The National Vaccine Advisory Committee Sponsored Workshop on Thimerosal Vaccines, August 12, 1999, Lister Hill Auditorium

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Abstract

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Contents

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Proceedings
8:33 A.M.

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

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

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

DR. MODLIN: Thanks, Marty, and good morning. Before we begin, just one or two quick housekeeping issues. Number one, Nancy Cherry and her staff have very graciously agreed to help us with taxicabs. So those of you who will be taking cabs to the airport directly from the center here, if you would check with either Nancy or one of her staff members out at the table, either at the break or at lunchtime, they will be happy to arrange a cab for you. Secondly, Harry Greenberg clearly set the standard yesterday by finishing up early. Those of you who attend the ACIP meetings know that I also have an obsession for staying on time and sticking to the agenda. So I will warn today's speakers of that in advance, and you all are so warned.

Yesterday we heard how this problem with Thimerosal in vaccines has developed. We learned more about mercury toxicity from some very excellent background presentations. Today the focus will be on where we go from here. We don't have all the data that we'd like to have. We still need to make some important decisions in the near future, and this is certainly the case for vaccine manufacturers, it's a case for the FDA, it's a case for advisory committees, and we will hear from representatives from all of these groups today. We'll also hear from a representative, one of our European colleagues, on how they have chosen to deal with this issue.

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

DR. ADLAM: Well, good morning, ladies and gentlemen. Thank you, Mr. Chairman, for that introduction. What I should like to do today is to expand on some of the points made by earlier speakers, with particular reference to the manufacturing issues surrounding the use of Thimerosal in vaccines and, as Dr.

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Modlin pointed out, moving a little bit to the future as to where we might be going. So, as you see, *Opportunities and Challenges* is the thrust of this part of the meeting.

Thimerosal is used in two different areas in the manufacturing process, and the first, which is the main concern of this meeting, is, of course, its use in final containers of vaccine as a preservative. Now, the reason it is used in that situation is, of course, to guard against contamination which might be introduced during the filling process. The second area, though, where it's still used is in vaccine development; for example, where we need to produce pilot batches of product for testing purposes, or we may require to validate equipment, scale up equipment, for example, but also, we still use Thimerosal in full-scale manufacturing processes for some vaccines, and particularly where the method of antigen purification, for example, might be complex, and where manufacturing people may consider that there would be potential risk for contamination if a preservative wasn't present.

Now, historically, Thimerosal has been used as a blanket cover for most liquid-inactivated vaccines, but as techniques have improved in manufacturing and the concept of good manufacturing practices over the years has come to the forefront, companies have reviewed their use of Thimerosal and, indeed, have come under pressure from environmental agencies to reduce the quantities of Thimerosal that they use in their vaccine manufacturing processes.

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

I won't deal on point two very much because Dr. Clements gave an excellent overview of the particular problems faced by the international agencies. As we have heard, they have particular problems, which, of course, vaccine companies, most of whom these days are international, have to address. It's worth making the point, though, that if we have to remove Thimerosal for, if you like, developed country markets, we still will have to make a second product containing the preservative for multi-dose containers in the international markets. So that is, of course, an added cost to the industry.

Finally, and to my mind most important, is that although quality of manufacture has greatly improved over the last 20 years—good manufacturing practices have, of course, improved out of sight since I first joined the industry—and the data and figures that were shown in terms of numbers of filling lots that were contaminated yesterday, these would of, course, not be tolerated by today's standards. Nevertheless, it has to be said that good manufacturing practice remains pretty good but not 100% perfect. And to expand on that just a little, it should be borne in mind that today's vaccines, in contrast to those of years ago, contain highly purified antigens and that these products may go through very many stages in the purification cycle. Sophisticated equipment, column chromatography would be used, where as, of course, 20 years ago these techniques were just considered totally unnecessary for vaccine manufacture. As many as 9 or 10 bulks, different bulk antigens would have to be stored. 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 type of sensitization which run somewhere between 1 and 3 million doses administered and 1 in 20 million doses administered. So we're talking of a very rare event, and the majority of those cases are not life threatening sensitizations.

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

So what are the alternatives open to the industry as we move away from the age of Thimerosal? Of course, the first option is to eliminate even from mono-dose vaccines—we can't do it for multi-dose, but we could eliminate from mono-dose vaccines all preservatives and to rely on good manufacturing practices. This is a laudable objective, and it may be, indeed, possible for some products and some processes, and it certainly is a road down which the FDA is pushing the companies. However, as I've stated already, we should maintain caution when we do this, if indeed we're not to replace one set of problems with another.

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

This slide just lists the vaccines produced by SmithKline Beecham Biologicals and which are commercialized in the U.S. together with their preservatives. And as you can see, only the earliest licensed product, which is the hepatitis B vaccine launched in 1989, contains Thimerosal. And since that time, it has been a decision within the company to move away from Thimerosal and to use the alternative 2-phenoxyethanol. And as we heard, again, a little bit on this substance yesterday, it has an excellent safety record and is pretty good as a preservative.

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

Now, as far as the vaccines that are commercialized which contain Thimerosal, as we heard, companies have been ap-

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proached by the agencies and are in discussion with agencies, both in the U.S. and in Europe, as to what their plans are for reducing or eliminating Thimerosal. And like other companies, I would guess, we have submitted our plans for removing Thimerosal as a preservative from this vaccine.

So to conclude this brief résumé and by returning a little bit to the title of this part of the talk, *Opportunities and Challenges*, as I've said, I think one of the first opportunities and challenges, if you like, lies in the continued development of new multi-component products, which, of course, will result in fewer injections that need to be given, which, as we're all aware, is a good thing.

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

And thirdly and finally, of course, our main objective is to continue to improve the efficacy and the safety of all of our vaccines. So I think I'd like just to leave it there, Mr. Chairman, and if there are questions, either take them now or at the end of this section. Thank you. (APPLAUSE)

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

DR. EGAN: You touched on the use --

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

DR. EGAN: Bill Egan from Office of Vaccines, CBER.

You commented about the use of preservative even in a single-dose vials. Could you expand a little bit on what you feel is the need or the advisability of having preservatives in them and what kind of levels? Thank you.

DR. ADLAM: Thank you. This is, of course, a little bit of a contentious issue. I think we would all like to be able to say that we can remove all preservatives from mono-dose containers, and as I said, they are laudable objective[s] to try to achieve. My only caveat to that is, as I say, I think we have to [be] very careful that it can be achieved. I mean, as you're well aware, all companies will submit media fill control data to the agency. This information is out there. We can look at it and we can see whether we are yet in a position to totally remove all preservatives from the vaccine. In terms of quantity, we use the standard quantities of 2-phenoxyethanol in these more recent products. It's a point for debate. We could discuss that, I think, the advisability of dropping it out, keeping it in, but it's something which we should be, in my view, careful. It should be approached carefully on a case-by-case basis.

DR. CLEMENTS: Thank you. John Clements, WHO, Geneva.

I thank you for bringing the issue of combination vaccines up. WHO is firmly in favor of developing strategies which will enable developing countries to use combination vaccines for the sorts of reasons you've identified. My question is: What opportunities do you think developing countries will have for producing combination vaccines, bearing in mind their desire so often to have local production? What are your ideas on the possibility of technology transfer and local filling, for instance?

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

DR. MODLIN: Further questions?

DR. BRIDGES: Carolyn Bridges, CDC.

Are there any special issues for producing preservative-free single-dose vaccines for vaccines produced in eggs or viruses grown in eggs?

DR. ADLAM: Yeah. That would be one example that I would look at. If you think about it, what you're doing when you make an inactivated influenza vaccine is to process and purify your influenza antigen from eggs, as you say, from embryonated eggs. Now, that is a whole lot of very rich protein that you have around, plus the fact can you be sure that each one of those eggs does not carry a contaminate of one sort or another. We know, for example, that hens' eggs in the outside world—of course, we don't use farmyard eggs to make these vaccines, okay? But, nevertheless, the theoretical possibility is still there that you may have the odd egg with the odd contaminate. Okay? And if you have that, then you have to have something in your system to prevent that becoming a real problem in the final vaccine.

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

DR. MODLIN: Dr. Daum?

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

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

It seems to me that no matter how try to minimize this problem—and minimize it we must because it's not acceptable to have an overly reactive (inaudible)— we're never going to get it to zero. I wonder. We live in an era now of numerator amplification where one side (inaudible), it instantly becomes -- CNN helps do that and some of our support groups help do that. It just becomes instantly news all over the place. I wonder if the proper way to think about this is to just realize that we're not going to ever solve this problem with taking the side effect or toxicity rates to zero. We're going to pick the method to get it as low as we possible can and then also have an education campaign that says, you know, there's no free lunch in this world.

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We have a wonderful preventative strategy here, we're offering it to all children, and in the end, like any medical intervention, there are rare occasional problems.

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

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

DR. SNIDER: Dixie Snider, CDC.

Actually, two questions.

First, if I understood you correctly, and I'd like to know if I did understand correctly, that combination vaccines present us with both a plus and a minus in terms of a preservative, that is, that you would have to give a smaller amount of—per antigen that you were using, but because of the complexity of the manufacturing process, it might be more important to include a preservative when making a combination vaccine.

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

DR. ADLAM: The first question was regarding the combinations, and I think you're right there. Obviously, the more complex the manufacturing process is, the more pressure there would be, I would say, to include some kind of preservative in the vaccine. So I think that analysis that you made there is correct.

In terms of 2-phenoxyethanol, it is fairly widely used, not just by us, but by others and in the pharmaceutical arena. It has a pretty clean tox profile as a material, and it's fairly effective at doing its job. Of course, we don't yet have 60 years experience with it. That's a given, but it looks to be very effective, and it is accepted by the agencies involved with preservatives.

DR. SCHWARTZ: John Schwartz from CDC.

I also wanted to focus on your use of 2-phenoxyethanol. Yesterday we heard from a couple of the speakers, when looking at the in vitro tests with the USP agents that it performed less well than Thimerosal. So I was wondering what type of testing has been done specifically that suggests that it's adequate as a preservative, and your company clearly has made a decision that it, indeed, is adequate to accomplish that particular function.

With respect to the -- the potential adverse reactions, you spoke in very general terms about what's known, but I think one of the things that we've learned from Thimerosal is that even in a product that has been used for 60 years that there hasn't been a lot of research about its use. So I would expand on Dixie's question and say, well, if the safety profile, quote, "looks good," what research has actually been done and are there areas? Are there gaps where we need to look further to get a better understanding of potential toxicity?

DR. ADLAM: Okay. An answer to the first point, the 2-phenoxyethanol as all other preservatives, in fact, it seems does satisfy for example, the USP regulations surrounding the use of preservatives in vaccines. It's true that as I said we don't have 60 years' experience with this material. There have been studies done. There is a literature on 2-phenoxyethanol. It's probably outside the -- you know, without having another symposium on 2-phenoxyethanol. Nevertheless, there's a significant body of information. But you're quite right, we don't have 60 years experience with this material.

As far a Thimerosal is concerned, I think that the fact that 60 years has gone by with it being used as a useful product has probably meant that people haven't spent a great deal of time going back over the old data, which is what we heard yesterday. Now, this meeting and recent resurgence of interest in the topic may stimulate some of this research, and I guess that's going to be a situation to be discussed in this afternoon's session as to where we go with Thimerosal, 2-phenoxyethanol, and maybe future alternative preservatives.

DR. MODLIN: Last question. Dr. Klein?

DR. KLEIN: Jerry Klein, Boston University.

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

DR. ADLAM: That is one option that could be taken. You could say, well, we have X amount of Thimerosal in this product, can we reduce it by half and still have a safe effective product? I mean, I think those – or couldn't we eliminate it completely? Can we substitute? These are the kinds of debates that are being held now with the agency in this particular area for particular products, and, you know, the discussions continue, and there will be, you know, discussions along what will be needed to show that your product is still efficacious if we remove or we reduce Thimerosal. Those questions have to be addressed on a case-by-case basis and data will have to be supplied.

DR. MODLIN: Thank you, Dr. Adlam.

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

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

Before I begin, I would like to emphasize a few points. As stated yesterday by Dr. Egan, the FDA has not banned the use of Thimerosal as a preservative in vaccines. Secondly, there's no evidence has been presented that would suggest that the

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amount of Thimerosal in individual vaccines is unsafe. Lastly, our goal or objective is to assist in decreasing the exposure of humans to mercury-containing compounds by reducing or eliminating, where feasible, Thimerosal from vaccines, and this is also stated or an objective of the Food and Drug Administration Modernization Act of 1997.

Basically, the regulatory issues involved in reducing and eliminating Thimerosal from vaccines is no different than the regulatory concerns of making any other manufacturing change to a vaccine. I think the issue here is, what are the implications involved in removing Thimerosal at this time and also for reducing the amount of Thimerosal. The options that we have, there are basically three that we can choose from. I think Dr. Adlam touched on these.

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

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

For all of these options, the regulatory requirements will differ slightly for each of these. As Dr. Egan mentioned in his talk yesterday, there are no regulatory requirements to include a preservative in a vaccine contained within a single dose or a single-dose vial. However, vaccines that are filled in multiple dose vials do require, by regulation, the use of a preservative with the exception of some live viral vaccines. The elimination of Thimerosal from multiple dose vials will require the exclusive use of single dose vials or the replacement of Thimerosal with an alternative preservative.

If we begin with the assumption that manufacturers will continue to use multiple-dose vials for vaccines, then we must assume that Thimerosal will either be replaced or the amount used will be reduced as I stated in my outline earlier in the options.

Let us begin with the substitution of an alternative compound for Thimerosal. One must first determine where in the manufacturing process the Thimerosal is used, and I think Dr. Adlam also touched on this. Thimerosal may be used as a bacteriostatic agent in the production process. So in processing the various steps involved in manufacturing may require the use of some type of preservative, and in this case, perhaps Thimerosal as a bacteriostatic agent. This is the case with some of the influenza vaccines. The use of Thimerosal may also be used as an inactivating agent, and an example of that would be whole cell pertussis vaccine. Then Thimerosal is also, as we all know and why we're here, is used as a preservative and that preservative may be in bulk/final containment or it be in the diluent. In other words, the replacement of Thimerosal with an alternative compound will depend on how and where the Thimerosal is used in the manufacturing process. In turn, the regulatory requirements for substituting an alternative compound for Thimerosal will depend upon whether the compound is used solely as a preservative or as a bacteriostatic agent for in-process manufacturing or as an inactivating agent.

Now, looking further into the regulatory requirements, I think it's necessary to explain a little bit about how the regulatory process works. The regulatory reporting category for a manufacturing change will depend upon whether the substitution of Thimerosal results in a complete formulation change in the final product or whether the removal or substitution of Thimerosal is, for example, only for a buffer used to reconstitute a vaccine.

So the reporting categories will be different. We have what is known as a prior approval supplement. The prior-approval manufacturing supplement has a maximum review time, and emphasizing the review time, of 6 months, although we have a target of reviewing a percentage of those in 4 months. Then the other extreme is a minor manufacturing change where you could have distribution of that product containing that change within 30 days or after a 30-day period if the manufacturer does not hear from the Agency that there are problems.

So what I'm getting at here is depending on the type of change, that removing this Thimerosal from the product, depending on where you remove it, it will dictate how much or how long the review time will be. In other words, if it's a new formulation, that's a full prior-approval supplement. Whereas, if your formulation does not contain Thimerosal and you are only adding the Thimerosal to a buffer that's to be used to reconstitute the vaccine, that may be a lesser change that will require less time.

So prior approval supplement versus changes being effected in 30 days, the timing on the—depending on where and how the Thimerosal is used, will dictate the review time. Preclinical data may be necessary for some of these changes, including reproductive and toxicological studies on new compounds, compounds that we have no experience with, may require repro/tox studies. Data on the compatibility of the new compound with other components in the vaccine will definitely be required, but depending on where in the process, the amount of data, again, will be dictated by that.

Of course, validation of the bacteriostatic and bacteriocidal type of properties of the new compound, as well as inhibition of yeast and fungi will have to be—data will have to be submitted to support the use of the new or alternative preservative. In addition, batch analysis of consistency lots will be required to be submitted to support a change of removing Thimerosal. Stability data will also be required and, preferably, we require real-time stability data for those submissions. Again, all of this we're going to try to work with the companies to work out the amount of data that's needed and what's available from the manufacturers. Stability data would also be required when you're changing from a multi-dose vial to a single-dose vial or syringe.

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

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Now, in some cases, Thimerosal may not be easily replaced by an alternative preservative. An option would be to reduce the amount of Thimerosal in a vaccine, especially if exclusive production of single dose vials is not an option. But, basically, the regulatory requirements for reducing the amount of Thimerosal are the same as those for substituting an alternative preservative. However, most important here is the validation of the inhibition of microorganisms using the reduced concentration of Thimerosal, as well as stability data supporting the desired shelf life of the final product. Now, some of the options we could take here is by—well, let me back up.

Most importantly, as I stated, the manufacturers would have to validate the reduced amount of Thimerosal has a given effect, i.e., bacteriostatic/bacteriocidal, with the given preservative. Now, those would not meet the USP requirements, but as stated yesterday, we're not really bound by the USP requirements. The USP requirements are accepted, but we would work with the manufacturer and look at the validation data, and what we may come to a point where we would reduce the shelf life on that product. So if you had a 30-month dating period and you could validate—you could substitute or reduce the amount of Thimerosal and shorten that dating period, that would be an option also.

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

Thank you. (APPLAUSE)

DR. MODLIN: Questions for Dr. Baylor?

DR. ABRAMSON: Jon Abramson from the American Academy of Pediatrics.

It would seem to me that scientifically what had to happen prior to all of this is that as for each vaccine you were figuring out how much Thimerosal was needed that there is data on the lower side of what was finally put in there that would tell us that. I mean, I can't believe that people would pick a number and did the studies just with that concentration and didn't do (inaudible) factors.

