break down things that I  
6 thought might help from a risk assessment perspective.

7 The first is really more of a common sense thing and  
8 it could easily be an in vitro study if it has not  
9 already been done. This is just to look at the  
10 effectiveness as a preservative of reduced amounts of  
11 Thimerosal. Again, that would -- if it has not already  
12 been done by the manufacturers, it'd be an easy thing  
13 to do.

14 Metabolic and biomarker studies are also important.  
15 Again, these have pretty much been covered, but we know  
16 that Thimerosal is actually water-soluble. So as a  
17 water-soluble substance, it's possible that it could be  
18 excreted through the kidneys as Thimerosal. So how  
19 rapidly is that bond between the group, the sulfur, and  
20 the ethylmercury broken? If it's not broken quickly,  
21 then there may not be the level of exposure

1       theoretically that there would be as if it were quickly  
2       broken.

3       Then, of course, we've already discussed the  
4       measurement of both ethylmercury and mercuric ion in  
5       the feces and urine. Having had three kids, I'm glad  
6       I'm not going to be a part of having to dip into that  
7       one.

8       Ethylmercury in the hair of the Seychelles Island  
9       population -- Well, the Faroe I'm not sure about. Dr.  
10      Grandjaun is not here, but Dr. Clarkson has already  
11      addressed the ethylmercury in the Seychelles  
12      population. So they might look into that.

13      Another thing regards one of the differences in looking  
14      at this Thimerosal is not only the fact that it's a  
15      bolus, we're talking about most of our knowledge  
16      relating to either the unborn or to adults, and I just  
17      want to really quickly explain something and then  
18      suggest that it might be looked into.

19      In adults, the primary source of excretion of organic  
20      mercury -- Primarily methylmercury is what most of the  
21      information about -- is through an enterohepatic

1       circulation. That is that the mercury is absorbed from  
2       the gut and it goes up through the circulation into the  
3       liver where it's conjugated with glutathion and leaves  
4       the liver in the bile salts back down to the  
5       gallbladder, through the bowel, and then back into the  
6       intestine where it continually gets recycled. So it's  
7       not always bowel available. Now, in rodents we know  
8       that during the suckling period, which is about twenty-  
9       one days in rats, that the glutathion, which is needed  
10      to conjugate the mercury, is not produced in sufficient  
11      quantities to lead to the circulation. There's been  
12      some studies in primates that have shown that in real  
13      young primates that that might also be the case. In  
14      humans, we really don't know, it may be the case or it  
15      may not be, but I think it would be interesting to find  
16      out when that enterohepatic circulation is to the  
17      extent that glutathion is produced and can conjugate  
18      the mercury and actually comes into being. That ties  
19      into again with excretion.

20      Longer-term things: A lot of classic toxicology-type  
21      studies; neurodevelopmental studies of Thimerosal which

1 would do dose-response studies and research animals and  
2 also look at different ages of animals, particularly  
3 after the animal is born and how the early stages of  
4 development compares to adulthood; the next one,  
5 contribution of Thimerosal from vaccines to total and  
6 individual tissue burdens. Kate Mchaffey from EPA and  
7 others were stressing the importance of looking at the  
8 total body burden of mercury. We're not just being  
9 exposed to Thimerosal. We're getting some in our food  
10 and some from other sources. ATSDR is involved in a  
11 Great Lakes research project that it's been sponsoring  
12 for years or co-sponsoring, and we may have some of  
13 this data and this may -- we may have the mechanism for  
14 getting some of this data.

15 The last thing is the immunologic effects of Thimerosal  
16 need to be investigated in laboratory animals as well.

17 I'm sure that's five minutes plus.

18 **DR. RABINOVICH:** And last is Dr. Bernard Schwetz.

19 **DR. SCHWETZ:** Thank you. It's always fun to be the  
20 last of a series of speakers who, for the most part,  
21 vigorously agree with each other. It's very hard to

1 say something that's new and unique. On the other  
2 hand, I want to offer some thoughts as the Senior  
3 Science Advisor to the Commissioner of the FDA and the  
4 Director of the FDA National Center for Toxicological  
5 Research.

6 As you might expect within an organization of the  
7 nature and size of the FDA, there will be different  
8 research agendas on almost everything, and that  
9 certainly would be true for ethylmercury as well, but a  
10 point I want to make is that I think that because of  
11 the nature of the exposures, these converge for  
12 something like ethylmercury.

13 If Thimerosal or mercury is taken out of vaccines, I  
14 think further work on ethylmercury for the Center for  
15 Biologics would not be a very high priority, especially  
16 in comparison to the need for data on the replacements  
17 for Thimerosal. I think this isn't just a question of  
18 a research agenda for ethylmercury, it's an even more  
19 important question that if we succeed, then the problem  
20 starts of knowing how successful the replacements are.

