regulations do not apply to veterinary drug products, exemptions for such products are stated in that section.

c. Radiopharmaceutical drug products. The general CGMP regulations are suitable requirements for the preparation of radiopharmaceutical drug products. When the Commissioner was aware of situations where the requirements are not appropriate, exemptions were made from these final regulations. Supplemental requirements specific for radiopharmaceuticals will be proposed in the future.

d. Biological drug products. The Commissioner notes that section 902(c) of the act parallels section 351(g) of the Public Health Service Act (42 U.S.C. 262(g)), which provides that section 351 does not affect, modify, repeal, or supersede the Federal Food, Drug, and Cosmetic Act. The agency has consistently interpreted these provisions to be additive; that is, although they preclude duplicative or inconsistent regulation under the two acts, where one statute speaks to a matter regarding biological products and the other statute is silent, the express statutory provisions govern, regardless of the statute in which they appear. Thus, for example, the provisions of section 505(i) of the act regarding investigational use of new drugs have been consistently held to apply to biological products because no part of section 351 of the Public Health Service Act addresses investigational use of biologics (21 CFR 312.1(g)). Because section 351 of the Public Health Service Act does not refer to current good manufacturing practice and because biological products are considered to be drugs subject to section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, the Commissioner believes it is consistent with both laws to apply current good manufacturing practices to biological drug products.

Biological products are now manufactured according to current good manufacturing practice and regulated under parts 600 through 680 (21 CFR parts 600 through 680), in particular the establishment license and product license provisions. Sections 210.2 and 211.1 clearly provide that the more specific biologic regulations prescribed in 21 CFR Parts 600 through 680 will supplement or supersede, where appropriate, the more general drug CGMP regulations. ..."

Thus, point "**d.**" recognized that:

a. "Biological products are now manufactured according to current good manufacturing practice" **[Note:** In general, these regulations started being issued prior to 1973[173] and were re-codified as parts 600 through 680 of Title 21 of the U.S. Code of Federal Regulations (21 C.F.R. Parts 600 through 680)**]** "and regulated under parts 600 through 680 (21 CFR parts 600 through 680) ...";

b. "Sections 210.2 and 211.1," which incorporate parts 600 through 680 by reference, "clearly provide that the more specific biologic regulations prescribed in 21 CFR Parts 600 through 680 will supplement or supersede, where appropriate, the more general drug CGMP regulations"; and **c),** given **a)** and **b),** all these regulations establish minimum requirements for compliance with "current good manufacturing practice" (CGMP), including the applicable CGMP regulation

[173] ***FR* 38**: 32048, (Nov. 20, 1973).

minimums, as CGMP compliance is a requirement *minimum* with respect to "safety" in **21 U.S.C. § 351(a)(2)(b).]**

On December 22, 1987, the "**National Vaccine Injury Compensation Program**" (NVICP), **42 U.S.C. §§ 300aa-10** through **300aa-34**, became law.

This statute includes **Sec. 300aa-27. Mandate for safer childhood vaccines**, that, *in subsection 27(a)(2)*, states (with underlining added for emphasis):

> "(a) General rule
> In the administration of this part and other pertinent laws under the jurisdiction of the Secretary, the Secretary shall -
> (1) ..., and
> (2) make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines."

Based on this statutory requirement and the subsequent expansion of the NVICP to cover all influenza vaccine doses, *including those for adults*, this statute made it illegal for the Secretary (of the Department of Health and Human Services [HHS] or any subordinate organization [including, but not limited to, the NIH, CDC, and FDA]) to:

a. Refrain from taking any action with respect to any vaccine covered by the NVICP that would reduce the risks of adverse reactions to vaccines and/or

b. Take any action that would increase the risks of adverse reactions to any vaccine that may be administered to "children."

4. Limits on the Administrative Discretion of the FDA

In general, the FDA has wide administrative discretion with respect to the administrative actions that it does or does not take.

Until 1988, there were no limits on the FDA's administrative discretion other than those explicitly established by law.

However, in a U.S. Supreme Court case[174] where the United States of America (U.S.) was being sued for the harm caused to one Kevan Berkovitz by a polio vaccine lot released under a discretionary decision rendered by an FDA official, the government maintained that the FDA official's "administrative discretion" authority protected the U.S. from being held liable for the harm done to Kevan Berkovitz.

Disagreeing with the view of the defendants (Department of Justice acting on behalf of the federal government), the U.S. Supreme Court *unanimously* held that an administrative official has no discretion when it comes to complying with any applicable official policy, law (regulation) or statute governing said administrator's actions.

Based on this finding, the U.S. was held to be liable for the harm to Kevan Berkovitz and his family; and the case was remanded to the lower courts to determine the extent of liability and the damages that should be awarded.

Therefore, the FDA's legal administrative discretion only begins after the FDA has *fully* complied with all applicable policies, laws (regulations) and statutes.

Moreover, *as a corollary*, *knowingly* failing to comply with, or, *where appropriate*, require a manufacturer to comply with, all applicable policies, laws and statutes may subject the accountable FDA officials involved to prosecution for their actions or inactions.

5. Summary of Current Requirements For Drugs Containing Mercury-Compounds Added At Any Step During Drug Product Manufacture

1. Given that the organic mercury compounds, *usually* Thimerosal (or *occasionally* a phenylmercury salt), added to the manufacturing processes for drugs and drug products are highly toxic, bioaccumulative with half-lives that exceed a decade for their mercury-containing end-stage metabolite (tissue-bound inorganic mercury") and these are highly (at

[174] Kevan *Berkovitz*, a Minor by his Parents and Natural Guardians Arthur Berkovitz, et ux., et al., Petitioners, *v. UNITED STATES.* Case No. 87-498. 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USL W 4549. (Cite as: **486 U.S. 531, 108 S.Ct. 1954.**)

mercury levels below 0.5 part per million) tetratogenic, mutagenic, carcinogenic, and immune system disruptive to susceptible humans, the applicable safety standard for all such should be the explicit CGMP *minimum* set forth in **21 C.F.R. Sec. 610.15(a), "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to"** (any) **"recipient."**

2. To be licensed and/or approved, by law, the drug manufacturer must conduct the appropriate toxicity studies and clinical trials to prove that the drug is "safe" in a manner that fully complies with the minimums set forth in all directly and/or indirectly applicable CGMP regulations. The drug manufacturers have an absolute non-dischargeable duty to prove their drugs are safe to all applicable established standards.
3. Under *Berkovitz v. U.S.*, the FDA has no administrative to waive any safety requirement and license and/or approve a drug whose manufacturer has knowingly failed to conduct any safety test required to establish that the drug is "**sufficiently nontoxic ...**"
4. Any drug that is adulterated[175] and subsequently distributed, *a prohibited act*,[176] must be recalled. **[Note:** The distribution of such drugs renders the drug and its manufacture subject to the legal penalties established in the FFDC Act.[177]**]**
5. *For drugs that are also vaccines covered by the NVICP*, the applicable statutory language[178] essentially prohibits the approval of any covered vaccine formulation containing any level of Thimerosal, ***in 1988 and after***, because adding Thimerosal to any vaccine formulation has been proven to increase the risk of adverse reactions, *including anaphylaxis*, and the statutory language states that "the Secretary shall ... make or assure improvements in, and otherwise use the authorities of the Secretary ... to reduce the risks of adverse reactions to vaccines."

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[175] **21 U.S.C. Sec. 351(a)(2)(b)**
[176] **21 U.S.C. Sec. 331 Prohibited acts.**
[177] **21 U.S.C. Sec. 333 Penalties.**
[178] **42 U.S.C. Sec. 300aa-27(a)(2).**

6. Similarly, the NVICP also mandates that, *since all vaccines containing Thimerosal, which were approved before the NVICP was enacted in December of 1987, are "Thimerosal preserved,"* the Secretary was under a mandate to replace these vaccines with ones that contained no Thimerosal because doing so would reduce the risks of adverse reactions to those receiving such "Thimerosal preserved" vaccines.

b. Federal Government's Actions – 1940s To The Present

1. Introduction

Since the U.S. FDA's ability to "enforce" safety is limited to the authorities delegated to them by statute, the FDA was in a position of "playing catch-up" when proof of safety was mandated for "new drugs" in 1938.

Moreover, when it came to existing drugs, which contained Thimerosal or any other mercury compounds, the FDA started out treating these drug products as "grandfathered" because they were used prior to 1938.

Further, *even though these drugs were reformulated and new drugs containing added mercury were being continually submitted for approval or licensing*, the FDA continued to *myopically* and *inappropriately* treat these reformulated or new drug formulations as being "grandfathered."

Thus, even though there was, and is, an ever increasing body of evidence showing the harm organic mercury compounds cause, the FDA has *repeatedly, and incorrectly*, testified, that all uses of Thimerosal and other mercury compounds in the formulation of drug products are "grandfathered."

However, under the FFDC Act of 1938, the statute, *by limiting its reach to "new drugs,"* <u>only</u> "grandfathered" the actual drug products that existed prior to the passage of the FFDC Act of 1938.

It did <u>not</u> "grandfather": **a)** any reformulation of said existing products or **b)** the further usage of any ingredient in any "existing" drug.

In spite of this obvious reality, the FDA has persisted in testifying to Congress that, *for example*, the use of Thimerosal as a preservative in influenza vaccines is "grandfathered" even though: **a)** no Thimerosal-containing influenza vaccine was in use in the U.S. in 1938, and **b)** each influenza vaccine formulation is a **new or reformulated drug** containing some "new" active ingredient (e.g., new influenza strain) that differs from the previous formulation.

Further, such twisted logic, as that embodied in the FDA's "it's grandfathered" defense of the use of Thimerosal as a preservative in vaccines without the requisite "proofs of safety," is contrary to American law, which fundamentally "expects" the FDA to protect, and not to jeopardize, the public health by requiring that manufacturers of each new drug product provide all of the requisite "proofs of safety" before the FDA approves that new drug product.

2. 1973: Changes to the CGMP Regulations for Biological Drug Products

In 1973, current good manufacturing regulations were enacted for biological products that included the following requirement for preservatives:

> "... Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, ..."[179]

In spite of explicitly incorporating this legally binding CGMP requirement minimum by reference into the CGMP regulations for finished pharmaceuticals (**21 C.F.R. Part 211**) in 1978, the FDA did not enforce this requirement on all existing vaccine products preserved with Thimerosal, and, *to date*, has neither enforced this requirement nor stopped approving preserved biological products until their sponsor has provided the scientifically sound and appropriate toxicity studies that prove their preserved biological drug product met the requirement minimum set forth in this regulation.

Furthermore, the FDA has not instituted product recall and legal sanction actions against those biological product manufacturers who continued to distribute preserved biological products that,

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[179] **21 C.F.R. Sec. 610.15(a).**

because they failed to meet a clear CGMP requirement minimum since 1973, are *clearly* adulterated by statute (**21 U.S.C. Section 351(a)(2)(b)**). [**Note:** Apparently, the FDA justified the Agency's *knowing* failure enforce this regulation (law) as a decision within the wide latitude of the FDA's view of its "administrative discretion." However, a unanimous U.S. Supreme Court decision in 1988, *Berkovitz v U.S.*,[180] *significantly* curtailed the FDA's "administrative discretion." Under *Berkovitz v. U.S.*, the FDA has no administrative to waive any safety requirement and license and/or approve a drug whose manufacturer has knowingly failed to conduct any safety test required to establish that the drug is "**sufficiently nontoxic ...**" In spite of this unanimous Supreme Court finding in 1988, the FDA continues to ignore the manufacturers' *knowing* failure to comply with **21 C.F.R. § 610.15(a)** and failed to take the legal action required by statute against all manufacturers who knowingly manufacture and distribute adulterated drugs.]

3. 1977: Proof of Harm from Thimerosal in Antiseptics and FDA "Recommendations"

The first large-scale prospective human epidemiological study, *in which the FDA participated*, clearly reported a significant risk of harm defects from Thimerosal was the "Collaborative Perinatal Project"[181] published in 1977.

As discussed earlier, the purpose of this book was "to present data on drugs used by 50,282 gravidae in relation to birth defects identified in children."

For Thimerosal, the study concluded:

> "The measure of association presented is a standardized relative risk (SRR) with its 95% confidence limits. The SRR is the ratio of the observed number to the expected number of malformed children. Since the SRR takes into account potential confounding variables, it represents the best estimate of the relationship between a drug and a malformation... Finally, thiomersal...was associated with malformations overall and with uniform malformations."

Factually, that study reported that Thimerosal exposure during the first 4 months of pregnancy was associated with a statistically significant increased risk (SRR = 2.69) for birth defects.

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[180] Kevan *Berkovitz*, a Minor by his Parents and Natural Guardians Arthur Berkovitz, et ux., et al., Petitioners, *v. UNITED STATES*. Case No. 87-498. 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USL W 4549. (Cite as: **486 U.S. 531, 108 S.Ct. 1954.**)

[181] Heinonen OP, Slone D, Shapiro S. **Birth Defects and Drugs in Pregnancy**. Littleton, Massachusetts: Publishing Sciences Group, Inc., 1977.

Coincidentally, in late 1977, the FDA made the following recommendations as proposed rules regarding the use of Thimerosal as a preservative:

> "There is now evidence that thimerosal may (1) induce cell mediated hypersensitivity and (2) affect the size of the delayed skin test reaction in some subjects. Therefore, (1) when other preservatives have been demonstrated to be safe, effective, nonsensitizing (as well as not causing deterioration of the product), products containing thimerosal should be discontinued; and (2) a search for safe, effective and nonsensitizing preservatives as alternatives to thimerosal should be initiated."

In spite of these FDA recommendations, the U.S. Department of Health and Human Services (DHHS) and its subordinate organizations, the CDC, the FDA and the NIH, took no action to direct the vaccine manufacturers to replace Thimerosal with another preservative compound even though 2-phenoxyethanol, *another compound suitable for use as a preservative*, was, and is, not only "safe, effective and nonsensitizing" but is also a compound whose metabolites, phenol and ethanol, do not bioaccumulate.

4. 1982: FDA Review of OTC Topical Uses of Thimerosal Leading to: 1998 Ban on Thimerosal in OTC Topical Products

In 1982, a scientific panel, convened by the FDA to review the over-the-counter (OTC) use of Thimerosal, concluded,[182] "that thimerosal is not safe for [over-the-counter] topical use because of its potential for cell damage if applied to broken skin and its allergy potential."

[Note: This FDA-sponsored panel only addressed the epidermal and dermal effects of Thimerosal.**]**

Based on the results of their review, that scientific panel recommended the removal of Thimerosal from over-the-counter products.

In 1998, *16 years later*, the FDA *finally* banned[183] the use of: **a)** Thimerosal and any other ingredient containing mercury in OTC topical antimicrobial products, and **b)** phenylmercuric acetate, phenylmercuric nitrate, and any other ingredient containing mercury in vaginal contraceptive products. **[See 21 C.F.R. Section 310.545.]**

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[182] **47 *FR*** 436, Jan 5, 1982.
[183] **63 *FR*** 19799-19802, April 22, 1998.

5. 1997: Food and Drug Administration Modernization Act of 1997: Sec. 413 Food and Drug Administration Study of Mercury Compounds in Drugs and Food

Section 413 of FDAMA contains three mandates legislated by Congress that the FDA is charged to fulfill.

In general terms, those mandates are:

(a) Within 2 years of November 21, 1997, the FDA was to:

i. compile a list of drugs and foods that contain intentionally introduced mercury compounds, and

ii. provide a quantitative and qualitative analysis of the mercury compounds in the list that they compiled.

(b) Conduct a study of the effect on humans of the use of mercury compounds in nasal sprays. Such study shall include data from other studies that have been made of the use if nasal sprays.

(c) Study mercury sales and, if the use of elemental, organic, or inorganic mercury offered for sale as a drug or dietary supplement poses a threat to human health, the Secretary shall promulgate regulations restricting the sale of mercury intended for such uses.