DR. BAYLOR: I think you have to estimate. When we receive the data, we're going to evaluate that data on the safety and efficacy of that vaccine. So looking at the amount of Thimerosal and -- Again, some of these products were licensed decades ago and the review was somewhat different, but, even then, there was concern about the toxicity of these compounds. So we did look at that in the whole package, but I think also that you have to -- the point that was made yesterday about the requirements in the United States versus Europe, some of those requirements, some of the Pharmacopeia requirements in Europe are higher. And looking at what the manufacturers are going through, producing multiple formulations for the world or taking the option of producing one formulation and that formulation happens to have a slightly higher amount of Thimerosal than needed for the U.S. or to beat the USP, as long as it's safe and effective, we're not going to disapprove that vaccine, but, you know, we are going to look at the toxicity. I think the bar is much higher now than it was when some of these old vaccines were approved.

DR. MODLIN: Dr. Gellen?

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

DR. MODLIN: Could you just introduce yourself?

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

There may not be a blanket answer to this, but when you use Thimerosal in the process, does it necessarily stay in the end product?

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

DR. GELLEN: Okay. And my second question, you were quite careful in your introductory remarks about—I may have not quoted this perfectly, but you said there's no evidence presented that Thimerosal in individual vaccines is unsafe. You were cautious to talk about individual vaccines. Is there a stance about the vaccination process, that there's a feeling that as given currently that there's evidence presented that Thimerosal content overall in infants is unsafe?

DR. BAYLOR: No. The point I was trying to get out there is that this issue that we're dealing with today and that we've been dealing with revolves around the cumulative amount of Thimerosal, a mercury-containing compound, to individuals receiving several vaccines, but if you look at the vaccines individually, there are no—whether you look at EPA or FDA, levels that are exceeded on those vaccines. The issue comes about when you administer a number of the vaccines, for instance, when a child receives all the recommended vaccines on time within the first six months. That's really the issue we're dealing with. We're not really dealing with -- I don't know if there's --

We, as an agency, don't have concerns that there's an amount of a compound in these products that are unsafe. It's the cumulative receipt.

DR. MODLIN: Dr. Myers?

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

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

DR. BAYLOR: Okay. Basically, the answer is, since we have the current regulations, no. However, that is a possibility if the manufacturers can validate that they can actually make or produce a multi-dose vial without a preservative and validate that that product would maintain its integrity as far as absence of contamination. We could consider that. However, the only way to consider that at this time is to eliminate that regulation. As long as the regulation is on the books, we have to require that, but that's not something that can't be done. We've eliminated regulations before. So . . .

DR. MODLIN: Yes, Dr. Horowitz?

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

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As an entity that works in collaboration with USP receiving medication errors, which, of course, we forward to FDA as a med watch partner, over the years we've received numerous incidences of adverse drug events related to multi-dose vaccines, confusion with (inaudible), cross-contamination up to, in one incident, 468 patients. You had mentioned 4 different alternatives that the Agency may do if I understood your presentation. It seems to me that with the sole exception of moving into a single-dose, essentially a unit dose, those same problems that are reported to us and that have been reported to us are likely to occur.

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

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

DR. HOROWITZ: As opposed to reducing the amount of Thimerosal or seeking an alternative?

DR. BAYLOR: At this time, we are not considering mandating single-dose vials. To do that has a number of implications and we feel that basically with the multi-dose vials in their current state, they're safe. I mean, the manufacturers have validated that with using the current preservatives in those products. They maintain their integrity. See, the complicated part here is we have no question that the manufacturer can produce a vaccine in a multi-dose vial or single-dose vial or any kind of vial that's going to be sterile. The issue is when you get out in the field. And we don't know if everyone is practicing aseptic techniques. That's something we can't control as an agency, but by requiring -- I mean, that's part of the rationale for requiring preservatives in multi-dose vials. We're trying to address that issue, but we'll never be able to address that issue across the board because we just can't—we cannot police aseptic techniques in the field.

DR. HOROWITZ: Thank you.

DR. ENGLER: Dr. Engler from Walter Reed.

I was just wondering in the options why there's no consideration of leaving the concentration of Thimerosal the same, but increasing the concentration of the active antigen and giving a smaller dose, which would also reduce the pain of the injection, facilitate jet injector technology development, and would potentially be a win/win. The half cc comes from the era when syringes did not have small enough markings and you couldn't readily measure more than a half cc. From a clinical perspective, it seems we might move to a new era considering we have tuberculin syringes.

DR. BAYLOR: I think that's a viable option. I mean, again, it would have to be validated and if the data supports it, I don't see why that – you know, we would definitely consider it.

DR. MODLIN: Dr. Daum?

DR. DAUM: Bob Daum from the University of Chicago.

I may have missed something in the logic here and I just need to clear --

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

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

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

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

DR. DAUM: But is the Agency committed to asking manufacturers to do something about Thimerosal or is the Agency just having discussion at this point?

DR. BAYLOR: The Agency is committed in asking the manufacturers what are they doing to address Thimerosal in vaccines. We sent out a letter this summer to all vaccine manufacturers asking them to address this issue. Again, our objective is to -- It's just like anything. Our objective is to remove or to decrease the exposure of humans to mercury. Thimerosal is a mercury-containing compound. So if that's feasible, and I did use that word in my discussion, then we want a dialogue with the manufacturers to find out if that can be done.

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

DR. BAYLOR: No, it doesn't. But it says that – I mean, any -- If we lived in a perfect world, none of us would want to be exposed to mercury. So if we have an opportunity to decrease our exposure to mercury or any other harmful chemical, we would do it. So we would like to know from the manufacturers what are they doing to address this issue. Can they address this issue? We have not issued any mandates at this time and this was not the purpose of (inaudible) in Section 413. It was not to issue any kind of mandate. It was exploratory.

DR. KIM: Kwang Sik Kim, Los Angeles.

You indicated that preservatives must have about bacteriostatic and bacteriocidal activities, and the question to you is that: Does FDA have any specific guidelines how to do those assays? For example, if the compounds are being tested with let's say bacteria of 103 instead of traditional 105, is this sort of acceptable? That may be the way to reduce the concentration of preservatives.

DR. BAYLOR: Again, as I stated, that's going to have to be validated. If the manufacturers want to go that route, they will have to validate -- I think the guidance is in the USP. You can start with that and then go back, but you have to validate the amount of preservative that you're going to use. In that validation, what are the inhibitory properties resulting from a reduced amount of preservative? And then we, as an Agency, will decide whether that's acceptable or not. In that decision, we may say, well, based on the data that you've accumulated, we need to cut your shelf life in half, or whatever.

DR. MODLIN: Dr. Plotkin?

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

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

DR. PLOTKIN: Plotkin, consultant, PMC.

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

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

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DR. PLOTKIN: -- and my question is, would you require clinical studies as well, in other words, to show that the material is still immunogenic and safe?
DR. BAYLOR: Again, depending on where that preservative is used will dictate whether we will --
DR. PLOTKIN: As a preservative?
DR. BAYLOR: As a preservative. As a -- Your question is, as a preservative?
DR. PLOTKIN: Yes.
DR. BAYLOR: Well, if your preservative is in the final formulation versus, say, you've made your final formulation and you have in your diluent, we may not require clinical data, but if it's in your final formulation, we may require clinical data because your final formulation has changed. But, again, that statement does not go across the board about products. We have to look at the individual product that you're speaking of and determine it from there, determine how you're adding—or where the Thimerosal is and the parameters that are involved in incorporating that into your final product. I mean, another example is you may have a preservative in your bulk and decide to leave that in, but as you're doing your final fill, you may remove that from your bulk at the time of final fill and demonstrate that it's at a level of, or below, the level of detection.
DR. MODLIN: Yes, Dr. Clements?
DR. CLEMENTS: Thank you. I'd like to come back to a question that Dr. Myers has just made about multiple dose MMR vaccines, and I really offer this as a comment.

I'm concerned that the meeting may be under a misapprehension about such vaccine vials. At WHO, we encourage countries to use the measles vaccine, which is a multi-dose, ten-dose vial, but once the vaccine is reconstituted, then we give strict training that this vaccine must be discarded up to six hours from the start of reconstitution and failure to do that has, in many, many instances, resulted in contamination, overgrowth of staph, and what is known as the toxic shock syndrome. The tragedies that result from that are the deaths of multiple—2, 3, or 6 children at a time from overgrowth of staph in the vaccine. So I would caution the enthusiastic procedure of multi-dose MMR vaccines.
DR. MODLIN: As well as lost potency, which is a little bit different issue than it is with perhaps some other vaccines.
DR. BAYLOR: Right.
DR. MODLIN: This is an important line of questioning. Are there others? Dr. Egan?
DR. EGAN: I would just like to make a very quick comment on the MMR vaccine itself.

First of all, it's a freeze-dried preparation. It does contain some neomycin, a preservative, and perhaps the representative from Merck can correct me, I believe the package insert says that it must be utilized within eight hours of reconstitution. So it's similar to the WHO. I think it's eight and not six.
MR. GUITO: Ken Guito from Pasteur Merieux Connaught.

I appreciate your attempts to try and shed some light on this challenging situation. If I can go back to your option four, if I might, and expand on your comments and Dr. Daum's comments.

You see a potential for, I guess, a hybrid of that situation where you could have a product such as flu where you would produce single-dose vials for a very specific population, women of childbearing potential, pregnant mothers, and the occasional infant. You had a multi-dose presentation that kept the existing level of Thimerosal.
DR. BAYLOR: I'm not going to rule that out. I think what we're going to be faced with in the short run is that situation anyhow, because as manufacturers move toward removing Thimerosal from some of their products, we're going to be in a situation where there are going to be Thimerosal-containing and Thimerosal-free products, the same products, same manufacturer on the market at the same time. So we're going to have a period where that's going to happen anyhow. Now, whether we're going to prolong that period, that's up for discussion.
DR. MODLIN: Okay. Thanks very much.
Our next speaker is going to give us a perspective on how our European colleagues have dealt with this issue very recently. She is Mary Teeling, who is Medical Director of the Ireland Medical Boards. Dr. Teeling, welcome.
DR. TEELING: First of all, just to say that we have in Europe been looking at the issue of Thimerosal for -- We've been doing this, in fact, for a year and a half. So it's a great honor and privilege for me to come here to share with you our deliberations and, more importantly, how we are coping and what we are doing on an ongoing basis with Thimerosal. And thank you to Dr. Myers. And I did say to him that I do have the facility, being a good Irish woman, to use many words rather than a few, but I really didn't think that my introduction was going to be as long as this. (LAUGHTER)

So to put into perspective exactly what we do in Europe -- Because I think this is very important and it's an important issue when we're looking at Thimerosal -- we have in Europe two methods of licensing. Now, there are 15 member states in the European Union and each member state has its own national agency. So you can imagine 15 FDAs, albeit all different sizes and shapes. And that's important because that means that it is possible to have a national license for medicines, including vaccines.

We also have a European Agency for Evaluation of Medicinal Products called the EMEA, and that is responsible for community authorization. So that means it's a one-stop shop. If you go the agency with a particular type of medicine, you can get a license that's valid in the 15 member states.

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

Now, the European agency has two main arms. The first is the Secretariat. Quite an extensive secretary is taken from all over the European Union, and these are mostly people who will have worked in agencies within the 15 member states and a scientific committee called the Committee for Proprietary Medicinal Products, the CPMP. Now, as I said, the CPMP is a scientific committee. It's made up of two members per member from each member state, but you leave your national hat outside the door when you come into the CPMP. It is a truly scientific

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committee where science is evaluated. So national issues are not discussed at the CPMP.

Now, if you were to ask me what the role of this scientific committee is, I think you can get many, many different views, but I think, in general, it's to ensure the provision of safe and efficacious medicines to the market place in a timely fashion. Now, that's very important. I know the FDA have time limits. In fact, Norman Baylor mentioned some time limits before, and we have implemented time limits, 210 days from beginning of the authorization to approval, positive opinion, or otherwise, from the CPMP. And that's for the community licenses, for the ones that get the European license.

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

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

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

Okay. Now, the CPMP has a number of permanent expert groups and, again, these are important because they've all been involved in the Thimerosal. There is a Biotechnology Working Party looking at the pharmaceutical aspects of biotech products, an Efficacy Working Party looking at the effectiveness of drugs, a Quality Working Party looking at the chemistry and pharmacy of chemicals, a Pharmacovigilance Working Party that's clinical safety of medicine, a Safety Working Party, preclinical issues are discussed there, and we can also have ad hoc expert groups as appropriate. But the other working parties are permanent working parties and they work very closely with the CPMP.

And my final introduction slide, if you like, this puts very much into context what we are discussing. Before 1995, life did exist in the European Union, before the implementation of the European agency, and prior to that we had purely national authorizations. The further you go back, the more national the authorizations were. And it is very likely that for the older medicines, particularly vaccines, in Europe, that you would have 15 different licenses for the same vaccine. I know that sounds crazy, but that's the way it worked. The playing field is not a level one when you're looking at these issues, particularly for products prior to 1995.

And, of course, in the same vein, although the CPMP is not involved with the National Immunization Programs, it is important to note that the National Immunization Programs vary between the member states. I'm not even sure that you would have two identical immunization programs in the member states. So you are dealing with a very uneven surface to start off with.

Many of these issues have been covered already and that's very good, because, you see, we're all thinking the same way. I mean, Thimerosal is a widely used preservative and it has been used in biologicals and multi-dose preparations for chemicals, as well as biologicals. Of course, this big issue and the reason why we're all here is that it's a mercury-containing compound.

Now, how we actually got involved with this at the European level was that in January of 1998, the biotechnology working party, who has ongoing dialog with the vaccine manufacturers and reviews vaccines on a regular basis brought up the possibility of a safety hazard using Thimerosal and, in fact, other organomercurial compounds, although to my knowledge there are very few of those left and only in the very old products. This was referred to the Safety Working Party to look at the preclinical evidence associated with use of such compounds in products in general, in medicines in general, and they reported to the CPMP.

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

Now, the most multi-disciplinary group posed three questions on behalf of the CPMP to the various working parties: what was the rationale for inclusion of Thimerosal; Are there suitable alternatives available; and the implications of removal of Thimerosal from medicinal products. So they were the three issues that the individual working parties had the review from their perspective.

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

Now, what we asked the member states to do was not only to tell us what vaccines were recommended, but the actual vaccine types if that was possible. It's certainly possible in Ireland because of the 3½ million population. The Department of Health in Ireland buys all of the vaccines for any particular year. So although we may have licensed 7 or 8 DPTs and two or three DTaPs, it is likely that one, or at most two, of those only will be in use in the country at any particular time. And so it's quite similar in the other member states, so it was possible to actually get actual usage information from this particular immunization questionnaire.

Now, the safety issues have been extensively discussed yesterday by people far more appropriate to discuss this than me, but, of course, the issues that we did focus on were the neurotoxicity. Again, we're talking about a potential here, a potential neurotoxicity. Hard data are certainly absent with regards to use in vaccines or, indeed, other medicinal products, but it's the potential because of the mercury content. And we especially focused on certain at-risk groups, pregnant women, to the risk for the fetus, and also infants and toddlers.

Sensitization was also looked at. Here we do have some pharmacovigilance data. And as you know, the type of sensitization is delayed hypersensitivity. I think it was particularly important because, remember, we were looking at all medicinal products and not just vaccines and we had information on the eye preparations. We also had some very minor information from the intramuscular immunoglobulin multi-doses which require a preservative, and some of which contain Thimerosal.

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And I think with regards to the vaccinations, we looked at the issue of the type of injection that was to be used, and basically the deeper you go, the less likely you are to get the reaction, and I think that's something that is generally accepted.

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

Now, again, all of these were discussed yesterday. I think with regard to the distribution, we were very much aware of the fact that this crosses the blood/brain barrier. Again, I have to draw your attention to the fact that we're talking about methylmercury data here, so we're extrapolating. And the brain and placental transfer was obviously something that was very important for the possibility of neurotoxicity. And we also, based on WHO data and their technical reports, noted that the hair concentration was a very good indicator because a very high concentration of mercury occurred in hair after administration, and so that hair levels could be used as perhaps as a reasonably valid marker and, of course, a non-invasive marker.

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

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

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

Infants were even more difficult. And as you can see yesterday, this issue is, is the newborn as sensitive as the unborn? We did a calculation based on the fact that if you take the worst possible case scenario, we came up with a working figure of 200 micrograms in the first year of life. However, and I must say the issue of the spiking or the episodic versus the chronic administration was something that we couldn't actually come to grips with, because I don't think anybody can give advice on that because we actually don't know.

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

So if we go back to the three questions that the group posed to the experts working on behalf of the CPMP, the first is the rationale for inclusion of Thimerosal, and you've heard all of this before, particularly from this morning's speakers. Vaccines consisting of protein and polysaccharide in a solution or a suspension may potentially support bacterial or fungal growth. Fact. So if you add a preservative, this will hopefully prevent contamination, and this can be done either during the manufacture or in the end product, in the case of multi-dose preparations, and this prevents contamination which could be harmful for the recipient.

We heard of the fatal contamination cases yesterday. So if you add a preservative, is it just to prevent contamination? I think we also looked at this idea of maintaining the integrity of the vaccine and to maintain the desired biochemical properties or functions of the active component. Obviously, the whole cell pertussis is an example here. Also, we did look at this issue of its use in single dose vials, and we felt that it could even have a role in single-dose in certain cases. For example, in the influenza vaccine, where you're using the eggs as starting materials. So we felt there is a rationale for including a preservative in some circumstances.

