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

convenes

**THE NATIONAL VACCINE ADVISORY COMMITTEE  
SPONSORED WORKSHOP ON THIMEROSAL VACCINES**

**DAY ONE - VOLUME I  
AUGUST 11th, 1999**

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1 across the street, which has a much larger cafeteria  
2 than is in this building.

3 Thimerosal has been used as an additive to a number of  
4 biologics since the 1930s, including some vaccines  
5 routinely recommended for use in young children.  
6 Because of multiple doses of vaccine, it is possible  
7 that some children could be exposed to a cumulative  
8 level of mercury that exceeds guidelines for  
9 methylmercury.

10 Nationally and internationally, manufacturers and  
11 regulatory agencies are working to replace or reduce  
12 thimerosal-containing vaccines.

13 The purpose of this workshop is to review the pertinent  
14 data on thimerosal: its use; its potential for  
15 toxicity; and steps that can be taken to increase the  
16 margin of safety, especially during the period of  
17 transition to greater availability of vaccines without  
18 thimerosal or with reduced thimerosal.

19 It's very -- It's important to discuss, as we discuss  
20 these issues, to balance these with the very real risks  
21 of disease resurgence if we have a reduction in vaccine  
22 utilization or a loss of confidence in vaccines.

1 We're a very diverse group of people here today, but  
2 let me say that the primary audience to whom this  
3 information is directed, the members of the Federal  
4 Advisory Committees that relate to vaccines. These  
5 include the National Advisory -- National Vaccine  
6 Advisory Committee that is sponsoring the workshop, the  
7 Advisory Committee on Immunization Practices, the  
8 Vaccines and Related Biologic Products Advisory  
9 Committee, and the Advisory Commission on Childhood  
10 Vaccines.

11 The workshop is convened specifically for the exchange  
12 of information. It is not a policy meeting nor is it  
13 designed to provide advice.

14 I'd like to say a little bit about the format of what  
15 we're trying to do today. The first is, we're going to  
16 talk about thimerosal, why we have preservatives in  
17 vaccines and some of the issues that surround the  
18 inclusion and experience of now over sixty years with  
19 thimerosal.

20 Then we're going to talk about organomercurials, both  
21 thimerosal as an organomercurial-containing additive as  
22 well as organomercurials in general.

1 We're going to end the afternoon talking about  
2 potential disease impact of the diseases that are --  
3 the vaccines that would be primarily affected during a  
4 transition to a reduced thimerosal vaccine supply.  
5 Tomorrow we're going to talk about the transition to a  
6 greater supply of thimerosal-free vaccines in reduced  
7 thimerosal-containing vaccines. We're going to talk  
8 about issues that relate to the manufacturer and  
9 regulatory activities, the European initiative, and  
10 then we're going to talk about the transitional vaccine  
11 options, the flexibility within the recommended  
12 schedule.

13 At that time, we're going to -- we have a number of  
14 groups and individuals who would like to participate by  
15 giving their perspectives on these options. We have  
16 allowed time in that session for others who would like  
17 to give their perspective on this, as well. We didn't  
18 know how much time to allow. We have limited time. We  
19 have a very full agenda for the next couple of days.  
20 So if there are individuals or groups that would like  
21 to give a perspective on this, if they'd put together a  
22 one- or two-sentence summary, we've asked Dr. Modlin,

1 who is going to be our moderator tomorrow, to triage  
2 these and work that last minute changes on the agenda.  
3 And then, finally, many of us feel that  
4 the -- one of the most important parts of this meeting will  
5 occur at the end, which is a discussion of knowledge  
6 gaps that exist.

7 We've tried to ensure a discussion time after each  
8 presentation, and speakers have been asked to limit  
9 their talks to allow five or ten minutes of discussion.

10 To use the microphones, the individual microphones at  
11 your seats -- I've got to read this here, and it's  
12 tough with bifocals -- you need to depress the "Request  
13 to Talk" button, and red and green lights will come on,  
14 and that means that the microphone is on, and then you  
15 depress it again to turn it off, and both lights will  
16 go off. We'll ask our moderators to triage the  
17 questions and also to keep us focused and on time.  
18 Dr. Georges Peter, who is Chair of the National Vaccine  
19 Advisory Committee, asked me to extend his sincere  
20 regrets at his inability to be here today and to  
21 express his appreciation to Dr. Klein for serving as  
22 both a convener and rapateur (sic).

1 Dr. Harry Greenberg will be our moderator today. Dr.  
2 Greenberg is the Chair of the VERPAC. Dr. John Modlin  
3 will be our moderator tomorrow, and he is the Chair of  
4 the ACIP. Again, they're going to make every effort to  
5 keep us on time.

6 We are going to develop proceedings from this meeting.

7 Therefore, even though everybody knows you in the  
8 room, if that's the case, please tell us who you are  
9 and your affiliation, so our transcriber will be able  
10 to put that together.

11 So, with no further ado, I will ask Dr. Klein to  
12 convene the meeting.

13 **DR. KLEIN:** Thank you, Dr. Myers. It's a privilege to  
14 be a participant in this very -- what I anticipate will  
15 be a very informative experience for all of us. I  
16 think we start out with a relatively limited base of  
17 information about organomercurials and, particularly,  
18 about concerns for these products in vaccines.

19 The specific issue of thimerosal is one that is -- has  
20 history of about sixty years. Its use as preservative  
21 in biologics and pharmacologic preparations goes back  
22 to the 1930s, and it is present, or has been present,

1 not only in vaccines, but in various cosmetics, contact  
2 lens solutions. So its use as a preservative goes  
3 beyond the specific area of vaccines.

4 Thimerosal is an ethylmercury salt, and it's important  
5 to keep the distinction about the disasters that have  
6 occurred with mercury with which we are familiar from  
7 the paucity of information about any harmful effects of  
8 ethylmercury, but we'll hear more about that.

9 Thimerosal is present in some but not all vaccines.

10 Most of the viral vaccines do not have thimerosal.

11 Both the oral and inactivated polio vaccines do not.

12 Measles/mumps/rubella does not. Varicella vaccine does  
13 not. Rotavirus, hepatitis A, and Lyme disease vaccines  
14 all do not preservatives. They don't have thimerosal.

15 Thimerosal is present in some but not all DTP and DTaP

16 preparations. Some of the hepatitis immune -- I'm

17 sorry -- amphophilous influenza B, polysaccharide

18 conjugate vaccine, the benignococcal and pneumococcal

19 polysaccharide vaccines, as well as hepatitis B. And

20 there will be more discussion about the focus of

21 changes for hepatitis B vaccine.

22 This product is antibacterial and prevents, as well as

1 may treat, infectious agents that are present in these  
2 various products. The antibacterial activity is  
3 related to release of ethylmercury after spontaneous or  
4 enzymatic breakdown of thimerosal into ethylmercury and  
5 thiosalicylate. It is bactericidal at acidic pH. It  
6 is bacteriostatic and fungistatic at alkaline or  
7 neutral pH.

8 The most frequent adverse events that have been  
9 identified with thimerosal are those of a  
10 hypersensitivity reaction, papular or vesicular  
11 disruptions. Some of the solutions for contact lenses  
12 have caused eye irritations.

13 It is methyl, not ethyl, toxicity that has been  
14 associated with the well-known events in Minamata,  
15 Japan, resulting from the contamination of fishing  
16 waters in the area and the severe consequences for  
17 people in that area.

18 Use of methylmercury has been as a fungicide, and the  
19 mistaken use in preparation of homemade bread rather  
20 than grain for planting in Iraq led to many -- severe  
21 morbidity and mortality.

22 In contrast then, thimerosal is ethylmercury; and to

1 underline, there is no evidence of harm from the  
2 amounts of mercury administered to infants and children  
3 in vaccines.

4 I think what we'll learn from this experience in the  
5 next two days I've categorized in six areas.

6 One, the use of preservatives in vaccines, are they  
7 necessary? Are they necessary for specific products?  
8 Are there are substitutes that can be made if they are  
9 necessary for the thimerosal that is now used?

10 Two, we'll talk specifically about mercury and the  
11 pharmacokinetics and toxicology in animals as well as  
12 some human data.

13 Three, the impact, and there will be considerable  
14 discussion later today on any issues that arise that  
15 may limit public confidence in vaccines and alter our  
16 current success in immunization program.

17 Four, what are the current plans to reduce or eliminate  
18 thimerosal in vaccines?

19 Five, the pragmatic issues about what to do during the  
20 transition from the current roster of vaccines that do  
21 contain thimerosal to a thimerosal-free vaccine,  
22 period.

1 And then finally, a review of appropriate priorities  
2 for research in these areas.

3 So I anticipate an educational experience for all of  
4 us.

5 To begin this morning's program, I'd like to introduce  
6 the moderator for the morning session, Dr. Harry  
7 Greenberg, who is Senior Associate Dean for Research at  
8 Stanford University and Chief of Staff of Research at  
9 the Palo Alto VA.

10 Dr. Greenberg.

11 **DR. GREENBERG:** Thank you, Dr. Klein, and thank you all  
12 for coming. I see my role as sort of the heavyweight,  
13 or bad guy, and I've been advised that I have the  
14 privilege of yanking anybody I want off the stage if  
15 they talk too long. I will tell all the speakers that  
16 there's an incredible little button up here that will  
17 eject you if you go beyond twenty-five minutes. And if  
18 it doesn't function, I will eject you.

19 The purpose, I think Dr. Myers really hit the nail on  
20 the head when he said the main purpose of this meeting  
21 is to get all of us on the same page as far as our  
22 database as to what the issues are here, and I look

1 forward to a very, very informative meeting.  
2 We're ahead of time, and maybe we'll be able to keep  
3 ahead of time during the meeting, but if, by chance,  
4 that doesn't occur, like it never does, I may have to  
5 cut off some of you who I am sure have the most  
6 important question to ask. It is nothing personal, but  
7 I will use my prerogative to keep the meeting on time.  
8 And so, trying to keep it -- keep on schedule, I'd like  
9 to introduce the first speaker, who is Dr. William  
10 Egan, Acting Director, Office of Vaccine Research and  
11 Review at CBER, FDA, and he's going to start off that  
12 first session that we're talking about: Where Are We  
13 Now: A Review of the Data -- Thimerosal in Vaccines.  
14 His perspective is from the FDA.  
15 Bill? First, I'm starting his time. Instruction is on  
16 your time.

17 (LAUGHTER)

18 **DR. EGAN:** Okay. Thank you very much. We'd like to  
19 thank you, Dr. Myers, for the opportunity to come here  
20 and say a few words about preservatives in a FDA  
21 perspective.

22 Let me begin by relating one incident that's described

1 in Sir Graham Wilson's classic book, "The Hazards of  
2 Immunization." It goes:

3 "In January, 1928, in the early stages of an  
4 immunization campaign against diphtheria, Dr. Ewing  
5 George Thomson, Medical Officer of Health at Bundaburg,  
6 in Australia, began the injection of children with  
7 toxin-antitoxin mixture. The material was taken from  
8 an India rubber-capped bottle containing 10 mLs of the  
9 toxin-antitoxin mixture. On the 17th, 20th, 21st, and  
10 24th of January, Dr. Thomson injected subcutaneously a  
11 total of twenty-one children without ill effect.  
12 On the 27th, a further twenty-one children were  
13 injected. Of these children, eleven died on the 28th  
14 and one on the 29th."

15 The death of these twelve children was investigated by  
16 the Royal Commission, and the final sentence in the  
17 summary of their findings reads as following:

18 "The consideration of all possible evidence concerning  
19 the deaths at Bundaburg points to the injection of  
20 living staphylococci as the cause of the fatalities."