Acting on mandate "(a)," in December of 1998[184] and April of 1999[185], the FDA published legally binding announcements requiring all manufacturers of food and drug products to respond, *pursuant to Section 413(a) of the Food and Drug Modernization Act of 1997 (FDAMA)*, in the form of "a call-for-data to identify food and drug products that contain intentionally introduced mercury compounds, e.g., mercurous chloride, mercuric chloride, phenylmercuric acetate, Thimerosal. The agency is seeking both quantitative and qualitative information about the mercury compounds in these food and drug

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[184] **63 *FR*** 68775-68777, December 14, 1998.
[185] **64 *FR*** 23083-23086, April 29, 1999.

products." [**Note:** In November of 1999, *to meet the mandated deadline in FDAMA*, the FDA posted[186] a notice of the availability of a document, entitled "**Mercury Compounds in Drugs and Food,**" that discussed drugs (including biologics) and foods that contain intentionally introduced **mercury** compounds. Unfortunately, apparently not all manufacturers of drug products containing intentionally introduced mercury compounds responded to this notice as, in 2004 and 2005, petitioners found and reported to the FDA evidence of at least one non-complying drug product (that was subsequently reformulated without any published action being taken against the manufacturer) whose manufacturer not only failed to report a Thimerosal-containing antimicrobial OTC drug product it was making but apparently continued to make that drug product even though the use of Thimerosal in it was banned in 1998.]

Unfortunately, since provisions "(b)" and "(c)" of section 413 of FDAMA lacked deadlines, *as of March 2006*,[187] the FDA has *apparently* failed to address the mandates set forth in provisions "(b)" and "(c)."

Thus, *in* spite of mandates to take other actions, beyond banning the use of Thimerosal in some topical OTC drug products in 1998, the FDA has, *as of June 30, 2007*, taken no action to ban, restrict, or require the mandated proofs of safety for vaccines and other drug products which contain added mercury, including, *but not limited to*, eye and ear drops, and nasal sprays.

6. 1999: Joint Pledge to Remove Thimerosal-containing Vaccines As Soon As Possible

In July of 1999, *shortly after the FDA's second "call-for-data" notice*, the federal government issued a press release (entitled "**Thimerosal in Vaccines: A Joint Statement of the American Academy of Pediatrics and the Public Health Service,**" which was subsequently *posted on the CDC's* ***Morbidity and Mortality Weekly Reporter (MMWR)*** *web site*,[188]) that, *in part*, stated:

> "... because any potential risk is of concern, the Public Health Service (PHS), the American Academy of Pediatrics (AAP), and vaccine manufacturers agree that thimerosal-containing vaccines should be

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186 **64 *FR*** 63323-63324, November 19, 1999.

187 http://www.fda.gov/po/modactchart/modact97fini.html, last visited on 15 June 2007.

188 ***Morbidity Mortality Weekly Report*** 1999; **48**(26): 563-565 (July 09, 1999 [original press release issued on July 7, 1999]) – can be found by searching the MMWR subsite (http://www.cdc.gov/mmwr/).

removed as soon as possible. Similar conclusions were reached this year in a meeting attended by European regulatory agencies, European vaccine manufacturers, and FDA, which examined the use of thimerosal-containing vaccines produced or sold in European countries."

Unfortunately, *eight (8) years later*, petitioners and the American public are still waiting for this "thimerosal-containing vaccines should be removed as soon as possible" promise to be fulfilled.

7. *1999: Illegally Closed "Lister Hill" Meeting Of Government, Medical and Industry Officials: "NVAC-sponsored Workshop on Thimerosal Vaccines"*

i. Day One

Following on the heels of that press release, *on 11-12 August 1999*, the CDC convened a closed-door workshop, *from which the general public and the news media were unlawfully excluded*, between members of the FDA, CDC and vaccine manufacturer representatives concerning the use of Thimerosal in vaccines.[189]

The first day of this workshop began with Dr. Martin Myers (Deputy Director of the National Vaccine Program Office in the CDC) who welcomed the participants.

The volume-one[190] transcript of first day of the workshop listed most of the participants and outlined the workshop topics addressed as follows:

"I. WELCOME
Martin Myers 11
II. INTRODUCTION
Jerome Klein 16
Harry Greenberg 20
III. WHERE WE ARE NOW: A REVIEW OF THE DATA
A. Thimerosal in Vaccines
1. Preservatives in Vaccines I: FDA Perspective
William Egan 21
2. Preservatives in Vaccines II:
Manufacturer Perspective
Stanley Plotkin 39
3. Preservatives in Vaccines III:

[189] 11-12 August 1999 (Confidential Transcript) The National Vaccine Advisory Committee Sponsored Workshop on Thimerosal in Vaccines convened by the US Department of Health and Human Services, the Public Health Service, and the Centers for Disease Control and Prevention (National Institutes of Health, Lister Hill Auditorium, Bethesda, Maryland)

[190] Unable to comment on what transpired in the last of day one because the petitioners do not have access to volume two of day one.

Global Perspective
John Clements 58
4. Toxicology and Metabolism of Thimerosal (Merthiolate) in Animals
Jeffery Englhardt 89
5. Thimerosal in Vaccines
Leslie Ball 105
B. Organimercurials:
1. Ethyl and Methylmercury: Pharmacokinetics and Toxicity
George Lucier 132
2. Guidelines for Safe Levels of Exposure"
[**Note:** Dr. William Raub, Deputy Assistant Secretary for Science and Policy in the Office of the Assistant Secretary for Planning and Evaluation, HHS, actually presented "Guidelines for Safe Levels of Exposure." His presentation actually begins on page 183. Dr. Kathryn Mahaffey of the EPA, Michael Bolger from the FDA, Tom Clarkson from University of Rochester and Christopher DeRosa from the Agency for Toxic Substances and Disease Registry were panelist who addressed specific exposures issues.]
"Kathryn Mahaffey 189
Michael Bolger 196
Tom Clarkson 201
Christopher DeRosa 212
END VOLUME I - DAY ONE ..... 222"

Tellingly, in his welcome, Dr. Myers remarked (with underlining added for emphasis):

"Because of multiple doses of vaccine, it is possible that some children could be exposed to a cumulative level of mercury that exceeds guidelines for methylmercury. Nationally and internationally, manufacturers and regulatory agencies are working to replace or reduce thimerosal-containing vaccines. The purpose of this workshop is to review the pertinent data on thimerosal: its use; its potential for toxicity; and steps that can be taken to increase the margin of safety, especially during the period of transition to greater availability of vaccines without thimerosal or with reduced thimerosal. It's very -- It's important to discuss, as we discuss these issues, to balance these with the very real risks of disease resurgence if we have a reduction in vaccine utilization or a loss of confidence in vaccines."

Here this FDA official circumspectly admits that some children "could be" mercury poisoned ("exposed to a cumulative level of mercury that exceeds guidelines for methylmercury").

However, he cautioned the participants to balance the "potential for toxicity" and "the steps that can be taken to increase the margin of safety" against "very real risks of disease resurgence."

Continuing his remarks, Dr. Myers stated:

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

In concluding, Dr. Myers announced that Dr. Harry Greenberg, Chairman of the Vaccines and Related Biologic Products Advisory Committee would be the moderator for the first day of the workshop and turned the convening of the meeting over to Dr. Jerome Klein from the Boston University School of Medicine.

Dr. Klein then convened the meeting and made introductory remarks that included the following key passages (with underlining added to highlight key points):

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

[**Note:** Here, Dr. Klein admits that there are recognized "most frequent adverse events" that are caused by Thimerosal, which extend far beyond the "local reactions" that most of today's governmental press releases claim are the "reactions to Thimerosal."]

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

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

[**Note:** Here, Dr. Klein fails to recognize, for example, that ethylmercury chloride was also used as a fungicide and mercury poisoning has also been associated with its usage, and that of other ethylmercury compounds, as a fungicide.]

"In contrast then, thimerosal is ethylmercury; and to underline, there is no evidence of harm from the amounts of mercury administered to infants and children in vaccines. I think what we'll learn from this experience in the next two days I've categorized in six areas.

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

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

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

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

Five, the pragmatic issues about what to do during the transition from the current roster of vaccines that do contain thimerosal to a thimerosal-free vaccine, period.
And then finally, a review of appropriate priorities or research in these areas.
So I anticipate an educational experience for all of us."

Following Dr. Klein's remarks, FDA CBER's Dr. William Egan presented the FDA's perspective, Dr. Stanley Plotkin of Pasteur Merieux presented the industry's perspective, and Dr. John Clement of the World Health Organization presented the "global perspective" on the use of Thimerosal as a preservative in vaccines.

Next, though Eli Lilly and Company had exited the vaccines business in the 1970s, Dr. Jeffery Englhard of Lilly presented on the toxicology and metabolism of Thimerosal (Merthiolate) in animals because, *at that time*, Lilly was still manufacturing Thimerosal.

Then, closing out the morning session on "Thimerosal In Vaccines," Dr. Leslie Ball, an FDA CBER Medical Officer, discussed an "FDA safety assessment of thimerosal in vaccines" that focused on "vaccines that are used in infants."

In the first afternoon session, entitled "Organimercurials," Dr. George Lucier, Director of the Environmental Toxicology Program at the National Institutes of Health began with a discussion of the toxicity and pharmacokinetics of ethylmercury and methylmercury compounds.

Speaking about his presentation, Dr. Lucier began by stating:

"My presentation will be, in a sense, two parts. And the first part is a summary of the interagency activities that we've had regarding methylmercury, particularly the areas of agreement and the findings that emerged out of our workshop in 1998. And the second is what we know, and that's written very small, it probably should be written smaller, and don't know About ethylmercury." That'll be a shorter part of the presentation because, as you heard this morning from a number of the speakers, there just isn't too much information out there on ethylmercury. I'll discuss a few issues that perhaps weren't presented this morning."

Next, he spoke about the process by which the "safe dose," 0.1 microgram of mercury per kg of body mass per day, was set for mercury in methylmercury "compounds" beginning with (with underlining added for emphasis):

"The purpose of the workshop was to discuss and evaluate the major studies, epidemiologic studies, associating methylmercury exposure with an array of developmental measures in children. It was in

response to the requirement that the emerging data from the Seychelles and Faroe Islands undergo a level of scrutiny beyond journal peer review if they are to be used in policy setting.

So, keep in mind, this was an extraordinary rigorous review in such a way that I think is rarely done in terms of individual papers. This workshop involved presentations by the groups who were conducting the studies, really a barrage of questions about what they did, how they did it, how they analyzed the data, information that really isn't found in the published literature, and can't be found, because the journals would never allow publication of that volume of information.

This was really done under the impetus of the White House Science Office, the Office of Science Technology Policy. Fran Sharples (phonetic) there was the point person. It involved a number of different agencies shown here. I hope you can read it okay. A number of institutes, agencies within DHHS; the NIEHS, which is where I'm from, Bill Raub's Office of the Assistant Secretary for Planning and Evaluation, and, of course, he'll give the next presentation and share the panel discussion; parts of CDC; ATSDR; FDA; again EPA; NOAA; OSTP; and also the Office of Management and Budget who was involved in this.

So you should keep in mind, as I go through what I'm going to say, in terms of the points that I make, they're really not my points. It's really the points of this interagency activity that basically was approved by all these various agencies and, in a sense, also approved by the major investigators whose studies we were reviewing, and generated by the reports, sub-reports, that were prepared by each of the panels, and I'll get to those later."

In his presentation, it became clear that, although much was "known" about the toxicity of "methylmercury" in fish for adults and some information was available from "methylmercury" fungicide poisoning incidents, "methylmercury" was known to be significantly more toxic to the developing fetus and somewhat more toxic to babies and children than it was to adults:

"One, methylmercury is a developmental neurotoxin in people. There's multiple publications, from Minamata, Iraq, and others to document that. The developing fetus is roughly ten times more sensitive than adults. This is a rough estimate, but probably not too bad of one. I think Tom Clarkson made that original estimate, and from my read of literature it can't be too far off.

The relative sensitivity of infants to methylmercury is unknown, but they are likely more sensitive than adults. We really don't have information in infants. We have to keep in mind that the central nervous system and the brain is still undergoing assembly and it's likely it would be sensitive to toxic insult, but we really have very little information, nothing near the extent that we have for prenatal exposures of the developing fetus and also for adults. We just don't have much for infants."

However, when it came to the toxicity of the related "ethylmercury" compounds, Dr. Lucier stated:

"Ethylmercury or Thiomersal? You'll notice I'm using the European spelling, because it was in the reprints had, so I used that spelling. Now, I'll make a few points here that I think most of them have already been made, maybe some of them haven't, regarding ethylmercury and possible comparisons with methylmercury.

Exposure. Depending on the vaccination schedule and bodyweights, a two-month-old infant receives a bolus injection of 3 to 18 micrograms per kilogram. This was information I got by Bill Raub via Neal Halsey, and assume that those calculations are correct. They seem similar to what was presented later on this morning, so I believe they're roughly correct.

This dose of mercury on vaccination day is much higher than daily exposure in the Seychelles and the Faroes, although the total dose received from vaccines is less than the mean exposures in the Faroes and Seychelles. Infant mercury intake per day from dietary sources is estimated to average .05 micrograms per kilogram per day in a chronic exposure, and this would be primarily through lactation as well as some other sources. And there's a few pieces of information in the scientific literature that support that estimate of infant uptake of methylmercury, exposure to methylmercury.

Biological half-life, similar to methylmercury. This is a little bit different than what was said this morning. For methylmercury, it's 40 to 150 days, and this was based on a number of different studies that have been presented. I think different agencies use slightly different numbers, but I think the average -- Chris, would it be right, it's about 70 -- 60 or 70, in that range? The one study I got ahold of regarding thimerosal, or ethylmercury, came from a suicide attempt. This was published three years ago actually, in "Clinical Toxicology," and this one lived. He also got about 80 milligrams per kilogram of thimerosal, and the half-life -- and Chris (inaudible) had sent me this reprint on Friday. It was estimated that the half-life, the second phase of the half-life, which is the one we need to look at here, was roughly 40 days in this one individual who survived that episode. Of course, we don't know what a near-death experience does in terms of the physiological factors that govern half-life, so I wouldn't guarantee that that's the half-life.

The information that we have in total suggests that it might be slightly shorter than methylmercury. And there is really no definitive information on potential differences that I could uncover between infants, children, or adults regarding biological half-life. I don't know, Katie, if you have some more information on that.

Metabolism -- And I think this was brought out in the presentations this morning -- that demethylation of methylmercury appears to occur more slowly than deethylation of ethylmercury. I think there's a growing body of knowledge that suggests that that is, in fact, true, and it's significantly different. In other words, the demethylation occurs much more slowly than deethylation in terms of the conversion to inorganic mercury.

What about the toxicity of ethylmercury or thimerosal? Again, we talked about the adult squirrel monkey study today, which was -- this was adults again and not a developmental study. Again, significant conversion to inorganic mercury; high levels in the kidney, as was presented this morning; lower levels in the brain; and no evidence of toxicity. And the doses that were given were equivalent to 1 or 6 micrograms per kilogram per day.

A second study, which was not discussed this morning, is that adult male and female rats were administered five daily doses of equimolar concentrations of ethyl or methylmercury by gavage and tissue distribution, neurotoxicity, and nephrotoxicity assessed. This was a Magos study in 1985 in the Archives of Toxicology. And the key points of that paper were: neurotoxicity of methyl and ethylmercury were similar, although higher levels of inorganic mercury were seen in the brains of ethylmercury-treated rats consistent with what we'd said about metabolism; and likewise, because of that, the renal damage was greater in the ethylmercury-treated rats. Unfortunately, neither time-course nor dose response was attempted in these studies, nor was any developmental studies attempted.

And after having said that, there are a number of critical toxicology studies that could be conducted to address some of the uncertainties that -- and you probably all know about and we talked about this morning. Unfortunately, all of these take time and, you know, clearly, if we embarked upon these studies now, we're not going to have results until long after some of the initial and significant decisions have to be made regarding the vaccine program. I think we have to acknowledge the paucity of data and move forward with the decision-making process, but I think it's good to think about what knowledge gaps do exist that really limit our ability to make those assessments in a way that we would like to make them.

Developmental neurotoxicity, we need to assess those response and age dependent responses in appropriate systems. We need to, for the reasons I discussed earlier regarding the PCBs and methylmercury, look at mechanistic studies, and we need to focus on critical changes in gene function and cellular pathways. In all the toxicology studies we do in the national toxicology program, and we do 30 or 40 of these a year as part of that interagency program, we're starting to take increasing

advantage of the human genome project and what that allows us to do in terms of looking at patterns of gene expression following exposure to various toxicants to compare potency of different agents and also mechanism of action, as one agent going through a similar mechanism of action as another agent. That might be particularly relevant to the issues at hand for the ethyl/methyl issue.

Evaluation of possible sensitive subpopulations based on either genetic predisposition, diet, or cumulative risk. Again, we're exposed to other developmental neurotoxicants. Are they additive? Are they synogestic? Are they antagonistic towards each other? Do they block each other's effect? And biomarkers of exposure, including hair, need to be evaluated.