Okay. So does it have to be Thimerosal? Well, what are the alternatives to Thimerosal? And we have some listed here. Phenol, we heard yesterday that that's no longer acceptable by the WHO. Cresol, I'm not sure that I'm too impressed with cresol. 2-phenoxyethanol. Perhaps I'm getting old and a bit cynical, but I'm really not sure that we have the full safety picture on 2-phenoxyethanol. It certainly does look to be a safe and efficacious vaccine preservative, but we're actually not 100% sure about either of these at this point in time. Formaldehyde has also been used. Now, there are other preservatives that have been used in other medicinal products, like benzochromium [sic; benzalkonium] chloride. I think the important thing is that for a preservative to be used, they must fulfill the European Pharmacopeia specifications. That's a requirement in order to get a license either nationally or at community level in the European Union. So they will, more or less, fulfill the PH Euro requirements. But we're not really -- Ever how much information we have on Thimerosal, I think we have less on the others.

So you're into a situation. You know the phrase, "The devil you know is better than the devil you don't know." And I think

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that's a very important aspect oft his whole review. So, well, of course, the real alternative is to get rid of the need for preservatives, and that's why using a good manufacturing practice and get a preservative-free product.

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

Right. The final question that the group posed to the experts was the implication of the removal of Thimerosal from medicinal products. Well, the group still maintained its position that GMP adherence should reduce the need for preservatives, certainly reduce the need for preservatives. And there will be a need in certain cases, and this is particularly in the multi-dose preparations where the seal is repeatedly breached. I think we did hear some examples of where the multi-dose preparations might be used from Dr. Clements yesterday, and I think we in the European Union are certainly very much aware of the WHO need in 1 this regard.

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

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

So the group recommended that we would have adequate labeling for the sensitization on all Thimerosal-containing medicines. Now, this is not something that was universally applied in the European Union. There is a requirement that Thimerosal or other preservatives are included routinely on the label, but a warning statement has not been mandatory. So it was agreed that this should be drawn up in the interest of informing patients and health care professionals. For vaccination in infants and toddlers, the use of vaccines without Thimerosal or other mercurial-containing preservatives was to be encouraged. However, we were very concerned that the continuing supplies and vaccination programs would be jeopardized, and so it was agreed that we would have a workshop with interested parties. That took place in April of this year with representatives from the WHO. We had Norman Baylor from the FDA. We had representatives from the European Pharmacopeia because, as you can see, the European Pharmacopeia requirements are mandatory to get a license in the European Union, either nationally or community level, and so we need to have the European Pharmacopeia on board if we're recommending changes. We also had the vaccine manufacturers and the other manufacturers, the eye manufacturers, the plasma protein fractionaters [sic; fractionators], and we also had the representatives from the CPMP and our experts. In the working party, this interested parties meeting, we did reach agreement in principle to labeling, obviously a standardized wording, and we addressed this issue of whether it's used as a preservative so it's added in a known amount at the end of the procedure or whether it's used in the manufacturing procedure where it's still present in trace amounts, but this, of course, may be important for sensitization purposes. And we also had an agreement in principle to work towards reducing or eliminating Thimerosal and, indeed, other mercurial-containing preservatives in the production of vaccines. So we've now moved forward, and we are in the process working to achieve those issues.

Now, I would like to draw your attention to the public statement that we issued in July regarding this. As I say, this is very much a working procedure. We haven't come to the end. We have a lot more work to do, but it's ongoing. Now, the background points to our public statement were, again, Thimerosal has been used for many years. The level of ethylmercury in any single medicinal product is not considered a risk. I think that's something that Norman Baylor said, that the last speaker said, and I think we would agree. However, it's the cumulative exposure from a range of sources, not just from medicines, but from food, and, indeed, if you read the WHO reports, intake from the air and from water. So there are many sources of mercury. So therefore, we could have a situation where this would lead to a potential cause for concern. I don't have the bullet point that Dr. Klein so rightly mentioned yesterday, and I think it is an important one, and I'll actually read it out to you because I have the document here. "Data on methylmercury has been used in the assessment of risks associated with ethylmercury as the toxicity profile of the two compounds would appear to be similar." I think that's a great use of the English language, but I think it's as far as we can go because we don't have the information on ethylmercury and we're doing the best we can with the information that we have, and I think it's probably the same for all of the workers who are doing this at the moment.

Now, the remainder of this, I'm actually going to read for you what we said because each line is very important. "For vaccination in infants and toddlers, the CPMP concluded that although there is no evidence of harm caused by the level of exposure from vaccines, it would be prudent to promote the general use of vaccines without Thimerosal and other mercurial-containing preservatives, particularly for single-dose vaccines. This should be done within the shortest possible time frame."

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

Now, this is, I think, very important. "The CPMP would like to stress that this is only a precautionary measure. There is no evidence of harm from the use of such Thimerosal-containing medicinal products. While reformulation work on vaccines proceeds, it is imperative that vaccination continues in accordance with national vaccination schedules to prevent disease outbreaks." That was a very important message that we wish to get across.

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

Where are we now? Okay? August, 1999? Well, our Pharmacovigilance Working Party has drawn up standard warnings on sensitization for all Thimerosal-containing medicines. Now, we need an agreed implementation procedure here, and remember the vast majority of these medicines are licensed at national

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level, and we all have different time limits and time levels, and that's what makes the European Union so wonderful. It's so varied. But the problem is, we have to agree to a time frame for implementation here.

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

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

Thank you very much for your attention. (APPLAUSE)

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

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

Now, I'm impressed with how oftentimes we tend to be very vertical and look at and consider issues that are only related to our area, and I'm not thinking about what happens in Europe. I'm thinking about what we might do here in the U.S. But when you were considering the issue of cumulative exposure, was there any discussion about issuing any sort of strict guidelines or information to pregnant women regarding ingestion of, let's say, you know, mercury-containing fish? Is that something that is --

DR. TEELING: No, no. And it's not a particular issue for us, obviously, because we're not a food and drug administration. The agency is not a European FDA. I think we deal specifically with medicines. From a public health point of view, that is important. I think we didn't want to add to the burden. And the reason why pregnant women were particularly investigated was not just from the point of view of the vaccines and any vaccinations that they may get, but because of the possibility that they could be getting anti-D immunoglobulin prior to delivery, which would affect the fetus. So we specifically honed in on those.

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

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

DR. GELLER: Bruce Geller from the Infectious Disease Society.

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

DR. TEELING: Yes, yes, yes. And I even have the website for you. I am computer illiterate, as you may have gathered. It's a disease, I can't help it, but I actually have the website. I have a copy here, if anybody would like a copy from the photocopy machine, but it is available on the EMEA website. Interestingly enough, we got very few comments, in fact, from this.

We have a website. We have a publication every month from the CPMP. So everything that we do is put on. This was a specific public statement that was put out. We actually got very little requests. In fact, we got more requests from the MMWR statement than we did from European statement, which I don't know what that says about European doctors. Certainly, you can -- I'll give you this later on.

DR. MODLIN: One final. Neal?

DR. HALSEY: Neal Halsey from John Hopkins again.

I notice that you have gone a little further than our Public Health Service and the Academy of Pediatrics have and that you have encouraged the use of Thimerosal-free products in the use of infants and toddlers. Was there any discussion about those particular populations in Europe which do have a fairly high background of fish consumption and a presumed higher background of mercury exposure with regard to even going beyond that?

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

DR. MODLIN: Dr. Teeling, thank you. We'll break for coffee and other things, and start precisely at 10:30. Thanks.

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

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

DR. BERNIER: I had some questions about whether this topic or title would still be appropriate this late in the workshop because I thought that this might be fairly clear by now. But I think that it's still valuable. I think Bob Daum's question during the last session, and as well, the last presentation by Mary Teeling, I think indicates that it would still be helpful to have a presentation from the public health service point of view, or in the U.S. what is the position that we have evolved to on this Thimerosal question.

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

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And I think one of the points I want to make is that in some ways something is different, that there is not a business-as-usual view of this matter, and I think that that's one of the things that we're trying to hold together in our minds, the idea that somehow it's not business as usual, yet, in another way, we are trying to do our usual business during the transition period.

And how can we keep together these two difficult concepts, if you will, or, the concepts are not difficult, but holding them together is difficult, that we're in a non-business-as-usual mode and we are trying to do some of our business as usual?

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

Now, in the U.S. there are—again, people caution me not to use the word "standards", and half the time I remember and half the time I forget. These guidelines, I think is the best term that people seem to feel is the best term to describe them. In the U.S. we have three different sets of guidelines. Again these were mentioned yesterday, as well, from EPA, ATSDR, and FDA, and there are also some from WHO. They are different, from 0.1 in the U.S. for the EPA, which is the lowest, to 0.4 with the FDA.

Now, one of the concepts that—and, again, I knew very little about this before and I still am learning about this every week, but this represents my understanding of what we mean by safety margin in relation to these guidelines. This represents the level of zero exposure. And I'm using here as an example the ATSDR guideline, but, apparently, there are safety margins, large safety margins, associated with all of the three guidelines in the U.S. If you take this level as the zero exposure level, the current ATSDR guideline is 0.3 micrograms. In fact, in the data that the ATSDR relied in the Seychelles, the average exposure in the high-risk group, where no effect was observed in the moms, where I believe it was 15 parts per million, approximately. That translates to 1.3 micrograms, which is four times above the ATSDR guideline level. So this much safety margin exists on this ATSDR guideline. In addition, if you'll at the highest exposure group in the Seychelle, again, this is the highest exposure in the high-risk group, where again no effect was observed, that equals to approximately 2.5 micrograms, which is eight times over the base line ATSDR guideline.

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

After the highest exposure group with a no-effect level, then you get into this grey area because, presumably, between this exposure level where there's no effect and the first level where you begin to see a mild effect, that is a grey zone. We don't know how wide that grey zone is. It might be very narrow or it might be very wide, but there is a grey zone when you begin to see a mild effect. Then at an exposure level that produces very serious effects, obviously, that's represented by this black area in the bar, but this represents the safety margin that we've heard so much about and that why we've heard that these guidelines, .in the case of ATSDR, or 0.1 or 0.4, why interpreting them as bright-line types of thresholds is probably not an appropriate way to interpret them, but rather to think more about them as starting points or screening levels or whatever most appropriate adjective, but not as a threshold, a bright-line-type of value.

Now, again, if 187.5 represents the potential exposure, what are the potential limits that might be allowable? And if you use the different standards, the different guidelines from EPA, ATSDR, and FDA, the -- Dr. Ball's group has calculated -- And we have somewhat slightly different assumptions, so I'm going to show the results that Dr. Ball's group did as well as the one at CDC. They're very similar, but they are slightly different. These are the results from Dr. Ball's calculations. From the calculations that we did at CDC, they are just a little bit higher. The major difference is that we calculated out to 30 weeks, again, thinking that what you wanted in coming up with your suggested limits was the limits during the period of time that children are most likely to be exposed. For most children, they're not going to be vaccinated exactly at six months. I think this is the question that Stan Plotkin raised yesterday: Why don't you calculate it at seven months?

I told Dr. Ball I didn't really plant that question. But if, in fact, you do that, you'd come up with slightly different limits. Now, comparing these two, then, here's the potential exposure as calculated by Dr. Ball from the vaccines on the routine schedule. And if you look at the three guidelines that we have in the U.S., you can see that the total exposure that some children might receive would be in excess of the guidelines suggested by the EPA but would be within the limits of the guidelines suggested by ATSDR and FDA. This is for children at the fifth percentile. Well, that's the potential exposure for some children.

What do we know about what children are actually being exposed to? Well, we don't have a lot of information on that at this time, but what we did do is look at the potential number of combinations of vaccines in the United States for DPT, HIB, and hepatitis B, and look at, of all the possible combinations of ways that infants could be vaccinated, what are all the potential total endpoints in terms mercury exposure that these combinations might lead to. And what it shows is that there's approximately, I think it's 100, different ways that infants can be vaccinated, but about, say, 15 or 20 total mercury exposure endpoints that they can end up with.

If you'll look at the vaccine combinations, most of the vaccine combinations that are available in the United States, about a quarter of the combinations produced would produce mercury exposures of about 100 micrograms over the first seven months, or 112. And I've put on here the guidelines where you can see that for some of the combinations, if children got these, they would exceed this EPA guideline but would for all the combinations available in the U.S., children, if they got any of these, would still be below the guidelines.

Well, we do have one set of data from the California Kaiser that is part of our vaccine safety data link, and, basically, what this shows is what mercury exposures 85,000 children received

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at this HMO, and what you can see is very similar to what you would have predicted based on the existing number of combinations, namely that approximately 90% of the children got 112 micrograms or less, 91%, 125. Again, for some of these, they were in excess of the EPA guideline, but below the ATSDR and the FDA.

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

So it was based on those kinds of considerations that public health service groups and others deliberating about these matters recently basically came to the conclusion that it would be worthwhile to reduce or eliminate Thimerosal in vaccines. While we did not and FDA, there was some excess relative to the EPA guidelines, and given that uncertainty and the possibility of a potential risk, I think there was this agreement that it would be prudent to reduce or eliminate Thimerosal in vaccines.

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

And here, then, captures in policy terms -- Because we can talk all about this, and bottom line is, at some point we have to make a recommendation that makes everything very specific -- you capture -- You have to deal with the uncertainty and make it specific. And what it boiled down to was the following.

That the U.S. has recommended that there be no change during this transition period in the use of DTaP, HIB, or hepatitis B for antigen positive mothers, or for hepatitis—no change in hepatitis for mothers whose antigen status is unknown, or for infants who come from high-risk populations. However, again, in light of this potential risk and concerns raised by that, there was a feeling that some action should be taken at this time, and the decision was made, or recommendation made, to postpone the initiation of hepatitis B in mothers whose antigen status is negative and for whom that status is proven or documented to be negative. In those mothers, the infant vaccination could be postponed until two to six months. This statement was issued jointly by the American Academy of Pediatrics and the Public Health Service. In subsequent guidance, the Public Health Service expressed a preference for initiating this postponed immunization at the lower end of this agreed-upon range, and the American Academy of Pediatrics expressed a preference for starting at the upper end of this range. The Academy did recommend that if you had a Thimerosal-free vaccine available, then you could begin at the lower end of the range with that product.

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

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

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

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

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

Another important issue that has permeated these discussions is that the guidelines are based on chronic exposures. What we are dealing with is an acute exposure and the guidelines may not be applicable. I think, on that score, it still remains unknown. I've heard data on both sides, or observations, I should say, or speculation on both sides, and in my mind this still remains an unknown. In the Department of Health and Human Services, there were three guidelines. I think it's fair to say that because of a two-year process that has been going on in the Department of Health and Human Services, while there were three existing guidelines in the U.S. more weight or preference was given to the ATSDR guideline as the primary guideline to be guided by, if you will, than the other two. That was a decision that was made, as I say, in the Department of Health and Human Services because of a two-year process. I've heard nothing to make us believe that we ought to have done that any differently.

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

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

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

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

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

One other area has to do with communication, and perhaps we need to look at improving communication with providers and parents about this change. We heard from a speaker in the audience from Philadelphia about confusion that is being caused, and even some mothers of infants of antigen-positive mothers may not be getting vaccine. That clearly is not a change. There has been no change for antigen-positive mothers, and maybe in the communication arena something needs to be revisited.

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

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

And, fourthly, there are issues around flu vaccination. You've heard there have been no recommendations yet. I think that's in the works and, perhaps, not something that we need to be overly concerned with. That will take place.

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

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

Thank you very much. (APPLAUSE)

DR. MODLIN: Thanks, Roger.

In the interest of time, I'm going to ask we not take questions, but I'm certainly going to ask Roger to join the panel up here at the end, and I'm almost certain that we will have a fair amount of time for discussion and questions at that time. So we'll ask some of the other presenters to go next.

And the first presentation will be by Dr. Jon Abramson. Dr. Abramson is Professor and Chair of the Department of Pediatrics at Bowman Gray School of Medicine. He is the brand-new Chair of the Committee on Infectious Diseases of the American Academy of Pediatrics, which, of course, has been out front, if not protagonistic, on this issue. So we're happy to have Jon here. Thanks.

DR. ABRAMSON: Thank you, John.

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

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

The next morning there were 50 people out by the pool. Everybody was standing around. The millionaire comes out, thanks them for coming, and then he says, "The only thing I haven't told you is there are 12 alligators in the pool." And everybody's standing around buzzing and saying, you know, "This isn't worth it. It's not worth dying over."

All of a sudden there's a splash in the pool, and the alligators converge, and guy dives down, comes up about halfway, the alligators converge, he dives down and comes up. And he's pulling himself out of the pool, the alligator bites him on the leg, and he's lying on the pool bleeding, and the millionaire comes up to him and says, "That's the bravest thing I've ever seen." He said, "I assume you want the million dollars."

"No."

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

"No."

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

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

So he says, "What do you want?"

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

(LAUGHTER)

Well, it was an interesting conversion from sitting on the committee to actually being the Chair. (LAUGHTER)

And I'd like to highlight a few of the issues. I think there was major areas of agreement.

In fact, I think for the Public Health Service and the American Academy of Pediatrics the vast majority of issues were agreed upon. Number one, we all agreed that the risk of not vaccinating children for every one of the diseases that we try to prevent with vaccines far outweighed any potential risk of giving the vaccine containing mercury. Two, that we should eliminate or reduce as quickly as possible the amount of mercury in vaccines. And three, which hasn't really been pointed out this morning, is that we agreed that we should delay the use of the vaccine in the baby who is born at term and not use it at term. And why is that? And the reason is that even if you take a full-term baby who weighs 3 kilograms and you take any of the standards, from the EPA standards to the FDA standards, you are exceeding on that day the amount of mercury that is – that guidelines recommend you give, by greater than tenfold. And we don't know what the safety margin is. This was pointed out today, and I'm sure it was pointed out yesterday, we don't really know whether it's cumulative dose or what that really matters. So both the Public Health Service and the American Academy of Pediatrics agreed that the hepatitis B vaccine

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should be delayed in a mom who is hepatitis B surface antigen negative.