21 As Sir Graham Wilson also notes in his book, staph  
22 toxin was very likely also present in the bottle, thus

1 accounting for the rapid deaths of the children.  
2 Obviously, the bottle became contaminated on the 24th  
3 of January, the bacteria multiplied, toxin was  
4 produced, and the bacteria then injected into the  
5 children on the 27th.

6 Among the recommendations of the Royal Commission is a  
7 very important one, that biological products in which  
8 the growth of a pathogenic organism is possible should  
9 not be issued in containers for repeated use unless  
10 there is a sufficient concentration of antiseptic to  
11 inhibit bacterial growth.

12 The number of similar examples of bacterial  
13 contamination, either during manufacturing or during  
14 product use, are detailed in Sir Graham Wilson's book,  
15 "The Hazard of Immunization." And, sadly, many  
16 additional examples of the consequences of bacterial  
17 contamination have been revealed since the publication  
18 of that book.

19 However, from these disasters, these and similar  
20 disasters, have arisen the regulations that require  
21 preservatives in multi-dose, multi-entry containers of  
22 biological products. Indeed, if I may offer a general

1 comment, many of the requirements that now exist for  
2 biological products have arisen not from foresight, but  
3 from mishaps.

4 The U.S. Code of Federal Regulation contains a  
5 requirement for preservatives in multi-dose containers.

6 This requirement was placed into the Code of Federal  
7 Regulations in January of 1968, although biological  
8 products had contained preservatives, including  
9 thimerosal, prior to this date. Indeed, Eli Lilly had  
10 thimerosal in their diphtheria toxoid vaccines in the  
11 1930s.

12 Specifically, the CFR states that: "Products in multi-  
13 dose containers shall contain a preservative, except  
14 that a preservative need not be added to Yellow Fever  
15 Vaccine; Polio-Virus Vaccine, live oral; viral vaccine  
16 labeled for use with the jet injector; dried vaccines  
17 when the accompanying diluent contains a preservative;  
18 or to an allergenic product in fifty percent or more in  
19 volume of glycerine."

20 The CFR also requires that a preservative that is used  
21 shall be sufficiently nontoxic so that the amount  
22 present in the recommended dose of the product will not

1 be toxic to the recipient, and in combination used it  
2 shall not denature the specific substance in the  
3 product to result in a decrease below the minimal  
4 acceptable potency within the dating period when stored  
5 at the recommended temperature.

6 The CFR does not specifically address the use of  
7 preservatives in single-dose containers. Currently,  
8 some single-dose presentations contain preservatives.  
9 Some do not. In the past, it was thought that single-  
10 dose containers, like multi-dose containers, should  
11 contain preservatives, the rationale being that the  
12 addition of a preservative during the manufacturing  
13 process or during the filling operation served to help  
14 ensure that the product was free of microbial agents  
15 and their toxins.

16 Indeed, at the International Symposium on Preservatives  
17 in Biological Products held twenty-five years ago, in  
18 San Francisco -- This was under the auspices of the  
19 IABS -- Dr. Edward Seligman, Jr., at that time the  
20 Director of the Bureau of Biologics Division of Product  
21 Quality Control, had the following comment:

22 "Because of the numerous complex processing stages in

1 the manufacture of biological products, good  
2 manufacturing procedures include the addition of  
3 preservatives early in the manufacture of many types of  
4 products to aid in preventing contamination during  
5 production. Even if products are sterilized by  
6 filtration prior to filling into final containers,  
7 contamination during earlier stages can result in  
8 soluble products that alter the purity of the product,  
9 increase toxicity, and result in pyrogens, all of which  
10 cannot be removed without alteration of the product  
11 itself."

12 Now, today, GMPs are viewed differently, and it would  
13 be argued that a well-controlled process does not  
14 require the addition of a preservative to ensure  
15 sterility. However, I think at this point, it's  
16 worthwhile noting that sterility is not an absolute  
17 term. Sterility does not mean zero microbial organisms  
18 in one hundred percent of the containers.

19 Let me show some data that was presented by Koerner and  
20 Kindt from the (inaudible) in Germany at this symposium  
21 twenty-five years ago. Well, this is filling data, so  
22 number of lots that were filled and the percentage of

1 non-sterile filling lots. And with no preservatives in  
2 ampules, 5.6 percent of the lots were found to be non-  
3 sterile. This is using the test that's in the CFR.  
4 For multi-dose containers, somewhat better, 2.2  
5 percent. And even when preservatives were used, if we  
6 look at the ampules, the number of lots that were  
7 rejected went from 5.6 to 4.4 with phenol, to 2.1 with  
8 an organomercurial. In the multi-dose containers, it  
9 went from 2.2 down to 0.3 with phenol and 0.8 with the  
10 organomercurial.

11 While formaldehyde was in there, they rejected  
12 seventeen percent of the lot. This was not  
13 statistically different than the 5.6, the small  
14 numbers. The numbers in parentheses refer to the  
15 number of lots rejected over the total number of lots  
16 that were examined.

17 And even in the -- with no preservatives, with the  
18 multi-dose containers with some residual formaldehyde,  
19 it was the same as no preservative. Formaldehyde does  
20 nothing.

21 The reason I show these data is simply to point out  
22 that even with the preservatives, there was still a

1 number of lots that were rejected because of issues of  
2 stability.

3 Now, today, these numbers are significantly lower, and  
4 if manufacturers would, you know, would do media fills  
5 to test the -- you know, the filling, and we're looking  
6 at numbers like one in ten to the three or one in ten  
7 to the four containers that might have microbial  
8 growth.

9 However, I point this out simply to say that the  
10 numbers will not be zero and the risk of no  
11 preservative will be slightly greater than with the  
12 preservative. No matter how small they are, the  
13 numbers are not zero. There may be some discussion  
14 later on this point.

15 Now, I've spoken for the past nearly ten -- five, ten  
16 minutes about preservatives, but have yet to say what a  
17 preservative is and what precisely we expect a  
18 preservative to do. If I may come back and quote Dr.  
19 Seligman again, he mentioned that the sole reason for  
20 adding a preservative is to protect the recipient.  
21 Thus, a preservative must be able to protect the  
22 recipient from the consequences of inadvertent

1 microbial contamination while at the same time being  
2 nontoxic to the recipient and not denaturing the  
3 product.

4 Sodium azide is a good preservative, but its use in  
5 (inaudible) would not be allowed because of toxicity.  
6 Thimerosal is a good preservative, but not for IPV. It  
7 inactivates the vaccine. Hence, we have the  
8 regulations that I showed before, that a preservative  
9 must be nontoxic and must not denature the particular  
10 substance.

11 But what needs a preservative to do? Obviously, as  
12 I've said, a preservative must prevent the consequences  
13 of inadvertent contamination by microorganisms  
14 introduced during use of the product.

15 However, does this mean that a preservative must be  
16 bactericidal or fungicidal, or is it sufficient that  
17 the preservative assure microbial stasis? And whether  
18 a preservative should be cidal or simply ensure stasis,  
19 we need to ask as well, against what organisms, at what  
20 levels, and if a preservative must be cidal, how  
21 rapidly. These issues are not addressed in the Code of  
22 Federal Regulations.

1 Now, under proper conditions of storage, usually  
2 refrigerated, and with good medical practice, the  
3 extent of potential inadvertent contamination should be  
4 minimal. The number of -- The number of the types of  
5 potentially contaminating organisms is quite large, and  
6 there are long lists in various texts on preservative  
7 and stabilities. And there could be and there has been  
8 considerable argument regarding which organisms a  
9 preservative should be able to exclude. However, if we  
10 look at past examples, past tragedies, that list would  
11 certainly include the staphylococci and streptococci.  
12 Now, preservatives are also discussed in the United  
13 States Pharmacopeia, and the USP regards antimicrobial  
14 preservatives as substances added to dosage forms to  
15 protect them from microbial contamination. They are  
16 used mainly in multi-dose containers to inhibit the  
17 growth of microorganisms that may be introduced  
18 inadvertently during or subsequent to the manufacturing  
19 process.

20 The USP further states that any antimicrobial agent may  
21 exhibit the protective properties of a preservative.  
22 However, all useful antimicrobial agents are toxic

1 substances. For maximum protection to the consumer,  
2 the concentration of the preservative should be  
3 considerably below the concentrations of the  
4 preservative that may be toxic to human beings.  
5 These discussions of a preservative that are in the USP  
6 are thus quite similar to those in the CFR. The USP,  
7 however, does provide a functional definition of  
8 preservative, whereas the CFR does not.

9 I should add also that the USP tests a preservative  
10 only in the original unopened container in which the  
11 product was distributed by the manufacturer. So it's  
12 not a preservative, per se, as an entity, but only that  
13 entity in a specific product.

14 Now, an ample number of examples may be found in  
15 literature wherein a substance at a particular  
16 concentration functions as a preservative, per the USP  
17 definition, for one biological product but fails in  
18 another. For example, a preservative at a -- a  
19 material at a particular concentration may be a good  
20 preservative for a vaccine, but in a blood product or  
21 in serum does not function -- does not function, does  
22 not meet the USP requirements.

1 Now, let me outline briefly the USP definition of  
2 "preservative." It's a functional definition wherein a  
3 specified amount of the product is challenged with a  
4 known quantity -- Actually, 0.1 milliliters of  
5 approximately  $10^5$  to  $10^6$  per ml of the following  
6 organisms, or spores: candida albicans, aspergillus  
7 niger, escherichia coli, staphylococcus aureus, and  
8 pseudomonas aeruginosa, and it specifies the strains  
9 from the American-type culture collection.

10 The test sample is incubated at 20 to 25 degrees, and  
11 the number of viable organisms determined on days 7,  
12 14, 21, and 28. And a preservative is then acceptable  
13 if bacteria are reduced to less than 0.1 percent of the  
14 challenge dose by day 14; yeast and mold remain at or  
15 below the initial inoculum on day 14, and the number of  
16 organisms -- This should be on day 28 -- are the same  
17 or below that on the day 14 level.

18 Now, for bacteria, the USP definition is a bactericidal  
19 one. For yeast and mold, the definition is one of  
20 stasis. Although the choice of challenge organisms  
21 might be argued, most people would agree that the USP  
22 challenge assay is quite stringent in that the

1 challenge doses are much greater than might ordinarily  
2 be expected to occur through inadvertent contamination  
3 during use. Thus, a preservative, as defined by the  
4 USP, provides a large margin of safety.

5 Now, the question may be raised whether the term  
6 "preservative" as used in the CFR is defined as per the  
7 USP. In other words, must we take the USP definition?

8 The preservative that is in the CFR is a preservative  
9 as defined in the USP.

10 The simple answer to this question is no. A material  
11 that does not meet the USP requirements may still be  
12 deemed by CBER to satisfy the CFR requirements for a  
13 preservative. Although a material satisfying the USP  
14 definition will certainly be acceptable as a  
15 preservative, other definitions are possible.

16 However, if a different set of requirements are to be  
17 met -- different organisms, different concentrations,  
18 different times to kill, et

19 cetera -- then the rationale for their use must be presented  
20 to CBER for approval in the products.

21 Now, we're at the workshop today to discuss thimerosal  
22 and its reduction and removal -- well, removal from

1 existing products. This will entail switching to  
2 single-dose vials without preservatives or using  
3 single-dose and multi-dose vials with different  
4 preservatives. Such changes may constitute a change in  
5 formulation of the product. Dr. Baylor, in his talk  
6 tomorrow, will discuss how CBER will handle these  
7 product formulation changes from a regulatory point of  
8 view.