21 That has got to be a high priority, along with



1       whatever we need to know about ethylmercury.

2       On the other hand, it isn't very likely that Thimerosal  
3       is going to be replaced in vaccines completely in a  
4       reasonable length of time. So that is still a need to  
5       have data on ethylmercury. Then look at the bigger  
6       picture of the FDA in total where the concern is for  
7       drugs, cosmetics, foods, as well as vaccines. Then  
8       it's a given that we need to have more data on  
9       ethylmercury to understand that kind of a complex  
10      picture. It must include considerations about  
11      additivity of ethylmercury from different sources, but  
12      a point that hasn't been made in this meeting so far is  
13      the need to consider the additivity between  
14      ethylmercury and methylmercury. We treat them as if  
15      they're not acting in the same cells, and at some times  
16      they are. So I don't think we can look at ethylmercury  
17      in isolation without considering methylmercury or other  
18      sources of ethylmercury other than vaccines.  
19      So one of the high priorities that I think is for us to  
20      reduce the uncertainties that surround the idea that  
21      methylmercury and ethylmercury are the same. We know

1 they're not, but that's where we are today and we don't  
2 have much data on ethylmercury to really confirm  
3 whether it's more or less toxic. We know for the  
4 kidney it's probably more, but we all seem to assume  
5 that methylmercury is the gold standard for concern and  
6 ethylmercury may not be as bad. We don't have enough  
7 data to say that with a hundred percent confidence.  
8 While there are some priorities that I would say maybe  
9 just a little bit differently than some of the  
10 preceding speakers, I would agree that the sensitivity  
11 of the fetus versus the neonate is very important, and  
12 for some of you who have forgotten about the sensitive  
13 windows during fetal development, the nervous system  
14 develops post-natally. So isn't unreasonable to expect  
15 there would be particular windows of sensitivity. So  
16 it isn't the matter of averaging the dose over the  
17 whole neonatal period, it's what's the week or what's  
18 the day or what's the series of hours that represent a  
19 particular event in the development of the nervous  
20 system when this whole thing might be dangerous. It  
21 may be weeks surrounding that when there isn't a major

1 problem. We don't have that information.

2 The idea of sensitive subpopulations, as I reviewed  
3 literature on ethylmercury, it appeared as though there  
4 were people who were much more sensitive than others --  
5 This is adults, and I don't know why, but the  
6 possibility that that would exist with neonates is not  
7 impossible -- the question of peak blood levels versus  
8 the blood levels -- I distinguish between a single  
9 exposure and chronic, because when you're talking about  
10 newborns, that's not chronic. That's what happens  
11 right then and the following days over which they're  
12 not exposed to a vaccine again.

13 So the real question in my mind is the peak -- the  
14 effect of the peak blood level versus the blood level  
15 during the distribution and elimination phase of the  
16 original exposure to ethylmercury. Then you add to it  
17 another exposure beyond that with another vaccination  
18 or from food or whatever, but it isn't a matter of  
19 chronic versus acute exposure for this neonate. We  
20 don't know the impact of the area under the curve  
21 during the elimination phase versus the impact on the

1 cells of nervous system during that peak level. Is it  
2 just a difference in the exposure? Is that just the  
3 dose response curve? Or is time important? That,  
4 again, gets into the windows of sensitivity and we  
5 don't have the kind of data to address that.

6 In addition, the intermittent versus the continuous  
7 exposure, there are examples where intermittent  
8 exposure is important because the rate of delivery to  
9 the cells is more important. The rate of delivery, the  
10 rate of change within cells, could be more important  
11 than the average concentration. That could explain the  
12 intermittent versus the continuous response.

13 The valid bar markers of exposure, I think we have to  
14 have that. That is obviously of considerable  
15 importance. The elimination from the neonate, we're  
16 using a conservative estimate when we say it's not  
17 being removed by anything other than dilution, but we  
18 need to get that information.

19 One that I haven't heard discussed, the fact that we  
20 know that ethylmercury is a skin sensitizer when it's  
21 put on the skin and now we're injecting this IM at a

1 time when the immune system is just developing, the  
2 functionality of the immune system is just being set at  
3 this age. So now we're injecting a sensitizer several  
4 times. During that period of time, what's the impact  
5 of a sensitizer -- of something that is known to be a  
6 skin sensitizer, what is the effect on the functional  
7 development of the immune system when you give a  
8 chemical of that kind repeatedly IM?