There are no studies in developmental toxicity that I was able to find in experimental models or people, and because of this, in my opinion, health assessments for ethylmercury at this time must assume that ethylmercury is producing the same effects at the same doses as methylmercury."

From what was said, it was clear that Dr. Lucier was not only relying on information provided by others but also was apparently still unaware, *as the petitioners were when we began our review of the literature*, of much of the literature in "ethylmercury" including the early 1970s study by Tryphonas and Nielsen [191] that had clearly established that, *at least in developing pigs*, ethylmercury chloride was significantly more acutely neurotoxic than methylmercury dicyandiamide and stated (with underlining added for emphasis):

"... ethylmercuric chloride (EMC) w(as) used to produce chronic alkylmercurial poisoning in young pigs. A dosage of 0.19 to 0.76 mg. of Hg / kg of body weight per day was used... The resulting toxicosis was primarily related to the nervous system, in which neuronal necrosis followed by secondary gliosis, capillary endothelial proliferation, and additional neuronal necrosis due to developing degenerative arteriopathy in the blood vessels supplying injured gray matter were seen. In other systems, degeneration of hepatocytes and renal tubular cells were commonly occurring lesions in pigs...edema of the mescolon, necrosis of the epithelium, and degenerative arteriopathy in the submucosa were seen most consistently in the esophagus and large intestine of pigs... The results proved that...EMC, if fed at low concentrations...were highly poisonous... Finally, since the alkylmercurial moiety is absorbed and stored as such for considerable lengths of time in...cells, the public health implications...cannot be overlooked."

After Dr. Lucier finished answering questions about his presentation, Dr. William Raub, who was then Deputy Assistant Secretary for Science and Policy in the Office of the Assistant Secretary for Planning and Evaluation of the Department of Health and Human Services (HHS), began a presentation, titled "**Guidelines for Safe Levels of Exposure**", with the following opening remarks (with underlining added for emphasis):

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[191] Tryphonas L, Nielsen NO. Pathology of chronic alkylmercurial poisoning in swine. ***Am J Vet Res.*** 1973; **34**: 379-392.

"Thank you very much, and I appreciate the opportunity to join you this afternoon. The format for the next hour, or a little bit less, is that I will make some introductory remarks around the health guidance values, and then I will be joined by a set of colleagues, including Dr. Clarkson, as a panel discussion, and they have promised to answer every question that I manage to raise.

We've heard repeated references or questions to the health guidance values this morning and issues around whether to use them, and if so, when and how to use them. I believe we will be able to do more to raise issues than to give sharp definitive information around some of those questions, but I thought it might be helpful to have some of the background around what these concepts are, what's the philosophy, and the generic approach to them.

All of these guidelines attempt to focus on a concept for which I made up a neutral name, the 'Safe Daily Exposure.' The emphasis is on long-term. The emphasis is generally is on very low levels of exposure. The usual units are the quantity per unit of bodyweight per unit of time. And, for example, for mercury, in its various forms, methylmercury, in particular, micrograms per kilogram of bodyweight per day.

These health guidance values are calculated individually for many different hazards, depending on the regulatory or other mission of the agency that's involved. They are calculated specifically for various primary routes of exposure, ingestion, inhalation, or dermal exposure. In general, they are projected either as a lifetime value or, more conservatively, at the very least, for some substantial indefinite period.

The three most common of these health guidance values are the reference dose, or RfD, of the U.S. Environmental Protection Agency; the minimum of risk level, or MRL, of the Agency for Toxic Substances and Disease Registry of the Department of Health and Human Services; or the acceptable daily intake, or the ADI, employed by the Food and Drug Administration.

Algebraically, these are essentially the same thing. They are used depending on the mission of the various agencies. They may be used as the starting point for health assessments in such situations as evaluating the risks presented by a superfund site. They may be used in a formal risk assessment of a particular hazard, including all of its distributional phenomena and the like. They may be used as a starting point for developing regulatory requirements for emissions in the air or water, for assessing the toxic levels in particular situations, or, in the FDA's case, for the regulation of commercial seafood. But, again, the common factor is the notion that these are starting points for those more specific assessments and applications, and, in virtually no case, is the guidance value considered the last word. It's usually considered the place to begin in terms of a specific use.

In all of this, there is a driving desire to have science-based values to the extent possible. And, in its simplest form, the algebra comes down to the notion of the safe daily exposure being a ratio of an estimated gleaned from real data, either experimental data on animals or epidemiologic observations with humans, divided by one or more uncertainty factors. And what this says is the science-based goal here involves two aspects of science. One is actual data, experimental or observed, and the other are informed judgments at to the utility of that data, the limitations of it, and the ways in which it might be applied, and that's everything from the selection from the particular studies from which to fill the numerator to the judgment about the number and size and the rationale for the uncertainty factors that constitute the denominator.

Certain priorities obtained in general with respect to how one chooses that numerator term. Other things being equal, there's a clear preference for the -- what is called from the direct data, the "no observed adverse effect level," or the NOAEL. If there's dose response information available, and one can indeed identify the level, usually the highest level at which no adverse effect is seen, then this is often an excellent beginning for this calculation.

More often than not, we find ourselves faced not with the "no adverse effect" level but rather observing adverse effects in many different levels and, therefore, being forced to choose the lowest observed adverse effect level. This has a bearing then on what uncertainty factor is chosen, because having seen the lowest observed one, one may have no certain information or no good basis to predict where the level of no effect actually is.

Another priority judgment around the selection of that numerator term is the type of information on which the experimental or observational data are based. Ideally, it's direct information on the most vulnerable human subpopulation, as we believe is the case with the Seychelles and the Faroes studies with respect to methylmercury, but sometimes one must settle for information on the general human population, not being sure at all that the most sensitive subpopulation has, in fact, been measured or that it can be discerned. Failing that, data from non-human primates are obviously desirable, and failing that, data from other mammals.

In the totality of these types of studies, we find ourselves, more often than not, relying on data from the bottom parts of this list, and, therefore, for all the uncertainties and complexity, as George was indicating, the methylmercury discussions and debates have been a relative pleasure in that we're talking about real data on real humans, in this case, the developing fetus, and a relatively rich source of pertinent information compared to many other areas of toxicology.

Getting to the denominator in that element of informed judgment, uncertainties are very much tailored to the particular situation at hand. When we must extrapolate from information on humans in general to the human vulnerable subpopulation, analysts usually determine that some uncertainty factor is appropriate for that. The same is true for having the lowest observed adverse effect level, but wanting to estimate where the "no adverse effect" level might be, or at least to take account of that difference. Acute exposures extrapolated to chronic exposures, animal data used where no human information is available. More often than not, the uncertainty factor chosen for any particular entry is 10, although the richer the data set the more relevant it is. Sometimes individuals doing these calculations choose a smaller value, such as 3 as a half-log unit, or sometimes 1 1/2. 2

If two or more uncertainty factors are employed, in my experience, more often than not, they're multiplied. But, in certain circumstances, if there is some mechanistic information, one might choose to do an additive of those instead. Again, there may be no right answers with any complete determination, but informed judgments as to how best to weigh the quality and relevance of the information to the task at hand. And finally, these are some, and only some, of the characteristics that affect these health guidance values. A number of my colleagues who will be speaking to you in a few minutes could give a week-long seminar on the intricacies of the assumptions and the calculations that go into these determinations. But, in general, these focus on chronic exposure, seeking that long-term, potentially lifetime level that is judged to be safe.

Most important, none of these are offered as a bright line between what is safe and what is unsafe. Rather, there's built in a substantial margin of safety, with the realization that the number proffered is almost certain to be a safe level. Values immediately above it are most likely to be safe as well, but the higher one goes above it, the greater the risk becomes.

From my point of view, they are most important the starting point for situation-specific assessments. That is, rather than giving the definitive answer to any generic set of situations, they are the values that raise the flag, they are the values that trigger curiosity or concern, and the values that cause one to look into the specifics of whatever the situation is.

In this case, I believe it's been quite appropriately applied as a takeoff point, and the challenge of attempting to understand what these estimated safe daily values mean into an exposure scenario that by its very nature is episodic and where there are blips of boluses of exposure.

The safe daily calculations generally assume that there's some modest excursion around that level on a day-to-day basis, but, in general, they do not assume that very large derivations on a daily basis from those are automatically included. And so, therefore, in this particular situation, I think we move very quickly from using the safe daily level as an indicator for concern to some focus on, in this case, the toxicokinetics of what the nature of these particular kinds of bolus exposures might mean.

Last, I stress the importance of a uniformity of precaution in making these calculations across various hazards. The precautionary principle always applies in doing these calculations in that, depending on the application at hand, one wants to be sure that the level is one that one is not likely to miss a potentially problematic situation.

On the other hand, most risk assessors and risk managers are willing to tolerate what I'll call a false positive, as are willing to tolerate the need to do further exploration on a particular situation, only to

find that it might be safe, but at least this value is set at a level that provides that degree of protection and extra caution.

But if each of the different hazards, say, at a superfund site, were somehow evaluated differently, if the level of precaution were extraordinarily greater or extraordinarily less from one to another, it can compound those situations tremendously, can cause risk managers to invest resources easily in the wrong place, or to be pursuing what is, in fact, the relatively lesser risk and missing a higher risk. So in all these calculations, a discipline of trying to make the precautionary uses as nearly uniform as possible becomes very important.

With that as a backdrop, I'll ask that my colleagues might join me here, and I believe they're prepared to make a few minutes of commentary from the perspective of their individual agencies, the nature of the guidance values and how they apply to the particular exposure situations we find with the vaccines. I thank you."

In light of the reality, those involved in setting the "Safe Daily Exposure" made, and have continued to make, the false assumption that the half-lives observed and reported for mercury in blood and hair were *universally* related to the half-life of mercury in the body.

This assumption has been repeatedly been shown to be false and, in indirect *post mortem* studies on humans killed accidentally,[192] an average value of 18 to 20 years was calculated for the mercury trapped in various areas in the brain.

Had they and subsequent researchers and health officials applied the "precautionary principle" and used a "20-year" ("7300-day") half-life with a worst-case retention of more than 90% of the mercury in a bolus dose's being retained in the brains of those individuals who, *for whatever reasons*, have *very limited* ("*almost no*") ability to excrete mercury instead of using the observed half-lives for mercury reported here for methyl- and ethyl- mercury (40 to 150 days) compounds, then, the petitioners find that the appropriate reference dose (RfD) for mercury would have been set at 0.01 microgram of mercury per kg of body mass per day, or lower, and not, *as it was*, 0.1 microgram of mercury per kg of body mass per day.

Moreover, the petitioners note that the RfD value alluded to was based on "dietary" intake, and not injection, with no apparent consideration for the gut's mercury-sequestering defense system

[192] Sugita M. The biological half-time of heavy metals. The existence of a third, "slowest" component. ***Int Arch Occup Environ Health*** 1978; **41**: 25-40.

that, *for cysteine-complexed methylmercury in fish*, appears to block absorption by the consumer of up to 80% of the mercury present in the fish consumed.

In fact, using the search string "metal" the petitioners found no mention of "metallothionein" and its roles in the sequestering of mercury compounds and the mediation of mercury toxicity; the searches only found the words, "metal" and "metallic."

However, a "PubMed" search limited to humans and mercury, found 30 "metallothionein" publications published in 1997 and before.

Of these, five (5) papers seem to contain information pertinent to the role of metallothioneins in: **a)** mercury toxicity and **b)**, in some cases, the mediation of the absorption of mercury in the gastrointestinal system:

1. Ohta H, Seki Y, Imamiya S. Possible role of metallothionein on the gastrointestinal absorption and distribution of cadmium. ***Kitasato Arch Exp Med***. 1993 Apr; **65** Suppl: 137-145.
2. Nordberg GF. Modulation of metal toxicity by metallothionein. ***Biol Trace Elem Res***. 1989 Jul-Sep; **21**: 131-135.
3. Chowdhury BA, Chandra RK. Biological and health implications of toxic heavy metal and essential trace element interactions. ***Prog Food Nutr Sci***. 1987; **11**(1): 55-113.
4. Cherian MG, Nordberg M. Cellular adaptation in metal toxicology and metallothionein. ***Toxicology***. 1983 Sep; **28**(1-2): 1-15.
5. Cherian MG, Goyer RA. Role of metallothioneins in disease. ***Ann Clin Lab Sci***. 1978 Mar-Apr; **8**(2): 91-94.

The petitioners also note that, *in the panel discussion that followed Dr. Raub's opening remarks*, Dr. Clarkson's closing remarks:

> "And my view is that it's the maximum level that determines the damage. Methylmercury is an irreversible poison. It knocks out the brain cells. So probably, it's not so much the length of exposure, it's the peak exposure that's really going to do the total damage. The Iraq dose response that the EPA used in their risk assessment was based on peak levels, not average levels, but peak levels. And so in this sense, it's the peak levels here I would imagine that are probably important to worry about. And this is obviously a worst-case scenario. These are the lowest possible bodyweights. And I heard this morning that you're not even supposed to give a vaccine to an infant at 1.8 kilograms, and this is 1.8 kilograms here. Okay? Thanks."

are particularly noteworthy in light of the current understanding of the immediate toxicity of Thimerosal and its initial ethylmercury metabolites in *in vitro* experiments on growing human neuron and fetal cell meshes which are: **a)** concentration dependent and **b)**, *in some respects*, similar to studies using inorganic mercury.

Based on the available "Day One" transcript, the following facts are clear regarding the level of Thimerosal in Thimerosal-preserved vaccines (typically, 100 micrograms per mL); the volume of each dose injected (0.25 mL or 0.5 mL) into babies and children; and, *in the case of Rho(D) products injected into pregnant women*, the level of Thimerosal (about 50% mercury by weight) in such was, typically, 30 to 100 micrograms per mL), and the volume injected for each dose was 0.6 mL to, *in some cases*, 1.5 mL or more):

1. The amount to which a 0.45 kg (1 pound) fetus may have been exposed exceeded the EPA RfD (0.1 microgram of mercury per kg per day [based on their dietary-intake and hair methylmercury studies]) from a single Thimerosal-containing Rho(D) injection by a factor of 20 to 200. **[Note:** Though these attendees were told that the fetus was the most sensitive human to mercury poisoning, no mention of these injected Rho(D) products occurs in the transcripts of the workshop. Apparently, the fact that Thimerosal-preserved Rho(D) products, *when they are Rh negative*, and, *in some instances*, flu vaccines were being administered to pregnant women was <u>not</u> addressed.]
2. The amount given to low-weight babies on a given day exceeded the EPA RfD by a factor of about 70 to about 200.

Thus, at the end of the available "Day One" transcript, the workshop attendees were clearly aware that Thimerosal-preserved vaccines (and other Thimerosal-preserved drug products) represented a clear danger to some, *if <u>not</u> all*, fetuses and children.

Unfortunately, since no transcript of the rest of the "Day One" discussions is available, the petitioners can *currently* only discuss the "Day Two" transcript.

ii. Day Two

[Note: Where appropriate, underlining has been added for emphasis.**]**

The transcript of the second day of the workshop again listed most of the participants and then outlined the workshop topics as follows:

"VI. REDUCING AND ELIMINATING THIMEROSAL IN VACCINES

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The moderator, Dr. John Modlin, Professor of Pediatrics and Medicine, and, more recently, the Acting Chair of Pediatrics at Dartmouth, and Chair of the CDC's Advisory Committee on Immunization Practices, began the second day by stating:

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

Thus, the moderator again recognized that Thimerosal in vaccines was a problem and stated that the focus on the second day of the workshop was "where we go from here."

Next, he introduced Dr. Chris Adlam, Associate Director of Regulatory Affairs at SmithKline Beecham Biologicals, as the presenter for the "manufacturing issues" under the "Opportunities and Challenges" section heading for the topics in the second day's workshop.

Dr. Adlam began by stating:

> "Thimerosal is used in two different areas in the manufacturing process, and the first, which is the main concern of this meeting, is, of course, its use in final containers of vaccine as a preservative. Now, the reason it is used in that situation is, of course, to guard against contamination which might be introduced during the filling process."

[Note: Here the petitioners observe that Dr. Adlam's stated reason for a preservative, "to guard against contamination which might be introduced during the filling process," is at odds with the FDA and CDC views and the rationale used to justify its inclusion in a vaccine formulation, namely that a "preservative" is added to multiple-dose containers to prevent microbial cross contamination during the removal of a dose from the multiple-dose container.]