So what were the two areas of divergence? And I must state up front that some of the confusion that has occurred has been because of the areas of divergence. We certainly get letters at the Academy asking us why we diverged, and at some point, we probably need to write an editorial just talking about the whole process that went on. Because one of the issues that I'm going to raise later on is: How do you deal with emergencies when the approval process for recommendations varies substantially between the American Academy of Pediatrics? How do we go through the process of getting our recommendations approved? We, as a technical committee, the Committee on Infection Disease go through the process of getting our recommendations approved, versus the ACIP or any part of the Public Health System which has to go through a very different process.

So where did we diverge? We diverged a little bit at when should you start the hepatitis B vaccine, and it simply was over a matter of how safe do you want to be. Everything we did with hepatitis B and the hepatitis B surface-antigen-negative mom related to how safe do you want to be, what kind of safety factor do you want to add? I don't think there's a right answer to it. I think the issue is the safety issue.

And the second is, the Academy did not comment about a hepatitis B surface-antigen-negative mom who is in a high-risk group or the family is in a high-risk group. In other words, someone from Africa, for instance. And the Public Health Service said vaccinate them, vaccinate them at term. We did not comment on it and we specifically didn't comment on it.

There's really two things that go into the equation about that. One is that the risk of horizontal transmission during the first two years of life is very, very small. And we are both, both the Public Health System and the American Academy of Pediatrics, strongly recommending that you finish out your immunization, your three-dose hepatitis B immunization by 18 months of age. But the Public Health Service had data at least when we were making the decisions we were not aware of, that said that if you do not start the vaccination at birth, that the completion of the three dose series goes down from 96% to 81%. So if you're talking as the American Academy of Pediatrics does to its pediatricians, and you're saying you can make that individual decision based on your family, what's the chance that they're going to come back versus not come back, versus you're dealing with it from a public health perspective and you know that number, you could understand where the difference comes from.

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

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

What is the mercury exposure from other sources? We still haven't dealt with that. And, I mean, we put the data in. I might as well say it. A six-ounce can of tuna has 17 micrograms of mercury in it, on average. There's obviously a range to it. What does that mean for a pregnant woman? What does it mean to the fetus? I sit on the ACIP Influenza Working Group, and we discussed the issue, what are we going to do with the pregnant mom? Well, the pregnant mom in the second and third trimester has a substantially higher risk for flu than does a non-pregnant mom. So based on our principles, we would recommend giving the flu vaccine, and that's what the working group is going to advise.

Now, that doesn't mean the Public Health Service has to agree to it, but that raises the question of "Is that the right decision?" I think so, but do we need to put other things in the consent form to inform a parent or an expectant mom about that.
The education of the public. I will tell you that we received a number of letters from angry pediatricians because they don't use computers and some of the public does, and the public learned about it before the pediatrician did.

And I don't know a way of solving it. We actually put out something that's called the PedsCom, which takes several days to get out and put out, but it is expensive and it's much better and much faster to do it by computer, and it's much cheaper to do it by computer. Those are all issues that come about when you're dealing with an emergent situation. I personally think that the AAP and the Public Health System worked well together during these two emergent situations, and I've actually learned a lot from the process and enjoyed working with them.

That's all.

DR. MODLIN: Thank you, Jon.

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

DR. WEBSTER: Thank you, Dr. Modlin.

Good morning. I just came to represent the National Coalition for Adult Immunizations this morning and give you a statement of where we stand on these issues of Thimerosal in vaccines. What I have here is nothing earth-shattering—I'll give you that—but let me just read to you what we put together here, and I appreciate any comments that you might have afterward.

While Thimerosal has been used as a preservative in many vaccines for many decades without apparent ill effect, it is nonetheless imperative that science and medicine continually seek safer and more effective medicines and procedures. With this in mind, we must make reasoned progress in the area of vaccines and vaccine research. On the one hand, each of us no doubt feels some level of concern in knowing that a small amount of a mercurial compound is present in the vaccines that we give to children, pregnant women, nursing women, and adults. On the other hand, it is also the case that it is difficult to find any definitive data suggesting that the use of such compounds has resulted in any direct harm to humans. We must also recognize that changing from one preservative to another is not without some level of risk itself, no matter how small, and may lead to other potentially unknown side effects. With this

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understanding, our organization would like to emphasize concerns about the use of Thimerosal in two settings.

First, the Advisory Committee on Immunization Practices has rightly made the national recommendation that women who will be beyond their first trimester of pregnancy during the influenza season receive the influenza vaccination. Those who have medical conditions that increase their risk for complications from influenza should be vaccinated before the beginning of the influenza season regardless of the stage of pregnancy. It is important to note that all of the licensed influenza vaccines in the U.S. do contain Thimerosal. There has been no reason to believe that there may be adverse fetal effects associated with using Thimerosal-containing vaccinations. The NCAI agrees with the ACIP that more data are needed in this special circumstance.

Second, there is a small population of vaccine recipients who have an allergic sensitivity to Thimerosal. Even when allergy testing does indicate hypersensitivity to Thimerosal, most patients do not develop reactions when given Thimerosal-containing vaccines. If reactions do develop, they almost always manifest as local reactions, but, nonetheless, can discourage both patient and provider from further immunization. In effect, the use of Thimerosal-containing vaccines means that a small proportion of the population cannot or will not receive vaccines which protect them against the morbidity and mortality of many otherwise vaccine-preventable diseases.

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

In the meantime, NCAI calls for and supports the following steps: First we support the recommendation from the Public Health Service and FDA that all vaccine manufacturers submit a plan for the elimination of all mercury-containing compounds from human vaccines as soon as possible. Second, we support and call for further research into the benefits and risks of these compounds in individuals and their potential impact on public health, particularly in regards to the possibility of neurodevelopmental effects on the developing fetus. Third, we support and call for the development of communication materials for health care providers and patients that clearly and fairly articulate the current controversy while maintaining public confidence in the enormous individual and societal benefits of immunization. Finally, we support the Public Health Service and the American Association of Pediatrics call for expedited FDA review of manufacturers' supplements to their product license applications which eliminate or reduce the mercury content of their vaccines.

Thank you for the opportunity to participate.

DR. MODLIN: Thank you, Dr. Webster.

Our next speaker will be Dr. Neal Halsey. Neal is representing the Institute for Vaccine Safety at Johns Hopkins University School of Public Health and Hygiene.

DR. HALSEY: Thank you very much, John.

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

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

The objective in the transition period is to minimize any potential risks that might be there, but, also, as many people have stated, to maintain public confidence in vaccines, the agencies, the federal agencies responsible for both vaccine safety and for delivery of vaccines, but also to the physicians who not only are responsible for providing those vaccines, but also for advice and guidance to parents of children who are going to be receiving these vaccines.

We do need to pay attention to what's happened in the public in recent years over the increased concern about product safety in general, and I won't spend the time to go through all of these examples, but we do need to be aware that there's been concern about environmental exposures of a variety of types, food contamination, automobile safety, toys, as well as drugs and vaccines.

Where these have been handled well, it increases the confidence of the Public Health Service and government in general, but there are several examples of where they have not been handled as well as they could have been, especially in Europe, with loss of public confidence in our government agencies that are responsible for protection of safety, and we don't want that to happen in this situation or any similar situation.

My personal belief is that we should follow the examples of what some of the producers of food, particularly children's food, baby food, in this case, from the representative of Gerber Foods, the CEO of Novartis, the parent company, in removing some chemicals, which, personally, I don't think carry any risk for those children. But their philosophy is that "We want a mother to buy our product and have no concern about this issue." We should adopt similar philosophies with regard to vaccines. I'm going to make seven points, and I will come back to each of these in detail and only mention them at the beginning.

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

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

Third, that I think hepatitis B has been unfairly targeted and assumed to be in some situations the only problem that occurs with regard to Thimerosal.

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

I think manufacturers should look very hard at providing unit dosing of vaccines whenever possible. I think there is a

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problem at the FDA that does need to be addressed and that we need additional resources and scientists to address vaccine safety. To go back over some of these issues, now, the first is the product labeling. I had to ask myself why someone who -- I felt I knew a fair amount about vaccines over the past 25 years and knew something about environmental exposures, why I didn't put it together. Why I didn't realize how much mercury was actually in vaccines. And I think it's because the product label indicates a concentration of Thimerosal of 1 to 10,000, or a 0.01%.

And as Leslie Ball walked us through, you have to go through a two- or three- or four-step calculation, and you have to know the molecular weight of Thimerosal to come up with the 25 micrograms for mercury. Since mercury is the biological agent, the biological product that's there, and we have guidelines for the amounts of mercury that people should be exposed to, that should be in the product label.

There are many factors that are associated with mercury toxicity, and that's what I mean by not all children are created equal with regard to their susceptibility. Many of these were discussed yesterday, so I won't go back over all of them, but there are differences in terms of the age of exposure, the weight of children, other mercury exposures, differences potentially in metabolism and excretion rates on an individual basis, not for the products. No one has really addressed very well the genetic predisposition to increased risk of potential toxicity. We can look most clearly at the weights of children, and I've picked girls here. Boys weigh slightly more than girls, but if we're looking at who may be the highest-risk population, the children who are the smallest, are the three standard deviations below the norm, their birth weight of 1.8 kg, there's a difference, a more than two-fold difference, in the weights of these children, and if exposure to mercury is a weight-based phenomenon when you get a fixed dose, then that two-fold—that is an important concern. That two-fold difference persists all the way out to almost six months of age. And we need to realize that it's the smallest children that I think that we have to be preparing our guidelines and decisions as to what we do with them.

If we take those weights of children and then apply the fixed doses and look at the worst-case scenario of children who may be getting all Thimerosal products, or prior to the most recent change in the recommendations, it plots out like this. And since sending Dr. Clarkson and Dr. Raub the data on the actual weights, I did adjust so that these children were getting hepatitis B when they weighed 2 kg. We have, through the recent guidelines, addressed this exposure here, but, in fact, the exposure that's occurring at 2 months of age is several-fold higher than that exposure that's occurring at birth. And, yes, the infant is slightly older and therefore may be somewhat less, if there is a risk per dose delivered at that time, then this is something that I think we still have to be concerned about and decide whether or not anything further with regard to advice needs to be given.

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

An exposure with a fixed dose, 62.5 micrograms at two months of age, is different than an exposure at six months of age, or if that was at nine months or twelve months. So I really question the philosophy that it doesn't matter when you got it or if you got a significant portion of that, one-third of it all in one day, that you really can take and look at that exposure over a six-month or a twelve-month period. So that's where I do differ.

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

Which guidelines should be applied? We've been through this too many times. You've seen this similar slide. The Public Health Service has chosen the ATSDR, which is a little more liberal with regard to the allowable exposures in the EPA. The WHO is quite similar to the EPA, as we have seen, with regard to those exposures. But over how much time can you take a single exposure and then say it's okay to get this over a day, a week, a month, or a year? We don't know. That's an unknown. The choice of the ATSDR guideline, which is based upon the Seychelle data, made sense at the time that it was done. The process was a good process that they used. But does it mean that we should ignore data that have been generated since then, and especially the follow-up in the Faroes Islands? And does it mean that it isn't going to change? The Faroe Island data were generated when these children were 5.5 years, and they were generated looking mostly at global I.Q. And as we heard from Dr. Lucier, there will be additional follow up and there will be harmonization of the methods to evaluate these children. So they'll do some of the more domain-specific analyses that were done in the Faroe Islands that revealed those very subtle defects that were picked up. So it's an older age in the Faroe Islands and a more specific analyses that were done. And equally, or, in fact, far more important, as Dr. Lucier mentioned and as Dr. Clarkson mentioned, there is the intermittent exposure that took place in the Faroe Island where it was coming a lot at one time or at monthly doses. And is that the explanation for finding problems in children at seven years of age that were not detected in the Seychelles at 5.5 years? Nobody knows that, but it certainly is one of the hypotheses that might explain the differences in the exposures and we must take it into account.

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

And again, these defects that are being detected are very subtle defects, and they're not going to be detected without these very sophisticated testings that was done. Some interesting observations is that the males are more susceptible than females. I think that's a whole area of research that these groups will potentially look at, and finding. This is the finger-tapping test that was done, cumulative amount, both hands, easier to measure differences than one hand. In other words, again, you won't find these with less sophisticated testing.

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If we accept or use the ATSDR guidelines and we superimpose those on these exposures and we put the daily, the weekly, or the monthly exposure here, we can see that at two months of age we're giving at a single day more than the total monthly allowable exposure for the ATSDR guidelines. And, in fact, the smallest of infants represented in the green bars are receiving almost three times, almost three months' worth of exposure on a single day. Is that really -- I haven't heard ATSDR say that that's really okay to do. I'm not convinced that it really is. And if we were to apply the EPA guidelines or the WHO more recent guidelines, they are one-third of this. We're giving eight times the maximum exposure that they would give you for a month. Can you get six or eight months exposure in a single day? I don't think that exposure at two months of age can --

You can't take all of these over six months or a year and average them. We haven't told physicians more precisely what they can do to help reduce that exposure. And if we simply limited it to one Thimerosal-containing product that was given at 2, 4, and 6 months of age, it would be DTaP or HIB, then you can reduce this to less than -- you can get less than the total monthly exposure for all but the very smallest of infants.

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

And we do have the option that, in many situations, where you don't have to give any Thimerosal. And everybody understands that goal, but it actually is an option that's available today. We really haven't told everybody that that's something that you can do. We've talked about all of the uncertainties. There are many. And again, there's not time to go through all of them, but we do need to focus on the other mercury exposures and which this exposure is added on top of.

We haven't really touched on any of the data on the potential effect on mild subtle things with regard to the immune system. Those data are going to be forthcoming in the next two years from various groups. With regard to other mercury exposures, this comes directly from the EPA report to Congress, the key point is that the majority of the population is getting relatively low-to-moderate exposures. But in this country we have some populations that have very high levels of fish intake on a regular basis. And as we heard yesterday, FDA estimates that about 7% of women of childbearing age are already consuming fish enough that it would give them more than their guidelines, 0.1 microgram per kilogram per day. So any additional exposure we give them from vaccines is on top of that baseline that they have set with a safety factor included.

But they also note in the report that 1% are receiving more than 0.37 micrograms per kilo per day. So there's 1% of pregnant women out there who are already getting more than what the ATSDR guideline is. And again, what we give them is added on top of that, and these children are being born with that exposure and some are getting this continued exposure through breast milk.

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

To change to one of the other topics about Thimerosal, it's not the perfect preservative. It doesn't totally solve the problem. There are numerous clusters of cases of group A strep disease and presumably other -- one, I think, of other bacteria that have occurred. So it doesn't solve the problem. I personally believe that the manufacturers need to move more toward unit dosing in this country whenever possible. And not only is the benefit from preservatives being not needed in most situations, but there are the reduced errors due to reconstitution that we heard a bit about earlier today. And again, we don't need to go through all of those. There will be another session this fall on some of those issues.

There are drawbacks, and these are major limitations that -- and that's increased space requirements in the refrigerator, but I don't think they're quite as bad as what John Clements was telling us. There are some technologies that can reduce the amount of space that's going to be required to store unit dosing. There will be increased costs, and I recognize that as a major problem for developing countries, but I think that we do need to help in terms of addressing that issue. We need to look at it from this country.

So to maintain public confidence in vaccines and people giving advice about vaccines, I think we should put the mercury content in the label. I think we need to modify the vaccine information statements. That is our primary means of communication with families about any potential or perceived risks. We don't have it in there now. I realize the process is long to put it in, but I think that has to be done as soon as possible. I also think physicians should be given more precise guidelines over maximum allowable exposures at each age. Can we really have recommendations for the highest risk and have physicians looking at fish consumption and other things? The Academy of Pediatrics is developing additional guidelines on reduction of mercury exposure from all sources. Those won't be available for 6 to 9 months. I don't know what the time will be there, but do we need to have separate guidelines for immunization for those children versus others? In general we have said, no, we can't do that. We must make guidelines for everybody that will be applicable to all of the populations.

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

The last point I'll make is that we need good science to be used in making these decisions, and that good science has to come from all of our federal agencies. As I looked into what was going on at FDA and research into alternative preservatives, research into other ways to approach this and who is going to be reviewing these applications that were all asking for or demanding rapid review, what is the research budget at CBER? The research budget has been cut in the last 5 years to one-third of what it was before. Instead of being 20% more just to keep up with inflation in that period of time, it's been cut to one-

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third. I don't know why. I don't know who's responsible, but I hope somebody goes to Congress and says that this is wrong.

Thank you very much. (APPLAUSE)

DR. MODLIN: Thanks very much, Neal.

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

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

Sitting through here for a couple of days, I'm impressed that you can never stop learning the lessons, and I think I'll talk a little bit about those, but one of the important lessons I learned this morning is that if you chair these AAP committees, you can never go on vacation. Poor Jon was strung out at every phone booth that was in Canada and Neal finds signs in the middle of Maine that tells him he needs to go back and do another PowerPoint presentation. And the final lesson I learned is it sounds like CBER needs to invest in Microsoft to try to help some of their budget requirements.

But I think that Sam outlined some of the highlights I want to just underscore, and he did that with his last slide, that the handwriting's on the wall. I think that that really tells us that it's our responsibility to see that it's there, to read it, to interpret it, and then to effectively communicate it to all the people who really need that. As has been outlined by several on the previous panel and at various points throughout this session, that's the public health community, the clinicians, the parents, the media, and to legislators.

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

As the face of the disease has gone away, there is increasing concern about the risks, both real and potential and imagined, of the vaccines, and that we need to address those in the same way the environmental risks come up all the time, and I'll bet you can't open any newspaper in this country where there's some headline about something that you may be exposed to that's causing some ill health. So I think that we've learned some lessons. We've learned some lessons about the development and approach to guidelines and how that can guide not only policy decisions, but should also guide communication about those decisions.