9 Now, regarding the question of feasibility and urgency,  
10 the kinds of studies that we're talking about, the  
11 pharmacokinetic studies, the distribution, the  
12 elimination, all these other things that we can do in  
13 rodents, we can do them in primates, so those are  
14 feasible. It just takes money and expertise and good  
15 work. We don't know need shotty work at this stage by  
16 people rushing in and doing something that they don't  
17 quite know what they're doing. This is a time when the  
18 rest of the data that we make new decisions on have got  
19 to be better than the quality of information that is  
20 normally available when people on a random basis begin  
21 to collect information and, in retrospect, it doesn't

1 fit into a real good picture when you analyze it.  
2 That's true of a lot of chemicals. There need to be  
3 some definitive studies now that are done very well.  
4 The urgency, from the standpoint of -- Now I'm speaking  
5 as a toxicologist. I think anytime there's an  
6 avoidable source of exposure to mercury, we need to  
7 look at it real hard, but, obviously, there are  
8 consequences in many cases of taking steps. I don't  
9 think this is an emergency, that mercury is being used  
10 in this manner, but if it's an avoidable exposure, we  
11 should do something about it. I also recognize that if  
12 we do something precipitous, we could create an  
13 emergency and that has got to be considered as equally  
14 important as the concern over mercury itself.  
15 Why mercury represents a priority concern for me as a  
16 teratologist and a developmental toxicologist who has  
17 been doing this kind of work my whole career is the  
18 fact that this can cause irreversible damage to the  
19 development of the nervous system. That's why, in my  
20 mind, it's different than nephrotoxicity. A reversible  
21 damage, whether it's in an adult or a neonate,

1       whatever, that's different than permanent damage to the  
2       function of the nervous system, permanent damage to the  
3       function of the immune system. So that's why I think,  
4       among the issues that we look at with mercury or with  
5       other heavy metals, the fact that you would cause  
6       irreversible damage to the nervous system, in  
7       particular, is something that makes the kind of  
8       priority where we shouldn't sit back and say, well, we  
9       got through this one and now we'll pay attention to  
10      other priorities. I think we've got to stay on  
11      mercury.

12      Thank you.

13      **DR. RABINOVICH:** Thank you. With that, I'd like to ask  
14      all the panel members to come up to the front table and  
15      I'd like to open the floor for discussion, and I see  
16      that they're lined up already. So you guys better  
17      hurry up.

18      Dr. Klein?

19      **DR. KLEIN:** Dr. Clarkson, I'd like you to amplify your  
20      remarks, particularly in regard to that graph that you  
21      showed, the figure, in terms of a potential first dose

1 of vaccine that has thimerosal in it given at birth.  
2 Now, you indicated that your -- that it would be about  
3 4 micrograms with that first dose. I wonder if you  
4 could -- If you eliminate that first dose, the rest of  
5 the curve presumably would be approximately the same;  
6 is that correct? In other words, what benefit do we  
7 gain in your model from eliminating that first dose?

8 **DR. CLARKSON:** Not a lot. I guess you've seen this  
9 before, but this basically -- As we said, all of these  
10 guidelines that we've talked about today don't start  
11 with the dose. Well, some of our Iraqi stuff did, but,  
12 basically, when you're making these risk assessments on  
13 human health, epidemiologists -- (inaudible) on  
14 ethylmercury, you start with a hair level or blood  
15 level, let's say a minimum toxic level or some  
16 threshold level, some level associated with toxicity.  
17 Then an expert committee may or may not apply safety  
18 factors. For example, originally, from the Japanese  
19 data, there was a blood level of 200 parts per billion.  
20 A committee comes along and applies a safety factor of  
21 10, so it's now 20 parts per billion in blood. Then



1 from that point, the committee will go on and figure  
2 out -- calculate what is the long-term daily dose that  
3 will give you a toxic level of 20. That's how it's  
4 done. There's various calculations.

5 The original data is not a dose. It's a blood level or  
6 a hair level. And the best way for us to compare a  
7 single dose to the chronic dose is to ask blood level  
8 results from that single dose or what blood level  
9 results from that chronic dose. The example I  
10 mentioned this morning with eating six ounces tuna  
11 fish, which has something like 17 micrograms of mercury  
12 -- Let's say 20. Well, if you consume one can, the  
13 effect on your blood level would be so tiny you can't  
14 measure it, but if that's taken day after day after day  
15 for six months to a year -- It takes about a year to  
16 get into a steady state where intake balances excretion  
17 -- that blood level will rise measurably to a level of  
18 about 20 parts per billion, which is one of the FDA  
19 safe limits.