Dr. Adlam then continued with:

> "The second area, though, where it's still used is in vaccine development; for example, where we need to produce pilot batches of product for testing purposes, or we may require to validate equipment, scale up equipment, for example, but also, we still use thimerosal in full-scale manufacturing processes for some vaccines, and particularly where the method of antigen

purification, for example, might be complex, and where manufacturing people may consider that there would be potential risk for contamination if a preservative wasn't present.

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

The petitioners note that, while Dr. Adlam mentioned "the concept of good manufacturing practices," he adroitly avoided the issue of his firm's knowing failure to comply with 21 C.F.R. Sec. 610.15(a) as it pertains to proving that the preservative systems used in biological products are "sufficient nontoxic ...", a *current good manufacturing practice* (CGMP) requirement *minimum* for *preserved* vaccines.

In addition, he noted that "environmental agencies," and not the FDA, had pressured companies "to reduce the quantities of thimerosal that they use in their vaccine manufacturing processes."

He continued by stating:

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

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

Here, the petitioners are compelled to note that Dr. Adlam's remarks presume that Thimerosal is the only compound that can be used as a preservative when there are other recognized compounds (e.g., 2-phenoxyethanol) that can be and have been used as preservatives in the manufacture of vaccines so that removal of Thimerosal does not necessarily require a "second product containing the preservative for multi-dose containers in the international markets" – the alternative non-mercury preservative could have been developed for all markets.

Returning to his presentation, he continued with:

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

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

As many as nine or ten bulks, different bulk antigens would have to be stored. Aseptically -- They would have to be blended together aseptically to make a modern multi-component combination vaccine. Elimination of preservatives then, even from mono-dose vaccine presentations, is a serious step, and the appropriate tests and validations have to be done to make sure that the resulting vaccine remains safe and efficacious.

Why thimerosal? Many people have said, as we've heard, it's been around a long time, and the industry is very used to using it.

...

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

This is a laudable objective, and it may be, indeed, possible for some products and some processes, and it certainly is a road down which the FDA is pushing the companies. However, as I've stated already, we should maintain caution when we do this, if indeed we're not to replace one set of problems with another.

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

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

The petitioners find that, with respect to the removal of preservatives from vaccines being "a road down which the FDA is pushing the companies," the recent approval of several Thimerosal-preserved vaccines clearly indicates that today's FDA is not only not pushing for single dose vaccine packaging but also continuing to:

- Approve additional Thimerosal-preserved vaccines[193] that, because the Thimerosal used has not been proven (as the presentations in first day of this workshop clearly establish) "sufficiently nontoxic ...," *as required by* ***21 C.F.R. Sec. 610.15(a),*** are adulterated drugs,
- *Knowingly* collude with the manufacturers of said adulterated Thimerosal-preserved vaccines to distribute these adulterated drugs in violation of the applicable sections of the Federal Food, Drug, and Cosmetic Act as amended, and
- Approve additional NVICP-covered Thimerosal-containing vaccines[194] that, contrary to the clear mandate to reduce adverse reactions to covered vaccines by any and all available means (a "refusal to approve" is certainly an available means) *unnecessarily* increased the risk of adverse reactions in violation of **42 U.S.C. Sec. 300aa-27(a)(2)**.

Finally, this presenter concluded by stating:

> "Now, as far as the vaccines that are commercialized which contain thimerosal, as we heard, companies have been approached by the agencies and are in discussion with agencies, both in the U.S. and in Europe, as to what their plans are for reducing or eliminating thimerosal. And like other companies, I would guess, we have submitted our plans for removing thimerosal as a preservative from this vaccine.
>
> So to conclude this brief résumé and by returning a little bit to the title of this part of the talk, "Opportunities and Challenges," as I've said, I think one of the first opportunities and challenges, if you like, lies in the continued development of new multi-component products, which, of course, will result in fewer injections that need to be given, which, as we're all aware, is a good thing.
>
> The second challenge, I think -- And this is a challenge for both the industry and the regulators -- would be: how can we speed up the production of good solid dossiers to support these changes and how can we get them through the agency review period in as short a time as possible? And I think we're all exercising our minds along those particular areas, as I said, in discussions with various agencies on this particular topic.
>
> And thirdly and finally, of course, all of objectives -- our main objective is to continue to improve the efficacy and the safety of all of our vaccines."

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193 **a.** Aventis Pasteur, Inc, inactivated "Thimerosal preserved" avian influenza vaccine approved on April 19, 2007.
b. ID Biomedical Corporation of Quebec (IDB), a subsidiary of GlaxoSmithKline, inactivated "Thimerosal preserved" human influenza vaccine, FluLaval®, approved October 5, 2006.

194 **a.** GlaxoSmithKline, inactivated "trace Thimerosal" human influenza vaccine, Fluarix®, approved August 31, 2005.
b. ID Biomedical Corporation of Quebec (IDB), a subsidiary of GlaxoSmithKline, inactivated "Thimerosal preserved" human influenza vaccine, FluLaval®, approved October 5, 2006.

Based on the preceding statements, it is clear that the manufacturer's plans in 1999 were for "removing thimerosal as a preservative from this vaccine" and not, *as the joint pledge had stated*, removing Thimerosal from vaccines as soon as possible.

Interestingly, though the workshop was about "Thimerosal Vaccines," this presenter thought that the first challenge was "the continued development of new multi-component products, which, of course, will result in fewer injections that need to be given, which, as we're all aware, is a good thing" – a challenge that is clearly peripheral to the challenge of removing Thimerosal from vaccines as the American public had been promised.

Similarly, in his view, the second challenge was "how can we speed up the production of good solid dossiers to support these changes and how can we get them through the agency review period in as short a time as possible?" – again a challenge that only *indirectly* bears on removing Thimerosal from vaccines to improve vaccine safety.

At least his final challenge, "... our main objective is to continue to improve the efficacy and the safety of all of our vaccines," did mention improving vaccine safety.

After a few questions, the moderator introduced Dr. Norman Baylor, Associate Director for Regulatory Policy for CBER at the Food and Drug Administration, who discussed some of the regulatory issues involved in reducing and eliminating the use of Thimerosal as a preservative in vaccines.

Dr. Baylor stated:

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

> **[Note:** Here, the petitioners are compelled to observe that Dr. Baylor's, "no evidence has been presented that would suggest that the amount of thimerosal in individual vaccines is unsafe," is a tacit admission of either:

a. Evidence exists that the amount of Thimerosal is not safe but that this evidence was not presented, and/or

b. The Agency was aware that the vaccine manufacturers have *knowingly* failed to conduct the toxicity studies required to meet the CGMP safety standard minimum, "sufficiently nontoxic ..." established in **21 C.F.R. Sec. 610.15(a)** for a component used as a preservative in a biological drug product formulation for, *at that time*, more than 25 years.]

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

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

The first is to eliminate the use of thimerosal as a preservative in vaccines – That gets into the issue of single-dose vials versus multiple-dose vials, and I'll touch on that a little bit further in a minute –"

[Note: Here, the petitioners observe that the elimination of Thimerosal as a preservative in vaccines is what was promised to the American people. Thus, if the FDA meant to keep that pledge, this is one of the two options that the Agency could pursue.]

"or we can substitute alternative preservatives for thimerosal,"

[Note: The petitioners again observe that this is a second promise-keeping option that can be considered.]

"and the third option is to reduce the amount of thimerosal in vaccines. This option, the last option, will involve using criteria other than those outlined in the U.S. Pharmacopeia."

[Note: Given the reality that Thimerosal is, *at best*, only a marginal long-term preservative at the 100-ppm level, any significant reduction would invalidate considering Thimerosal as a preservative in vaccine formulations.]

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

[Note: The "keep using it" option presented here not only breaks the promise made but also would continue to render all lots of a Thimerosal-preserved vaccine adulterated under **21**

U.S.C. § 351(a)(2)(B) unless, *as the vaccine manufacturers have failed to do*, the vaccine manufacturers: **a)** conducted the requisite scientifically toxicity studies required to satisfy all of the applicable safety standards, including the CGMP minimum for "sufficiently nontoxic ..." set forth in **21 C.F.R. § 610.15(a)**, and **b)** found, *at a Thimerosal level at least 100-fold higher than 0.01% (about the 1% to 2% level that was banned for topical antiseptics)*, that such vaccine formulations are "sufficiently nontoxic ..." to the most sensitive humans to which such vaccines are permitted to be given. From reports on preliminary toxicity studies conducted by Eli Lilly in the early 1970s, the petitioners and the FDA "know" that Thimerosal has been shown to be toxic to humans at concentrations of 0.001% [1 ppm]. Thus, were the requisite scientifically sound and appropriate toxicity studies to be conducted, the result would clearly be that Thimerosal at 0.01% (requiring a toxicity test concentration of 1.0 % Thimerosal) or even 0.001% (requiring a toxicity test concentration of 0.1% Thimerosal) in a vaccine formulation would not be "sufficiently nontoxic ..." – explaining the manufacturers' reluctance to comply with the law. Finally, the petitioners note that the option to ban all uses of Thimerosal in vaccines was not even mentioned despite the fact that this is the option that other "developed" (e.g., Sweden, Denmark, and, must recently, the United Kingdom) and a few "developing" (e.g., Russia) nations seem to have pursued.]

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

...

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

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

validate -- you could substitute or reduce the amount of thimerosal and shorten that dating period, that would be an option also.

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

[Note: In addition to again mentioning the FDA's failure to address the unmet CGMP requirement to prove Thimerosal-preserved vaccines are "sufficiently nontoxic ...," the petitioners must observe that Dr. Block failed to mention, much less, address the statutory mandate to reduce the adverse effects of vaccines covered by the NVICP as set forth in **42 U.S.C. § 300aa-27(a)(2).]**

After a question and answer period, the workshop next heard a presentation by Dr. Mary Teeling, Medical Director of the Ireland Medical Boards, who discussed the actions taken by European countries to address the issues surrounding the removal of Thimerosal from vaccines and the actions that were being considered or had been taken.

Since this presentation did not directly address the United States of America, the petitioners see no need to address this presentation.

After a question and answer period about the European views, various views on the topic "**Immunization Issues During Transition to Thimerosal-free Vaccines**" were discussed by six presenters:

1) Dr. Roger Bernier (the CDC "point person" for Thimerosal issues), **2)** Dr. Abramson (Professor and Chair of the Department of Pediatrics at Bowman Gray School of Medicine and Chair of the Committee on Infectious Diseases of the American Academy of Pediatrics), **3)** Dr. Peggy Webster (Director of the National Coalition on Adult Immunization), **4)** Dr. Neal Halsey (Institute for Vaccine Safety at Johns Hopkins University School of Public Health and Hygiene), **5)** Dr. Bruce Gellen (Infectious Disease Society), and **6)** Claire Hannon (Director of Immunization Policy for the Association for State and Territorial Health Officials.

Several passages made by the first presenter, CDC's Dr. Bernier were instructive in revealing the commitments made and their rationale.

In addition, his remarks, in the clarity of hindsight, helped the petitioners to understand today's reality – the divergence of the various groups from the "remove Thimerosal" commitments they made in 1999.

Concerning the CDC's position as articulated in their joint press release, Dr. Bernier stated:

> "... what is the position that we have evolved to on this thimerosal question. Well, I think it can be expressed by the goals that we have articulated. The first is to reduce or eliminate thimerosal from vaccines as soon as possible. And second, to reduce exposure to thimerosal from vaccines during the transition period to thimerosal-free vaccines."

In addition, he confirmed:

> "when you look at DPT, HIB an[d] hepatitis B using three doses, the potential exposure to mercury from vaccines in the United States over approximately the first six months [of a baby's life] is this 187.5 micrograms, assuming there's not flu,"

and, *with one 0.25-mL influenza vaccine dose*, nominally 200 micrograms of mercury or, *with a prenatal 0.5-mL influenza vaccine shot to the mother during pregnancy and two 0.25-mL influenza vaccine doses*, nominally 250 micrograms of mercury by seven months.

After a convoluted discussion of risk based on acceptable limits under various dose-averaging scenarios using the guidelines (ATSDR, EPA and FDA) derived from uncertain studies of methylmercury ingestion from fish and whales and related issues, Dr. Bernier closed with (with <u>underlining</u> added for emphasis):

> "Vaccine supply issues. Issues have arisen about how to manage the stocks of thimerosal-containing and non-thimerosal-containing vaccines. There are issues about what's in the pipeline and what's going to happen to the stocks of vaccine. This may be an issue that we need to visit that we haven't fully addressed. Another one has to do with the supply of vaccines. We may, in the near future, have greater availability of thimerosal-free vaccines. If that happens, <u>will we want to express any preference for thimerosal-free vaccines as they become available? If they're only available from one or some manufacturers but not others, this has implications for the long-term supply of vaccines. Do we want to address that in any way?</u>
>
> And, fourthly, <u>there are issues around flu vaccination</u>. You've heard there have been no recommendations yet. <u>I think that's in the works</u> and, perhaps, not something that we need to be overly concerned with. <u>That will take place</u>.
>
> And finally, there are issues around research and a lot of unmet needs in the information area, and that will be the subject of Dr. Rabinovich's panel following later in the morning.

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

Here the petitioners note that Dr. Bernier was clearly sending signals that:

- Even when "thimerosal-free" vaccines become available, the CDC would be, at best, reluctant to express any preference for these vaccines over the Thimerosal-preserved ones that were clearly intended to be allowed to remain in distribution, and
- The CDC was in the process of formulating recommendations for universal influenza vaccination even though, in 1999 (and until 2004), all the licensed influenza vaccines for young children and pregnant women were Thimerosal-preserved.

Next, after an introductory joke, Dr. Jon Abramson, the second presenter began by stating (with underlining added for emphasis):

"And I'd like to highlight a few of the issues. I think there was major areas of agreement. In fact, I think for the Public Health Service and the American Academy of Pediatrics the vast majority of issues were agreed upon.

Number one, we all agreed that the risk of not vaccinating children for every one of the 11 diseases that we try to prevent with vaccines far outweighed any potential risk of giving the vaccine containing mercury."

[Note: Petitioners understand that his "we all agreed" view is not supported by any published long-term (20-plus-year) case-control study with matched unvaccinated controls of which we are aware. In addition, this statement is classic Orwellian doublespeak. If the Orwellian elements are removed, his Orwellian "the risk of not vaccinating children for every one of the 11 diseases that we try to prevent with vaccines far outweighed any potential risk of giving the vaccine containing mercury" phraseology would become "the [theoretical] risk of not vaccinating children for every one of the 11 diseases that we try to prevent with vaccines far outweighed the [known risks] of giving the vaccine containing mercury." In the U.S. today, the risk of getting any vaccine-covered childhood disease is a theoretical risk since: **a)** the risk of exposure is low, **b)** not all who are exposed contract a given disease, and **c)** the health of most who contract any of these childhood diseases is not severely impacted by having the

disease. On the other hand, the risks and incidence for adverse reactions are known and, *in most cases*, the risks of a severely adverse outcome from a given vaccine exceed the U.S. risk today of contracting the disease and having a severe adverse outcome.]

"Two, that we should eliminate or reduce as quickly as possible the amount of mercury in vaccines."

[Note: Petitioners notice that the 1999 promise to "eliminate or reduce as quickly as possible the amount of mercury in vaccines" has not yet been completely realized and, *contrary to the phrase "reduce or eliminate,"* the U.S. government has approved and recommended use of at least two new Thimerosal-preserved influenza vaccines (one human [in 2006] and one avian [in 2007]) and one new "reduced Thimerosal" vaccine human influenza vaccine (approved in 2005) since the promise was made in 1999.]

"And three, which hasn't really been pointed out this morning, is that we agreed that we should delay the use of the [hepatitis B] vaccine in the baby who is born at term and not use it at term. And why is that? And the reason is that even if you take a full-term baby who weighs 3 kilograms and you take any of the standards, from the EPA standards to the FDA standards, you are exceeding on that day the amount of mercury that is -- that guidelines recommend you give, by greater than tenfold. And we don't know what the safety margin is. This was pointed out today, and I'm sure it was pointed out yesterday, we don't really know whether it's cumulative dose or what that really matters. So we both -- Both the Public Health Service and the American Academy of Pediatrics agreed that the hepatitis B vaccine should be delayed in a mom who is hepatitis B surface antigen negative."

[Note: While the petitioners agree with and applaud this joint "delay hepatitis B vaccination" decision, we find that there is no scientific justification for universal hepatitis B vaccination since the disease is not highly contagious, and, *based on the long-term hepatitis-B-associated increases in MS in France and the United Kingdom*, this vaccine should only be used in the United States when there is a life-style-associated disease risk.]