And finally, I think, under the category of lessons learned, from the very beginning of this session yesterday, there were questions about whether or not the decisions that have been made are up for grabs or are reversible, depending on what we heard. I think that we all had the subtle hope that a meeting like this that brings together the world experts would give us the answer to guide us, and I think that if you had heard what I've heard, that we don't have absolutely clear answers and the hopes that a meeting like this would bring together all those people that would provide that kind of guidance wasn't going to happen because uncertainties remain. And while everybody keeps pointing to Gina to tell us what those uncertainties are, we've heard them and a number of people have highlighted them, but I think that we know that that's what this arena of risk communication is about, which is communicating making good decisions in the absence of complete information. And I think that we also understand that when faced with an issue, not making a decision or ignoring it or delaying it is, in fact, making a decision.

And I think finally what we also need to be more transparent and communicative about is the process that we undergo when these things come up. Jon highlighted that, and I think that that's really an issue that we really should be discussing: what do you do in these emergency situations? And there will be some that will be far more emergent than this, I imagine, in vaccines and other issues, but I do think that that's something that we really need to address, of how you can, when faced with an emergency, deal with that in a responsible fashion and make moves and communicate those moves despite uncertain information.

So I think that we've learned that there are health risks of mercury-containing compounds. We have the desire, all of us, to reduce those risks from all sources that we can, and that with a limited data, we are going to be forced to make assumptions and extrapolations, and there may be differences in how people handle each of those, but that we then need to continue to do our best to be as transparent about the process, and to let people know that there actually is a process in place that's looking at these things. I think we have heard that from a number of speakers as well, that it's not as though there are not systems in place that recognize this. And I think that, as Jon highlighted, the fact that this went on, essentially concurrent with the issue of rotavirus, highlighted that to all of us.

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

Thank you.

DR. MODLIN: Thank you, Bruce.

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

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

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

ASTHO doesn't have a specific policy at this time on Thimerosal, so I just wanted to give you some background, how

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we reacted, and a sense of what state health officials feel about the issue.

Vaccine policies are decided on a state level, and for that reason, ASTHO still maintains clear support for state flexibility. The ASTHO organization works to make sure that states have the best information available, and we provide an opportunity for health officials to work with partners and each other to build consensus. We did work quickly on the Thimerosal issue and gave state health departments to discuss the issues amongst themselves and with CDC.

As I said, we don't have existing policy. And amongst all these discussions with the state health officials, we were not able to reach consensus on specific new policies in such a limited amount of time in reaction to Thimerosal. So for that reason, states are using the available science, as well as the CDC and AAP recommendations, to formulate their own policy on a state-by-state basis.

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

We are very concerned with maintaining immunization coverage, protecting infants from disease, and maintaining public trust. And again, we, as the organization of ASTHO, support consensus building based on science, information sharing, communication among states and all the other parties involved.

Just to add a little bit of state perspective, I spoke with Dr. Natalie Smith, who is here today from the California State Health Department. She's a member of the Association of Immunization Managers, and they've also been holding discussions over the last two weeks or so about Thimerosal and vaccine safety issues. It does appear that states are taking a variety of approaches in the transition to Thimerosal-free vaccine, approaches which are sometimes very different.

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

Thanks.

DR. MODLIN: Thanks, Ms. Hannon.

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

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

DR. ANTHONY: My name is Bud Anthony. I'm with the Biologics Consulting Group in Alexandria. And although Neal has cautioned that hepatitis B has been singled out, and it's certainly not the only vaccine that we're concerned about, but it's my greatest concern, and those concerns were heightened yesterday by the presentation from Dr. Mast, so I have a couple of questions.

One has to do with the recommendations for deferring the hepatitis B vaccine in hepatitis B surface-antigen negative mothers, and that is this: Isn't this policy of selective immunization of infants based upon maternal antibody screening, one that we abandoned almost a decade ago because it did not work? I know the new policy is different. In a perfect world, I'd have no disagreement with it, but it seems to me we're going back to something that did not work very well.

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

Thank you.

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

DR. HALSEY: Jon is current chair, but --

Well, the Academy policy to give the vaccine at birth was based upon a number of issues, and the Academy policy was published in '92, but the Public Health Service was published in '91, and I don't sense from anybody that I've had any contact with that there's any abandonment of that policy. I believe the Joint Statement still has the language in it, although it was modified, that once the Thimerosal-free preparations were available, the preferred age will be at birth.

The Academy's policy has been that you can initiate it between birth and two months of age, so there was flexibility within the schedule. That's the terminology that was used. But my belief is it makes sense to go back to birth immunization whenever possible as soon as we have a Thimerosal-free, but Jon is really the chair and should respond.

DR. ABRAMSON: Oh, I agree. Let's make it clear why we picked on hepatitis B. It is the one disease in the hepatitis B surface-antigen-negative mom that the infant is at very low risk for. The infant is at risk for pertussis. The infant is at risk for HIB disease. So that is why we picked on hepatitis B, not for any other reason. And we've stated clearly in numerous places that once we have Thimerosal-free vaccines, we will go back to recommendations for giving it at birth.

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

DR. ABRAMSON: I don't see us as selectively immunizing. I see us as immunizing at just a delayed period of time. The recommendation is still to get three doses in by 18months of age.

DR. MODLIN: Dr. Daum?

DR. DAUM: Bob Daum from University of Chicago.

I've also been impressed -- I think Bruce made the comment of how much out there there is to learn (inaudible) is that there is a big mercury vacuum in your brain and we don't know much about it and (inaudible) learn a lot in a couple of days. And there's obviously a long way to go in terms of understanding what the effects are on the brain and whether this ethylmercury has any effect at all, much less what the effect of methylmercury is.

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But I'm wondering how this got so quickly translated into a public and private immunization policy. And I read when the Beatles were doing public performance and they actually gave up performing before they broke up, and the reason they gave up performing is because they were having to perform in larger and larger stadiums. And what they found was they couldn't do anything subtle on stage, because if they tried to, no one would see it and no one would understand it. They were performing in 100,000-seat stadiums.

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

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

In addition to that, John, I don't know if you were here yesterday, but we know from our inner city population in Chicago that if you look at kids that received their first dose of hepatitis B vaccine at more than three months of age, only10.6% of those kids have finished the three-dose series by 19 months. We also know that if you delayed – whatever that first intervention is doing, if you delay it and take a (inaudible) in receipt of 4, 3, 1 by two years of age.

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

It certainly sounds as if mercury is an issue that we all ought to think about. It certainly sounds as if we all ought to be thinking about how to get a mercury-free vaccine. I'm the first one to stand up and want safer vaccines. I think that's a crucial part of our program, but I just don't understand why it was so urgent to shift this immunization policy so quickly. It creates a confusion that you're hearing only distant echoes in this room, because a very few of us are out on the front line doing vaccine implementation. But, nevertheless, I can tell you, it's beginning to sound like a louder and louder noise among the people that I take phone calls from and interact with every day.

So I guess that's my comment, and I'd certainly like to hear anybody's response to that.

DR. MODLIN: Roger?

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

I think what's happened is that -- I've told this to some people -- we've had a paradigm shift in how we think about this preservative. And when I went to leadership classes, I was told paradigm shifts take years. I think we experienced a paradigm shift in days, or maybe weeks at the most. And it has to do with our consciousness being raised about the potential, potential, effects of mercury. Once we had that realization -- And I think in some way there was a new realization for all of us, and some of us came to it for different reasons in different ways.

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

That's how I would tackle it.

DR. MODLIN: Yes?

DR. RICHARD: I'm John Richard from the Agency for Toxic Substances and Disease Registry.

For Dr. Halsey, you brought up some very good and very germane points that's consideration --

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

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

You raised some very good points, and I was just pointing out that those are things that the government health agencies that are involved in this and involved with the analysis for assessment of health effects of mercury have been concerned about and have considered. And I think this afternoon, in the research needs portion of the program, some of those will be addressed.

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

One is that in a series of three injections, three vaccinations, the total dose, as I understand it, is 62.5 micrograms per child. While that's to the child in the Seychelles study, we looked at the dose that the mothers received every day on the average throughout pregnancy, and that was 78 micrograms per day. Well, that's to the mother, of course, and on a milligram-per-kilogram basis, that's different. But if you take that 78, then that every week they're receiving almost 600 micrograms of mercury, and this goes on throughout pregnancy. Not only that, but the methylmercury is—all mercury, or most mercury is accumulated in the fetus at higher levels in the fetal circulation than it is in the maternal circulation. So these were fetuses being exposed throughout critical times in their development, and we're not saying one point of development is more important than the other, or whether it's the beginning of (inaudible) migration early in the third week, or whether it's further into cerebella or cerebral organization, but throughout all those critical points of fetal development, they were exposed to mercury, methylmercury, through high levels of maternal ingestion relative to the levels that we're talking.

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

Two other quick things, then I'd be happy to hear your response, sir. In the Seychelles, by and large, the tests were of global cognitive function. However, the McCarthy scales tests were conducted, and back in November when the workshop was conducted in Raleigh, one of the panels actually examined the data from the McCarthy subscales and they concluded -- And it's in that report that George Lucier said he had available -

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- that the data from that on a limited -- not limited, they didn't use the term -- but domain-specific effects indicated no domain-specific change in alteration and function as a result of methylmercury.

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

That's all I had to say.

DR. HALSEY: The one thing you haven't done is answered the key question that the physician and the parent have to face on the day of immunization. That is, how much of that exposure can they get on a single day? You haven't given us the answer to that. I would hope that your agency goes back and tries to address that question. Would you really accept getting three months worth of exposure at one time?

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

DR. PLOTKIN: Well, no.

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

DR. MAHAFFEY: Some comments and a couple of points. First of all, while on average the amount of mercury exposure through food is under the EPA 0.1 microgram per kilogram per day for adult women, it's certainly not an even distribution and, as Dr. Halsey pointed out, there are groups who are far higher with 1% above the ASTDR level. There are also groups within subpopulations who go a great deal higher, and we have some idea of who these subpopulations are. We know that there are people in this country, probably 2 or 3%, who eat fish just about every day. So while, on average, yes, it's true, the exposures are lower, they're certainly equal.

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

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

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

DR. ABRAMSON: Did I understand the question to be, what else we're looking at making recommendations about? It's really outside of the Committee on Infectious Disease. It's a question of should there be other guidelines as far as fish exposure, other sources of mercury exposure. So I'm really not in a position to comment about it.

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

DR. MODLIN: Yes?

DR. ROGAN: I'm Walter Rogan from the National Institute of Environmental Health Sciences and I'll briefly put my hat on as liaison to the Academy Committee on Environmental Health and say we are writing a new mercury statement. Wet think, but we haven't been cleared, the intention for the statement is in and we haven't been cleared to write it yet, but we will write a new mercury statement. All that other mercury stuff that isn't infectious diseases is ours, so we will do that. That's the only thing I have to say about that. So we'll do that. Take that hat off, I wrote the sentence about the McCarthy scale stuff. I think it's a little unfair to take that one sentence out of the context. I think that, broadly speaking, if you use the Faroe data as opposed to the Seychelle data, you would come up with a lower number because the Faroe data are positive and the Seychelle data are negative. So we, in that committee—I was the Chair of the Psychometric Endpoint Committee for that meeting—were uncomfortable dismissing the Faroe data on the basis of those objections that had been brought about on confounding domain-specific scores and things like that. So I don't want the impression left that we thought that because of some decomposition of the McCarthy scales, the Seychelle data were somehow preferable. We ended up saying these are both good studies and you have to take both into account when you look at them.

Finally, It's hard to keep more than two things in my mind at once. Finally, back to risk management and something Dr. Gellen said, I think the choice back in June was not between the Public Health Service and the Academy of Pediatrics saying something and, perhaps, producing a change that didn't benefit everybody, but, rather, between – and saying nothing which would have resulted in everything going along just fine. I think at least the perceived idea was that to say nothing and to have the information that the FDA, during the process of implementing the Modernization Act, had uncovered or analyzed or calculated that these numbers were higher than we had expected would have gone out. There would have been inquiries of physicians, of state health officers, of vaccine programs, of everybody, and that would have gone into a void with no statement from the Public Health Service or the Academy. So it wasn't a question of this could just sort of go along with nobody saying anything. We won't know what the effect of that kind of uncontrolled and unprepared sort of thing would be because it was circumvented by having something in place, however imperfect and done in whatever haste, but I think that the emergency was not a toxicological emergency. It was the fear that the professional people responsible for answering the questions would be unarmed unless something went out from the Academy of Public Health Services. I'm sorry I took so long.

DR. MODLIN: Thank you. Stan?

DR. PLOTKIN: At the risk of seeming to pick on Neal, who is partly paranoid by now -- Well, actually, it's a clarification. Neal suggested that the European attitude is to switch to Thimerosal-containing vaccines immediately, and I'd like really a clarification from Dr. Teeling because it's my understanding, as I read the CPMP statements, that the ideal is to switch to

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Thimerosal-containing vaccines as soon as possible in terms of working with manufacturers to eliminate the material from the vaccines. I am not aware, and I'd like Dr. Teeling to clarify, that any national or European authorities have instructed physicians to stop using vaccines containing Thimerosal.

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

What I said is I interpret the wording of that statement is that for infants and children there is a preference—I didn't say stop—there is a preference for the use of Thimerosal. And I have it written in front of me, but, perhaps, Dr. Teeling could deal with that sentence that I was referring to. I didn't say stop and there isn't any order, it's a preference.

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

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

DR. TEELING: I'm quite happy to let everybody else to answer my question. There's no problem. I mean, I think what you're referring to is the sentence, "For vaccination in infants and toddlers, the CPMP concluded that although there is no evidence of harm caused by the level of exposure from vaccines, it would be prudent to promote the general use of vaccines without Thimerosal and other mercurial-containing preservatives, particularly for single-dose vaccines."

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

So I think the prudence is to move to that. We are not recommending stopping vaccinations in the meantime. Now, it does state here that vaccinations should continue according to national legislation. And in reply to the second part of your question, this statement went out on the 8th of July. And certainly, my visit to the CPMP at the end of July, I had not been informed that any national authorities had made a change. However, we did look at -- And I think this is an issue that has been looked at not particularly in an hurry, but is an ongoing issue at the national level, and there is the instance of one particular country, Austria, which had a tick-borne encephalitis, which is a particular type of disease which is very specific to the Austrian population. They use a vaccine for that. And the addition of the tick-borne encephalitis vaccine added an additional burden of Thimerosal to their vaccination programs, and I am aware that they have now withdrawn that vaccine and are using a Thimerosal-free vaccine which has recently been authorized.

So I think it's an ongoing issue in Europe, much more so than it would appear to be here. I think we've been living with this for the last year and a half or so, with this move, and I think we have had communications. Indeed, we have had some vaccines where the companies have already started to put in variations to reduce or eliminate Thimerosal from the vaccines. So it's probably a more ongoing issue. I think this statement is from the 8th of the July and, as to hard facts as a result of that, we haven't had anything else yet.

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

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

One of the big issues, in a situation where you're trying to take something that you believe is safe to make it safer, you are introducing a change, but for the sake of the credibility of the program, there was a big concern about not creating a perception of good vaccines and bad vaccines. And I think that this issue of preference gets into that category, that as we transition, we're trying to avoid the perception that a label of bad vaccine that would be put on a vaccine that contains Thimerosal because it was considered to be a safe product. So there was a lot of discussion about this issue. So I think when we talk about preferences, we have to be careful. We all do prefer, but I don't think it's a preference in the sense that we're willing to call things good vaccines, bad vaccines. Now, that was a very important driver for a lot of the deliberations.

DR. MODLIN: Yes?

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

Yesterday, I was very impressed by the rapidity of the CDC surveying the hepatitis B screening practices, et cetera, in the wake of this change. That was really very impressive to have data like that. I wondered, given Dr. Daum's comments and also anecdotal things that I've heard about physicians misinterpreting the recommendations to assume that Thimerosal-free vaccines are indeed evil and they don't use them, whether there's any attempt or plan by CDC to look at the effect of these recommendations on immunization timing or the rates of immunization outside of hepatitis B?

Yesterday, Dr. Schwartz presented, I think, a pretty persuasive case, that if you delay DTP or HIB or whatever, you can clearly have a potential problem. I wonder, is the CDC going to be looking at that?

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

DR. MODLIN: Back of the room? Yes?

DR. GOODMAN: Yeah, Jessie Goodman from CBER.

Just to follow up on a couple of the comments, I think one of the things that may have occurred, and I guess luckily I was out of the country when all this happened, but if I was here I could speak more from firsthand knowledge, is that there is this spectrum of what our public health emergencies are, true public health emergencies, epidemics of pneumococcal disease or exposures to toxic or infectious substances, and then there are potential public health threats. I think this very clearly is a potential public health threat that warrants very careful consideration and, because of the kind of consequences people have talked about, very careful consideration of the response. But under the microscope of the media and public concern and all

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that, what has tended to happen is that whether something is a potential public health threat or a public health emergency, they're all being handled as public health emergencies. I think although I'm hearing that the agencies all work together well under the circumstances, I would second Bruce's comments, that I think, one, I'd think through carefully if there are any ones we can improve our responses to these kinds of issues, not necessarily critiquing the response to this issue in its particulars, but not falling into that particular trap of everything being a crisis and everything being an emergency. That's really all I wanted to say.

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

DR. MUSIC: Stan Music, working with Merck at the moment. (LAUGHTER)

I want to express some concerns about the epidemic of disease that I think we're beginning to see as a result of the controversy. When I hear John Abramson talk about a kilogram normal infant and say on that day we exceed the guide by ten-fold or when I heard Roger Bernier say "I haven't heard anybody say differently," I mean, I understand that the complexity is enormous and I think that that's an underestimate.