20 So a single dose is a very different situation than a  
21 chronic dose in terms of body burden.

1 Now, in this case, you go to the top, a single dose of  
2 12.5 micrograms here at birth, given the bodyweight --  
3 We took a bodyweight of 1.8 kilograms -- and we assume  
4 the blood volume was 8.5 percent bodyweight and you  
5 assume that

6 5 -- You do all this arithmetic and you will come out with a  
7 blood level of about 4 parts per billion, which is  
8 about where the equivalent blood level will be for the  
9 EPA guidelines. So you get with this one dose to about  
10 the EPA guideline. You certainly do not exceed, as I  
11 heard this morning, by a factor of 10. Okay?

12 As you continue with these doses over this six-month  
13 period, assuming there's no elimination of ethylmercury  
14 from the body and assuming ethyl behaves like methyl,  
15 you will -- eventually, you will exceed the EPA  
16 guideline. At month number 2, you will get up to a  
17 level of about 15. By six months, you may get up to a  
18 level in the 20s, which then starts to exceed the other  
19 guidelines, the FDA guidelines, the ASTDR, and so on.

20 **DR. KLEIN:** I'd like you to superimpose on this curve.

21 Let's say there is no vaccine given at birth, but the

1 same series of immunizations is given beginning at two  
2 months of age. Does that affect your curve at all?

3 **DR. CLARKSON:** Well, it would reduce every one of these  
4 points by about 4 parts per billion. Essentially, what  
5 would happen is you would have a line sort of parallel  
6 to this, which would start off -- Usually, background  
7 levels in blood are less than 1 part per billion  
8 depending on how much fish the mother may have  
9 consumed. So you would just draw a line more or less  
10 parallel to this with 4 parts per billion below it. So  
11 you would still get in six months, you know, close to  
12 about 20 parts per billion, close to the other  
13 guidelines.

14 **DR. RABINOVICH:** Thank you. Next question? Dr.  
15 Orenstein?

16 **DR. ORENSTEIN:** I was interested -- I guess I did --  
17 Walt Orenstein, CDC.

18 It's interesting that I didn't hear anybody talking  
19 about looking at outcome kinds of studies in vaccinated  
20 children. Roger Bernier presented data from the  
21 Vaccine -- one of the institutions in the Vaccine

1 Safety data link. Kaiser I think had over 30,000  
2 children in a distribution at least of different  
3 thimerosal intakes, and I presume most of those kids  
4 are now between two and four years of age or somewhere  
5 along that line.

6 Is there a reason why none of you considered that? Or  
7 is it I didn't hear you? Is it too many confounders,  
8 too difficult a study to do, or do you think it would  
9 be worthwhile trying to look at some outcome in a  
10 population such as that?

11 **DR. RABINOVICH:** Dr. Gerber?

12 **DR. GERBER:** Maybe one of the people who's been  
13 actually involved in the Seychelles or Faroe studies  
14 can comment on this, but my impression is that those  
15 studies were extremely difficult to do in those  
16 limited, very limited populations compared to the  
17 United States, and that to attempt to reproduce  
18 something like the Seychelles studies or the Faroe  
19 studies in this country with all the potential  
20 confounders would be -- the expense would probably be  
21 prohibitive and it would be extremely difficult to do

1 properly.

2 **DR. RABINOVICH:** Dr. Clarkson, do you have any comments  
3 based on the Seychelles experience?

4 **DR. CLARKSON:** Well, I agree. The number of covariants  
5 that we have to take into account in the Seychelles is  
6 really quite large anyway, and I imagine it will be  
7 much worse here. You can't do a randomized clinical  
8 trial, but that would be the ideal scientific way of  
9 dealing with it.

10 **DR. RABINOVICH:** Dr. Schwartz?

11 **DR. SCHWARTZ:** One of the things that I think we need  
12 to consider is, as a couple of the speakers have said,  
13 that the cat is out of the bag, the horse out of the  
14 barn, and that thimerosal is going to be out of the  
15 vaccines. In addition not only to looking at the  
16 replacement for thimerosal, which I think is very  
17 important, and the gentleman who spoke earlier from  
18 SmithKline didn't specify exactly what has been looked  
19 at with 2-phenoxyethanol, and I think we need to make  
20 sure that our potential concerns with that substance  
21 and with other substances are dealt with.

1 One of the other things that we haven't looked at is  
2 what other additives there are in vaccines or adjuvants  
3 that are used with vaccines and what the impact of  
4 those may be. I think if we're going to learn  
5 anything, it is that thimerosal has been in vaccines  
6 for a long time and nobody really thought a whole lot  
7 about it until all of a sudden it seemed to spring on  
8 everyone's consciousness, and there may very well be  
9 other things that are parts of the immunization program  
10 that are found in vaccines and we need to do, I think,  
11 a much better job thinking about what additional  
12 research may be done in order to be ready should any  
13 concerns arise in the future or to identify any  
14 problems before they're identified by the media or  
15 people who may misinterpret what those data mean.  
16 I think before I spent any money doing further research  
17 on thimerosal, I would be inclined to look very  
18 carefully and see what money needs to be spent on  
19 things that are going to be important to the  
20 vaccination program in the U.S. in the future.