9 A little later in this talk -- in this session, Dr.  
10 Ball from FDA will be discussing the vaccines that  
11 contain thimerosal, the content of thimerosal in those  
12 vaccines, and the guidelines that are now existing  
13 regarding mercury intake, and I believe that Dr.  
14 Plotkin will be following me and presenting some data  
15 on alternative preservatives.

16 Okay. Nineteen minutes, Harry. You got one extra  
17 minute.

18 **DR. GREENBERG:** Thank you, Bill. Stay up here because  
19 we have some time for some questions. I'd like to  
20 thank you for an excellent talk.

21 Can I ask the first question? I assume that thimerosal  
22 or thimerosal --

1 DR. EGAN: Actually, one's used -- one is the term used  
2 in Europe, the other is the term used in the U.S..  
3 They're the same chemical.

4 DR. GREENBERG: Good.

5 DR. EGAN: Next question.

6 (LAUGHTER)

7 DR. GREENBERG: I assume that that fits under the USP  
8 definition.

9 DR. EGAN: Yes.

10 DR. GREENBERG: Okay. Do we have any questions for Dr.  
11 Egan? You have a little mic in front of you that  
12 you're supposed to -- Yes, you're on. Neal, you're  
13 Number 8-A.

14 DR. HALSEY: Two questions, one -- the first one is,  
15 does that USP --

16 DR. GREENBERG: Could you stand up and identify  
17 yourself to the audience?

18 DR. HALSEY: Neal Halsey, John Hopkins University.

19 DR. GREENBERG: Then you can sit down.

20 (LAUGHTER)

21 DR. GREENBERG: I'm learning as we go along here.

22 DR. HALSEY: All right. Two questions. The first one

1 is: Does the USP test, the pharmacopeia test, require  
2 the product to be used -- that preservative to be  
3 tested in the final product, and is this being --

4 **DR. EGAN:** Yes.

5 **DR. HALSEY:** -- because of the -- If you might address  
6 the issue of the contamination of DTP with Group A  
7 strep, and Group A strep is not one of the organisms  
8 which you mentioned back there, but the basis for why  
9 that doesn't work as perfectly as we would like to,  
10 because there are multiple reports of clusters of those  
11 cases, and I have always assumed it was because of the  
12 particular matter that was in DTP that may have played  
13 a role in helping protect it.

14 The second question has to deal with the definition  
15 under the USP and whether it's your understanding in  
16 terms of the safety, and I don't have the words in my  
17 head exactly, but the toxicity for the recipient must  
18 be considerably below that that might be toxic, is the  
19 sort of language that you used. Is your interpretation  
20 of that definition with regard to thimerosal, does the  
21 current concentrations fall within that safety  
22 guideline or they exceed that safety guideline?

1 **DR. EGAN:** Okay. Let me try the first question first.

2 That related to the USP definition about whether it  
3 corresponds to the preservative in the material, and  
4 the answer to that question is yes. So, in other  
5 words, they take the final dosage formulation and then  
6 it's challenged with those five -- those five  
7 organisms.

8 Your second question was --

9 **DR. GREENBERG:** Bill, I --

10 **DR. EGAN:** Yes?

11 **DR. GREENBERG:** Neal, it seems to me that your second  
12 question is the purpose of this meeting. So rather  
13 than, in the first speaker, trying to -- I think maybe  
14 you'd be wise to ask that question at the end of the  
15 meeting.

16 Now, any other questions?

17 **DR. McINNUS:** Pamela McInnus, NIAID. I'd like some  
18 clarification following this first talk: Are we moving  
19 forward with this workshop on the basis that available  
20 data do support the decision to reduce and eliminate  
21 thimerosal? Is that up for discussion at all, or is  
22 that decision made and is nonretractable?

1       **DR. EGAN:** Okay --

2                               (LAUGHTER)

3       **DR. EGAN:** Well, let me speak for myself personally,  
4       and I believe that we -- you know, we, i.e., FDA, have  
5       made that decision to -- whenever possible, to  
6       eliminate thimerosal from products. We have asked  
7       manufacturers and sponsors in the development of their  
8       products to develop them without thimerosal; and if  
9       they're not able to do that, to specifically explain  
10      why.

11      So the use of thimerosal as a preservative is no long  
12      the default option.

13      And, you know, we did send out a letter earlier -- sent  
14      out a letter this summer again asking manufacturers and  
15      sponsors for their plans to reduce -- reduce or  
16      eliminate thimerosal in their products. So I think  
17      that's where we're heading. I'm not sure where the --  
18      this workshop will be headed.

19      **DR. GREENBERG:** Pam, I would like to say, also I think  
20      your question, at least for me, who is less well-  
21      informed than many of you, that part of the purpose of  
22      this meeting is to get a database in front of all of us

1 at the same time and then potentially to re-evaluate  
2 decisions that were made, but at least to have a very  
3 broad and deepening airing of available information so  
4 that your question can be answered in a scientific way.  
5 Any other questions? In the back?

6 **DR. CORDERI:** José Corderi, CDC. Bill, what  
7 preservatives are now available, other than thimerosal,  
8 that would meet the USP definition for preservative?

9 **DR. EGAN:** For the common childhood vaccines, the only  
10 one that I'm aware of that -- in the product  
11 formulations that is used is 2-phenoxyethanol.

12 **DR. CORDERI:** Any others?

13 **DR. EGAN:** Not that I'm aware of in the childhood  
14 vaccines. In anthrax, for example, there's  
15 benzalkonium chloride, which is an ammonium salt. I  
16 don't think we have phenol in any of the vaccines  
17 anymore, but I would have to go back and check that  
18 specifically for all of them.

19 **DR. GREENBERG:** Other questions?

20 (NO RESPONSE WAS HEARD)

21 **DR. GREENBERG:** If not, I'd like to thank you, Bill.  
22 And we are -- I'm going to get all of you home early.

1 The next speaker is Dr. Stanley Plotkin, who is now the  
2 Medical and Scientific Advisor to Pasteur Mérieux  
3 Connaught, and he is going to be talking to us about  
4 preservatives, the manufacturer's perspective.

5 **DR. PLOTKIN:** Well, Harry, first of all, let me stress  
6 that this talk does not represent the view of the  
7 entire manufacturing industry. I have not canvassed  
8 manufacturers' views and I would not presume to speak  
9 for them. This is my view, reflecting experience both  
10 in academic vaccine development and as a consultant to  
11 one manufacturer.

12 Indeed, after I am done speaking, manufacturers in  
13 general, and Pasteur Mérieux Connaught, in particular,  
14 may choose to disavow what I have to say.

15 (LAUGHTER)

16 **DR. PLOTKIN:** Vaccine manufacturers -- Vaccine  
17 manufacture is, as it should be, a highly regulated  
18 industry, designed to produce safe and effective  
19 vaccines. Like many of you, I first became aware of a  
20 perceived crisis with respect to thimerosal at the time  
21 of the ACIP meeting late in June through communications  
22 concerning a meeting held at the FDA.

1 Subsequently, there was an urgent meeting called by the  
2 American Academy of Pediatrics on June the 30th, at  
3 which it was announced that there was an emergency  
4 based on concerns about the presence of thimerosal in  
5 pediatric vaccines.

6 This was puzzling, as thimerosal has been used for at  
7 least fifty years, and, therefore, I expected to hear  
8 new data concerning its effects. At the end of the AAP  
9 meeting, I was largely disappointed. Nevertheless,  
10 there were some salient points that emerged from that  
11 meeting.

12 First, that the FDA and the EPA were apparently not in  
13 agreement with each other in regard to the guidelines  
14 for mercury exposure.

15 Second, that if the EPA guidelines were assumed to be  
16 preferable, some infants might receive a combination of  
17 vaccines with sufficient mercury to exceed those  
18 guidelines.

19 Third, that a small uncontrolled study, published only  
20 in abstract, showed significant blood levels after  
21 neonatal hepatitis B vaccination.

22 Thus, three changes had taken place with respect to the

1 use of thimerosal. First, the perception of danger,  
2 experience with methylmercury exposures, and increasing  
3 environmental concerns led the EPA to issue strict  
4 guidelines with respect to mercury exposure. These  
5 guidelines were designed to provide a margin of safety  
6 based on the available data concerning toxicity of  
7 methylmercury.

8 As various guidelines had been proposed, one could  
9 calculate differently the allowable mercury ingestion,  
10 and Leslie Ball, I believe, will later give these  
11 different calculations.

12 So here we have a situation of apparent disagreement  
13 between agencies and where industry may have been  
14 following a guideline that could be abandoned or  
15 altered.

16 It is important to understand, as I learned, what is  
17 meant by a guideline. The statement on this slide is  
18 from the recent EPA report which explains how the  
19 guideline was chosen. Now, I don't know that I should  
20 read this, but the point is that calculations were  
21 based on a hair concentration conversion to blood  
22 levels, and these were a blood level of 11 -- I'm sorry

1 -- of 44 micrograms per liter of blood; hair  
2 concentration you can read; and then an uncertainty  
3 factor of 10 was used to derive the acceptable dose,  
4 which was thought to be safe. It was stressed that  
5 this reference dose is likely to be without appreciable  
6 risk of deleterious effects during a lifetime.  
7 Exceedence (sic) does not mean that risk will be  
8 present.

9 There is an impression of a certain arbitrariness in  
10 the choice, but, of course, a choice must be made. All  
11 of us would like more data. And as science advances,  
12 we must be prepared to change the regulations in  
13 recognition of new data. I trust that we shall see  
14 these new data later in this meeting.

15 The second change is the increasing number of licensed  
16 vaccines recommended for infants. While some of us  
17 perceive that as a good thing, the concern is that this  
18 development may be associated with an accompanying  
19 increase and exposure to thimerosal. I would point  
20 out, however, that thimerosal containing DTaPs have the  
21 same concentration of thimerosal as whole cell DPTs, so  
22 there was no change there.

1 In single-dose presentations, HIB vaccines do not  
2 contain thimerosal, and IPV does not contain  
3 thimerosal. So the only significant addition is  
4 hepatitis B vaccine.

5 The third change, indeed, involves the hepatitis B  
6 vaccine, which we all know is recommended in infancy as  
7 the best way of preventing later infection, cirrhosis  
8 and liver cancer, as has been amply proved in other  
9 countries. The birth dose was recommended as a way of  
10 reducing the number of injections in two- four-, and  
11 six-month-old children, which is itself caused by the  
12 problems that few combination vaccines have been  
13 licensed in this country, and that some of others may  
14 not have been screened for hepatitis B infection during  
15 pregnancy.

16 However, and I will -- Well, however, routine neonatal  
17 vaccination of premature infants was never recommended.

18 The Redbook recommendation here is that infants be  
19 allowed to reach two kilograms of weight before being  
20 vaccinated against hepatitis B, unless their mothers  
21 are hepatitis B carriers.

22 Let me now touch briefly on the data that formed the

1 basis of concern regarding thimerosal. I must start  
2 with a disclaimer that I am certainly not a  
3 toxicologist and would never presume to give an opinion  
4 concerning acceptable levels of mercury. However, I do  
5 have a fair amount of experience in evaluating  
6 scientific evidence.

7 Well, first of all, there are apparently no data to  
8 show that ethylmercury in the concentrations normally  
9 used in vaccines is harmful to infants. The available  
10 data concern methylmercury, and we are asked to  
11 extrapolate the metabolism and toxicity of the former  
12 from the latter, which, on the face of it, introduces a  
13 scientific uncertainty.