I also want to make it clear that I am speaking professionally, as an epidemiologist with 30+ years now, and though I work for Merck, I'm not speaking for Merck. This has not been cleared. I spent 28 years at CDC, mostly infectious disease, mostly outbreaks, mostly training epidemiologists, but in '96, I became the Chief of Environmental Epidemiology from North Carolina and I learned a lot of NOELLs and LOELLs and mercury in fish and I was responsible for wording of the signs on the creeks that gave the warnings and was very unhappy with the way we had to interact with the regulators and the sort of emphasis on regulation without the true public health effectiveness of making those warnings heedable. It's all over the east coast. It's not just up in Maine. It's in Maryland, it's in North Carolina, it's all the way down to the Gulf Coast.

When a MRL, a minimum risk level, or other guideline is applied here, I think it's being misapplied and I think it's being misapplied because of the way we label slides and because of the shorthand way we have to speak, but we have no data for ethylmercury. So in addition to what has been said, and I respect the rights and the integrity of everybody that said it, I think it's also legitimate to say that when a MRL, which is for chronic exposure for ingestion or inhalation and for methylmercury, is applied to what we are injecting with vaccines, will we get it all on the same day and we, at the same time, ignore any excretion or we assume that it is all totally instantly bioavailable, I think that's an abuse of the MRL and I think we need to make slides say those things and say it the right way so that everybody understands that the shorthand doesn't confuse them. That's the concern, and I want to state it clearly because I am concerned about the epidemic of disease that this controversy is causing. That is, delayed vaccinations are not good.

DR. MODLIN: Thank you. Dr. Clarkson?

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

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

So there seems to be a tremendous misunderstanding as to what these guidelines mean, and with the benefit of hindsight, we should write a talk on the kinetics of mercury so that we have some understanding of what the meaning of a day dosage in terms of tissue levels versus the meaning of a six-month dose. I mean, in this learned audience, it worries me that there's such a misunderstanding of the guidelines.

Lord only knows what the general public views these as. (APPLAUSE)

DR. MODLIN: Yes?

DR. ENGLER: Dr. Engler.

I just want to speak from a clinician's perspective and from an educator, both for physicians and nursing staff. This event -- And I just want to emphasis the last two speakers; I agree a hundred percent -- has really stressed the front lines, once again, in ways that are hard to imagine until you sit in a clinic with a rapid rate of health care delivery challenges you where there is no adequate recognition of the complexity of immunization health care delivery and you very rapidly have 30-minute visits that are not being counted or are not paid for in any of our systems, trying to answer questions that this illustrious group can't answer. I think that the whole issue of how we translate what the questions are and the words we use have a huge impact, and I want to take a lesson from the latex allergy issue.

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

So just the language of saying Thimerosal-free does convict in the layperson's mind and most providers who already don't think much of the vaccines. Some of the worst people who don't want to be immunized are physicians and nurses as a group. Why aren't we talking about Thimerosal-safe and recognizing that there is a balancing of issues in that arena? If we're going to make edict, then what about information fact sheets for providers and for the public that are readily available and palatable and let's call them "Draft version 1," so that the edicts that come down are translatable and usable in a quick user-friendly fashion. I think we should enhance the funding for the CDC section that helps write in a language that people understand.

If AAP, ACIP, *et al.* -- And it is very hard to teach people about all these organizations and what they do. I'd love you to give me a teaching slide set on it that's user-friendly for our use. Why not use those people as you're working these rapid-response edicts to create those interim or early VIS versions that as you're evolving these issues, you take the rest of the world with you? When I've been to the Armed Forces Epide-

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miologic Board, I've said to them, "Do you all care that almost no one knows you exist or what you do and you're twixes never get to anybody who's doing the work?" And that is not just a problem in the military health care system. That is a problem throughout the health care system. Just speaking for, as I say, the nurses and physicians on the front lines, you know, we want to work with you, but it's awfully hard and also challenging.

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

DR. KLEIN: I think one of the positive aspects that we've learned from this experience is that introducing immunization in the nursery is a very positive feature of vaccine utilization and that that lesson should be carried through with hepatitis returning to the nursery at the earliest possible time, but the opportunity to introduce during that period where there is so much positive educational opportunity, I think, is one of the most important things we've learned in the last couple of days.

DR. MODLIN: Thanks, Jerry. I think on that very positive note, I'll ask that we wind things up and certainly thank our speakers, our panel, and all the participants for their comments. It, indeed, has been a terrific morning and we look forward to a terrific afternoon. We will start back again at 1:30 on the dot.

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

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

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

The panel members will each -- Dr. Clarkson, if you could join us up front, so that as each panel member speaks, they'll be up at the front. The panel members will each -- have been asked to speak for several minutes, no more than five or I will cut it off. I have Bill Egan's watch, good interagency collaboration here, and then the real work starts and all of you have to make sure that we have covered what it is we should be considering in terms of research priorities, important questions, what's doable, and what's answerable.

I chose to spell "Thimerosal" the way I finally learned to spell it, which is the U.S. way, and let me – Okay. This is just a little part of the vaccine R and D component that I happened to have a slide ready for, but it's to remind us that when we talk about individual vaccines and when we worry about the vaccine schedule that each of the vaccines has gone through an intensive process of evaluation from Phase I through Phase IV where safety is a consideration as the number of subjects goes up and the questions that you're answering, be it immunogenicity, efficacy, or effectiveness, alter. There's, in reality, a huge oversight process to this part of it, and I think it's true for preclinical and what manufacturers need to do with potency and establishment licensure applications, which you guys don't have to follow anymore, that kind of thing. But it includes people overlooking the trials, people looking at ethics, the safety monitoring boards, and as you go into Phase IV, which is kind of where we are now with the immunization schedule, the post-licensure period —this is 50 years or 60 years post-licensure—including the company, the federal agencies, the parents, interests groups, and we all have some interest or another, as well as those people from the National Vaccine Injury Compensation Program.

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

First of all, vaccines are not perfect. Everyone agrees with that, I would hope. Yet, we understand the enormous value of the role of vaccines in preventing disease. That was beautifully stated yesterday. I think what people don't realize unless they've been involved in some process development or evaluation of that process is that GMP, those standards defined by the field of good manufacturing process, are not perfect. Actually, I've seen some studies where you can quantify the rate at which you will have contamination of a vial given different GMP practices, but that it's not zero. It's a quantifiable risk. At the same time, there are both regulatory and field requirements for a preservative in multi-dose vials.

There are some questions that we'll come up and things that I still haven't learned after two days of discussion regarding use of multi-dose vials in the public sector, both domestically and globally. I have learned that the ideal preservative does not exist. I was trying to elucidate the characteristics of an ideal preservative. I've got that list for vaccines and antimicrobials, and I decided I really didn't know enough to do that, but, perhaps, it would be helpful to have someone help us by doing that. But the ideal preservative probably does not exist.

I think another principle that you should all acknowledge as we are attempting to come up with the required research agenda is that the data that you have heard and the data that we're having to deal with and listen to from the environmental community and the infectious disease community are qualitatively different. As you heard in the afternoon yesterday, you're talking vaccine efficacy. You've got relatively clear endpoints. You've got measurable health effects. And when you're talking to the environmental epidemiologists and environmental health people, they're talking a language which makes sense to them and for us, it's like parts per million and it's modeling with uncertainty factors. Yet, to them, and in the field of environmental epidemiology, many of those approaches, although not driven to consensus, have a validity and a validity that we, in the infectious disease community in evaluating the randomized clinical trials, the gold standard, have difficulty attributing them. It's probably just better to acknowledge that you've got two communities talking across each other.

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Now, there are some principles that I think I've learned from Thimerosal, and if I haven't, please feel free to speak up because this is what I learned and it should be correct. The first is that we have to look at Thimerosal in context, and the context is that children do not grow up in a mercury-free bubble. They don't grow up in a mercury-free bubble prenatally and they certainly don't do it postnatally. This is probably my third day-long or -- Well, I don't know if you can group all the conference calls we had in that two-week period into a two-day period, listening to a number of different people talk about Thimerosal and realizing that the efforts to decrease mercury exposure in childhood is not something new, that 20 years ago—don't remember the date exactly—there were diaper powders that had mercury in it, in which it wasn't until people recognized that those were deleted from there. This is not new.

We haven't dealt with it in vaccines. I think the principle is that the health goal is to decrease exposure to mercury overall before you get into the issue ethyl versus methyl or inorganic, etc.

The other principle is that -- Someone asked me on the way in, they said, "Is this thing about coffee not in the room, is that a regulation or a guideline?" I went, "It's a regulation. They'll throw you out of here." That's a regulation. This is not. This is a guideline. I think that I want -- Where's Roger? I want that slide that shows the gray zone, the white zone, because we got it from whoever presented that at the influenza meeting, and I think that's the best graphic to really present. It doesn't matter, 0.1 versus 0.3, until you start talking in smallest children and then I'm not sure how it matters, but the 0.1 versus 0.3 versus 0.4 are built into how the non-methyl people think about guidelines and what kind of question they're trying to answer when they create guidelines.

The environmental community, having listened to three different sets of them -- Or maybe at least three different sets of them -- are not unified in their assessment of ethylmercury. They may be a lot more in consensus about methylmercury, but they've done that on the basis of detailed review, and I don't think we have the data to look at that. This is the scientific issues [sic; issue] relevant to have effects from exposure to methylmercury.

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

So gaps? Now, gaps are in the context of what I thought were the general principles, and they're not necessarily in the most logical sequence. I sort of started pasting together my thoughts over the past day and a half and the past 2 hours. Let me just go through them and I promise to distribute them to anyone who wants something a little bit more logical here.

None of the mostly methyl exposure epidemiologic studies took into measurement of effect, although they have clinical hair samples, etc., an understanding of the potential role of immunization of the child of an additional bolus during the time of infancy. This all relates to mercury, in general, and not just necessarily just Thimerosal. I'll try to speak with some more relevance specifically to Thimerosal on the next slide.

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

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

Now, we spent several conference calls arguing about ethyl/methyl and, you know, I was going, "Is there a difference of carbon group? Is that organic concentrate ethyl/methyl?" A colleague of mine, Dr. DeBosky, said, "Yes, but think about it. It makes a really big difference. You're talking ethyl alcohol versus methyl alcohol." Okay. I will admit that I don't know. While it may be perfectly reasonable, in an effort to assure that we're doing is the safest possible, to take the data that we have for methylmercury and to extend the conclusions and the considerations to ethylmercury. I don't know. In thinking of methylmercury in the kinds of settings that are referenced here, the primate data printed on methylmercury exposure which has been associated with motor and sensory changes, alterations in primates, and much less with cognitive effects, led to their conclusion that they needed data on specific domains.

Not being a -- What's it called? -- not environmental, but a development specialist, I'm not quite sure what specific domains are. I just know it means more than global assessment of cognitive or any single parameter of development. We need to evaluate potential health impact of prenatal exposure and, if we're going to do that and figure out ways to answer those kinds of questions, it has to be in the context of timing of exposure as it's related to those critical windows of susceptibility during development. That was recommended by the methyl group and I think the ethyl group, and ethyl considerations need to include that.

Now, when I start talking about ethylmercury and especially ethylmercury presented intramuscularly, the question really is, how different is it from methylmercury? The potential differences, and I've heard everything from "mercury is mercury" to "it may be 20% less toxic" or "really, you need to use it as the model" to "we don't know." And the differences could relate to the potential health effects and the pharmacokinetics, the bio-

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logical activity, the clinical endpoints one must worry about, the effect of a route of administration, and the dose schedule. And even something as relatively simple to answer -- And we hope to have data not too long from now, Dr. Clarkson, is it excreted and how in infancy? We can't answer that today and we should be able to do that if we're doing our jobs very shortly from now.

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

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

The issue of cumulative levels, it's clear that – I was worried that after listening to all this, I still don't know what's new to vaccines versus background exposure and what is the most appropriate useful, accurate, truthful time frame for evaluating childhood exposure. You know, in statistics, you can take a dose level and divide it to an average daily dose over six months or over seven months and --Let's figure out before we start doing the math what the appropriate window is that we're worried about and do it in consultation with the environmental folks and then compare the different strategies to decrease mercury exposure, regardless of source, to that measure.

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

At the same time, there are gaps in our knowledge of vaccines and the vaccine field, and that has to do with alternative preservatives. I'm glad to hear that some of the manufacturers have a lot more information than we appear to have on specific pharmacokinetics of methylmercury for—What is it?—2-phenoxy, whatever. I'm not sure it's published. If it isn't, it should be published and we should evaluate it because we have a 60-year track record with these vaccines. And before we go around running to replace them with another preservative, I think we have lots of questions to be answered. Do that very carefully. It doesn't mean that the data can't be collected or at least wait to hear from our colleagues in the industry that the feasible goal and that this data, the safety data that we're interested in, can be collected.

Although we heard a lot about the cost of eliminating and the lack of feasibility of eliminating multi-dose vials, I didn't hear any data and I think it would be useful to know. Maybe we heard a little bit from WHO, but for the U.S.—what is the real cost of eliminating the multi-dose vials and going to single dose vials and what's the real cost in terms of space that's needed to maintain the cold chains for these vaccines? I think you need that for decision-making for the U.S. and I think there's other factors globally. In a country where we are—I have to quote Dr. Orenstein—paying three million dollars per dose—per case of wild-type poliomyelitis to avert poliomyelitis due to vaccine, we obviously value vaccine safety and we have the resources to support that kind of approach. So if it's an issue of eliminating multi-dose vials, what are the costs?

Can there be novel approaches to limiting mercury content? By this, I meant—the "novel" word is one that we use at NIH when we want to sort of reach in and have people come up with things that we haven't thought of. By "novel", I mean some suggestions made around how to play with formulation and a way to limit Thimerosal, but different kinds of delivery vehicles, total delivery vehicles, which may not need it. Dry powders, DNA vaccines, whatever, novel formulations and approaches to limiting mercury content. Notice that [I] say "limiting" without presumption of value to that of absolute elimination.

I think it is possible to get a little bit more data on when in the first two years of life are infants exposed to hepatitis B, because we keep having to come back and discuss that when it comes to the hepatitis B issues. This is not a question. There will be an ongoing need to conduct an assessment of the cumulative effect of the immunization schedule. And Bruce talked about lessons learned, and I think a lesson learned is as we add and recommend vaccines that we need to look not only at individual vaccines but at the schedule that we're recommending from every perspective. I'm sure we'll continue to be surprised, but we won't be caught with this one again. Data, people have raised "Who's going to do this?" and "Are you going to talk about it?" So let me ask: Do we have data—I don't think we do—on which to comment upon the long-term effects on vaccine-level exposure to ethylmercury? I think the first place to look, and I'd ask those scientific communities that have these databases, can some sort of assessment be made from analysis or evaluation of existing data sources? In other fields like the diabetes issue, we were able to provide, I think, useful analysis from an existing database resulting from a randomized clinical trial in a country in which there was a very detailed and validated diabetes registry to answer a specific question. Are there places we could be looking for information pertaining to this or do we need to go look for novel sources and at what point do we need to go? Do we have enough knowledge about what's going on from animal models or fairly simply measurement of levels in children to have a high enough level of concern that we need to worry about bad health effects as opposed to recognizing the levels that are being administered potentially through vaccines? And I think Roger presented the diversity of the vaccine schedules to say we need to limit exposure. There are different presumptions that lead you to different conclusions.

Finally, how to communicate controversial and inconclusive data and at the same time maintain confidence in vaccines. I think we began to hear today what becomes sort of second-guessing what was a very difficult time of a vaccine group trying to understand data that, as you heard over the past two days, was not conclusive, but what was quite worrisome, and to de-

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cide when it's compelling enough for some action and at what point and what timing information is distributed.

There are lessons learned about systems we need to put in place and how to access our advisory committees rapidly and how to maintain—where's Dr. Plotkin? What's the word?—sang-froid. The charge to the panel—and I'll ask each speaker to talk for three to 5 minutes and I have my FDA watch on— is, number one: What are priorities for research from your perspective? Number two, even if you don't include that in whatever you had thought you were going to present up to now, can you comment on the feasibility and the urgency to do so?

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

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

DR. CLARKSON: With regard to human studies, some suggestions that the group might want to consider, first of all, is this calculation that I did which I think the calculations like this have to be done to assess risk from ethyl and methylmercury. You have to base them on blood levels because all of these guidelines from these various government agencies and so forth all start with toxic blood levels and minimum toxic blood levels and so forth, and they work from them. So what I've given here, for example, is the blood levels that might develop in an infant given these schedules of vaccines. For example, the first shot only raises the blood level to about 4 parts per billion which is actually about the equivalent of the EPA guideline.

So I heard this morning a single dose will be ten times or something the EPA guideline. It's certainly not. It might approach about the EPA guidelines, but as you can see, as it builds up with subsequent doses from the vaccines, it does certainly exceed the EPA guideline by a factor of 4 or 5. But all this is based on all kinds of assumptions. One is that methyl is the same ethyl, which it probably isn't. It's based on the assumption that there's no excretion, and as the Chairperson pointed out, that's something that we should definitely check and I promised to do that, be a good boy.

We also should validate hair as a marker for exposure to ethylmercury. That would allow us to do some more population studies to see what hair levels are like in infants, but we have to validate it first. I think that can be done with the infants already available. Hair monitors methylmercury and not inorganic. The hair then could be very useful. It might just monitor the intact ethylmercury in the infant which is probably responsible for the neurological effects, and we'd have to have some other measure for inorganic mercury like a blood sample.

As I say, I learned an important thing—many things from this meeting, but one was that we didn't take into account vaccines in the Seychelles study. I think it's possible now—Thank you, Dr. Myers—that it's possible that we may now be able to go back and look at that. We have an enormous amount of behavioral data, clinical data, development data on these kids who are now 9 years of age. So we have a huge database. So we might be able to now take a look and see who got vaccines and how much and whether this has an impact on our data, and we might therefore get, I hope, some useful human data out of this.