21 **DR. RABINOVICH:** Yes, please, Peter?

1       **DR. PARADISO:** I think it's a misconception, at least  
2       to me, that the thimerosal issue or that the concerns  
3       about thimerosal were sprung on anybody. I mean, we --  
4       At least on the vaccine manufacturer side, this is an  
5       issue we've been dealing with for quite a number of  
6       years. And in Europe, we heard this morning, it's been  
7       a fairly major issue for a number of years, and we have  
8       been moving in the direction that in new vaccines in  
9       the future is actually to move away from the use of  
10      thimerosal because of -- because of the concerns and  
11      the potential unknowns about it.

12      So I think it's unfair to say that this was a surprise,  
13      that we, from a manufacturing perspective anyway,  
14      didn't know about the issues with thimerosal. I think  
15      the surprise was more the reaction to it and the  
16      immediacy in the U.S. particularly.

17      So I want to add to that to say that there is generally  
18      very great care taken to what is put into vaccines and  
19      the potential toxicity of what is put into vaccines.  
20      Perhaps, we can see that the most when we think about  
21      adjuvants and new technologies for improving immune

1 responses. That has been a process that we've been  
2 working on for probably the last ten years and it is a  
3 slow and careful process guided by toxicology and  
4 guided by our desire to make sure that we don't  
5 introduce anything that's not safe. So, you know, I  
6 think we are doing that.

7 **DR. RABINOVICH:** Dr. Zoon?

8 **DR. ZOON:** Yes, Dr. Zoon, CBER.

9 A point I would like to just mention, while I agree  
10 that we need to look at the future with respect to  
11 other potential preservatives, I do think we're looking  
12 at a transition period where even -- a very long  
13 transition period where thimerosal will continue to be  
14 used in a number of vaccines. So I probably share less  
15 -- I feel like the balance needs to be looked at on  
16 both ends. What are the risk factors and what is the  
17 information we need to know to make good scientific  
18 decisions and guidance with respect to the use of  
19 thimerosal and really understand that so that we can  
20 give good instructions and good advice. But as we  
21 heard, if we, if ever, go to zero, we need to still



1 deal with those issues.

2 So my sense is that we need to achieve a balance here.

3 We need to understand more about thimerosal because in  
4 the past two days, I think we have recognized there  
5 really is a paucity of data and I think some of the  
6 points made about looking at the developing nervous  
7 system, looking at the developing immune systems and  
8 the effects of these agents on that at critical times  
9 of development hasn't been -- hasn't been done, and I  
10 think that knowledge is very important.

11 So I would -- While I agree with some of the comments  
12 that we need to look to the future, I also think  
13 there's a lot of science that need to be done in  
14 looking at these organomercurials.

15 **DR. RABINOVICH:** Dr. Halsey?

16 **DR. HALSEY:** I just want to respond to Walt Orenstein's  
17 question and I would have said it anyway, but I think  
18 there is a problem of perception. I personally think  
19 it's very unlikely that any harm has been done. I  
20 don't think anybody believes -- most people don't  
21 believe that it has. I really -- I don't think so.

1 But I think the public perception will be that it might  
2 have, and we know from our experiences that we've been  
3 dealing with in the past five years with regard to  
4 alleged adverse events of a variety of type, that  
5 including things that we have learned some of the  
6 subtle neurologic defects that may come from the  
7 studies in the Faroe Islands, you can bet there will be  
8 many parents who believe their child may be affected.  
9 And they do need data to address that issue. I believe  
10 the data will be likely to be negative, but if we don't  
11 have the data, how can we say that it's not negative?  
12 This is one situation where there will have been  
13 exposure to something that might have done it. It's  
14 not the same as some of the other allegations that we  
15 have dealt with.  
16 So I do believe that there is a need and probably for  
17 much more than the study that Walt was talking about,  
18 which is a limited number of small -- a relatively  
19 small number, even though it's in the tens of thousands  
20 of children, to just take a look at some of the simple  
21 outcomes, but there probably is a need for a careful

1 study. I'm not that type of investigator, but the  
2 people who do these neurodevelopmental things very  
3 carefully need to determine the feasibility. They need  
4 to look at all of the other exposures. This is not a  
5 simple study. This would be very complicated and I  
6 don't look forward to being responsible for those, but  
7 I think if we don't have that, we're just going to have  
8 the continued public trust erosion that says you don't  
9 care or you don't think so. And what's going to happen  
10 to the Vaccine Compensation Program? There will be,  
11 undoubtedly, applications for that and who knows what's  
12 going to be the outcome of those deliberations by the  
13 Special Master.