After discussing two areas of diverging views between the Public Health Service and the AAP, and remarking on his views and some peripheral and concurrent problematic vaccine issues, Dr. Abramson closed with:

"Those are all issues that come about when you're dealing with an emergent situation. I personally think that the AAP and the Public Health System worked well together during these two emergent situations," [Thimerosal in vaccines and the rotavirus' severe adverse reactions] "and I've actually learned a lot from the process and enjoyed working with them. That's all."

Next, Peggy Webster presented National Coalition for Adult Immunizations' stand on these issues of Thimerosal in vaccines (with underlining added for emphasis):

"While thimerosal has been used as a preservative in many vaccines for many decades without apparent ill effect, it is nonetheless imperative that science and medicine continually seek safer and more effective medicines and procedures. With this in mind, we must make reasoned progress in the area of vaccines and vaccine research. On the one hand, each of us no doubt feels some level of concern in knowing that a small amount of a mercurial compound is present in the vaccines that we give to children, pregnant women, nursing women, and adults. On the other hand, it is also the case that it is difficult to find any definitive data suggesting that the use of such compounds has resulted in any direct harm to humans.

We must also recognize that changing from one preservative to another is not without some level of risk itself, no matter how small, and may lead to other potentially unknown side effects.

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

First, the Advisory Committee on Immunization Practices has rightly made the national recommendation that women who will be beyond their first trimester of pregnancy during the influenza season receive the influenza vaccination. Those who have medical conditions that increase their risk for complications from influenza should be vaccinated before the beginning of the influenza season regardless of the stage of pregnancy.

It is important to note that all of the licensed influenza vaccines in the U.S. do contain thimerosal. There has been no reason to believe that there may be adverse fetal effects associated with using thimerosal-containing vaccinations. The NCAI agrees with the ACIP that more data are needed in this special circumstance.

Second, there is a small population of vaccine recipients who have an allergic sensitivity to thimerosal. Even when allergy testing does indicate hypersensitivity to thimerosal, most patients do not develop reactions when given thimerosal-containing vaccines. If reactions do develop, they almost always manifest as local reactions, but, nonetheless, can discourage both patient and provider from further immunization.

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

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

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

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

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

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

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

Thank you for the opportunity to participate."

In general, the petitioners support the 4 "steps" that the NCAI's spokesperson discussed here.

The next presenter, Dr. Halsey, gave the perspective of the Institute for Vaccine Safety concerning what should transpire during the transition period.

Much of Dr Haley's presentation addressed the issues of safety espoused by the petitioners.

He stated (with underlining added for emphasis):

"Well, the position is fairly simple, and that is that all children should be protected against vaccine-preventable diseases using the safest possible vaccines. Actually, I think that everybody in the room would agree with that. The objective in the transition period is to minimize any potential risks that might be there, but, also, as many people have stated, to maintain public confidence in vaccines, the agencies, the federal agencies responsible for both vaccine safety and for delivery of vaccines, but also to the physicians who not only are responsible for providing those vaccines, but also for advice and guidance to parents of children who are going to be receiving these vaccines.

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

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

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

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

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

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

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

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

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

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

To go back over some of these issues, now, the first is the product labeling. I had to ask myself why someone who -- I felt I knew a fair amount about vaccines over the past 25 years and knew something about environmental exposures, why I didn't put it together. Why I didn't realize how much mercury was actually in vaccines. And I think it's because the product label indicates a concentration of thimerosal of 1 to 10,000, or a [0].01 percent. And as Leslie Ball walked us through, you have to go

through a two- or three- or four-step calculation, and you have to know the molecular weight of thimerosal to come up with the 25 micrograms for mercury [for a 0.5-mL dose]. Since mercury is the biological agent, the biological product that's there, and we have guidelines for the amounts of mercury that people should be exposed to, that should be in the product label.

There are many factors that are associated with mercury toxicity, and that's what I mean by not all children are created equal with regard to their susceptibility. Many of these were discussed yesterday, so I won't go back over all of them, but there are differences in terms of the age of exposure, the weight of children, other mercury exposures, differences potentially in metabolism and excretion rates on an individual basis, not for the products. No one has really addressed the very well the genetic predisposition to increased risk of potential toxicity."

We can look most clearly at the weights of children, and I've picked girls here. Boys weigh slightly more than girls, but if we're looking at who may be the highest-risk population, the children who are the smallest, are the three standard deviations below the norm, their birth weight of 1.8 kilos, there's a difference, a more than two-fold difference, in the weights of these children, and if exposure to mercury is a weight-based phenomenon when you get a fixed dose, then that two-fold -- that is an important concern. That two-fold difference persists all the way out to almost six months of age. And we need to realize that it's the smallest children that I think that we have to be preparing our guidelines and decisions as to what we do with them. If we take those weights of children and then apply the fixed doses and look at the worst-case scenario of children who may be getting all thimerosal products, or prior to the most recent change in the recommendations, it plots out like this. And since sending Dr. Clarkson and Dr. Raub the data on the actual weights, I did adjust so that these children were getting hepatitis B when they weighed two kilograms.

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

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

An exposure with a fixed dose, 62.5 micrograms at two months of age, is different than an exposure at six months of age, or if that was at nine months or twelve months. So I really question the philosophy that it doesn't matter when you got it or if you got a significant portion of that, one-third of it all in one day, that you really can take and look at that exposure over a six-month or a twelve-month period. So that's where I do differ. I do not know that any of the guidelines that have been written by any of the agencies say that it's okay. Can you really get all 200 micrograms in the same day? I don't see that written any place, and I don't hear that from the people who have been responsible for developing those guidelines.

Which guidelines should be applied? We've been through this too many times. You've seen this similar slide. The Public Health Service has chosen the ATSDR, which is a little more liberal with regard to the allowable exposures in the EPA. The WHO is quite similar to the EPA, as we have seen, with regard to those exposures. But over how much time can you take a single exposure and then say it's okay to get this over a day, a week, a month, or a year? We don't know. That's an unknown.

The choice of the ATSDR guideline, which is based upon the Seychelle data, made sense at the time that it was done. The process was a good process that they used. But does it mean that we should ignore data that have been generated since then, and especially the follow-up in the Faroes Islands? And does it mean that it isn't going to change? The Faroe Island data were generated when these children were 5.5 years, and they were generated looking mostly at global I.Q. And as we heard from Dr. Lucier, there will be additional follow-up and there will be harmonization of the methods to evaluate these children. So they'll do some of the more domain-specific analyses that were done in the

Faroe Islands that revealed those very subtle defects that were picked up. So it's an older age in the Faroe Islands and a more specific analyses that were done.

And equally, or, in fact, far more important, as Dr. Lucier mentioned and as Dr. Clarkson mentioned, there is the intermittent exposure that took place in the Faroe Island where it was coming a lot at one time or at monthly doses. And is that the explanation for finding problems in children at seven years of age that were not detected in the Seychelles at 5.5 years? Nobody knows that, but it certainly is one of the hypotheses that might explain the differences in exposures and we must take it into account. So I don't think that the Public Health Service means we should ignore all of these data, but we do need to be aware that they're there and take them into account and realize that more data will be forthcoming. And what will happen in two years' time if all of the experts review it and say, you know, we really should be using the Faroe Island data as the exposure, how will we be perceived? And again, these defects that are being detected are very subtle defects, and they're not going to be detected without these very sophisticated testings that was done.

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

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

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

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

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

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

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

With regard to other mercury exposures, this comes directly from the EPA report to Congress, the key point is that the majority of the population is getting relatively low-to-moderate exposures. But in this country we have some populations that have very high levels of fish intake on a regular basis. And as we heard yesterday, FDA estimates that about 7 percent of women of childbearing age are already consuming fish enough that it would give them more than their guidelines, [0].1 microgram per kilogram per day. So any additional exposure we give them from vaccines is on top of that baseline that they have set with a safety factor included.

But they also note in the report that 1 percent are receiving more than [0].37 micrograms per kilo per day. So there's 1 percent of pregnant women out there who are already getting more than what the

ATSDR guideline is. And again, what we give them is added on top of that, and these children are being born with that exposure and some are getting this continued exposure through breast milk.

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

To change to one of the other topics about thimerosal, it's not the perfect preservative. It doesn't totally solve the problem. There are numerous clusters of cases of group A strep disease and presumably other -- one, I think, of other bacteria that have occurred. So it doesn't solve the problem. I personally believe that the manufacturers need to move more toward unit dosing in this country whenever possible. And not only is the benefit from preservatives being not needed in most situations, but there are the reduced errors due to reconstitution that we heard a bit about earlier today. And again, we don't need to go through all of those. There will be another session this fall on some of those issues. There are drawbacks, and these are major limitations that -- and that's increased space requirements in the refrigerator, but I don't think they're quite as bad as what John Clements was telling us. There are some technologies that can reduce the amount of space that's going to be required to store unit dosing. There will be increased costs, and I recognize that as a major problem for developing countries, but I think that we do need to help in terms of addressing that issue. We need to look at it from this country.

So to maintain public confidence in vaccines and people giving advice about vaccines, I think we should put the mercury content in the label. I think we need to modify the vaccine information statements. That is our primary means of communication with families about any potential or perceived risks. We don't have it in there now. I realize the process is long to put it in, but I think that has to be done as soon as possible. I also think physicians should be given more precise guidelines over maximum allowable exposures at each age. Can we really have recommendations for the highest risk and have physicians looking at fish consumption and other things? The Academy of Pediatrics is developing additional guidelines on reduction of mercury exposure from all sources. Those won't be available for six to nine months. I don't know what the time will be there, but do we need to have separate guidelines for immunization for those children versus others?

In general we have said, no, we can't do that. We must make guidelines for everybody that will be applicable to all of the populations. So my personal belief is that we should do what was done in Europe, that we should give a preference for thimerosal-free vaccines for immunization of infants in this country.

The last point I'll make is that we need good science to be used in making these decisions, and that good science has to come from all of our federal agencies. As I looked into what was going on at FDA and research into alternative preservatives, research into other ways to approach this and who is going to be reviewing these applications that were all asking for or demanding rapid review, what is the research budget at CBER? The research budget has been cut in the last five years to one-third of what it was before. Instead of being 20 percent more just to keep up with inflation in that period of time, it's been cut to one-third. I don't know why. I don't know who's responsible, but I hope somebody goes to Congress and says that this is wrong. Thank you very much."

Here, petitioners notice that, though Dr. Halsey's suggestions were based on his concerns for improved vaccine safety and improved communication so that there might be informed consent, his suggestions to:

a. Improve vaccine safety (remove Thimerosal and move to single-dose vaccines without any preservative), and

b. Communicate the risk (display mercury content on label and modify the vaccine information statements to include mercury-content information)

have been either incompletely implemented, *when it comes to improved vaccine safety*, or, *for improved communication*, ignored.

Next, Dr. Gellen, representing the Infectious Disease Society, who began by stating:

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

After discussing the concepts of communication, education and decision-making in terms of "risk" and what amounts to damage control when it comes to vaccine safety issues, this presenter concluded with (with <u>underlining</u> added for emphasis):

> "So I think that <u>we've learned that there are health risks of mercury-containing compounds</u>. <u>We have the desire, all of us, to reduce those risks from all sources that we can</u>, and that with a limited data, we are going to be forced to make assumptions and extrapolations, and there may be differences in how people handle each of those, but that <u>we then need to continue to do our best to be as transparent about all the -- about the process, and to let people know that there actually is a process in place that's looking at these things</u>. I think we have heard that from a number of speakers as well, that it's not as though there are not systems in place that recognize this. And I think that, as Jon highlighted, the fact that this went on, essentially concurrent with the issue of rotavirus, highlighted that to all of us.
> <u>We have had a number of these</u>, as we've discussed in the past, quote, '<u>case studies</u>,' and <u>I think that we really need to take a hard look at the case studies that we've been presented to see what lessons we can learn for the next time and how we can go about making good decisions based on the best available science and communicate those decisions though there's still uncertainty</u>. Thank you."

Here, the current petitioners agree, "we've learned that there are health risks of mercury-containing compounds."

In 2007, we know that these health risks for Thimerosal are <u>at least</u> an order, if <u>not</u> two orders, of magnitude greater than admitted by the U.S. government and/or revealed by most studies published in the late 1990s and early 2000s.

Petitioners also observe that, in spite of this and the previous presenters' calls for improved communication of the risk and transparency, the Agencies charged with overseeing all aspects of drug safety and the Department to whom they report have rejected these suggestions and elected to reduce the communication of risk and the transparency of the decision-making process.

That having been said, the last presenter, Claire Hannon, Director of Immunization Policy for that the Association of State and Territorial Health Officials (ASTHO) began by stating (with underlining added for emphasis:

> "ASTHO doesn't have a specific policy at this time on thimerosal, so I just wanted to give you some background, how we reacted, and a sense of what state health officials feel about the issue.
>
> ...
>
> As I said, we don't have existing policy. And amongst all these discussions with the state health officials, we were not able to reach consensus on specific new policies in such a limited amount of time in reaction to thimerosal. So for that reason, states are using the available science, as well as the CDC and AAP recommendations, to formulate their own policy on a state-by-state basis.
>
> At this point, my discussions with state health officials I think would indicate that they don't see a serious cause for concern at the current level of thimerosal but believe it is prudent to reduce or eliminate thimerosal, given that new vaccines with varying manufacturing needs can be expected in the future."

Then, she admitted that ASTHO's main concerns were "maintaining immunization coverage, protecting infants from disease, and maintaining public trust," and not vaccine safety.

She closed by stating:

> "Just to add a little bit of state perspective, I spoke with Dr. Natalie Smith, who is here today from the California State Health Department. She's a member of the Association of Immunization Managers, and they've also been holding discussions over the last two weeks or so about thimerosal and vaccine safety issues. It does appear that states are taking a variety of approaches in the transition to thimerosal-free vaccine, approaches which are sometimes very different. I think both of our associations are eager to hear the most up-to-date information, including reports from this conference, and share those with the states. The states benefit from clear direction and lead time to implement policy changes. Thanks."

A question and answer (Q&A) period followed the last presentation.

The petitioners would like to highlight the statements that bear directly on the issues of proving safety and upholding bodily integrity (through informed consent) that were made during this Q&A period (with underlining added to emphasize the key portions of the statement).

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

DR. BERNIER: "I was thinking you probably expected Neal to answer that question, but I'll probably surprise you by trying to tackle it myself. I think what's happened is that -- I've told this to some people -- we've had a paradigm shift in how we think about this preservative. And when I went to leadership classes, I was told paradigm shifts take years. I think we experienced a paradigm shift in days, or maybe weeks at the most.

And it has to do with our consciousness being raised about the potential, potential, effects of mercury. Once we had that realization -- And I think in some way there was a new realization for all of us, and some of us came to it for different reasons in different ways. I think Neal likes to talk about how, you know, the concentration and the dilution were not an easy way to realize this, but all of us in some way have had a sort of heightened awareness now, and we can't do business as usual. I mean, that's -- While there's not a lot of evidence about harm, and it's a potential thing, it does become a matter of choice and goal and direction that you want to go into. That's how I would tackle it."

DR. RICHARD: "Yeah, for Dr. Halsey. I'm John Richard from the Agency for Toxic Substances and Disease Registry. You raised some very good points, and I was just pointing out that those are things that the government health agencies that are involved in this and involved with the analysis for assessment of health effects of mercury have been concerned about and have considered. And I think this afternoon, in the research needs portion of the program, some of those will be addressed. You also raised some questions or asked questions of ATSDR, and real quickly I'd just like to point out three things.

One is that in a series of three injections, three vaccinations, the total dose, as I understand it, is 62.5 micrograms per child. While that's to the child in the Seychelles study, we looked at the dose that the mothers received every day on the average throughout pregnancy, and that was 78 micrograms per day. Well, that's to the mother, of course, and on a milligram-per-kilogram basis, that's different. But if you take that 78, then that every week they're receiving almost 600 micrograms of mercury, and this goes on throughout pregnancy. Not only that, but the methylmercury is -- all mercury, or most mercury is accumulated in the fetus at higher levels in the fetal circulation than it is in the maternal circulation. So these were infants or neo -- excuse me, not neonates -- fetuses being exposed throughout critical times in their development, and we're not saying one point of development is more important than the other, or whether it's the beginning of (inaudible) migration early in the third week, or whether it's further into cerebella or cerebral organization, but throughout all those critical points of fetal development, they were exposed to mercury, methylmercury, through high levels of maternal ingestion relative to the levels that we're talking. For what it's worth, methylmercury is believed to be absorbed close to 100 percent, 95 to 100 percent, through the gastrointestinal tract. So those 78 micrograms a day is actually an absorbed dose.