14 Second, with respect to methylmercury, it appears that  
15 there are only two large epidemiologic studies  
16 concerning methylmercury exposure, both occurring after  
17 eating fish, and they are in disagreement. The study  
18 in the Seychelles was reassuring in that chronic  
19 exposure of mothers to more mercury than is present in  
20 vaccines was not followed by abnormalities in children.

21 Whereas, in the Faroe Islands, perhaps because of  
22 binge eating of pilot whales or because of concomitant

1 ingestion of PCBs, subtle effects in learning  
2 correlated with blood levels of mercury. The blood  
3 levels, just to remind you, were on the order of 23  
4 micrograms per liter, with an interquartile range of  
5 13.4 -- It's a mistake on the slide -- to 41. The mean  
6 was 22, as I said, and 75 percent of infants had cord  
7 blood levels over 13 micrograms. Also noteworthy is,  
8 it appeared to me, that the hair mercury levels in the  
9 mothers were similar to those in the Seychelle study.  
10 So no data have been produced to suggest that  
11 vaccinated children have suffered from thimerosal  
12 toxicity aside from the allergic reactions already  
13 mentioned.

14 Admittedly, the effects found in the Faroe Islands  
15 exposure to methylmercury are subtle and might be  
16 missed by passive reporting. At least, however, one  
17 epidemiologic study done in the United Kingdom  
18 comparing scholastic achievement in pertussis-  
19 vaccinated children versus unvaccinated children, as  
20 quoted in the IOM report on adverse reactions to  
21 pertussis vaccine, show that vaccinated children were  
22 doing better in school, an effect that was attributed

1 to their parents being smarter.

2 (LAUGHTER)

3 **DR. PLOTKIN:** I mentioned -- It's true. I mentioned  
4 previously the study reported in abstract for memory in  
5 which blood levels of mercury were measured before and  
6 after neonatal hepatitis B vaccination in five full-  
7 term infants and fifteen premature infants. The post-  
8 vaccination blood levels averaged 7 micrograms in very  
9 low birth weight infants, compared to 2 to 3 micrograms  
10 in full-term infants. The mean gestational age of the  
11 premature infants is given in the abstract as 25 weeks.

12 This would mean the infants were mostly below a  
13 thousand grams in weight and should not have received  
14 the vaccine in the first place.

15 However that may be, a few percent of those prematures  
16 had peak blood levels in the range of cord bloods  
17 associated with learning defects in the Faroe Islands  
18 study. No pharmacokinetics follow-up was done, but the  
19 Emory data would seem to reinforce the earlier  
20 recommendation, not to vaccinate premature infants of  
21 very low birth weight.

22 Plus, there seems to be a paucity of data in the

1 literature to show that infants receiving ethylmercury  
2 accumulate mercury in excess of infants who are simply  
3 exposed to mercury in the environment.

4 Now, what are the responses of the manufacturers to  
5 this situation? First, well, it should be recalled --  
6 And Dr. Egan has already well covered this -- why  
7 thimerosal was introduced into vaccines in the first  
8 place -- I don't think I need to repeat that -- and it  
9 was chosen indeed because it is the best preservative  
10 available.

11 Many chemicals have been tested, and on the next slide  
12 we see a short list of the favorite ones: 2-  
13 phenoxyethanol, benzyl alcohol, phenol, cresol.

14 Each preservative must pass tests prescribed by the  
15 U.S. or European Pharmacopeia, as Bill Egan has already  
16 stressed. And he already pointed out that, although in  
17 real life situations, the preservative simply has to  
18 keep organisms from growing. When tested for  
19 regulatory approval they must show an ability to  
20 decrease the number of viable bacteria.

21 Now, I just wanted to show a few slides on comparisons.

22 Here we see a study that was done in the U.S. in 1981

1 in which we see that thimerosal actually in this test  
2 failed against staph aureus, failed against the USP  
3 criterion. 2-phenoxyethanol also failed against e.  
4 coli. In this particular test, phenol was the best.  
5 Two more recent studies done in Europe gave the  
6 following results. On these slides, "A" means  
7 fulfilling the Pharmacopeia's requirement, "B" means a  
8 slower killing effect than is stated in the  
9 Pharmacopeia, and "C" means stasis. "Inc" is  
10 incomplete.

11 So we see here in this comparison that thimerosal was  
12 the best. 2-phenoxyethanol mixed with formol was next,  
13 and let's say phenol and 2-PE were more or less the  
14 same.

15 And another comparison done by another manufacturer  
16 again shows thimerosal to be the better of the three,  
17 the best of the three, when you look at the As, Bs, and  
18 Cs.

19 Undoubtedly, new preservatives, or combinations of  
20 preservatives, are under study, but any sudden decision  
21 to eliminate thimerosal would create a number of  
22 potential problems. The first concern is that, at

1 least temporarily, vaccine available would be disturbed  
2 and vaccination delayed or omitted.

3 If physicians or state public health authorities insist  
4 on immediate access to thimerosal-free vaccines, chaos  
5 will ensue. This is not a commercial issue. Each  
6 manufacturer will have gains and losses in terms of  
7 marketshare. The overall loss is to the vaccine -- is  
8 to vaccination programs.

9 Second, there is the risk that substitute preservatives  
10 will not be as compatible with the vaccines or have  
11 less antimicrobial activity and, therefore, lead to an  
12 increased possibility of accidents.

13 In the absence of preservatives, filling of vaccine  
14 vials must depend more on aseptic filling. Although  
15 the technology for aseptic filling grows more and more  
16 sophisticated, as illustrated on this slide, which  
17 shows a filling apparatus in which the operator  
18 operates in a sterile atmosphere through these  
19 portholes -- although, as I say, this technology gets  
20 more and more sophisticated, it must be admitted that  
21 the absence of a preservative deprives us of a safety  
22 net to maintain sterility in later use.

1 Fourth, as thimerosal participates in the inactivation  
2 and detoxification of Bordetella pertussis in whole  
3 cell DTP, elimination of thimerosal would require  
4 reformulation and re-evaluation of the product.

5 Fifth, as influenza vaccine requires rapid production  
6 of large amounts of vaccine, elimination of a  
7 preservative will shift filling to single-dose vials  
8 and may slow or reduce influenza vaccine production.

9 Finally, if manufacturers must choose between preparing  
10 single-dose vaccines without preservatives and multi-  
11 dose vaccines with preservatives, thimerosal or other,  
12 in general, they are likely to privilege single doses  
13 and therefore reduce the availability of multi-dose  
14 vaccines. The effect on vaccination in the developing  
15 world may be dramatic, as I am sure John Clements will  
16 discuss. In the United States, we should not forget  
17 the effects of loss of multi-dose preservatives and  
18 multi-dose forms on the function of public health  
19 clinics and on the cost of vaccines.

20 The immediate response of manufacturers to this crisis  
21 atmosphere will be the usual one. They will respond as  
22 fast as possible to a perceived public health and

1 consumer demand. In this case, for thimerosal-free  
2 vaccine. As I understand the situation, HIB single-  
3 dose and IPV vaccines are already free of thimerosal,  
4 and hepatitis B vaccines free of thimerosal will soon  
5 be brought to the FDA for approval. DTaP is a mixed  
6 bag, but the manufacturers who use thimerosal will seek  
7 to bring single-dose preparations without preservatives  
8 to the FDA within months.

9 Much will depend on the attitude of the FDA regarding  
10 evaluation of existing data. For example, if removal  
11 of a preservative is considered to potentially alter  
12 stability, there will be delays while real-time  
13 stability studies are undertaken by manufacturers and  
14 then the results reviewed by the FDA. And, of course,  
15 we're looking forward to what Norm Baylor has to say  
16 tomorrow.

17 It is interesting that European regulatory authorities  
18 met to discuss this issue in April of this year, as  
19 many of their vaccines also contain thimerosal. A  
20 working group on thimerosal formed by the European  
21 Medicines Agency issued documents on the subject. Two  
22 of their statements are excerpted on the next slides.

1 As you can read: "For vaccination in infants, the  
2 use of vaccines without thimerosal should be  
3 encouraged. However, in order not to jeopardize  
4 vaccine supplies and immunization programs, it is  
5 advisable to introduce requirements for the elimination  
6 of organomercurials in vaccines on a gradual basis."

7 And another excerpt, the group concluded that  
8 thimerosal should not be banned from medicinal  
9 products; however, taking into account the identified  
10 and theoretical risks, precautionary measures should be  
11 considered. And the most desirable alternative they  
12 mention is preservative-free formulations.

13 It is important to stress that until now European  
14 countries that also used neonatal hepatitis B  
15 vaccination, such as France, Germany, and Italy, have  
16 not changed their recommendations. That includes  
17 Spain, which, like the U.S., recommends universal  
18 neonatal hepatitis B vaccination.

19 So, in summary, what is the manufacturers' view, in  
20 quotes, of the situation as interpreted by me. Frankly  
21 -- And I think it is important to be frank early in  
22 this meeting to promote a useful discussion -- I think

1 that FDA did not give manufacturers sufficient warning  
2 that thimerosal is no longer acceptable, that panic  
3 entered into the deliberations of the AAP, and that CDC  
4 was partly handcuffed by regulations that prevented  
5 adequate consultation with the ACIP.

6 The published evidence that the thimerosal contained in  
7 vaccines is dangerous is unconvincing. Nevertheless,  
8 manufacturers, like everyone else, would prefer to have  
9 a less controversial preservative. Many vaccines  
10 currently sold do not contain thimerosal. And even in  
11 the absence of any regulatory changes, new vaccines  
12 will not be manufactured with it. Yet, it remains the  
13 most active preservative and no equivalent substitute  
14 is available. Political concerns aside, it may be  
15 justified to keep in some vaccine formulations,  
16 particularly those in multi-dose preparations.

17 Beyond the factual scientific issues, the process of  
18 decision in this matter has been flawed. This meeting  
19 should have taken place before a public health decision  
20 or a public announcement was made. There should have  
21 been adequate consultation and discussion.

22 This point of view probably gives offense to some, and

1 I'm sorry that this should be the case as my remarks  
2 are not directed against any person in particular.  
3 Reasonable people may disagree on all of these points,  
4 and I, for one, am prepared to modify my opinion based  
5 on data displayed later in this meeting. However, so  
6 far, manufacturers have seen no evidence for a clear  
7 and present danger, but, rather, a rush to judgment.  
8 At the earlier private meeting called by the AAP, I  
9 tried to recommend to the participants a bit of what  
10 the French call "Sang-Froid." I found it difficult to  
11 give an adequate English translation of the term, but,  
12 recently, I came across the French definition given by  
13 Denis Diderot in the 18th century.

14 He wrote: "Sang-froid, that quality so necessary to  
15 those who govern, without which one would rarely apply  
16 justly the means to the circumstances, without which  
17 one would lack presence, presence of mind; sang-froid  
18 which submits the activity of the soul to reason and  
19 which preserves one, in every event, from fear, from  
20 frenzy, and from precipitation."

21 I believe we could all benefit from such dispassionate  
22 reflection. Thank you.

1 (APPLAUSE)

2 **DR. GREENBERG:** Thank you, Stan. That was an  
3 interesting talk. We now can take some questions.

4 **DR. ENGLER:** Dr. Engler from Walter Reed. I was  
5 wondering if in those discussions there was any  
6 consideration of the hundreds of children and adults  
7 who between the '60s and until 1981, when intravenous  
8 gamma globulin became available, received weekly or  
9 every two weeks, 10, 15, 30 cc's of intramuscular gamma  
10 globulin, and in my calculation there's probably a  
11 significant cluster of a couple hundred patients or  
12 more who have received 10,000 milliliters of gamma  
13 globulin, which is probably more than three logfolds,  
14 if not four, more than what are given in standard  
15 childhood immunizations, and that does contain  
16 thimerosal.