14 So I think there is a need and probably for more than  
15 one study based upon the problems that we've seen  
16 elsewhere by the interpretation of different studies  
17 and in different populations who have a very different  
18 baseline rate of exposure to mercury. You can't just  
19 pick those populations that are at the low background  
20 of other environmental exposure because you're likely -  
21 - you're then -- it'll be stated, perhaps correctly,

1 that you biased it in your favor in saying that there's  
2 no effect from those.

3 **DR. RABINOVICH:** Comments from the panel or from  
4 anybody in terms of need for such a study?

5 **DR. MAWLE:** I wouldn't disagree with you, but in terms  
6 of public trust, it's an important question to ask. I  
7 feel quite strongly that we have -- there's a lot of  
8 data that we need to know just about what happens to  
9 the thimerosal before we can even get into those  
10 studies. So I think it's something to bear in mind.  
11 I was very happy to hear that Dr. Clarkson will be able  
12 to look or possibly be able to look at what happens to  
13 vaccines in the Seychelle where there is a huge burden  
14 of mercury. If that's possible to do in the Faroe  
15 Islands, I would want to do it there, too, where you  
16 already have the careful outcome measures looked at. I  
17 agree it's not the U.S. population, but it would  
18 certainly give you a parameter and a range for where  
19 you can start to apply that to this population and to  
20 get an idea of whether we really need to do them. The  
21 biggest problem I have with that is that if we find a

1 negative, then there will be so many confounders that  
2 people will say "Well, you just didn't do the study  
3 right." And for the time and expense, I would say that  
4 that was -- that's the kind of study that you want to  
5 keep in the back of your mind, and Gina talked about  
6 looking for populations, databases that may have been  
7 collected for other things that we could possibly get  
8 that kind of data from that wouldn't involve setting a  
9 study de novo.

10 **UNIDENTIFIED SPEAKER:** Bill (inaudible) from Wyeth. I  
11 have sort of similar comment maybe since you said  
12 exactly what I was going to say. My question is  
13 actually for Neal which is that, since you seem to  
14 think there is a clear and present sort of danger here  
15 that should be taken out immediately, what data would  
16 you need personally to be convinced otherwise?

17 **DR. HALSEY:** Let me clarify, I do not think that there  
18 is evidence of a clear and present danger. That was  
19 not my intent by anything that I have said, but I have  
20 participated in writing in the Academy statement and  
21 elsewhere that there is no evidence that harm has been

1       done. There is a clear problem with regard to the  
2       potential or the perceived potential for harm, and I  
3       believe that the correct steps have been taken by the  
4       FDA at this time of requesting within the realm of what  
5       they're capable of in the absence of any data of  
6       requesting action to determine what can be done and how  
7       fast it can done to remove this.

8       So the corrective step from that standpoint has been  
9       taken. What I do believe has not been done adequately  
10      to date is a showing of the uncertainties that we have  
11      at this time and provision of more specific guidance to  
12      physicians with regard to what options are available.

13      I mean, the basic principles that I learned a long time  
14      ago about dealing with perceived risks is that you do  
15      take an action, but you also have to inform people of  
16      what additional steps they may take and this is not too  
17      different than some other vaccine safety issues that  
18      we've dealt with in the past five years. We have DTP  
19      whole cell and DTaP, the acellular pertussis. We have  
20      given a preference to that vaccine that we think is  
21      safer with regard to some side effects. With regard to

1        inactivated polio vaccine versus oral polio vaccine, we  
2        have moved in a fairly rapid process toward the vaccine  
3        that seems to be safer, but one of the first steps we  
4        did was to inform people that there were two different  
5        vaccines and that there are these benefits and risks of  
6        each one. We haven't taken that step yet with this  
7        process, but I think we have an obligation to  
8        physicians and the public to at least talk about the  
9        actions that are there.

10       **DR. RABINOVICH:** I guess I'd like to comment having  
11       heard part of the process. The web pages have had for  
12       a long time the concern about thimerosal and that we're  
13       giving children mercury. Those have been up for a long  
14       time. My groups have known that vaccines contained  
15       mercury. What was new then and sort of gave rise to  
16       the urgency was not knowledge that it was mercury or  
17       mercury-derivative, but the content, the volume. And I  
18       think it was the assessment of the potential highest  
19       exposure given the immunization schedule and the  
20       products available.