Two other quick things, then I'd be happy to hear your response, sir. In the Seychelles, by and large, the tests were of global cognitive function. However, the McCarthy scales tests were conducted, and back in November when the workshop was conducted in Raleigh, one of the panels actually examined the data from the McCarthy subscales and they concluded -- And it's in that report that George Lucier said he had available -- that the data from that on a limited -- not limited, they didn't use the term -- but domain-specific effects indicated no domain-specific change in alteration and function as a result of methylmercury. One thing

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

[**Note:** Petitioners observe that subsequent reviews of the information available on intakes have reduced them by at least a factor of 2 to 5 and the absorption of the putative mercury-storage compound in fish, "methylmercurycysteine" is closer to 20 % than it is to the "95 to 100 percent" value stated here. Taken together, the pregnant women's weekly absorption of mercury from fish is closer to 3 to 15 micrograms and, factoring in fetal partitioning, the fetus' exposure is no more than 50% of the dose. Further, since this population has been exposed to this environment for generations, those individuals who were susceptible to clinical mercury poisoning from dietary consumption of fish would died out leaving a mercury-resistant population.]

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

DR. MAHAFFEY: "Some comments and a couple of points. First of all, while on average the amount of mercury exposure through food is under the EPA [0].1 microgram per kilogram per day for adult women, it's certainly not an even distribution and, as Dr. Halsey pointed out, there are groups who are far higher with one percent above the ASTDR level. There are also groups within subpopulations who go a great deal higher, and we have some idea of who these subpopulations are. We know that there are people in this country, probably two or three percent, who eat fish just about every day. So while, on average, yes, it's true, the exposures are lower, they're certainly equal.

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

[**Note:** Here, petitioners observe subsequent studies on the correlation between mercury in hair and mercury intake have found that these numbers are not a constant nor do they fall within a narrow range. Furthermore, there exists identified

individuals who have near-zero levels of mercury in hair no matter what their level of mercury exposures – these are "non-excretors" with respect to mercury in hair. Given the proven existence of a subpopulation of mercury non-excretors, it is obvious that the EPA daily intake "guideline" has a negative safety factor for these individuals as well as no real safety factor for the mercury "excretors" because the actual mercury exposures from fish were lower than presumed and the reference compound used "methylmercury hydroxide" has a much higher absorption than the actual protein bound compound (methylmercurycysteine) found in the fish consumed. Based on 2007's understanding of these factors, the "guideline" daily intake dose for mercury in vaccines should be at least an order of magnitude lower (0.01 micrograms of mercury per kg of body weight per day) than the dietary intake guideline for fish eaten by adults.]

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

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

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

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

that there is this spectrum of what our public health emergencies are, true public health emergencies, epidemics of pneumococcal disease or exposures to toxic or infectious substances, and then there are potential public health threats. I think this very clearly is a potential public health threat that warrants very careful consideration and, because of the kind of consequences people have talked about, very careful consideration of the response.

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

DR. MUSIC: "I want to express some concerns about the epidemic of disease that I think we're beginning to see as a result of the controversy. When I hear John Abramson talk about a 3 kilogram normal infant and say on that day we exceed the guide by tenfold or when I heard Roger Bernier say 'I haven't heard anybody say differently,' I mean, I understand that the complexity is enormous and I think that that's an underestimate.

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

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

[**Note:** Petitioners agree that using an MRL for ingested organic mercury (that is based on "methylmercury hydroxide") for injected Thimerosal is a bad idea not only because there are "no data for ethylmercury" but also because there are absorption issues that do not apply when we are injecting a bolus dose. However, the commenter's concern for an "epidemic of disease" is and was a baseless concern. Finally, we note that his real

concern, "delayed vaccinations are not good," seems to be a worry about Merck's potential loss of revenue more than a true concern for the health of the public.]

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

A comment was made about eating six ounces of tuna fish which contains 17 micrograms of mercury. Now, if you take that once, as a pregnant female weighing 60 kilograms, the increase in mercury level in blood or tissues would be so small you couldn't measure it. If you took that six ounces day after day for six months to a year, her blood levels would slow rise until they reach the level consistent with these guidelines, about 20 parts per day. So there seems to be a tremendous misunderstanding as to what these guidelines mean, and with the benefit of hindsight, we should write a talk on the kinetics of mercury so that we have some understanding of what the meaning of a day dosage in terms of tissue levels versus the meaning of a six-month dose. And this is -- I mean, in this learned audience, it worries me that there's such a misunderstanding of the guidelines. Lord only knows what the general public views these as."

[**Note:** While petitioners agree that "MRLs" and "guidelines" have been misused, we do so more on the basis that: **a)** they are not for Thimerosal and **b)**, given all human mercury-protective systems have inherent limits, they do not address the "near instantaneous" bolus-dose situation that vaccines present. However, we find that both the example and the interpretation are misguided. Today, we know the example that should be considered is a 25 microgram dose Thimerosal being injected at birth into a 1.8 kg infant who has impaired mercury-excretion ability followed by 100-microgram doses of Thimerosal at 2 months and 4 months of age and up to a 175-microgram dose of Thimerosal being injected into that same mercury non-excretor at 6 months.

Since:

a. Cellular and tissue studies have shown that the acute cellular toxicity of Thimerosal (49.55% mercury by weight) is the same as, or worse than, the toxicity of ionic mercury (II) salts

b. Like ionic mercury, Thimerosal is an immune system disruptor, and non-excretors retain most of the mercury to which they are exposed, and

c. Severe mercury poisoning has been proven in some children where mercury-containing biological products administered to their mothers and/or themselves are the principal sources of the mercury,

d. There are no published toxicity studies for Thimerosal that have established a human no-effect level or a "sufficiently nontoxic ..." level in humans (as required by **21 C.F.R. § 610.15(a)** since 1973) and unpublished studies by Lilly (who *coincidentally* abruptly sold off its vaccines business in the mid 1970s) in the early-1970s *reportedly* found toxicity at levels 100-times lower than the 100-ppm level in the vaccines they were making, it is, *or should be*, obvious that the only amount of Thimerosal that has been proven to be "sufficiently nontoxic ..." in a biological drug product is zero ("0") Thimerosal.

Until and unless, *scientifically sound* and *appropriate* toxicity studies can find it "sufficiently nontoxic ..." as required by **21 C.F.R. § 610.15(a)**, Thimerosal must be banned from any use in the manufacture of all biological drug products and should be banned from all uses in medicine.]

Following the Q&A session, the moderator for the workshop then moved to start the last scheduled event, the panel discussion on "**Filling the Gaps: Developing a Research Agenda**" in which the "**Gaps**" were presented by Dr. Regina Rabinovich and Drs. Tom Clarkson, Michael Gerber, Alison Mawle, Peter Paradiso, John Risher, and Bernard Schwetz presented their views on the "Priorities for a Research Agenda." [**Note:** As we have done previously, the petitioners will use underlining to highlight key points that bear on the issues being raised in our citizen petition.]

In her opening remarks, Dr. Rabinovich, from the National Institutes of Health (NIH), stated:

"... because I'm going to attempt to define the landscape as I understand it right now. I am not going to attempt to devise or force consensus because I don't think it's doable. Then I'm going to define

some of the questions that remained in my mind as I listened to the presentations of pre-clinical, clinical, and public health and industry perspectives.

The panel members will each -- Dr. Clarkson, if you could join us up front, so that as each panel member speaks, they'll be up at the front. The panel members will each -- have been asked to speak for several minutes, no more than five or I will cut it off. ..."

Then, after some introductory commentary, she continued by stating:

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

First of all, vaccines are not perfect. Everyone agrees with that, I would hope. Yet, we understand the enormous value of the role of vaccines in preventing disease. That was beautifully stated yesterday. I think what people don't realize unless they've been involved in some process development or evaluation of that process is that GMP, those standards defined by the field of good manufacturing process, are not perfect. Actually, I've seen some studies where you can quantify the rate at which you will have contamination of a vial given different GMP practices, but that it's not zero. It's a quantifiable risk. At the same time, there are both regulatory and field requirements for a preservative in multi-dose vials. There are some questions that we'll come up and things that I still haven't learned after two days of discussion regarding use of multi-dose vials in the public sector, both domestically and globally. I have learned that the ideal preservative does not exist. I was trying to elucidate the characteristics of an ideal preservative. I've got that list for vaccines and antimicrobials, and I decided I really didn't know enough to do that, but, perhaps, it would be helpful to have someone help us by doing that. But the ideal preservative probably does not exist.

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

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

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

The other principle is that -- Someone asked me on the way in, they said, 'Is this thing about coffee not in the room, is that a regulation or a guideline?' I went, 'It's a regulation. They'll throw you out of here.' That's a regulation. This is not. This is a guideline. I think that I want -- Where's Roger? I want that slide that shows the gray zone, the white zone, because we got it from whoever presented that at

the influenza meeting, and I think that's the best graphic to really present. It doesn't matter, [0].1 versus [0].3, until you start talking in smallest children and then I'm not sure how it matters, but the [0].1 versus [0].3 versus [0].4 are built into how the non-methyl people think about guidelines and what kind of question they're trying to answer when they create guidelines.

The environmental community, having listened to three different sets of them -- Or maybe at least three different sets of them -- are not unified in their assessment of ethylmercury. They may be a lot more in consensus about methylmercury, but they've done that on the basis of detailed review, and I don't think we have the data to look at that. This is the scientific issues relevant to have effects from exposure to methylmercury. Two-day meeting full of preclinical primate/human epidemiologic -- we haven't done that for ethylmercury and we won't have the data to do it at this point.

I think the last thimerosal principle that the vaccine community -- we're faced [sic; forced?] to deal with is different from what the environmental folks have to deal with. It's what I call the Caesar's wife principle. And some of those things my dad taught me, but you sort of remember, is that not only did Caesar's wife have to be pure, she had to appear pure. This issue of appearance being everything, that we have to not only be doing what we think we're doing, but to appear and to be able to inform and to be open and transparent about it. I think it's something we need to keep in mind as we go on and define the research.

So gaps? Now, gaps are in the context of what I thought were the general principles, and they're not necessarily in the most logical sequence. I sort of started pasting together my thoughts over the past day and a half and the past two hours. Let me just go through them and I promise to distribute them to anyone who wants something a little bit more logical here. 3

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

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

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

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

We need to evaluate potential health impact of prenatal exposure and, if we're going to do that and figure out ways to answer those kinds of questions, it has to be in the context of timing of exposure as it's related to those critical windows of susceptibility during development. That was recommended by the methyl group and I think the ethyl group, and ethyl considerations need to include that.

Now, when I start talking about ethylmercury and especially ethylmercury presented intramuscularly, the question really is, how different is it from methylmercury? The potential differences, and I've heard everything from 'mercury is mercury' to 'it may be 20 percent less toxic' or 'really, you need to use it as the model' to 'we don't know.' And the differences could relate to the potential health effects and the pharmacokinetics, the biological activity, the clinical endpoints one must worry about, the effect of a route of administration, and the dose schedule.

And even something as relatively simple to answer -- And we hope to have data not too long from now, Dr. Clarkson -- is, is it excreted and how in infancy? We can't answer that today and we should be able to do that if we're doing our jobs very shortly from now.

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

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

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

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

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

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

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

I think it is possible to get a little bit more data on when in the first two years of life are infants exposed to hepatitis B, because we keep having to come back and discuss that when it comes to the hepatitis B issues. There will be -- There will be -- This is not a question. There will be an ongoing need to conduct an assessment of the cumulative effect of the immunization schedule. And Bruce talked about lessons learned, and I think a lesson learned is as we add and recommend vaccines that we need to look not only at individual vaccines but at the schedule that we're recommending from every perspective. I'm sure we'll continue to be surprised, but we won't be caught with this one again.

Data, people have raised 'Who's going to do this?' and 'Are you going to talk about it?' So let me ask: Do we have data -- I don't think we do -- on which to comment upon the long-term effects on vaccine-level exposure to ethylmercury? I think the first place to look, and I'd ask those communities that have -- the scientific communities that have these databases, can some sort of assessment be made from analysis or evaluation of existing data sources? In other fields like the diabetes issue, we were able to provide, I think, useful analysis from an existing database resulting from a randomized clinical trial in a country in which there was a very detailed and validated diabetes registry to answer a specific question. Are there places we could be looking for information pertaining to this or do we need to go look for novel sources and at what point do we need to go? Do we have enough knowledge about what's going on from animal models or fairly simply measurement of levels in children to have a high enough level of concern that we need to worry about bad health effects as opposed to recognizing the levels that are being administered potentially through vaccines? And I think Roger presented the diversity of the vaccine schedules to say we need to limit exposure. There are different presumptions that lead you to different conclusions.

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

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

The charge to the panel -- And I'll ask each speaker to talk for three to five minutes and I have my FDA watch on -- is, number one: What are priorities for research from your perspective? 17

Number two, even if you don't include that in whatever you had thought you were going to present up to now, can you comment on the feasibility and the urgency to do so? I ask you to do this in the constant context of a comment that George Kirwan would make if he was here and he would say, 'You know, the most expensive words in the English language are, I wonder if.' So you have to put some value on if the 'if' that you're trying to answer is, indeed, important for science, for public health, or public policy."

The petitioners will now present pertinent excerpts from the comments by each presenter and, *where appropriate*, underline key points, and comment on "what was said" in light of "what is known today."

The first commenter, Dr. Clarkson, began with:

"With regard to human studies, some suggestions that the group might want to consider, first of all, is this calculation that I did which I think it -- the calculations like this have to be done to assess risk from ethyl and methylmercury. You have to base them on blood levels because all of these guidelines from these various government agencies and so forth all start with toxic blood levels and minimum toxic blood levels and so forth, and they work from them. So what I've given here, for example, is the blood levels that might develop in an infant given these schedules of vaccines. For example, the first shot only raises the blood level to about four parts per billion which is actually about the equivalent of the EPA guideline. So I heard this morning a single dose will be ten times or something the EPA guideline. It's certainly not. It might approach about the EPA guidelines, but as you can see, as it builds up with subsequent doses from the vaccines, it does certainly exceed the EPA guideline by a factor of four or five. But all this is based on all kinds of assumptions. One is that methyl is the same ethyl, which it probably isn't. It's based on the assumption that there's no excretion, and as the Chairperson pointed out, that's something that we should definitely check and I promised to do that, be a good boy."

[Note: Petitioners must observe that, unlike lead, *where post-exposure elevated blood levels of lead persist for months in most cases*, the levels of mercury in blood are not valid markers for the level of mercury burden or toxicity (poisoning) in the human body because Thimerosal and its metabolites are rapidly absorbed into the tissues where they tend to become "tissue bound." To date, the only valid, readily measured markers for mercury poisoning that have been validated are the abnormal levels and pattern of certain porphyrins measured in an analysis of a urine sample protected from exposure to light. This urine porphyrin profile analysis ("UPPA") test had be proven to be a valid indicator of occupational mercury poisoning (toxicity) in humans for more than 20 years at the time of this workshop. However, it was not until recently[195] that this test was proven to be valid for identifying mercury poisoned children in studies on children with a diagnosis in the ASD spectrum, their neurotypical siblings, and matched controls. Thus, Dr. Clarkson's approach is not valid and, *though it has been pursued*, should be abandoned in favor of using the UPPA test to assess: **a)** mercury poisoning, **b)** mercury-poisoning severity, and **c)**, perhaps, mercury body burden in those injected with Thimerosal or having other relevant mercury exposures.

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[195] **a.** Nataf R, et al. Poryphyrinuria in childhood autistic disorder: implications for environmental toxicity. ***Toxicol Appl Pharmacol*** 2006; **214**: 99-108.
b. Geier DA, Geier MR. A prospective assessment of porphyrins in autistic disorders: a potential marker for heavy metal exposure ***Neurotox Res*** 2006; **10**: 57-64.

In addition, *as some of the existing literature indicated,*[196] *and subsequent studies have confirmed,*[197] the metabolism and excretion of "methylmercury" and "ethylmercury" are indeed different; the immune toxicity profile for Thimerosal differs from that of "methylmercury"; and Thimerosal's autoimmune triggering potential is much worse than that of the methylmercury compounds that have been evaluated.

Finally, since: **a)** some children have been shown not to excrete mercury in their hair or fingernails even when they have significant exposures and **b)** the half-life for "inorganic mercury" in the brain has been shown to be about 20 years,[198] any "risk" guidelines must be based on a "no excretion" model to protect those "non-excretors" who are most at risk.]