17 As far as I'm aware, there's only two cases, and these  
18 are patients who had received this in excess of twenty  
19 years in these kinds of doses who developed some  
20 cerebelli ataxia secondary to accumulated mercury  
21 toxicity. Now, the incident is a separate issue,  
22 certainly, in regards to also the difference in the

1 immune system of the infant from older children or  
2 adults, but in other age groups separate from infants,  
3 that seems to be overwhelming data in terms of the  
4 safety to support some of what you're suggesting.

5 **DR. PLOTKIN:** Yes, thank you. I would agree that in  
6 looking over the literature, as far as I've seen, the  
7 only instances of acute thimerosal toxicity have been  
8 where a gross error was made, I think, in the use of  
9 chloramphenicol and, otherwise, the literature show  
10 conspicuous absence of acute toxicity.

11 But to be fair, as you pointed out, of course the issue  
12 here has focused on the very young infant and the  
13 effects on the central nervous system of the very young  
14 infant.

15 **DR. GREENBERG:** In the back? Could you identify  
16 yourself?

17 **INAUDIBLE SPEAKER:** Stan (inaudible) from Merck. You  
18 covered the other chemical, but did you run across any  
19 studies using radiation as a preservative?

20 **DR. PLOTKIN:** The question that Stan is asking is the  
21 use of radiation as a preservative. That's a good  
22 question. I must admit ignorance. I have not seen

1 those studies. I imagine that under some circumstances  
2 it might be possible, although, with particulate matter  
3 in vaccines, I think there could be some issues about -  
4 - about sterilization and, of course, the effects of  
5 radiation on the active product. So the short answer  
6 the your question is no.

7 **DR. BAYLOR:** I just wanted to add what the real issues  
8 --

9 **DR. GREENBERG:** Identify yourself, please?

10 **DR. BAYLOR:** Oh, I'm sorry. I'm Norman Baylor. I'm  
11 with the CBER Office of Vaccines.

12 The real issue is going in and out of that vial. To  
13 produce the vial, a final fill, that's sterile, that's  
14 not really a problem. But going in and out of that  
15 vial, that wouldn't address that problem.

16 **DR. GREENBERG:** Any other questions?

17 (NO RESPONSE WAS HEARD)

18 **DR. GREENBERG:** Well, Dr. Plotkin had a pretty  
19 controversial talk there. You folks aren't rising to  
20 the bait.

21 (LAUGHTER)

22 **DR. PLOTKIN:** I'm glad to be able to get off the podium

1 and still in one piece.

2 **DR. GREENBERG:** The last speaker before the coffee  
3 break is Dr. C. John Clements, from the Expanded  
4 Program on Immunization, Vaccines, and Other Biologics  
5 at the WHO, and the title of his talk will be  
6 "Preservatives in Vaccines: The Global Perspective."  
7 So he will encompass everything.

8 **DR. CLEMENTS:** Good morning, ladies and gentlemen.  
9 First of all, I want to thank the organizers for  
10 inviting me to come and speak. It's a great privilege  
11 to be here in Washington.

12 Before I actually start the presentation, I want to  
13 acknowledge that in assembling some of the materials  
14 for this I was helped by a colleague of mine, Gary  
15 Schatz, who is a consultant that has been working with  
16 us from CDC and who tragically was killed in a road  
17 traffic accident last Monday. I just want to  
18 acknowledge his contribution to this.

19 As I speak to you this morning, I want you to think of  
20 me both as somebody speaking from a global perspective  
21 from WHO, but also as an advocate for a hundred million  
22 such children as this every year. This young gentleman

1 is sitting in a cardboard box with a hole cut for his  
2 legs and he is very interested in what we're going to  
3 say this morning.

4 As you can see from this molecular description of  
5 thimerosal, it's the mercury which is the pride and the  
6 downfall of this gentleman, and we can all agree, I  
7 think, right away, that the mercury here is not what we  
8 want in preservatives. There's ample evidence that it  
9 is an undesirable molecule which is taken in by the  
10 human through food and drink and pharmaceuticals and  
11 vaccines. In general terms, we're without hesitation  
12 in saying we don't want it, and that is a strong basis  
13 for further action. However, I think we need to  
14 examine the issues a little bit more.

15 And I must say that I'm delighted being third in a row  
16 of three, and I hope you'll find that what I have to  
17 say is very synoptic with the previous two speakers. I  
18 make no apologies for covering similar ground, although  
19 I hope you'll remember my friend from Africa as we  
20 speak. And I keep pressing the wrong key. Never mind.  
21 Okay. The United States has gone through its due  
22 process to identify a problem and take action to remedy

1 it. However, there is a knock-on effect which the rest  
2 of the world must bear as a consequence. And what I  
3 want to do is to draw out in the next few minutes some  
4 of these consequences for you and examine the knock-on  
5 effect. And I want to really say how privileged I am  
6 to be here, and I feel that I'm looking over your  
7 shoulders as you make -- go through this discussion and  
8 make some of these decisions.

9 But also, I'm looking over your shoulder anxiously  
10 because there is an knock-on effect, and I want to be  
11 really sure that each one of you involved in these  
12 decisions understands fully some of the implications of  
13 those knock-on effects.

14 Like Stan, I'm concerned with the scientific process  
15 which has gone on to date. There is a lack of  
16 agreement about the safe cutoff levels for mercury and  
17 there's a variance between the control bodies in the  
18 United States, and certainly between WHO, as to what  
19 those levels should be. And the infant maximum intake  
20 level has been extrapolated only.

21 As far as toxic effects go, it's not clear what levels  
22 of exposure to mercury in the fetus, the neonate, and

1 the infant are harmful. We know that there are harmful  
2 levels, but we certainly don't know at what point we  
3 have to be concerned.

4 Now, what does WHO say about this? Well, if we look at  
5 the most authoritative voice that I can find, the 33rd  
6 Report of the Joint FAO/WHO Expert Committee on Food  
7 Additives, JFOA, pronounced on this in 1989. The  
8 committee confirmed the previously recommended the  
9 provisional tolerable weekly intake of 200 micrograms  
10 of methylmercury. That is equivalent to 3.3 micrograms  
11 per kilo of bodyweight for the general population, but  
12 noted that pregnant women and nursing mothers are  
13 likely to be at greater risk from adverse effects of  
14 methylmercury.

15 And I should point out that the discussions which have  
16 gone over the last two or three months really suggest  
17 that possibly we should be looking at a five-fold lower  
18 cutoff point for pregnant women and nursing mothers in  
19 order to protect the fetal brain.

20 And even though the JFCA committee that met in Rome in  
21 June was aware of the issues regarding thimerosal, they  
22 were not in a position to offer any stronger guidelines

1 regarding cutoff levels for pregnant women and didn't  
2 even trespass into the dark waters of recommending  
3 levels for infants.

4 So the figures that I've been able to get hold of,  
5 then, are for WHO 3.3, for FDA 2.8, and for EPA 0.7  
6 micrograms per kilo bodyweight. But I do stress that  
7 WHO recommendations are based on the adult level and  
8 make no special concessions for pregnant women or  
9 infants.

10 A question already asked: Do we need preservatives in  
11 vaccines? And the way that things are going in the  
12 United States, there's the clear possibility that as  
13 you move to monitor those preparations then there may  
14 be a possibility that they are not needed. However,  
15 this is not the case for the majority of the world.  
16 And in tests that we've undertaken recently in  
17 vaccines, it is clear that the lack of preservatives  
18 pose a serious threat to the integrity of multi-dose  
19 vials which have already been opened and penetrated by  
20 at least one needle through the cap.

21 These lists vary a little bit depending on who's  
22 presenting, but I think we're fairly consistent in

1 identifying some alternatives to thimerosal. 2-  
2 phenoxyethanol is -- looks like the forerunner, but we  
3 have limited information on comparative effectiveness.

4 Formaldehyde, cresol, possibly others. Phenol, I  
5 should draw your attention to, in the WHO regulations,  
6 is not permitted any longer.

7 If thimerosal is not available, what alternative  
8 strategies are there for developing countries? Well,  
9 we can move to a mono-dose vial without preservatives  
10 or we can seek a replacement to the preservatives. But  
11 as is already pointed out by Stan, there are serious  
12 consequences for both options. The product must be  
13 reformulated, new clinical data must be presented, and  
14 new submission for license must be made, and for  
15 vaccine supplied through UNICEF, then a special  
16 WHO/UNICEF approval must be processed. All in all, a  
17 long time interval before availability of either of  
18 these alternatives.

19 You've heard already, and you'll hear I know in a lot  
20 more detail, how the regulatory bodies in the United  
21 States go through their debates. In terms of WHO, we  
22 have an Expert Committee on Biological Standardizations

1 which meets regularly, which is composed of outside  
2 experts. Although it is hosted by WHO, it is not an  
3 internal committee, it is an external committee, and it  
4 results in WHO producing WHO technical report series,  
5 which I've already quoted from once.

6 Expert Committee on Biological Standardizations, ECBS,  
7 what does that say about DPT and thimerosal?

8 "If the vaccine is to be dispensed into multi-dose  
9 containers, a suitable antimicrobial preservative shall  
10 be added. The amount of preservative in the final bulk  
11 shall have been shown to have no deleterious effect" --  
12 Never put that on a slide if you have the say it in  
13 public --

14 (LAUGHTER)

15 **DR. CLEMENTS:** -- "on the toxoid or on any other  
16 vaccine components with which the toxoid may be  
17 combined, and to cause no unexpected adverse reactions  
18 in humans. The preservative in its concentration shall  
19 be approved by the national control authority and don't  
20 include phenol."

21 The other vaccine that we're particularly concerned  
22 about is hepatitis B, and the ECBS says about that:

1 "Each final bulk or final lot shall be tested for the  
2 presence of preservative. The method used and the  
3 permitted concentration shall be approved by the  
4 national control authority. The most common  
5 preservative used for hepatitis B is thimerosal," and  
6 then it goes on to describe the analytical methods.  
7 So, in summary, through the expert committee at WHO is  
8 saying that the task of the  
9 preservative -- the task that the preservative is designated  
10 for -- In other words, to be antimicrobial -- must be  
11 defined and fulfilled.  
12 Again, as Stan has already pointed out, it must not  
13 damage the vaccine in any way, like thimerosal and IPV,  
14 and it must not damage the human recipients, although  
15 that is not spelled out how. The level is set not by  
16 WHO but by the national control authorities.  
17 Now, what implications has all this to do for the  
18 global supply of vaccines? Since Stan has begun to  
19 open up this discussion, I need to just clarify for  
20 some of you who may not be familiar with it, the  
21 majority of the world, particularly developing  
22 countries, looks to three main sources to get their

1 supply of vaccines.

2 The first is the local producer, and that may surprise  
3 some of you who are not familiar with this subject;  
4 secondly, UNICEF-supplied vaccines; and thirdly, they  
5 may go directly to the manufacturer and buy directly  
6 through them.

7 And if you look at this graph, the red at the top is  
8 the local production. I'm sorry I don't have more up-  
9 to-date information to show you, but the trend has  
10 continued where a large proportion of the world's  
11 vaccines are produced in-country and consumed in-  
12 country.

13 If you look at this description of DPT sources by WHO  
14 region, you can see that in the Eastern/Western Pacific  
15 Region and the Southeast Asia Region, a vast proportion  
16 of the vaccine is made locally and consumed locally.  
17 We'll discuss the implications in a moment.