21       You raised questions about communicating uncertainty

1 and at what point you send that out further. Bruce,  
2 you've been dealing with this for a year. Maybe there  
3 are other experts here on risk communication. How do  
4 you take something which has been out in the community,  
5 it's on the web pages, where we have a little bit more  
6 information which give rise to concern and which our  
7 vaccine information statements already contain  
8 everything from hypersensitivity to death on every  
9 single statement -- how do you more appropriately  
10 answer concerns? Can you comment upon that?

11 **DR. GELLER:** Well, if somebody has the answer to your  
12 question, they should be speaking and not me.

13 But I will say that one of the things that we've heard,  
14 and I think that while this session is designed to sort  
15 of sketch out a potential research agenda which people  
16 can go back and figure out what's feasible and not,  
17 what's fundable and not -- One of the things that we  
18 heard at the hearing and that we hear repeatedly and I  
19 think Neal echoed in some of his comments just a minute  
20 ago was the sense that you need to actually demonstrate  
21 that you're taking these concerns seriously and doing



1 something about them. I think the fact that we have  
2 recommendations for vaccines and people have a  
3 perception that they've been harmed in some way and  
4 nobody cares about harm is really a big part of the  
5 problem. So I think that as these various studies get  
6 sketched out, I think we all need to know what they  
7 are. So that when someone -- when people ask us, they  
8 say, "Well, what are you doing about it?" that we can  
9 be very clear about all that's going about it. There's  
10 a lot going on already. We've highlighted a number of  
11 things that are deficit, but I think we also have to be  
12 clear that all of this is going on because, though this  
13 is the information age, we'll never have complete  
14 information. We're always going to live in some sort  
15 of uncertainty and I'm sure that nobody would have ever  
16 dreamt that this would have been the issue of the day  
17 and now we see all the gaps in this. So I think as we  
18 begin to move along, there will be other things like  
19 that and we always recognize that there are more things  
20 to fill in, and I think what we're doing about those is  
21 something that we have to communicate quite vigorously.

1       **DR. RABINOVICH:** Plotkin?

2       **DR. PLOTKIN:** Well, as this meeting draws to a close, I  
3       am -- we're talking about perceptions, perceptions of  
4       danger and so on, I must say that I'm reminded of Alice  
5       in Wonderland. Now, I don't happen to remember the  
6       exact story, but at one stage I think Alice is talking  
7       about a situation and she says, "Well, we'll have a  
8       trial and then we'll have a sentence." And the Red  
9       Queen says, "No, first the sentence and then the  
10      trial."

11      So, you know, it strikes me that a perception has  
12      certainly been created through the change in the  
13      vaccine schedule and so on and that there is a real  
14      problem. Now, after these two days, I must say that  
15      I'm actually less sure that there is a problem while I  
16      was when this meeting started. I do have to repeat my  
17      comment that I think this meeting should have been held  
18      sometime ago before the announcements.

19      **DR. RABINOVICH:** I think that's a point well-taken.  
20      I'd like to thank the panel and turn it back to Dr.  
21      Marty Myers.

1       **DR. MYERS:** Dr. Modlin had to leave to make a plane  
2       just a little bit ago and asked me if I would take over  
3       at this point and ask Dr. Klein, our rapateur, to give  
4       us a summary. We're a little bit ahead, though we seem  
5       to be at that point. Dr. Klein?

6       **DR. KLEIN:** My job has been made easier by this  
7       afternoon's discussion. I think it was the best  
8       summary of this meeting. It included almost everything  
9       that I had noted. So I will touch on only a few  
10      points.

11      One, the goals of the meeting were to inform and have  
12      dialogue among experts from different disciplines, and  
13      I think we've achieved that very successfully.  
14      Certainly, for those of us whose knowledge of ethyl,  
15      methyl, or other forms of mercury was limited or none,  
16      we've learned a lot. I think we'll all be able to find  
17      the Seychelles and Faroe Islands on the map and be able  
18      to discuss them with authority.

19                               (LAUGHTER)

20      **DR. KLEIN:** Dr. Myers and I will develop a summary that  
21      will be published in MMWR. We'll have to call on some

1 of you to clarify and make sure that we don't write  
2 something that is either unintelligible or incorrect.  
3 So we'll be calling on you for your help.

4 I think we've learned that preservatives are critical  
5 in the preparation of vaccines and there will be  
6 preservatives, even if they are different from the ones  
7 that are currently used, but they are important during  
8 the manufacturer process, during administration, and  
9 particularly during multi-dose vial usage. Even there,  
10 the concerns that the multi-dose vials be used as  
11 instructed on the label and that they have a relative  
12 limited period of time for their usage and the  
13 contamination may overwhelm the preservative if those  
14 instructions are not followed.