Then Dr. Clark suggested hair studies:

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

[**Note:** Though a recent study by Marques et al. has proven that hair levels of mercury track vaccine exposure as well as mercury depletion in lactating mothers,[199] the studies by Holmes et al. have shown that this is not a viable population-wide method for mercury-exposure monitoring because some children are non-excretors.[200]]

Finally, Dr. Clarkson suggested a review of the existing data gathered in the Seychelles study and animal studies.

"As I say, I learned an important thing -- many things from this meeting, but one was that we didn't take into account vaccines in the Seychelles study. I think it's possible now -- Thank you, Dr. Myers -

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196 Tryphonas L, Nielsen NO. Pathology of chronic alkylmercurial poisoning in swine. ***Am J Vet Res.*** 1973; **34**: 379-392.

197 Burbacher TM, et al. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing Thimerosal. ***Environ Health Persp*** 2005; **113**(8): 1015-1021.

198 Sugita M. The biological half-time of heavy metals. The existence of a third, "slowest" component. ***Int Arch Occup Environ Health*** 1978; **41**: 25-40.

199 Marques RC, Dórea JG, Fonseca MF, et al. Hair mercury in breast-fed infants exposed to thimerosal-preserved vaccines. ***Eur J Pediatr*** 2007 Sep; 166(9): 935-941. Epub ahead of print on 20 Jan 2007.

200 Holmes AS, Blaxill MF, Haley BE. Reduced levels of mercury in first baby haircuts of autistic children. ***Int J Toxicol*** 2003; **22**: 277-285.

- that it's possible that we may now be able to go back and look at that. We have an enormous amount of behavioral data, clinical data, development data on these kids who are now nine years of age. So we have a huge database. So we might be able to now take a look and see who got vaccines and how much and whether this has an impact on our data, and we might therefore get some -- I hope some useful human data out of this. Of course, this will be a vaccine on top of a substantial dose of methylmercury. So this could be useful, too. When we heard about all other kinds of mercury exposures that kids are exposed to, here you've got a population that really is getting an exposure, on the average, ten times higher than the U.S. population. If we superimpose vaccines on top of that, if we're going to get any effect, we'll get it in the Seychelles as I mentioned. If we don't get an effect, I think it will be very reassuring for this situation."

[Note: First, he admits the impact of vaccines was <u>not</u> considered in the original study. However, the petitioners also notice that he is ignoring the genetic effect of generations of population pressure from ingested mercury when he states, "here you've got a population that really is getting an exposure, on the average, ten times higher than the U.S. population" and "If we superimpose vaccines on top of that, if we're going to get any effect, we'll get it in the Seychelles as I mentioned. If we don't get an effect, I think it will be very reassuring for this situation."**]**

"As far as animal experiments are concerned, I understand that it's really not going to be practical to do a major Seychelles type study in this country with regard to vaccines, but I think that animal experiments are feasible. I mean, one can do a lot of neurobehavioral tests and kidney function tests on animals. There are three or four papers in the literature on ethylmercury, so we've got good guidelines to start with for ranging effects. So I would suggest we could do that or somebody could do that. We'd be happy to make them an offer. I'm in my elements this afternoon. I'm after research money. The other point is that -- especially with regard to this figure here, the salicylic acid may be playing a role here. I've talked to some of my colleagues here today and yesterday. We don't know how rapidly it may go from the intramuscular side. I've assumed in this figure here that it's a very rapid, almost instantaneous distribution, but it may not be and that's something we could test in animals, too. All our previous animal work has been done with ethylmercury chloride, which is a very lipid soluble commodity that diffuses readily from tissues. It will be interesting to see if the salicylate compound" [Thimerosal] "behaves the same way. For example, if you're looking at the transport of methylmercury into the brain, methylmercury-L Sistine" [sic; cysteine] "gets in the brain rapidly. The disomer, the optical isomer, the only difference is the optical activity. The d[-]isomer does not go into the brain. So the chemical compound, not just the mercury itself, but the chemical compound when mercury is present may play a very important role in its distribution and kinetics. This may -- If it was a slower release, for example, these peaks may not be as high as they are in this figure. So I think it's worth considering. So with that, Madam Chairman, I hope I've earned myself a little grant of some sort. I don't know."

[Note: Petitioners are surprised that Dr. Clarkson was apparently unaware of the patent findings that Thimerosal fairly rapidly solvolizes in body fluids to ethylmercury chloride and ethylmercury chloride with the reaction being driven by two thiosalicylate molecules being converted to a

disulfide. Based on the preceding reality, there is no need for a study of the ability of Thimerosal to cross the blood-brain barrier.

For animal testing, the petitioners note that the published (in 2005) baby monkey study[201] in which he is one of the authors not only suffers from a different mode of delivery for the test animals (fed for methylmercury hydroxide and injected for Thimerosal) but also the failure to report any behavioral alterations or comparative tissue slides for all treatments even though the study by Hornig et al.[202] (published in 2004) observed and reported data for both altered outcomes in the affected mice that she studied. If, *as was suggested here by Dr. Clarkson and has been suggested by others*, this "effect" data exists but was not published, then, this failure, *when it is revealed to the public*, will further undermine the public's trust in claimed "lack of evidence of harm" for the use of Thimerosal in vaccines.]

The next commenter, Dr. Gerber, from NIH, stated:

"Thank you. Well, as we've heard several times yesterday, as well as today, we can speculate on what the mercury levels may be in infants who've received immunizations with thimerosal-containing vaccines, but as far as the actual data demonstrating what those levels are, there really is very little. In fact, the only data that we have comes from stages of study at the nursery at Emory. We heard yesterday about the limitations of that study, the fact that it hasn't been published except in abstract form, the fact that there are only five term infants and fifteen premature infants, that the fifteen premature infants had a mean weight of only 750 milligrams, concerns about the methodology of that study. So, needless to say, with that being the only data that we have, we really have very little.

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

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

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

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201 Burbacher TM, et al. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing Thimerosal. ***Environ Health Persp*** 2005; **113**(8): 1015-1021.

202 Hornig M, Chian D, Lipkin WI. Neurotoxic effects of postnatal Thimerosal are mouse strain dependent. ***Mol Psychiatry*** 2004; **9**: 833-845.

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

But, in any case, in addition to the premature infants, we would then want to look at a cohort of term infants[,] kinds of pediatric practices, one practice in which the routine immunization had been providing the patients with vaccines that had a relatively high amount of thimerosal. We would want to look at a second group of practices where the cumulative exposure from vaccination of thimerosal would be relatively low, and then, finally, practices or a group of practices where only thimerosal-free vaccines had been used. Again, we would want to look at these infants within one month to several months following the two-month immunization and at that point determine what the exposure, what the combined exposure had been at that two-month visit, as well as all of the possible previous exposure to thimerosal from earlier immunizations, and collect blood, stool, urine from those patients, as well as maternal hair samples if we could.

We would also want to look at a similar group of infants from those same three types of pediatric practices after the sixth-month immunization and, again, make a determination of the total thimerosal exposure at that six-month immunization, as well as any exposure from previous immunizations and again collect blood, stool, urine specimens from those infants, as well as maternal hair samples if we could.

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

Is this feasible? I think it is feasible. One limitation of the feasibility is trying to do this as soon as possible while children are still receiving thimerosal-containing vaccines. Why is this important? If we're moving towards -- hopefully moving towards a situation where infants in this country would no longer be receiving thimerosal-containing vaccines, I think there are three reasons.

First of all, I think the information that would be obtained would be helpful for those parents whose infants have already or will continue to receive thimerosal-containing vaccines.

Number two, as we heard from Dr. Clements, although we may be approaching thimerosal-free vaccines in the near future, for much of the world, this is something that's not going to happen for several years, at least several years, so this information would be important for those populations.

Finally, as one of the charges in the Joint Statement from the American Academy of Pediatrics and the Public Health Service, this type of research was one of the things that we had committed ourselves to performing. Thank you."

[Note: Unfortunately, *as far as the petitioners have been able to ascertain*, **a)** these studies have not been conducted or, *if conducted*, not published and **b)** Thimerosal-containing vaccines, including multiple doses of Thimerosal-preserved influenza vaccines, starting *in utero*, continue to be given without the requisite toxicological proofs of safety (reproductive toxicity studies for the fetus and UPPA-test and neurological deficit assessments for the infants vaccinated with Thimerosal-containing vaccines). Apparently, the government, the source of the funding for the proposed studies, either:

a. Felt that was no need to conduct these studies to prove safety of Thimerosal in vaccines to the standard "sufficiently nontoxic ...," even tough the law (**21 C.F.R. § 610.15(a)** requires such be conducted, or

b. Knew that the outcomes observed would establish that the Thimerosal exposure was toxic and, to varying degrees, the infants exposed to Thimerosal are mercury poisoned and did not want that information to be generated.]

Next, Alison Malwe, of the CDC, spoke:

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

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

At this point, Dr. Clarkson interjected: "Why don't you come? It's a nice island"; Ms. Malwe responded: "I'd be delighted to come. I just don't eat the seafood" and then she continued by stating:

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

This is coming from the fact that we live in a mercury-contaminated environment and seeing the contribution of vaccines within that context I think is critical. From CDC's perspective, I think it's very important and very urgent that we monitor any changes on immunization practices. The data that

Eric Mast presented yesterday I found very disturbing, that in such a short time you can already see an effect of this. We heard from -- I don't know if they're going to address this, but we've heard from the manufacturers over the last few weeks that we could not go to a thimerosal-free schedule right now without introducing dramatic vaccine shortages, which would totally disrupt the current schedule. So we clearly want to keep our current immunization program in place, we want to reassure people, and we also want to -- in some way, come up with a time line for reducing or removing thimerosal. I think that that is something that CDC can contribute to in terms of doing surveillance on what effect is being had on the schedule itself.

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

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

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

[Note: Petitioners simply observe that, as far as we can ascertain none of the recommended studies have been conducted and Thimerosal has not been removed from all vaccines recommended for children (generally, defined in the US as humans under the age of 18). Moreover, CDC spokespeople have been increasingly less than truthful about the presence and import of Thimerosal in vaccines as time has elapsed to the point that today the media often reports "Thimerosal was removed from vaccines in 2002" or some other similar less-than-truthful statement. So much for communication and transparency.]

Then Dr. Paradiso, of Wyeth-Lederle, spoke:

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

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

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

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

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

Lastly, I just want to comment, Norman Baylor talked this morning about the FDA review process and the desire to expedite review. I need to point out that on those two slides, the list of potential requirements for the presentation for a new preservative or the presentation of any new formulation is potentially not a small task, and if you're talking about doing stability studies in real-time, usually that's a two-year real-time stability study. If you're talking about doing consistency studies and if you're talking about efficacy trials, you're talking about several years and fairly major programs for the presentation of new preservatives. So all of that needs to be put together before the review process can start, obviously. So I just wanted to tell you that when we think about these changes in formulations, we think about the time lines that are required prior to that submission and those are fairly long time lines from a manufacturing perspective. That's all I've got to say. Thanks."

[**Note:** First, the petitioners notice that Dr. Paradiso argues against doing any safety/toxicity studies on several grounds. Moreover, he ignores the reality that the information needed is still required for those developing countries who continue to use Thimerosal-preserved multi-dose vials. While he correctly realizes that we should eliminate Thimerosal "because it makes sense not to inject mercury," he thinks that the data is not "going to tell us too much about potential

rare adverse events that may occur as a result of having thimerosal" as a preservative in a vaccine formulation.

Moreover, we agree with him when he states, "things that I would like to know, it would be: How do we assess cumulative effect when we talk about vaccination? The only data, I guess, that would be convincing to me would be data that actually measured levels in the blood or in an appropriate bodily fluid that could be related to the potential toxic effects that we're worried about. Those are mostly neurological" and, *as petitioners have stated*, recognize that the "UPPA" test on appropriate urine samples has been proven to be the recognized standard that should be used to assess any person's current level of mercury intoxication.

With respect to his, "I think we need to, however, then think, what if it's undetectable?," the published UPPA-based studies of neurologically damaged children have more than answered that question and have established that the harm caused to some children by Thimerosal-derived mercury poisoning is certainly detectable.

With respect to his, "Multi-dose vials are greatly favored. I mean, the reason we use them in the United States is because that's what the physicians' offices prefer," petitioners note that the lower per dose price is the true driver and not any innate preference that drives "what the physician's offices prefer." For liquid vaccines formulations requiring no reconstitution, this preference could easily be overcome by pointing out to them that the overall costs and risks of dose loss are lower. For vaccines requiring reconstitution with a diluent, there are pre-fillable syringe devices that could actually reduce the overall costs and dose losses for such vaccines. His real concern is that the time and costs to not only retool the existing aseptic filling suites but also to upgrade them to the standards required for "riskless" aseptic single-dose filling.

With respect to his, "If you're talking about doing consistency studies and if you're talking about efficacy trials, you're talking about several years and fairly major programs for the presentation of new preservatives. So all of that needs to be put together before the review process can start, obviously," the petitioners note that these barriers were, and are, illusory because the "no Thimerosal" or "reduced Thimerosal" vaccine formulations developed and approved for the European

markets in the early 1990s can easily be licensed for the U.S. market in a much shorter period. Moreover, the fact is that U.S. manufacturers were able to market their "reduced Thimerosal" vaccines within 2 years of the workshop. Furthermore, the CDC even turned down offers from what is now GlaxoSmithKline of millions of doses of a Thimerosal-free DPT vaccine, which was licensed in Europe, to bridge the gap until the U.S. manufacturers could get their "reduced Thimerosal" DTaP vaccines approved by the FDA.]

Then, Dr. John Risher, from the ATSDR, gave his views of the research needed:

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

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

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

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

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

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

In adults, the primary source of excretion of organic mercury -- Primarily methylmercury is what most of the information about -- is through an enterohepatic circulation. That is that the mercury is absorbed from the gut and it goes up through the circulation into the liver where it's conjugated with glutathione[e] and leaves the liver in the bile salts back down to the gallbladder, through the bowel,

and then back into the intestine where it continually gets recycled. So it's not always bowel available. Now, in rodents we know that during the suckling period, which is about twenty-one days in rats, that the glutathione[e], which is needed to conjugate the mercury, is not produced in sufficient quantities to lead to the circulation. There's been some studies in primates that have shown that in real young primates that that might also be the case. In humans, we really don't know, it may be the case or it may not be, but I think it would be interesting to find out when that enterohepatic circulation is to the extent that glutathione[e] is produced and can conjugate the mercury and actually comes into being. That ties into again with excretion.

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

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

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

Finally, Dr. Bernard Schwetz, Senior Science Advisor to the Commissioner of the FDA and the Director of the FDA National Center for Toxicological Research, offered the following:

"As you might expect within an organization of the nature and size of the FDA, there will be different research agendas on almost everything, and that certainly would be true for ethylmercury as well, but a point I want to make is that I think that because of the nature of the exposures, these converge for something like ethylmercury. If Thimerosal or mercury is taken out of vaccines, I think further work on ethylmercury for the Center for Biologics would not be a very high priority, especially in comparison to the need for data on the replacements for Thimerosal. I think this isn't just a question of a research agenda for ethylmercury, it's an even more important question that if we succeed, then the problem starts of knowing how successful the replacements are. That has got to be a high priority, along with whatever we need to know about ethylmercury.

On the other hand, it isn't very likely that Thimerosal is going to be replaced in vaccines completely in a reasonable length of time. So that is still a need to have data on ethylmercury. Then look at the bigger picture of the FDA in total where the concern is for drugs, cosmetics, foods, as well as vaccines. Then it's a given that we need to have more data on ethylmercury to understand that kind of a complex picture. It must include considerations about additivity of ethylmercury from different sources, but a point that hasn't been made in this meeting so far is the need to consider the additivity between ethylmercury and methylmercury. We treat them as if they're not acting in the same cells, and at some times they are. So I don't think we can look at ethylmercury in isolation without considering methylmercury or other sources of ethylmercury other than vaccines. So one of the high priorities that I think is for us to reduce the uncertainties that surround the idea that methylmercury and ethylmercury are the same. We know they're not, but that's where we are today and we don't have much data on ethylmercury to really confirm whether it's more or less toxic. We know for the kidney it's probably more, but we all seem to assume that methylmercury is the gold standard for concern and ethylmercury may not be as bad. We don't have enough data to say that with a hundred percent confidence.