18 And for hepatitis B, many countries in the developing  
19 world have HBV transmission by the neonatal route. In  
20 other words, the first week, first two weeks of life  
21 are crucial in protecting the infant; and if there is  
22 no birth dose of hepatitis B given, then there is

1 likely to be transmission of the virus. And this means  
2 that without a birth dose in China, between 10 and 15  
3 percent of all births are likely to result in chronic  
4 infection.

5 What immediate impact on developing countries would  
6 there be if thimerosal were removed from vaccines? As  
7 Stan has already said, existing suppliers would be  
8 unable to supply such vaccines and supplies would  
9 rapidly dry up.

10 Locally-produced vaccines, and remember I've identified  
11 them as being a major source in developing countries,  
12 would be unable to substitute for this preservative.  
13 Local production would either stop or -- I'm not sure  
14 whether it's worse or about the same level of  
15 significance, but they might turn to producing without  
16 the preservative.

17 We've mentioned another strategy of moving to mono-dose  
18 vial preparations, but at the moment, basically all  
19 vaccines in developing countries are drawn from multi-  
20 dose vials.

21 The cold chain could not cope with a five- to twenty-  
22 fold increase in volume which would be resulting from

1 this. It would double the cost of the cold chain, and  
2 result in a cold chain costing around half a billion  
3 dollars a year. There would be a six- to ten-fold  
4 increase in vaccine prices for these countries, which  
5 could not be borne by them. Even if there was a switch  
6 to mono-dose, those products still need relicensing.  
7 The one hope in the dark tunnel at this moment in this  
8 scenario is that we are watching the development of a  
9 pouch-and-needle hepatitis B delivery system in its  
10 field trials, and there is at least the possibility  
11 that that will fill a niche as being a disposable  
12 single-dose delivery system.

13 What happens -- The alternatives open to developing  
14 countries. They could obtain vaccine through their  
15 regular UNICEF supply with a new preservative if a new  
16 preservative became available. They could purchase  
17 directly from industrialized countries. They could use  
18 locally-produced vaccine, or they could use vaccine  
19 which is imported in bulk and filled locally, or they  
20 could switch to mono-dose with no preservatives.  
21 And what about the time and the impact of these  
22 decisions they would make? If they waited for a

1 preservative to be introduced into UNICEF vaccines,  
2 that is going to be a long wait. If they purchase  
3 directly from industrialized countries, not only do  
4 they have the wait, but they will certainly have an  
5 increased cost. If they rely on locally-produced  
6 vaccines, they have to try and obtain the new  
7 preservative, perhaps under license, again a long wait  
8 and an increased cost. If they go for local filling  
9 from bulk purchased overseas and the license, there's a  
10 long wait and an increased cost. And if they switch to  
11 mono-dose, it may be relatively quick, but it will be  
12 far too expensive, both in terms of purchasing the  
13 vaccine and in managing the cold chain.

14 Now, there may be some discrepancy in the time sequence  
15 that I put up here. It's the best we could come up  
16 with in WHO on a sort of Gallup Poll basis, and this  
17 isn't something that you should take as finite, but it  
18 gives you some feel. To find a new preservative -- If  
19 a new preservative is found, there's no guarantee, but  
20 between one and five years. Clinical trials, another  
21 two years. Licensing, a year if it's put on fast  
22 track. To reformulate an existing vaccine to a mono-

1 dose would probably take around one year.

2 In summary, then, my Executive Director, Michael  
3 Scholtz put out a press release a few weeks ago: WHO  
4 will continue to recommend thimerosal-containing  
5 vaccines. We see no reason for changing that given the  
6 present amount of information and the scientific  
7 debate. Mono-dose hepatitis B vaccine will continue to  
8 be administered in the birth dose and all the other  
9 doses from multi-dose vials. At this point, there is  
10 no option about using mono-dose. Although, as I said,  
11 a light in the end of the tunnel is the patch-and-  
12 needle device.

13 And as I indicated already that mercury is a highly  
14 undesirable chemical to have in biological products  
15 anyway, and we are determined to work with industry and  
16 regulate the authorities to eliminate thimerosal.

17 One thing I've observed doing this over the last few  
18 months is a concern, and I asked the question: Instead  
19 of the onus being on the scientist to demonstrate there  
20 is a problem, has the onus now shifted to the pro-  
21 vaccine community to show that there isn't a problem?  
22 And remembering my patron sitting there in Africa, what

1 does it all mean for him or her? Well, there is  
2 balancing scales out there, and there is a theoretical  
3 risk from thimerosal that we are all aware of and have  
4 been discussing. On the other hand, there is the known  
5 risk from vaccine-preventable diseases if we stop  
6 immunization and if we're no longer able to use the  
7 vaccines that we have at the moment and which have been  
8 used successfully for fifty to sixty years. And there  
9 is the known risk from contamination of vaccines. I  
10 put it to you that it is not a nearly equal balance.  
11 It is a balance which is, without hesitation, in favor  
12 of continued use on a global scale of vaccines which  
13 now contain thimerosal. Thank you.

14 (APPLAUSE)

15 **DR. GREENBERG:** Thank you, Dr. Clements.

16 Do we have any questions?

17 **DR. GELLEN:** Bruce Gellen from the Infectious Disease  
18 Society.

19 John, has this -- the decision that's been made here  
20 and some of the recommendations, has this trickled into  
21 developing country programs and has there been some  
22 discussion to date at local levels?

1       **DR. CLEMENTS:** When the United States generated this  
2 interest and it went public on the Internet and in the  
3 journals, then WHO put out a press release and  
4 distributed information and backup information to all  
5 EPI managers throughout the world and to WHO regional  
6 offices and country representatives. And to my delight  
7 and amazement, I had only one e-mail query of  
8 clarification following that.

9       So at this point the world is quiet, and I'm very happy  
10 to say that. So it doesn't seem to have had any impact  
11 at all, Bruce.

12       **DR. HALSEY:** John, the cost of --

13       **DR. GREENBERG:** Identify yourself, Neal.

14       **DR. HALSEY:** Neal Halsey. The cost that you put in for  
15 the potential use of single-dose or mono-dose vials and  
16 so forth, because of the increase in space  
17 requirements, you estimated it would increase to five  
18 hundred million per year, but you didn't give us what  
19 the current cost is and whether that increase in cost  
20 is a single time or whether that's recurring year after  
21 year after year. I recognize that more refrigerators  
22 would need to be purchased at multiple points in the

1 cold chain, but once those are purchased, then that --  
2 is that -- I asking, is that a one-time cost and, you  
3 know, what is the recurring cost?

4 **DR. CLEMENTS:** Okay. There are two parts to that.  
5 It's approximately doubling the cost of the cold chain  
6 to half a billion, and most of that would be capital  
7 investment, not recurring costs.

8 **DR. KATZ:** Sam Katz from Duke University and the  
9 Infectious Disease Society of America.

10 John, one of the issues that we have heard repeatedly,  
11 and this may not be a fair analogy, but that is what  
12 the United States policy determines regarding vaccine  
13 use has effects on the WHO program. That came up with  
14 smallpox vaccine when we discontinued use six years  
15 before WHO. More recently, concerns switching to IPV  
16 and rejecting OPV as the vaccine of choice in this  
17 country. And one side, of course, is your pragmatic  
18 issue: Do thimerosal-containing vaccines remain  
19 available?

20 The other is, perhaps, related to what Bruce Gellen was  
21 asking, which is its influence on policymakers in other  
22 countries, particularly the developing nations. Do you

1 see this as an issue?

2 **DR. CLEMENTS:** It's potentially an issue. I think a  
3 lot of countries use whatever the FDA does as a  
4 benchmark, and in my own country, New Zealand does the  
5 same. It looks to FDA, and if it passes a vaccine,  
6 that in itself is crucial in the vaccine being accepted  
7 in that country.

8 Do they accept it without process? No. And I think  
9 our job has been in this last few weeks to be the  
10 moderator of the information coming out of the United  
11 States and to say that has been deliberated in the  
12 United States and it has relevance to that country, but  
13 it needs to be processed and seen in the light, in this  
14 particular light, for the rest of the world.

15 So, yes, it has a powerful influence, but countries  
16 make their judgments. The end call is that they make  
17 their own judgments.

18 **DR. SNIDER:** Dixie Snider, CDC.

19 John, How do you see moving forward on this from a  
20 global perspective? I mean, it seems to me, as you've  
21 indicated, it's going to be a long process, and I'm  
22 very concerned about the trends, as you pointed out,

1 were to use local producers, and there are a lot of  
2 reasons for that, which we -- you may want to elaborate  
3 on. But there seems to be, by doing that, an increased  
4 need for a preservative if you're going to rely on a  
5 variety of local producers, unless somehow GMP, Good  
6 Manufacturing Practices, can be upgraded in many of  
7 these countries.

8 And so I wonder, realistically, how do you see this  
9 playing out to achieve the goal of maintaining the  
10 availability of these necessary vaccines while at the  
11 same time getting the mercury out?

12 **DR. CLEMENTS:** I think we have perhaps a different  
13 perspective on the urgency. I think the United States  
14 is faced with a different set of pressures from some  
15 other countries and it must respond to them.

16 But I think our job in WHO is to guide in as wise a way  
17 -- I wish I could remember what Stan's quote was -- to  
18 have the wisdom to guide countries in making decisions  
19 in an appropriate time base.

20 And what we'll be doing is working with the Experts  
21 Committee on Biological Standardization to come up with  
22 something similar to the European vaccine manufacturers

1 in encouraging a gradual shift towards mercury-free  
2 preservatives, but it will be something which is  
3 measured in due time and with due consideration of as  
4 many factors as necessary.

5 So I think that's how I'd answer it. We will  
6 definitely be encouraging the process. We will  
7 probably be funding research from researchers who wish  
8 to investigate the potential for new preservatives.  
9 We'll be looking at industry and encouraging them to do  
10 the research.

11 There will be -- We'll be putting out feelers in many  
12 directions to try and encourage the development, the  
13 rapid development of that preservative, because for us  
14 there is no turning back from multi-dose vials and  
15 there is no getting away from the fact that due to  
16 human error, potential for human error, it is essential  
17 that those multi-dose vials have some preservative  
18 system in them.

19 **DR. PLOTKIN:** Plotkin, PMC.

20 I'd just like to point out that there's been kind of a  
21 subtle fall down the slippery slope here. That is to  
22 say, the discussions have started out by talking about

1 limits, tolerable limits, to the amount of mercury, and  
2 now we're talking about zero tolerance. So we've now  
3 progressed -- I'm generalizing here, of course. We've  
4 now progressed to the point where no mercury is  
5 tolerable at all, whether it meets EPA requirements or  
6 not.

7 Now, in the particular situation of the developing  
8 world, John, I mean, could you not envision a situation  
9 where there would be an allowable amount of mercury  
10 given in the multi-dose vaccines, considering that in  
11 the developing world the number of vaccines being used  
12 in not the same as in the U.S.?

13 **DR. CLEMENTS:** Well, I think, Stan, you made a  
14 rhetorical statement there which I certainly don't  
15 agree with, that we're wanting zero dose mercury. That  
16 has not been established in any scientific setting. It  
17 may be an emotional response which you're talking about  
18 on a slippery slope, but mercury ingestion and  
19 environmental mercury that we have around us now make  
20 it impossible to think that we'll be mercury-free.  
21 What we're talking about is how much mercury is  
22 acceptable. That doesn't negate the desire -- the

1 desirability of having mercury-free vaccines, but we  
2 certainly are not targeting that as -- that is not  
3 necessarily our immediate goal, although it may be our  
4 long-term desirability.