Of course, this will be a vaccine on top of a substantial dose of methylmercury. So this could be useful, too. When we heard about all other kinds of mercury exposures that kids are exposed to, here you've got a population that really is getting an exposure, on the average, 10 times higher than the U.S. population. If we superimpose vaccines on top of that, if we're going to get any effect, we'll get it in the Seychelles as I mentioned. If we don't get an effect, I think it will be very reassuring for this situation.

As far as animal experiments are concerned, I understand that it's really not going to be practical to do a major Seychelles type study in this country with regard to vaccines, but I think that animal experiments are feasible. I mean, one can do a lot of neurobehavioral tests and kidney function tests on animals. There are 3 or 4 papers in the literature on ethylmercury, so we've got good guidelines to start with for ranging effects. So I would suggest we could do that or somebody could do that. We'd be happy to make them an offer. I'm in my elements this afternoon. I'm after research money. The other point is that—especially with regard to this figure here, the salicylic acid may be playing a role here. I've talked to some of my colleagues here today and yesterday. We don't know how rapidly it may go from the intramuscular side. I've assumed in this figure here that it's a very rapid, almost instantaneous distribution, but it may not be and that's something we could test in animals, too.

All our previous animal work has been done with ethylmercury chloride, which is a very lipid soluble commodity that diffuses readily from tissues. It will be interesting to see if the salicylate compound behaves the same way. For example, if you're looking at the transport of methylmercury into the brain, methylmercury-L cistine [sic; cysteine] gets in the brain rapidly. The "d" isomer, the optical isomer, the only difference is the optical activity. The "d" isomer does not go into the brain. So the chemical compound, not just the mercury itself, but the chemical compound when mercury is resent may play a very important role in its distribution and kinetics. If it was a lower release, for example, these peaks may not be as high as they are in this figure. So I think it's worth considering.

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

DR. RABINOVICH: Can I understand from your presentation that you think answering all of these are doable?

DR. CLARKSON: Yes.

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

DR. GERBER: Thank you. Well, as we've heard several times yesterday, as well as today, we can speculate on what the mercury levels may be in infants who've received immunizations with Thimerosal-containing vaccines, but as far as the actual data demonstrating what those levels are, there really is very little. In fact, the only data that we have comes from stages of study at the nursery at Emory. We heard yesterday about the limitations of that study, the fact that it hasn't been published except in abstract form, the fact that there are only 5 term infants and 15 premature infants, that the 15 premature infants had a mean weight of only750 milligrams, concerns about the methodology of that study. So, needless to say, with that being

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the only data that we have, we really have very little. As little as we have about the levels, we have even less about the distribution, about the kinetics, about the metabolism, about the excretion of ethylmercury. In fact, we know essentially nothing about those things in ethylmercury.

So what we at the NIH are proposing to do, and we're proposing to do this in conjunction with our colleagues, Dr. Ball and Dr. Pratt at the FDA, and we're proposing to do this through our vaccine and treatment evaluation units at Maryland and at Rochester, working with Dr. Clarkson at that same institution. What we're proposing to do is to attempt to obtain this data and we attempt to do this by getting together a cohort, first of all, of premature infants who have been vaccinated with the hepatitis B vaccine sometime within the last week to several months. These would be infants whose mothers were hepatitis B surface-antigen positive, infants whose mother's hepatitis surface-antigen status was unknown, or infants who were born at hospitals that were not following the current recommendations of withholding the hepatitis B vaccine until a later time and those infants born to hepatitis B surface-antigen negative mothers.

And what we've proposed to do after identifying these premature infants is to obtain blood, stool, and urine specimens from them, as well as maternal hair samples. The maternal hair samples would be to get a baseline idea of what the *in utero* exposure had been. Maybe as a point of clarification, and we can get it from Dr. Clarkson later, I understood you to say that we could not measure inorganic mercury in hair, only organic, but I was unclear as to whether we could distinguish ethyl from methyl and maybe you could address that later. But, in any case, in addition to the premature infants, we would then want to look at a cohort of term infants and look at term infants coming from three different kinds of pediatric practices, one practice in which the routine immunization had been providing the patients with vaccines that had a relatively high amount of Thimerosal. We would want to look at a second group of practices where the cumulative exposure from vaccination of Thimerosal would be relatively low, and then, finally, practices or a group of practices where only Thimerosal-free vaccines had been used. Again, we would want to look at these infants within one month to several months following the 2-month immunization and at that point determine what the exposure, what the combined exposure had been at that 2-month visit, as well as all of the possible previous exposure to Thimerosal from earlier immunizations, and collect blood, stool, urine from those patients, as well as maternal hair samples if we could. We would also want to look at a similar group of infants from those same three types of pediatric practices after the sixth-month immunization and, again, make a determination of the total Thimerosal exposure at that six-month immunization, as well as any exposure from previous immunizations and again collect blood, stool, urine specimens from those infants, as well as maternal hair samples if we could.

Hopefully, with that information, we would be in a position to make some determinations about what the expected mercury levels would be after immunization with Thimerosal-containing vaccines, about what the distribution, what the metabolism, what the excretion of ethylmercury in these infants would be. Is this feasible? I think it is feasible. One limitation of the feasibility is trying to do this as soon as possible while children are still receiving Thimerosal-containing vaccines. Why is this important? If we're hopefully moving towards a situation where infants in this country would no longer be receiving Thimerosal-containing vaccines, I think there are three reasons. First of all, I think the information that would be obtained would be helpful for those parents whose infants have already or will continue to receive Thimerosal-containing vaccines. Number two, as we heard from Dr. Clements, although we may be approaching Thimerosal-free vaccines in the near future, for much of the world, this is something that's not going to happen for several years, at least several years, so this information would be important for those populations. Finally, as one of the charges in the Joint Statement from the American Academy of Pediatrics and the Public Health Service, this type of research was one of the things that we had committed ourselves to performing.

Thank you.

DR. RABINOVICH: Alison Mawle.

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

I work at CDC. I'm part of the National Centers for Infectious Diseases, and as we have listened over the past two days, but also over the last several weeks, to some of the issues that have been brought up around Thimerosal, I have been repeatedly struck by the fact that we really don't know how this compound breaks down. We heard yesterday from Jeffrey Englhardt that there's very little kinetic data on Thimerosal, but the one paper that we have seen in squirrel monkeys suggests that a fair proportion of this breaks down not into ethylmercury but breaks down into inorganic mercury. And we've heard the data on methylmercury. We're now hearing a little bit about how we want to do the studies on ethylmercury. I think it's absolutely critical that we know how this compound breaks down, because if what we're looking at is inorganic mercury, we're looking at a different thing again. We've heard very little at all about inorganic mercury. Dr. Clarkson mentioned that if we want to do studies in hair that we cannot use inorganic mercury as a marker. I have learned more about how you do these studies over the last few weeks than I ever wanted to know and I still feel very ignorant about many of these things, but I do feel that that is, in terms of both feasibility and urgency, one of the first things we should be doing. It's, certainly in animals, a fairly straightforward experiment to do.

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

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

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

But I think that that's a real important study to do, clearly from the Faroe Island studies and the Seychelles Island studies.

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If there are effects of the mercury from the vaccines, they're going to be subtle. It's going to be very hard to do any kind of study in current populations that are being immunized, especially as we have heard from FDA that the commitment is to move towards mercury-free vaccines if at all possible. I've certainly not heard any argument against that. If we need preservatives in certain cases, if we need to keep Thimerosal there for a specific reason, FDA will be willing to discuss that, but, clearly, the move is to get rid of mercury if we can. That comes in the context of the environmental mercury load. I think it's very easy for us to focus on our little issue of vaccines, but that's not where this is coming from.

This is coming from the fact that we live in a mercury-contaminated environment and seeing the contribution of vaccines within that context I think is critical.

From CDC's perspective, I think it's very important and very urgent that we monitor any changes on immunization practices. The data that Eric Mast presented yesterday I found very disturbing, that in such a short time you can already see an effect of this. I don't know if they're going to address this, but we've heard from the manufacturers over the last few weeks that we could not go to a Thimerosal-free schedule right now without introducing dramatic vaccine shortages, which would totally disrupt the current schedule.

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

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

Lastly, I just want to leave you with the idea that we really, really need to increase our ability to communicate with our constituents. I think that we can certainly be faulted in terms of being complacent about the efficacy and safety of vaccines, and it's become clear over the last 2 or 3 years that the public's concern about vaccine safety has risen. We've seen congressional hearings recently on that issue, and I think the way that we communicate, both with the public and also with providers, is critical in terms of maintaining confidence in our program and in giving them information to give to their constituents in order to reassure them, or not, if that's what we need to be doing as we've seen in the case of the rotavirus issue, which has been going along parallel with that. So I hope that's given a few thoughts from our perspective. Thank you.

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

DR. PARADISO: Thank you, Gina. Gina said I only have a half-an-hour to talk, so I'll try to go quickly. I have to first apologize for the fact that I was not here yesterday. I couldn't make it, so I missed a lot of the detailed discussion. I want to tell you that during the course of the several weeks and also during the course of this morning, when thinking about research in this area, particularly as it relates to Thimerosal and what we need to know and what we don't know, I have a little trouble getting past what we're going to do with any data at this point that we collect with Thimerosal. I think that we have made a judgment—or a judgment has been made on the basis of a desire to eliminate Thimerosal because it makes sense not to inject mercury. And there is not, to my knowledge, a specific outcome besides that that we're trying to avoid. So in designing studies to look at Thimerosal, it's hard for me to think specifically about outcomes that I would have any confidence in or that I would think about to counterbalance the decisions that have been made so far. I'm not trying to be flip about this, but I think we have to be a little careful about thinking that data that we collect on Thimerosal, while I think it will be useful in our understanding of Thimerosal and its metabolism, it's not clear to me that it's going to tell us too much about potential rare adverse events that may occur as a result of having Thimerosal.

Now, having said that, at the end of this morning, I heard Dr. Clarkson, who knows far more about Thimerosal and mercury than I do and also is from Rochester like I am, so that raises him a little bit higher on the scale—Rochester, New York, that is—it seems clear to me that we, infectious disease vaccinologists, perhaps have no idea how to use these numbers that we're using and using as our guidelines. So if I were to back off what I said at first and think about things that I would like to know, it would be: How do we assess cumulative effect when we talk about vaccination? The only data, I guess, that would be convincing to me would be data that actually measured levels in the blood or in an appropriate bodily fluid that could be related to the potential toxic effects that we're worried about. Those are mostly neurological. You know, I think we need to, however, then think, what if it's undetectable? Would that change what we're thinking? If it wouldn't, then we have to accept that the outcome of these studies is going to be for our understanding and not going to really help us in terms of future use of Thimerosal.

So I think we, as manufacturers—or our company is looking more towards potential new formulations or new preservatives that could be used or towards the elimination of the use of preservatives, and that obviously gets us to single-dose vials. I think it's important for us not to underestimate the practice that was just mentioned in the United States. Multi-dose vials are greatly favored. I mean, the reason we use them in the United States is because that's what the physicians' offices prefer. In Europe, that's not the case. They, in fact, prefer single-dose vials. So that is the market there. So this is not an overnight change from a multi-dose dose presentation to single-dose only because of the capacities that have been developed in our manufacturing around those needs.

In thinking about new preservatives, I think we need to think hard about what outcomes we'd be looking for from a safety perspective when we use new preservatives, and it seems clear to me that tests for toxicity that Thimerosal passed are obviously not enough for the next preservative. So we need to think about what outcomes we're specifically looking for. Somebody said this morning, for the unknown, the new preservatives are really the unknown, and without experience, and we need to

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think in our research, when we think about research, what those outcomes would be.

Lastly, I just want to comment, Norman Baylor talked this morning about the FDA review process and the desire to expedite review. I need to point out that on those two slides, the list of potential requirements for the presentation for a new preservative or the presentation of any new formulation is potentially not a small task, and if you're talking about doing stability studies in real-time, usually that's a two year real-time stability study. If you're talking about doing consistency studies and if you're talking about efficacy trials, you're talking about several years and fairly major programs for the presentation of new preservatives. So all of that needs to be put together before the review process can start, obviously.

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

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

DR. RABINOVICH: Dr. John Risher?

DR. RISHER: This will be a little bit of a challenge for me. I teach biology classes for 6 hours on Saturday and I always run out of time before I get the information through. So 5 minutes is really going to be a challenge.

Most of what I have to say, and I'm approaching from a toxicology and human health risk assessment perspective, has already been said, but I just wanted to put a couple of points of clarification that I don't know -- This may help. This is just from a general introductory biology textbook. I don't know how many people really understand when we're talking about the main specific effects versus global effects. An example of the global effect is I.Q. The main specific effects -- This is 1999, so we know a lot more about the brain than we did a 100 years ago and we know that specific areas of the brain are associated with specific cognitive or motor functions. I don't have a pointer here -- Oh, great, thanks. If you can just look, where it says "language structure" on the upper left and go down, we know that certain areas of the brain are associated with that. So specific neuropsychological tests are designed to probe specific cognitive functions and the ultimate intent is to find out if -- even although you may not have been exposed to enough of a substance to have an effect on global function cognitively, there still might be enough effect in a particular area of the brain associated with a certain function. So when they talk about domain-specific effects versus global effects, that's, in general, the difference between the two.

Again, the first one on here is just common sense, but what I did is I tried to break down things that I thought might help from a risk assessment perspective. The first is really more of a common sense thing and it could easily be an in vitro study if it has not already been done. This is just to look at the effectiveness as a preservative of reduced amounts of Thimerosal. Again, that would -- if it has not already been done by the manufacturers, it'd be an easy thing to do.

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

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

Ethylmercury in the hair of the Seychelles Island population -- Well, the Faroe I'm not sure about. Dr. Grandjaun is not here, but Dr. Clarkson has already addressed the ethylmercury in the Seychelles population. So they might look into that. Another thing regards one of the differences in looking at this Thimerosal is not only the fact that it's a bolus, we're talking about most of our knowledge relating to either the unborn or to adults, and I just want to really quickly explain something and then suggest that it might be looked into.

In adults, the primary source of excretion of organic mercury -- Primarily methylmercury is what most of the information about -- is through an enterohepatic circulation. That is that the mercury is absorbed from the gut and it goes up through the circulation into the liver where it's conjugated with glutathione and leaves the liver in the bile salts back down to the gallbladder, through the bowel, and then back into the intestine where it continually gets recycled. So it's not always bowel available. Now, in rodents we know that during the suckling period, which is about 21 days in rats, that the glutathione, which is needed to conjugate the mercury, is not produced in sufficient quantities to lead to the circulation. There's been some studies in primates that have shown that in real young primates that that might also be the case. In humans, we really don't know, it may be the case or it may not be, but I think it would be interesting to find out when that enterohepatic circulation is to the extent that glutathione is produced and can conjugate the mercury and actually comes into being. That ties into again with excretion.

Longer-term things: A lot of classic toxicology-type studies; neurodevelopmental studies of Thimerosal which would do dose-response studies and research animals and also look at different ages of animals, particularly after the animal is born and how the early stages of development compares to adulthood; the next one, contribution of Thimerosal from vaccines to total and individual tissue burdens. Kate Mchaffey from EPA and others were stressing the importance of looking at the total body burden of mercury. We're not just being exposed to Thimerosal. We're getting some in our food and some from other sources. ATSDR is involved in a Great Lakes research project that it's been sponsoring for years or co-sponsoring, and we may have the mechanism for getting some of this data.

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

I'm sure that's five minutes plus.

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

DR. SCHWETZ: Thank you. It's always fun to be the last of a series of speakers who, for the most part, vigorously agree with each other. It's very hard to say something that's new and unique. On the other hand, I want to offer some thoughts as the Senior Science Advisor to the Commissioner of the FDA and the Director of the FDA National Center for Toxicological Research.

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

If Thimerosal or mercury is taken out of vaccines, I think further work on ethylmercury for the Center for Biologics would not be a very high priority, especially in comparison to the need for data on the replacements for Thimerosal. I think this isn't just a question of a research agenda for ethylmercury, it's an even more important question that if we succeed, then the problem starts of knowing how successful the replacements are. That has got to be a high priority, along with whatever we need to know about ethylmercury.

On the other hand, it isn't very likely that Thimerosal is going to be replaced in vaccines completely in a reasonable length of time. So that is still a need to have data on ethylmercury. Then look at the bigger picture of the FDA in total where the concern is for drugs, cosmetics, foods, as well as vaccines. Then it's a given that we need to have more data on ethylmercury to understand that kind of a complex picture. It must include considerations about additivity of ethylmercury from different sources, but a point that hasn't been made in this meeting so far is the need to consider the additivity between ethylmercury and methylmercury. We treat them as if they're not acting in the same cells, and at some times they are. So I don't think we can look at ethylmercury in isolation without considering methylmercury or other sources of ethylmercury other than vaccines.

So one of the high priorities that I think is for us to reduce the uncertainties that surround the idea that methylmercury and ethylmercury are the same. We know they're not, but that's where we are today and we don't have much data on ethylmercury to really confirm whether it's more or less toxic. We know for the kidney it's probably more, but we all seem to assume that methylmercury is the gold standard for concern and ethylmercury may not be as bad. We don't have enough data to say that with a hundred percent confidence.

While there are some priorities that I would say maybe just a little bit differently than some of the preceding speakers, I would agree that the sensitivity of the fetus versus the neonate is very important, and for some of you who have forgotten about the sensitive windows during fetal development, the nervous system develops postnatally. So isn't unreasonable to expect there would be particular windows of sensitivity. So it isn't the matter of averaging the dose over the whole neonatal period, it's what's the week or what's the day or what's the series of hours that represent a particular event in the development of the nervous system when this whole thing might be dangerous. It may be weeks surrounding that when there isn't a major problem. We don't have that information.