15 In relationship to the manufacturer processing, I was  
16 particularly impressed with Dr. Clements' discussion  
17 and presentation that there are a lot of manufacturers  
18 in countries with different standards and that perhaps  
19 some of the data that will come from these areas of  
20 research will be universally available for local  
21 manufacturers and perhaps give them an additional

1       safeguard.

2       The regulation issues, I raise a question of timing in  
3       the sense that any new product or change in formulation  
4       is substantial in terms of new studies that will be  
5       needed and this is a process that will be gradual and  
6       take place over a period of years. Dr. Clements gave  
7       the timetable. Dr. Paradiso added to that, but,  
8       certainly, in terms of finding the preservative, the  
9       clinical trials for the products containing that  
10      preservative, the regulatory issues in terms of  
11      approval and, subsequently, reformulation, we're  
12      probably talking about a minimum of five years before  
13      new preservative preparations are on the market. And  
14      that may be, give or take, two or three years.  
15      In terms of thimerosal, by either spelling, it works  
16      and has worked for these many years and one can at  
17      least have some confidence that disasters have not  
18      occurred to our knowledge from such usage, but the  
19      toxicity data are limited. And what has been presented  
20      to us by our colleagues in toxicology is that the data  
21      on methylmercury has been used in the assessment of

1 risks associated with ethylmercury and the toxicity  
2 profile of the two compounds should be considered to be  
3 similar so that, even though it may be a stretch that  
4 ethyl and methyl are similar, the absence of  
5 information dictates what we need to use the data about  
6 methyl at least is a starting point and surrogate for  
7 our discussions.

8 In terms of thimerosal, again, that it's not the amount  
9 of the preservative in each vaccine, but it's now with  
10 the burst of new product and the cumulative amount of  
11 mercury that is present that has raised the concern.

12 I think most important is the words "eliminate/reduce"  
13 and that the perception should be, particularly keeping  
14 in mind the timetable of years, that our goal is to  
15 achieve elimination but first reduction and that those  
16 terms always be used in a paired fashion and that the  
17 gradual changes, rather than precipitous changes, is a  
18 reality.

19 Finally, we talked a lot about delivering the message  
20 and I think that's an increasing part of our decision-  
21 making, and at anytime we do come to a change in

1 current policy, we need to anticipate the reception of  
2 that change among caretakers, physicians, health care  
3 workers, parents, consumer advocates, legislators,  
4 manufacturers, and particularly, I think, our role as a  
5 leader in these discussions throughout the world.  
6 So every action will have a reaction. I think a lot of  
7 the discussion yesterday about the action that was  
8 taken in changing the schedule of the hepatitis B  
9 vaccine from birth bears on that, making sure that that  
10 message and the reason for the change is delivered to  
11 those who are actually responsible for the change, the  
12 hospitals in altering their policies are cognizant of  
13 the reasons for the changes, that the clinics  
14 understand that any gaps that would be created -- I  
15 think Bob Down's data and the CDC data that suggest  
16 that that first immunization in the nursery is very  
17 important in subsequent vaccine utilization by selected  
18 families leads us to believe that delivering the  
19 message and the caretaker's delivering the message to  
20 the parents becomes a very critical part in decision-  
21 making.

1 I think Gina said it very well, that the generic issue  
2 is to become more capable, more skilled in how to  
3 communicate controversial and inconclusive data so that  
4 we maintain confidence of our public. And as long as -  
5 - the time that I've been on the Red Book and  
6 subsequently, this has been and will be a continued  
7 challenge, and I think we need all the help we can get  
8 in making sure that our decisions not only are  
9 appropriate scientifically, but they are communicated  
10 to the public in a manner that the constituency  
11 understands the reasons for the change and is accepting  
12 of those changes.

13 I'd like to congratulate Dr. Myers and staff for  
14 putting together a meeting that I find to have been one  
15 of the most informative and interesting programs that  
16 I've attended in a long time. So thank you very much,  
17 Marty.

18 (APPLAUSE)

19 (CONCLUSION OF WORKSHOP AT APPROXIMATELY 3:14 P.M.)

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C E R T I F I C A T E

G E O R G I A )

FULTON COUNTY )

I, Pamela T. Lennard, being a Certified Court Reporter in and for the State of Georgia, do hereby certify that the foregoing, consisting of pages 1 through 238 (DAY TWO - VOLUME I) inclusive, was reduced to typewriting by me personally or under my supervision and is a true, complete, and correct transcript of the aforesaid proceedings reported by me.

I further certify that I am not related to, employed by, or attorney or counsel for any parties, attorneys, or counsel involved herein; nor am I financially interested in this matter.

WITNESS MY HAND AND OFFICIAL SEAL, this 5th day of September, 1999.

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Pamela T. Lennard, CCR-CVR  
CCR No. B-1797

[SEAL]