5 Thimerosal has been a fantastic preservative for fifty  
6 to sixty years, and it has done a fantastic job.

7 **DR. WANACOTT:** I'm not sure whether we have  
8 representation -- I'm Dave Wanacott from Merck. And  
9 I'm not sure if we have representation from the  
10 Pharmacopeia decisionmakers in this meeting, but have  
11 you considered at WHO talking to some of the  
12 pharmacopeias? Because they have really been a large  
13 driver for the higher levels of preservatives to meet  
14 the antimicrobial effectiveness testing, and they  
15 consider backing off on both levels. Has that  
16 consideration been discussed?

17 **DR. CLEMENTS:** Yes. I'm speaking from a particular  
18 unit in WHO, the Immunization Unit. We work hand-in-  
19 hand with Biologicals. So I'm not privy to everything  
20 to the Chief, L. Wynn Griffith, has been doing in that  
21 area, but I know he has been in contact with them, and  
22 absolutely, I think it's a good point.

1       **DR. GREENBERG:** Well, we're actually a little bit  
2 early. So I'd like to ask whether there are any  
3 questions for our last two speakers, after you've heard  
4 all three, or whether any of the speakers have anything  
5 to say to the other speakers that might be informative  
6 or help clarify this issue?

7 Bill?

8       **DR. EGAN:** If I could just make a comment. First of  
9 all, thimerosal, or if you want to go on the other side  
10 of the Atlantic, thimerosal, has not been banned. So  
11 we're not talking about that it must come out of all  
12 vaccine. So, you know, thimerosal has not been banned.

13       We are, nonetheless, concerned about the cumulative  
14 doses of mercury and we prefer to have mercury-free  
15 vaccines and preservative-free vaccines, i.e., single-  
16 dose presentations in the United States.

17       We have asked manufacturers for their -- you know, for  
18 their plans for elimination of thimerosal and that  
19 it'll still be a -- you know, if they cannot eliminate  
20 it, to justify it and be allowed where justified. So,  
21 you know, we haven't gone to that point of saying, you  
22 know, as of such and such a date, mercury cannot be in

1 any preservative -- in any vaccine.

2 **DR. SNIDER:** Dixie Snider. I just wanted to raise one  
3 additional point that I think has been implied but  
4 really hasn't been made explicit, and that is that I  
5 think the -- there is an important issue here around  
6 the credibility of immunization programs nationally and  
7 globally, and that although it may not be in the best  
8 interests of everyone to eliminate mercury entirely  
9 because the risk or the price of doing so might be a  
10 price we don't want to pay, I think the concern about  
11 the integrity of the entire immunization effort, if you  
12 will, has been on many people's minds and has been a  
13 part of the decision-making process up to this point  
14 and will continue to be a part of the consideration  
15 here. Not that people do not want to react to  
16 scientific information that is available in an  
17 appropriate way, but, in addition, when there are  
18 choices that can be made to move from a thimerosal-  
19 containing vaccine to one which is -- can be found to  
20 be just as safe and effective without that agent, then  
21 it's to the immunizations programs' advantage to be  
22 seen as not adding to the mercury that people are

1 ingesting all the time, not be adding to mercury  
2 burden.

3 So I think the credibility of all immunization programs  
4 is important to maintain, and one aspect of the reason  
5 why we have declared concern, if you will, about the  
6 amount of mercury that we are delivering.

7 **DR. ZUNE:** Kathy Zune, CBER.

8 I just wanted to make one comment regarding the issue  
9 of the timing here, and it was alluded to that this was  
10 rather sudden. The issue and concern over thimerosal  
11 has been an ongoing discussion, and I think the  
12 discussions with manufacturers looking at the reduction  
13 and/or elimination of thimerosal is not a new issue. I  
14 think some of the aspects which triggered some of the  
15 current information that has been discussed has been  
16 during the FDA Modernization Act of 1997. We were  
17 directed at the FDA to do an evaluation of mercurials  
18 in all FDA-regulated products. As part of that  
19 initiative we worked cooperatively with the  
20 manufacturers to get the data, which is what you will  
21 be hearing later in the workshop. The issues are then  
22 looking at cumulative levels, as was discussed by Dr.

1 Snider, I think became the issue of concern. The  
2 vaccines are believed, when looked at, safe and  
3 effective, but when you're looking at cumulative does  
4 in small neonate typing, I think the issue and the  
5 concern was raised and should be looked into, both from  
6 a scientific as well as a public health issue.

7 My sense is that this workshop is very valuable to the  
8 public health service, FDA included, in order to have a  
9 very important scientific evaluation of the data  
10 available and what data we need to get. So, thank you.

11 **DR. GREENBERG:** Dr. Plotkin.

12 **DR. PLOTKIN:** Well, several points. One, actually, in  
13 responding to Dr. Zune, I think

14 the -- there is general agreement that mercury is not going  
15 to be used in future vaccines. I think the issue is  
16 more whether it needs to be removed immediately from  
17 currently licensed vaccines.

18 In relation to Dixie Snider's comment, I would like to  
19 say that if anti-vaccinationists did not have mercury,  
20 they would have another issue, and one cannot prevent  
21 them from making hay regardless of whether the sun is  
22 shining or not. So I don't think that's really a valid

1 reason for making decisions.

2 Lastly, I don't want to lose sight of the comment by, I  
3 think Dr. Wannake from Merck. I am certainly not a  
4 vaccine production person, but in looking at the  
5 Pharmacopeia regulations, I was struck by their, let's  
6 say, apparent excessiveness, and whether one could --  
7 And this is actually be considered in Europe, whether  
8 one could adopt different criteria which would allow  
9 reduction of the concentration of preservatives in  
10 vaccines. In other words, that you would require only  
11 stasis rather than cetyl activity against  $10^5$  or  $10^6$   
12 organisms, as Bill Egan mentioned.

13 **DR. GREENBERG:** I know less about this than Dr.  
14 Plotkin, but it certainly seems to me that the biologic  
15 experiment, there's a lot to be said for that, but it  
16 doesn't seem to me that usually contamination should be  
17 occurring at quite that level and that you might be  
18 able to get exactly the same effect with less than --  
19 If somebody in the audience knows how that criteria --  
20 what the thought process behind it was, that would be  
21 an interesting thing to hear about.

22 Bill?

1       **DR. EGAN:** I can't comment about, you know, the thought  
2 process, and it goes back quite a few years, I think  
3 somewhere around 1970, when the USP introduced those  
4 requirements, their definition of a preservative, but I  
5 would like to add again what I mentioned during my  
6 talk, that I did think that, you know, those are very  
7 stringent requirements and that the -- that in the  
8 United States, it is not necessary that a preservative  
9 per, you know, the CFR must meet the USP definition.  
10 Certainly, that's -- you know, that's acceptable, and  
11 it has been, but it's not a requirement that it meet  
12 the USP to satisfy the CFR. I did run that through our  
13 general counsel.

14       **DR. GREENBERG:** All the pharma -- Did the big pharma  
15 hear that last statement?

16       **UNIDENTIFIED SPEAKER:** Just one comment. Usually when  
17 we're manufacturing, we think on the international  
18 level, and, particularly, it's the European  
19 Pharmacopeia that is the mandatory one, and their  
20 requirements are perhaps even more strict than the USP.  
21 therefore, you know, I'm thinking in the international  
22 scheme of things, that becomes an issue.

1 Let me give you an example. A few years ago, quite a  
2 few years ago, we were working with the Europeans and  
3 taking a product that's no longer -- a diluent that's  
4 no longer on the market that had a preservative in it,  
5 and it was a single-dose vial, but there was a very low  
6 level of thimerosal in it which would not pass the  
7 European Pharmacopeia. And we said, well, basically  
8 this is a single dose, it's there as assurance for  
9 misuse after it leaves the manufacturer. And they  
10 said, well, no, still got to meet European  
11 Pharmacopeia.

12 so I think that needs to be brought into the equation  
13 here in looking to evaluate some of these requirements  
14 that may not be a requirement in the U.S., but our  
15 impact on the international basis.

16 **DR. SNIDER:** Dixie Snider again.

17 I just wanted to respond to Stan by saying that I  
18 wasn't speaking -- in talking about credibility, I  
19 wasn't speaking to try to address issues that anti-  
20 vaccine groups might raise because I do realize that  
21 there are incredibly an unending list of complaints or  
22 charges that could be made.

1 I'm more concerned, though, about scientists at the  
2 Agency for Toxic Substances and Disease Registry and  
3 the National Center for Environmental Health and the  
4 Environmental Protection Agency and others who have  
5 expressed concerns about the mercury that we are  
6 delivering and was only trying to suggest that, in view  
7 of concerns of scientific groups, it is reasonable to  
8 consider how we can lower or eliminate the mercury that  
9 we deliver through vaccines since people will get it  
10 through, unavoidably, a series of food supply.

11 **DR. GREENBERG:** Dr. Klein?

12 **DR. KLEIN:** Jerry Klein, the Boston University.  
13 Stan, as a point of information, could you clarify the  
14 many products that do not have thimerosal? Now, do  
15 they have other preservatives, or are they free of any  
16 preservatives? And if so, what is the basis for their  
17 success and is it just something that is necessary for  
18 the manufacturing products in selected vaccines? As  
19 example, there's one pneumococcal vaccine that has  
20 thimerosal, as the alternative product does not, and  
21 the same thing with amphophilous influenza.

22 **DR. PLOTKIN:** Well, there are many parts to that

1 question. The best table on the list of vaccines  
2 containing thimerosal is the one published by the AAP,  
3 and I refer to it often. But as Bill mentioned, IPV  
4 contains 2-phenoxyethanol because thimerosal will  
5 inactivate the polio component. Other than that, I  
6 think -- I think, but I'm not absolutely certain, that  
7 benzyl alcohol may be in some unusual vaccines, but in  
8 terms of common vaccines, I think those are the only  
9 two.

10 Now, why is TM, to give a nondenominational name -- why  
11 is it present? Usually because manufacturers are  
12 making multi-dose and single dose and prefer to have  
13 one product that they fill from.

14 Now, of course, as I stressed, where single-dose  
15 presentations are the only form, you can, in fact, do  
16 simple aseptic filling with the risks that Bill  
17 mentioned.

18 So the choice of whether there's TM in it or not  
19 depends on largely what forms are being made, whether  
20 bulks have to sit around for some time before they're  
21 combined for filling, and issues which relate to the  
22 perceived production process and the subsequent use --

1 that is, the subsequent use by physicians -- whether in  
2 the single-dose form or in the multi-dose form, and  
3 also capacity of the manufacturer to make one or the  
4 other.

5 I'm not sure that I've answered your question very  
6 precisely, but I -- that's about the closest I can  
7 come.

8 **UNIDENTIFIED SPEAKER:** But there are a number of  
9 products that appear to be in multi-dose form that do  
10 not have preservatives?

11 **DR. PLOTKIN:** No.

12 **UNIDENTIFIED SPEAKER:** So any multi-dose form does have  
13 a preservative?

14 **DR. GREENBERG:** Well, I think we're almost back exactly  
15 on schedule, which is good. You can all take a thirty-  
16 three-minute break, so 11:00 o'clock, and be back in  
17 your seats then. Thank you.

18 (RECESS FROM 10:30 A.M. TO 11:00 A.M.)

19 **DR. GREENBERG:** If everybody could take their seats,  
20 please? In the back, sit down.