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

So the real question in my mind is the peak – the effect of the peak blood level versus the blood level during the distribution and elimination phase of the original exposure to ethylmercury. Then you add to it another exposure beyond that with another vaccination or from food or whatever, but it isn't a matter of chronic versus acute exposure for this neonate. We don't know the impact of the area under the curve during the elimination phase versus the impact on the cells of nervous system during that peak level. Is it just a difference in the exposure? Is that just the dose response curve? Or is time important? That, again, gets into the windows of sensitivity and we don't have the kind of data to address that.

In addition, the intermittent versus the continuous exposure, there are examples where intermittent exposure is important because the rate of delivery to the cells is more important. The rate of delivery, the rate of change within cells, could be more important than the average concentration. That could explain the intermittent versus the continuous response. The valid bar markers of exposure, I think we have to have that. That is obviously of considerable importance. The elimination from the neonate, we're using a conservative estimate when we say it's not being removed by anything other than dilution, but we need to get that information.

One that I haven't heard discussed, the fact that we know that ethylmercury is a skin sensitizer when it's put on the skin and now we're injecting this IM at a time when the immune system is just developing, the functionality of the immune system is just being set at this age. So now we're injecting a sensitizer several times. During that period of time, what's the impact of a sensitizer -- of something that is known to be a skin sensitizer, what is the effect on the functional development of the immune system when you give a chemical of that kind repeatedly IM?

Now, regarding the question of feasibility and urgency, the kinds of studies that we're talking about, the pharmacokinetic studies, the distribution, the elimination, all these other things that we can do in rodents, we can do them in primates, so those are feasible. It just takes money and expertise and good work. We don't know need shoddy work at this stage by people rushing in and doing something that they don't quite know what they're doing. This is a time when the rest of the data that we make new decisions on have got to be better than the quality of information that is normally available when people on a random basis begin to collect information and, in retrospect, it doesn't fit into a real good picture when you analyze it. That's true of a lot of chemicals. There need to be some definitive studies now that are done very well. The urgency, from the standpoint of -- Now I'm speaking as a toxicologist. I think anytime there's an avoidable source of exposure to mercury, we need to look at it real hard, but, obviously, there are consequences in many cases of taking steps. I don't think this is an emergency, that mercury is being used in this manner, but if it's an avoidable exposure, we should do something about it. I also recognize that if we do something precipitous, we could create an emergency and that has got to be considered as equally important as the concern over mercury itself.

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Why mercury represents a priority concern for me as a teratologist and a developmental toxicologist who has been doing this kind of work my whole career is the fact that this can cause irreversible damage to the development of the nervous system. That's why, in my mind, it's different than nephrotoxicity. A reversible damage, whether it's in an adult or a neonate, whatever, that's different than permanent damage to the function of the nervous system, permanent damage to the function of the immune system. So that's why I think, among the issues that we look at with mercury or with other heavy metals, the fact that you would cause irreversible damage to the nervous system, in particular, is something that makes the kind of priority where we shouldn't sit back and say, well, we got through this one and now we'll pay attention to other priorities. I think we've got to stay on mercury.

Thank you.

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

Dr. Klein?

DR. KLEIN: Dr. Clarkson, I'd like you to amplify your remarks, particularly in regard to that graph that you showed, the figure, in terms of a potential first dose of vaccine that has Thimerosal in it given at birth.

Now, you indicated that it would be about 4 micrograms with that first dose. I wonder if you could eliminate that first dose, the rest of the curve presumably would be approximately the same; is that correct? In other words, what benefit do we gain in your model from eliminating that first dose?

DR. CLARKSON: Not a lot. I guess you've seen this before, but this basically -- As we said, all of these guidelines that we've talked about today don't start with the dose. Well, some of our Iraqi stuff did, but, basically, when you're making these risk assessments on human health, epidemiologists -- (inaudible) on ethylmercury, you start with a hair level or blood level, let's say a minimum toxic level or some threshold level, some level associated with toxicity. Then an expert committee may or may not apply safety factors. For example, originally, from the Japanese data, there was a blood level of 200 parts per billion. A committee comes along and applies a safety factor of 10, so it's now 20 parts per billion in blood. Then from that point, the committee will go on and calculate what is the long-term daily dose that will give you a toxic level of 20. That's how it's done. There's various calculations. The original data is not a dose. It's a blood level or a hair level. And the best way for us to compare a single dose to the chronic dose is to ask blood level results from that single dose or what blood level results from that chronic dose. The example I mentioned this morning with eating 6 ounces tuna fish, which has something like 17 micrograms of mercury. Let's say 20. Well, if you consume one can, the effect on your blood level would be so tiny you can't measure it, but if that's taken day after day after day for 6 months to a year—it takes about a year to get into a steady state where intake balances excretion—that blood level will rise measurably to a level of about 20 parts per billion, which is one of the FDA safe limits. So a single dose is a very different situation than a chronic dose in terms of body burden. Now, in this case, you go to the top, a single dose of 12.5 micrograms here at birth, given the bodyweight -- We took a bodyweight of 1.8 kilograms—and we assume the blood volume was 8.5% bodyweight and you assume that 5—you do all this arithmetic and you will come out with a blood level of about 4 parts per billion, which is about where the equivalent blood level will be for the EPA guidelines. So you get with this one dose to about the EPA guideline. You certainly do not exceed, as I heard this morning, by a factor of 10. Okay? As you continue with these doses over this six-month period, assuming there's no elimination of ethylmercury from the body and assuming ethyl behaves like methyl, you will eventually exceed the EPA guideline. At month number 2, you will get up to a level of about 15. By six months, you may get up to a level in the 20s, which then starts to exceed the other guidelines, the FDA guidelines, the ASTDR, and so on.

DR. KLEIN: I'd like you to superimpose on this curve. Let's say there is no vaccine given at birth, but the same series of immunizations is given beginning at two months of age. Does that affect your curve at all?

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

DR. RABINOVICH: Thank you. Next question? Dr. Orenstein?

DR. ORENSTEIN: Walt Orenstein, CDC.

It's interesting that I didn't hear anybody talking about looking at outcome kinds of studies in vaccinated children. Roger Bernier presented data from the Vaccine—one of the institutions in the Vaccine Safety data link. Kaiser I think had over 30,000 children in a distribution at least of different Thimerosal intakes, and I presume most of those kids are now between two and four years of age or somewhere along that line. Is there a reason why none of you considered that? Or is it I didn't hear you? Is it too many confounders, too difficult a study to do, or do you think it would be worthwhile trying to look at some outcome in a population such as that?

DR. RABINOVICH: Dr. Gerber?

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

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

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

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DR. RABINOVICH: Dr. Schwartz?

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

One of the other things that we haven't looked at is what other additives there are in vaccines or adjuvants that are used with vaccines and what the impact of those may be. I think if we're going to learn anything, it is that Thimerosal has been in vaccines for a long time and nobody really thought a whole lot about it until all of a sudden it seemed to spring on everyone's consciousness, and there may very well be other things that are parts of the immunization program that are found in vaccines and we need to do, I think, a much better job thinking about what additional research may be done in order to be ready should any concerns arise in the future or to identify any problems before they're identified by the media or people who may misinterpret what those data mean.

I think before I spent any money doing further research on Thimerosal, I would be inclined to look very carefully and see what money needs to be spent on things that are going to be important to the vaccination program in the U.S. in the future.

DR. RABINOVICH: Yes, please, Peter?

DR. PARADISO: I think it's a misconception, at least to me, that the Thimerosal issue or that the concerns about Thimerosal were sprung on anybody. At least on the vaccine manufacturer side, this is an issue we've been dealing with for quite a number of years. And in Europe, we heard this morning, it's been a fairly major issue for a number of years, and we have been moving in the direction that in new vaccines in the future is actually to move away from the use of Thimerosal because of the concerns and the potential unknowns about it. So I think it's unfair to say that this was a surprise, that we, from a manufacturing perspective anyway, didn't know about the issues with Thimerosal. I think the surprise was more the reaction to it and the immediacy in the U.S. particularly.

So I want to add to that to say that there is generally very great care taken to what is put into vaccines and the potential toxicity of what is put into vaccines. Perhaps, we can see that the most when we think about adjuvants and new technologies for improving immune responses. That has been a process that we've been working on for probably the last 10 years and it is a slow and careful process guided by toxicology and guided by our desire to make sure that we don't introduce anything that's not safe. So, you know, I think we are doing that.

DR. RABINOVICH: Dr. Zoon?

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

A point I would like to just mention, while I agree that we need to look at the future with respect to other potential preservatives, I do think we're looking at a very long transition period where Thimerosal will continue to be used in a number of vaccines. I feel like the balance needs to be looked at on both ends. What are the risk factors and what is the information we need to know to make good scientific decisions and guidance with respect to the use of Thimerosal and really understand that so that we can give good instructions and good advice. But as we heard, if we, if ever, go to zero, we need to still deal with those issues. So my sense is that we need to achieve a balance here. We need to understand more about Thimerosal because, in the past 2 days, I think we have recognized there really is a paucity of data and I think some of the points made about looking at the developing nervous system, looking at the developing immune systems and the effects of these agents on that at critical times of development hasn't been done, and I think that knowledge is very important.

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

DR. RABINOVICH: Dr. Halsey?

DR. HALSEY: I just want to respond to Walt Orenstein's question and I would have said it anyway, but I think there is a problem of perception. I personally think it's very unlikely that any harm has been done. I don't think anybody believes—most people don't believe that it has. I don't think so. But I think the public perception will be that it might have, and we know from our experiences that we've been dealing with in the past 5 years with regard to alleged adverse events of a variety of type, that including things that we have learned some of the subtle neurologic defects that may come from the studies in the Faroe Islands, you can bet there will be many parents who believe their child may be affected. And they do need data to address that issue. I believe the data will be likely to be negative, but if we don't have the data, how can we say that it's not negative? This is one situation where there will have been exposure to something that might have done it. It's not the same as some of the other allegations that we have dealt with.

So I do believe that there is a need and probably for much more than the study that Walt was talking about, which is a limited number of small—a relatively small number, even though it's in the tens of thousands of children, to just take a look at some of the simple outcomes, but there probably is a need for a careful study. I'm not that type of investigator, but the people who do these neurodevelopmental things very carefully need to determine the feasibility. They need to look at all of the other exposures. This is not a simple study. This would be very complicated and I don't look forward to being responsible for those, but I think if we don't have that, we're just going to have the continued public trust erosion that says you don't care or you don't think so. And what's going to happen to the Vaccine Compensation Program? There will be, undoubtedly, applications for that and who knows what's going to be the outcome of those deliberations by the Special Master.

So I think there is a need and probably for more than one study based upon the problems that we've seen elsewhere by the interpretation of different studies and in different populations who have a very different baseline rate of exposure to mercury. You can't just pick those populations that are at the low background of other environmental exposure because it'll be stated, perhaps correctly, that you biased it in your favor in saying that there's no effect from those.

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

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DR. MAWLE: I wouldn't disagree with you, but in terms of public trust, it's an important question to ask. I feel quite strongly that there's a lot of data that we need to know just about what happens to the Thimerosal before we can even get into those studies. So I think it's something to bear in mind.

I was very happy to hear that Dr. Clarkson will be able to look or possibly be able to look at what happens to vaccines in the Seychelle where there is a huge burden of mercury. If that's possible to do in the Faroe Islands, I would want to do it there, too, where you already have the careful outcome measures looked at. I agree it's not the U.S. population, but it would certainly give you a parameter and a range for where you can start to apply that to this population and to get an idea of whether we really need to do them. The biggest problem I have with that is that if we find a negative, then there will be so many confounders that people will say, "Well, you just didn't do the study right." And for the time and expense, I would say that that's the kind of study that you want to keep in the back of your mind, and Gina talked about looking for populations, databases that may have been collected for other things that we could possibly get that kind of data from that wouldn't involve setting a study de novo.

UNIDENTIFIED SPEAKER: Bill (inaudible) from Wyeth. [Probably, Dr.Hausdorf based on earlier in transcript, page 25, column 2.]

I have sort of similar comment maybe since you said exactly what I was going to say. My question is actually for Neal which is that, since you seem to think there is a clear and present sort of danger here that should be taken out immediately, what data would you need personally to be convinced otherwise?

DR. HALSEY: Let me clarify, I do not think that there is evidence of a clear and present danger. That was not my intent by anything that I have said, but I have participated in writing in the Academy statement and elsewhere that there is no evidence that harm has been done. There is a clear problem with regard to the potential or the perceived potential for harm, and I believe that the correct steps have been taken by the FDA at this time of requesting within the realm of what they're capable of in the absence of any data of requesting action to determine what can be done and how fast it can done to remove this. So the corrective step from that standpoint has been taken.

What I do believe has not been done adequately to date is a showing of the uncertainties that we have at this time and provision of more specific guidance to physicians with regard to what options are available.

I mean, the basic principles that I learned a long time ago about dealing with perceived risks is that you do take an action, but you also have to inform people of what additional steps they may take and this is not too different than some other vaccine safety issues that we've dealt with in the past 5 years. We have DTP whole cell and DTaP, the acellular pertussis. We have given a preference to that vaccine that we think is safer with regard to some side effects. With regard to inactivated polio vaccine versus oral polio vaccine, we have moved in a fairly rapid process toward the vaccine that seems to be safer, but one of the first steps we did was to inform people that there were two different vaccines and that there are these benefits and risks of each one. We haven't taken that step yet with this process, but I think we have an obligation to physicians and the public to at least talk about the actions that are there.

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

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

DR. GELLER: Well, if somebody has the answer to your question, they should be speaking and not me. But I will say that one of the things that we've heard, and I think that while this session is designed to sort of sketch out a potential research agenda which people can go back and figure out what's feasible and not, what's fundable and not -- One of the things that we heard at the hearing and that we hear repeatedly and I think Neal echoed in some of his comments just a minute ago was the sense that you need to actually demonstrate that you're taking these concerns seriously and doing something about them. I think the fact that we have recommendations for vaccines and people have a perception that they've been harmed in some way and nobody cares about harm is really a big part of the problem. So I think that as these various studies get sketched out, I think we all need to know what they are. So that when people ask us, they say, "Well, what are you doing about it?" that we can be very clear about all that's going about it. There's a lot going on already. We've highlighted a number of things that are deficit, but I think we also have to be clear that all of this is going on because, though this is the information age, we'll never have complete information. We're always going to live in some sort of uncertainty and I'm sure that nobody would have ever dreamt that this would have been the issue of the day and now we see all the gaps in this. So I think as we begin to move along, there will be other things like that and we always recognize that there are more things to fill in, and I think what we're doing about those is something that we have to communicate quite vigorously.

DR. RABINOVICH: Plotkin?

DR. PLOTKIN: Well, as this meeting draws to a close, we're talking about perceptions, perceptions of danger and so on, I must say that I'm reminded of Alice in Wonderland. Now, I don't happen to remember the exact story, but at one stage I think Alice is talking about a situation and she says, "Well, we'll have a trial and then we'll have a sentence." And the Red Queen says, "No, first the sentence and then the trial." So, you know, it strikes me that a perception has certainly been created through the change in the vaccine schedule and so on and that there is a real problem. Now, after these two days, I must say

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that I'm actually less sure that there is a problem while I was when this meeting started. I do have to repeat my comment that I think this meeting should have been held sometime ago before the announcements.

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

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

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

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

(LAUGHTER)

Dr. Myers and I will develop a summary that will be published in MMWR. We'll have to call on some of you to clarify and make sure that we don't write something that is either unintelligible or incorrect. So we'll be calling on you for your help.

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

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

The regulation issues, I raise a question of timing in the sense that any new product or change in formulation is substantial in terms of new studies that will be needed and this is a process that will be gradual and take place over a period of years. Dr. Clements gave the timetable. Dr. Paradiso added to that, but, certainly, in terms of finding the preservative, the clinical trials for the products containing that preservative, the regulatory issues in terms of approval and, subsequently, reformulation, we're probably talking about a minimum of five years before new preservative preparations are on the market. And that may be, give or take, two or three years.

In terms of Thimerosal, by either spelling, it works and has worked for these many years and one can at least have some confidence that disasters have not occurred to our knowledge from such usage, but the toxicity data are limited. And what has been presented to us by our colleagues in toxicology is that the data on methylmercury has been used in the assessment of risks associated with ethylmercury and the toxicity profile of the two compounds should be considered to be similar so that, even though it may be a stretch that ethyl and methyl are similar, the absence of information dictates what we need to use the data about methyl at least is a starting point and surrogate for our discussions.

In terms of Thimerosal, again, that it's not the amount of the preservative in each vaccine, but it's now with the burst of new product and the cumulative amount of mercury that is present that has raised the concern. I think most important is the words "eliminate/reduce" and that the perception should be, particularly keeping in mind the timetable of years, that our goal is to achieve elimination but first reduction and that those terms always be used in a paired fashion and that the gradual changes, rather than precipitous changes, is a reality.

Finally, we talked a lot about delivering the message and I think that's an increasing part of our decision making, and at anytime we do come to a change in current policy, we need to anticipate the reception of that change among caretakers, physicians, health care workers, parents, consumer advocates, legislators, manufacturers, and particularly, I think, our role as a leader in these discussions throughout the world.

So every action will have a reaction. I think a lot of the discussion yesterday about the action that was taken in changing the schedule of the hepatitis B vaccine from birth bears on that, making sure that that message and the reason for the change is delivered to those who are actually responsible for the change, the hospitals in altering their policies are cognizant of the reasons for the changes, that the clinics understand that any gaps that would be created.

I think Bob Down's data and the CDC data that suggest that that first immunization in the nursery is very important in subsequent vaccine utilization by selected families leads us to believe that delivering the message and the caretaker's delivering the message to the parents becomes a very critical part in decision making.

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

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

(Conclusion of Workshop at approximately 3:14 pm)

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