21 Okay. We're now going to finish up the morning  
22 session. Before we start, I have one question that was

1 -- several people have asked, and I just wondered  
2 whether any of the speakers from the morning could  
3 answer it, and that was: For multi-dose vials --  
4 Measles/Mumps/Rubella is a multi-dose vial and does not  
5 have preservative in it -- do people know how the  
6 problems of preservation are dealt with in that  
7 vaccine? That's the question. Does anyone have an  
8 answer? A quick answer?

9 **UNIDENTIFIED SPEAKER:** (Unable to hear speaker)

10 **DR. GREENBERG:** There are no multi-dose vials of  
11 Measles/Mumps/Rubella? Somebody over there. Neal?

12 **DR. HALSEY:** My mic won't come on.

13 **DR. GREENBERG:** Okay. Then, Stan?

14 (LAUGHTER)

15 **DR. GREENBERG:** I'm not responsible. Okay. We're  
16 having -- If there's somebody in the back, the lights  
17 don't seem to be coming on. I'm going to save that for  
18 the end of the session, and people can think about  
19 that.

20 So the next speaker is Dr. Jeffery Enghardt, Senior  
21 Research Scientist at Eli Lilly, who are the -- which  
22 is the company that makes thimerosal, and his talk will

1 be "Toxicology and Metabolism of Thimerosal in  
2 Animals."

3 **DR. ENGLHARDT:** Thank you. I appreciate Dr. Myers'  
4 invitation to come to this. I am a veterinary  
5 pathologist, so I look at things from a slightly  
6 different perspective in that I work in the toxicology  
7 or drug safety component of Eli Lilly and Company.  
8 When the question came to me about toxicity of  
9 thimerosal, I had to scratch my head and wonder, what  
10 the heck is this? This is not a product that I have on  
11 my horizon very often, and I had to talk to one of my  
12 more senior colleagues who said, "Oh, that's  
13 Merthiolate." As I started getting into this  
14 particular topic, I had to go back into our corporate  
15 literature but also start searching the scientific  
16 literature. Though we keep information from a material  
17 safety data sheet standpoint, we don't keep an active  
18 research program going on this compound, mostly because  
19 of its historical perspective. If you'll bear with me  
20 a little bit, I'd like to take a few minutes to retread  
21 some of the ground that was covered this morning, but  
22 it's important to, I think, see where the database has

1 grown on the toxicity of this compound and where are  
2 the holes in terms of the toxicity of this compound.  
3 As was mentioned earlier, thimerosal is an  
4 organomercurial. It's ethylmercurithiosalicylate and  
5 it's just mercury that's part of the ethylmercury that  
6 has apparently become the issue that's being discussed  
7 here at this workshop. And just to note from a  
8 molecular standpoint, in this complex salt, the mercury  
9 composes about forty-nine percent of the molecule.

10 Looking back into the historical literature, thimerosal  
11 had a variety of chemical properties that made it very  
12 attractive. And one of the things also, as I was  
13 reading this literature, is that not all mercuries are  
14 alike, and I'd like to retread that again a little bit  
15 later in the talk. Now, thimerosal is found to be very  
16 water soluble. It was created stable solutions and  
17 also compatible with a variety of biological materials.

18 As Dr. Klein mentioned earlier, we were one of the  
19 first to be using thimerosal as a preservative in some  
20 of our older vaccine days in terms of the diphtheria  
21 vaccine. It was also used in some of our other toxoids  
22 that were produced back in the '30s and '40s. And as

1 mentioned also, this has been marketed since the '30s,  
2 and as I got into our literature, I found that there is  
3 very little in terms of toxicology in animals. Most of  
4 it is quite old -- The primary reference is a 1931  
5 reference in the American Journal of Hygiene -- and  
6 it's often in obscure journals or cited as one or two  
7 sentences within review articles, and it's very  
8 difficult to find very explicit information on  
9 thimerosal.

10 As has been well described this morning, it's been used  
11 as an antiseptic, fungistat, and a preservative for a  
12 number of years. The antimicrobial activity has been  
13 attributed to the release of this ethyl mercuric ion  
14 and thereby acting as an oxidizer for groups leading to  
15 changes in intracellular calcium and that is the  
16 mechanism that it causes cell death. I also found that  
17 it's very interesting that there are as many articles  
18 on using thimerosal as an in vitro reagent to study the  
19 calcium fluxes in cells as there are uses for -- or  
20 publications on use in vaccines.

21 One thing that I did find is that the ethylmercury and  
22 thiosalicylate are the primary metabolites which were

1 described in an article published from Lilly in 1956.  
2 In this particular issue, they were looking at the  
3 question around the inactivation of IPV with the use of  
4 thimerosal and had discovered that these metabolite  
5 ratios can be altered by the presence of copper within  
6 either the vials that are being filled or within the  
7 production materials and that the copper drives the  
8 reaction not to the mercuric ion, but to the mercuric  
9 oxide. That is one of the materials that is purported  
10 to inactivate the protein in the polio toxoid.

11 So, so much for the history. What I'd like to do now  
12 is talk a little bit about what do we know about the  
13 toxicity of this molecule. Again, these data are from  
14 some of these older articles. There's been nothing  
15 that I've been able to uncover published in about the  
16 past twenty-five years in terms of new animal data on  
17 this molecule.

18 Oral toxicity in rats has a MLD of about 73 mg/kg and,  
19 as you can see, when you look at the rodents and the  
20 lagamorphs (sic), there is a disparity in terms of  
21 what the bodyweight toxicity is, but the overriding  
22 morphological alteration that occurs in these animals

1 is renal necrosis. This is interesting in the fact  
2 that this type of toxicity is what has been described  
3 most widely with mercuric chloride studies, which is  
4 renal necrosis.

5 One human study -- And I should note that I found a  
6 couple of human correlates to go along with this during  
7 my searches. There was one human accidental or -- I  
8 can't say if it was accidental. It must have been  
9 intentional in this case. An individual consumed some  
10 liquid Merthiolate and successfully done himself in.  
11 He consumed an estimated 83 mg/kg showing that the oral  
12 toxicity in rats is pretty well on, but the  
13 presentation that this individual had was, again, very  
14 similar to what's been seen with mercuric chloride,  
15 that he presented with gastritis, renal failure, and  
16 gingivitis. It wasn't until the very late stages  
17 before he died of respiratory failure that any type of  
18 polyneuropathy was identified.

19 Also as mentioned earlier, thimerosal is a very  
20 exquisite antigen, not only in people but also in  
21 guinea pigs and rabbits, and it is also a dermal  
22 irritant as was described in some of the earlier

1 literature when thimerosal was used as a contact lens  
2 solution preservative. The ethylmercuric chloride is  
3 the purported allergen that's responsible for these  
4 phenomena not only in people but also in animals, and  
5 one of the disparities from the animal studies that's  
6 been identified is that, unlike people that can  
7 occasionally have a systemic hypersensitivity reaction,  
8 those particular phenomena have not been identified in  
9 either the rabbit or the guinea pig studies.

10 When we start looking at the non-rodent species, the  
11 only studies that I had found on toxicity were some in  
12 the 1931 publication on toxicity in dogs, where 2 mg/kg  
13 was administered every three days and then 10 mg once  
14 weekly over a six-week period, and at the end of that  
15 the animals were examined and there were no -- there  
16 was no clinical toxicity nor pathologic alterations  
17 that were identified.

18 I was also surprised to find that there was a two-year  
19 carcinogenicity study that had been conducted on  
20 vaccine preservatives and thimerosal was included in  
21 that particular study, and the outcome of that was that  
22 there were no compound-induced neoplasms. It should

1 also be noted that thimerosal does cross the  
2 blood/brain barrier. It also crosses the placental  
3 barrier. However, there has not been any evidence of  
4 turadnogenicity (phonetic) that's been shown with the  
5 compound in a study that was conducted with one of the  
6 contact lens preservatives.

7 It should also be noted -- And this is one of the gaps  
8 that I identified and this is part of the concerns that  
9 are raised here in looking at the neonatal vaccine  
10 issue -- is that typically now with the pharmaceutical  
11 agents, we do what's called a post-natal development  
12 study or a Segment III study, and there's nothing in  
13 the literature right now that has anything that looks  
14 at in utero exposure to thimerosal and in post-natal  
15 development in rodents. So we do not have any data  
16 that would indicate either a risk or a lack thereof.  
17 I did find one article that I found very informative  
18 and that was an article published in 1975 by Blair, et  
19 al., that was looking at the metabolism and excretion  
20 of thimerosal in adult squirrel monkeys and this was a  
21 chronic study, a chronic daily administration study.  
22 Thimerosal, at a concentration of .002 percent, and

1 this is, I believe, in the range of what's used as a  
2 preservative in the vaccines. I think that's allowed  
3 to go up to about .01 percent. This was administered  
4 in two ranges, either 2.2 or 12 micrograms per monkey  
5 per day for six months and that the total thimerosal  
6 dose was 418 or 2280 micrograms. If you remember, this  
7 has a 49 percent of mercury, so this means that these  
8 animals received roughly 200 micrograms of mercury or  
9 1100 micrograms of mercury.

10 Now, this is a classic tissue distribution study and,  
11 unlike what's done with pharmaceutical agents, they had  
12 to use atomic absorption to look for the mercury. So  
13 the tissues were dissected, analyzed for the presence  
14 of mercury and what form was that mercury in and also  
15 histologic evaluation of those tissues to see if there  
16 were any accompanying morphologic alterations due to  
17 the presence of absence of the mercury.

18 The data from this study showed that there was no  
19 evidence of toxicity either seen clinically during that  
20 six-month administration phase or during the pathology  
21 evaluations. There was variation in the mercury  
22 concentration in individuals. That is, within those

1 given groups, there was a disparity in how much  
2 mercury, even though they were given the same dose by  
3 the same period of time, on how much mercury was  
4 accumulated in different tissues, but what was of note  
5 was that the mercury that was present in the blood and  
6 tissues was primarily in the inorganic form and also  
7 that the distribution of the  
8 tissues -- or within the tissues had kidney as being the  
9 primary organ, followed by liver, muscle, brain, and  
10 the least of all, in blood.

11 Now, some of this conversion from the organic to the  
12 inorganic may lead to the point that I made earlier,  
13 that all mercuries are not alike and that within the  
14 organomercurials, there is a difference in the  
15 stability of that carbon/mercury bond, and I'm hoping  
16 that when Mr. Lucier presents later, talking about  
17 ethyl and methylmercury that he will be striking on  
18 that.

19 It also should be noted that the ethylmercury  
20 compounds, particularly thimerosal, will also undergo  
21 this biotransformation of organic to inorganic in human  
22 tissues, and that was described in a report by Suzuki

1 in 1971.

2 As I mentioned, the kidney had the highest  
3 concentration, and you can see we've got over 3000  
4 nanograms -- These are the mean values that were  
5 presented in this article -- and that the predominant  
6 form that was present within the kidney tissue was  
7 inorganic. And as you go through, you can see that  
8 from the kidney, as you move down, there is a quite a  
9 disparity between the average values that were present  
10 in the brain in terms of inorganic mercury and what was  
11 present in the major excretory organ and very little  
12 present in the blood.

13 Again, there was no evidence of toxicity seen  
14 clinically or evidenced morphologically that the  
15 presence of this mercury was causing any deleterious  
16 effect on these animals.

17 One thing that was brought out in this article is they  
18 mentioned that a critical brain level of mercury range  
19 from 3 to 9 micrograms per gram in the brain to cause  
20 toxic effects. What should be noted is that even  
21 though there were differences among all these animals,  
22 the highest level in the high-dose animals was only 245