While there are some priorities that I would say maybe just a little bit differently than some of the preceding speakers, I would agree that the sensitivity of the fetus versus the neonate is very

important, and for some of you who have forgotten about the sensitive windows during fetal development, the nervous system develops post-natally. So isn't unreasonable to expect there would be particular windows of sensitivity. So it isn't the matter of averaging the dose over the whole neonatal period, it's what's the week or what's the day or what's the series of hours that represent a particular event in the development of the nervous system when this whole thing might be dangerous. It may be weeks surrounding that when there isn't a major problem. We don't have that information.

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

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

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

The valid bar markers of exposure, I think we have to have that. That is obviously of considerable importance. The elimination from the neonate, we're using a conservative estimate when we say it's not being removed by anything other than dilution, but we need to get that information. One that I haven't heard discussed, the fact that we know that ethylmercury is a skin sensitizer when it's put on the skin and now we're injecting this IM at a time when the immune system is just developing, the functionality of the immune system is just being set at this age. So now we're injecting a sensitizer several times. During that period of time, what's the impact of a sensitizer -- of something that is known to be a skin sensitizer, what is the effect on the functional development of the immune system when you give a chemical of that kind repeatedly IM?

Now, regarding the question of feasibility and urgency, the kinds of studies that we're talking about, the pharmacokinetic studies, the distribution, the elimination, all these other things that we can do in rodents, we can do them in primates, so those are feasible. It just takes money and expertise and good work. We don't know need shotty [sic; shoddy] work at this stage by people rushing in and doing something that they don't quite know what they're doing. This is a time when the rest of the data that we make new decisions on have got to be better than the quality of information that is normally available when people on a random basis begin to collect information and, in retrospect, it doesn't fit into a real good picture when you analyze it. That's true of a lot of chemicals. There need to be some definitive studies now that are done very well.

The urgency, from the standpoint of -- Now I'm speaking as a toxicologist. I think anytime there's an avoidable source of exposure to mercury, we need to look at it real hard, but, obviously, there are consequences in many cases of taking steps. I don't think this is an emergency, that mercury is being used in this manner, but if it's an avoidable exposure, we should do something about it. I also recognize that if we do something precipitous, we could create an emergency and that has got to be considered as equally important as the concern over mercury itself.

Why mercury represents a priority concern for me as a teratologist and a developmental toxicologist who has been doing this kind of work my whole career is the fact that this can cause irreversible damage to the development of the nervous system. That's why, in my mind, it's different than nephrotoxicity. A reversible damage, whether it's in an adult or a neonate, whatever, that's

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

After the last commenter finished, Dr. Rabonivoch opened the discussion to the participants.

The following is the "verbatim" transcription of those exchanges with: **a)** underlining added for emphasis and **b)**, *where appropriate*, petitioners' comments.

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

DR. KLEIN: "Dr. Clarkson, I'd like you to amplify your remarks, particularly in regard to that graph that you showed, the figure, in terms of a potential first dose of vaccine that has thimerosal in it given at birth. Now, you indicated that your -- that it would be about 4 micrograms with that first dose. I wonder if you could -- If you eliminate that first dose, the rest of the curve presumably would be approximately the same; is that correct? In other words, what benefit do we gain in your model from eliminating that first dose?"

DR. CLARKSON: "Not a lot. I guess you've seen this before, but this basically -- As we said, all of these guidelines that we've talked about today don't start with the dose. Well, some of our Iraqi stuff did, but, basically, when you're making these risk assessments on human health, epidemiologists -- (inaudible) on ethylmercury, you start with a hair level or blood level, let's say a minimum toxic level or some threshold level, some level associated with toxicity."

[Note: Petitioners again observe that neither blood nor hair is a valid marker for mercury toxicity, the variable that should be being assessed. Since both blood and hair values have been shown to be non-valid measures of assessing a person's mercury toxicity, it should be obvious that any "guidelines" for mercury exposure derived from such are also non-valid.]

"Then an expert committee may or may not apply safety factors. For example, originally, from the Japanese data, there was a blood level of 200 parts per billion. A committee comes along and applies a safety factor of 10, so it's now 20 parts per billion in blood. Then from that point, the committee will go on and figure out -- calculate what is the long-term daily dose that will give you a toxic level of 20. That's how it's done. There's various calculations. The original data is not a dose. It's a blood level or a hair level. And the best way for us to compare a single dose to the chronic dose is to ask blood level results from that single dose or what blood level results from that chronic dose. The example I mentioned this morning with eating six ounces tuna fish, which has something like 17 micrograms of mercury -- Let's say 20. Well, if you consume one can, the effect on your blood level would be so tiny you can't measure it, but if that's taken day after day after day for six months to a year -- It takes about a year to get into a steady state where intake balances excretion -- that blood level will rise measurably to a level of about 20 parts per billion, which is one of the FDA safe limits.

So a single dose is a very different situation than a chronic dose in terms of body burden. Now, in this case, you go to the top, a single dose of 12.5 micrograms here at birth, given the bodyweight -- We took a bodyweight of 1.8 kilograms -- and we assume the blood volume was 8.5 percent bodyweight and you assume that -- You do all this arithmetic and you will come out with a blood level of about 4 parts per billion, which is about where the equivalent blood level will be for the EPA guidelines. So you get with this one dose to about the EPA guideline. You certainly do not exceed, as I heard this morning, by a factor of 10. Okay?"

[Note: Petitioners observe that injecting 12.5 micrograms of mercury into a 1.8 kg body would give a direct value of 6.9 micrograms/kg or 6.9_4 parts per billion (ppb). If you presume that the whole dose first enters the blood and accept Dr. Clarkson's 8.5% value for the weight of the blood in the newborn, then, the blood level would be 6.9_4 ppb divided by 0.085 or $81._7$ ppb. So, in the absence of excretion, the initial level of mercury in the blood is between 6.9 and 82 ppb – values that exceed EPA's "putative" guideline of "5 ppb" by a factor of from 1.3 to 16+ – indicating that the values can easily exceed the "EPA guideline" by more than a factor of 10. Since, *from the information given*, we cannot understand how Dr. Clarkson arrived at his 4 ppb value, we are compelled to find that Dr. Clarkson's line of reasoning is flawed and must reject his projected views of reality both because the value he reported does not seem valid and because the assumptions he is making are based on a "methylmercury" model and not, *as they should be*, based on a " no excretion" Thimerosal model to address those most at risk, the non-excretors.]

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

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

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

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

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

DR. RABINOVICH: "Dr. Gerber?"

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

[**Note:** Petitioners observe that, if Dr. Gerber is correct and, *as a recent NIESH review found*, the VSD database is not well-suited to assessing effects, then, any findings, including the report from the 2004 IOM committee, based on an evaluation of the VSD database or similar epidemiological studies on foreign population databases must be rejected.]

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

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

DR. RABINOVICH: "Dr. Schwartz?"

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

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

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

DR. RABINOVICH: "Yes, please, Peter?"

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

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

[Note: Petitioners observe that, *contrary to Dr. Paradiso's broad assertion that* "there is generally very great care taken to what is put into vaccines and the potential toxicity of what is put into vaccines," the requisite toxicity studies on Thimerosal that are required to satisfy the CGMP requirement for "sufficiently nontoxic ..." have either not been conducted or, if conducted, not reported. Thus, instead of being able to point to the required studies as proof of safety for Thimerosal-containing drugs, the manufacturers and the governmental agencies *continually* claim that there is no evidence of harm – *knowingly* avoiding: **a)** the reality of the vaccine manufacturers' failure to conduct and report the results from, scientifically sound and appropriate toxicity studies that prove the Thimerosal meets the "sufficiently nontoxic ..." CGMP requirement *minimum* set forth in **21 C.F.R. § 610.15(a)** and **b)** the reality that the FDA continues to approve and permit the distribution of vaccines formulations that are, by statute (**21 U.S.C. § 351(a)(2)(B)**), adulterated drugs because of the knowing failure of the manufacturers to comply with this CGMP minimum. Lest the FDA attempt to assert that their administrative discretion permits them to ignore the manufacturers' knowing and willful non-compliance with CGMP, in 1988 the Supreme Court unanimously upheld the reality that

the FDA's discretion is only permitted when it is not at odds with an applicable published policy, law (and the CGMP requirements are laws) or statute.[203]]

DR. RABINOVICH: "Dr. Zoon?"

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

[Note: Petitioners observe that Dr. Zoon's, "We need to understand more about thimerosal because in the past two days, I think we have recognized there really is a paucity of data and I think some of the points made about looking at the developing nervous system, looking at the developing immune systems and the effects of these agents on that at critical times of development hasn't been -- hasn't been done," is another admission that all in the workshop were aware that the toxicity studies, required (by **21 C.F.R. § 610.15(a)** since 1973) to meet the "sufficiently nontoxic ..." standard for safety, had not been conducted by the vaccine makers even though, in 1999, such toxicity studies had been required by law for more 30 years (since 1968) or, as codified in **21 C.F.R. § 610.15(a)** in 1973, for more than 25 years. As of 2007, the vaccine makers who use, or used, Thimerosal as a preservative apparently have yet to comply with **21 C.F.R. § 610.15(a)** – more than 34 years after it was first published.]

DR. RABINOVICH: "Dr. Halsey?"

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

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[203] Kevan *Berkovitz*, a Minor by his Parents and Natural Guardians Arthur Berkovitz, et ux., et al., Petitioners, *v. UNITED STATES*. Case No. 87-498. 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USL W 4549. (Cite as: **486 U.S. 531, 108 S.Ct. 1954.**)

don't think so. But I think the public perception will be that it might have, and we know from our experiences that we've been dealing with in the past five years with regard to alleged adverse events of a variety of type, that including things that we have learned some of the subtle neurologic defects that may come from the studies in the Faroe Islands, you can bet there will be many parents who believe their child may be affected.

And they do need data to address that issue. I believe the data will be likely to be negative, but if we don't have the data, how can we say that it's not negative? This is one situation where there will have been exposure to something that might have done it. It's not the same as some of the other allegations that we have dealt with. So I do believe that there is a need and probably for much more than the study that Walt was talking about, which is a limited number of small -- a relatively small number, even though it's in the tens of thousands of children, to just take a look at some of the simple outcomes, but there probably is a need for a careful study. I'm not that type of investigator, but the people who do these neurodevelopmental things very carefully need to determine the feasibility. They need to look at all of the other exposures. This is not a simple study. This would be very complicated and I don't look forward to being responsible for those, but I think if we don't have that, we're just going to have the continued public trust erosion that says you don't care or you don't think so. And what's going to happen to the Vaccine Compensation Program? There will be, undoubtedly, applications for that and who knows what's going to be the outcome of those deliberations by the Special Master. So I think there is a need and probably for more than one study based upon the problems that we've seen elsewhere by the interpretation of different studies and in different populations who have a very different baseline rate of exposure to mercury. You can't just pick those populations that are at the low background of other environmental exposure because you're likely -- you're then -- it'll be stated, perhaps correctly, that you biased it in your favor in saying that there's no effect from those."

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

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

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

DR. HALSEY: "Let me clarify, I do not think that there is evidence of a clear and present danger. That was not my intent by anything that I have said, but I have participated in writing in the Academy statement and elsewhere that there is no evidence that harm has been done. There is a clear problem with regard to the potential or the perceived potential for harm, and I believe that the correct steps

have been taken by the FDA at this time of requesting within the realm of what they're capable of in the absence of any data of requesting action to determine what can be done and how fast it can done to remove this.

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

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

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

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

DR. RABINOVICH: "Plotkin?"

DR. PLOTKIN: "Well, as this meeting draws to a close, I am -- we're talking about perceptions, perceptions of danger and so on, I must say that I'm reminded of Alice in Wonderland. Now, I don't

happen to remember the exact story, but at one stage I think Alice is talking about a situation and she says, 'Well, we'll have a trial and then we'll have a sentence.' And the Red Queen says, 'No, first the sentence and then the trial.' So, you know, it strikes me that a perception has certainly been created through the change in the vaccine schedule and so on and that there is a real problem. Now, after these two days, I must say that I'm actually less sure that there is a problem while I was when this meeting started. I do have to repeat my comment that I think this meeting should have been held sometime ago before the announcements."

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

Dr. Myers then asked Dr. Klein to give the workshop participants a summary of the workshop.

The following are Dr. Klein's remarks, with underlining added for emphasis where appropriate:

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

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

(LAUGHTER)

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

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

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

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

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

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

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

So every action will have a reaction. I think a lot of the discussion yesterday about the action that was taken in changing the schedule of the hepatitis B vaccine from birth bears on that, making sure that that message and the reason for the change is delivered to those who are actually responsible for the change, the hospitals in altering their policies are cognizant of the reasons for the changes, that the clinics understand that any gaps that would be created -- I think Bob Down's data and the CDC data that suggest that that first immunization in the nursery is very important in subsequent vaccine utilization by selected families leads us to believe that delivering the message and the caretaker's delivering the message to the parents becomes a very critical part in decision-making. I think Gina said it very well, that the generic issue is to become more capable, more skilled in how to communicate controversial and inconclusive data so that we maintain confidence of our public. And as long as -- the time that I've been on the Red Book and subsequently, this has been and will be a continued challenge, and I think we need all the help we can get in making sure that our decisions not only are appropriate scientifically, but they are communicated to the public in a manner that the constituency understands the reasons for the change and is accepting of those changes.

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

In summary, the petitioners are compelled to again point out that the problems associated with Thimerosal in vaccines stem from the *knowing* failure of the manufacturers to comply with the law requiring preservatives to be proven "sufficiently nontoxic ..." for more than three decades, and the *knowing* refusal of the FDA to compel the manufacturers to comply with the law or, when non-compliance persisted, to take legal action against the makers of drugs that used Thimerosal as a preservative without the requisite proofs of safety for more than three decades while continuing to illegally[204] approve Thimerosal-preserved vaccine formulations as well as permit the shipment of adulterated Thimerosal-containing vaccine lots.

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[204] Kevan *Berkovitz*, a Minor by his Parents and Natural Guardians Arthur Berkovitz, et ux., et al., Petitioners, *v. UNITED STATES*. Case No. 87-498. 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USL W 4549. (Cite as: **486 U.S. 531, 108 S.Ct. 1954.**)

Based on the verbal reports of the Eli Lilly finding, in the early 1970s, that Thimerosal was toxic below the level of 1 microgram per milliliter of vaccine formulation and Lilly's subsequent abrupt exit from vaccines in the mid-1970s, the petitioners understand that Lilly's findings are the "reason" the other manufacturers have *knowingly* failed to conduct and report the required toxicity studies for Thimerosal at one (1), ten (1), or, *as they should have*, one hundred (100) times the preservative level of 100 ppm – such studies would have simply confirmed that Thimerosal's toxicity was such that it could not meet the "sufficiently nontoxic ..." safety standard set forth in **21 C.F.R. § 610.15(a)** with even a true 10-fold safety margin.

To meet the required "sufficiently nontoxic ..." CGMP minimum, *based on the reported Lilly finding of toxicity at 1 ppm*, the level of Thimerosal in the vaccine formulation would have to be reduced to below 0.1 ppm (< 0.1 microgram of Thimerosal per mL of vaccine formulation [<0.05 microgram of mercury per mL of vaccine formulation), a level well below the level where Thimerosal could be considered to meet the USP's requirements for a preservative.

8. 2000: Illegal Closed Meeting of Government, Medical and Industry Officials. "Scientific Review of Vaccine Safety Datalink Information" June 7-8, 2000, Simpsonwood Retreat Center, Norcross, Georgia

Since the petitioners have made in-depth comments about this meeting previously, we see no need to rehash those comments but only observe that this meeting was a closed meeting which was not announced in the Federal Register, as required by law, and from which the public and the media were illegally excluded.

9. 2001: Institute of Medicine's Committee on "Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders"[205]

In 2001, the Institute of Medicine, contracted by the CDC and charged with reviewing immunization safety,[206] convened a committee (the Immunization Safety Review Committee) to review selected issues related to immunization safety.

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[205] http://www.iom.edu/CMS/3793/4705/4717.aspx, last visited June 23, 2007.

The second review focused on a potential relationship between thimerosal use in vaccines and neurodevelopmental disorders (IOM 2001).

This latter issue was brought to the fore primarily as the result of the hypothesis, formulated by S. Bernard and others from Cure Autism Now, that autism is a novel form of mercury poisoning (Bernard et al. 2001).

This hypothesis, linking autism to mercury, was based on a comprehensive review of the scientific literature on mercury toxicity.

In its report of October 1, 2001, the IOM's Immunization Safety Review Committee found that the evidence was inadequate to either accept or reject a causal relationship between thimerosal exposure from childhood vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder (ADHD), and speech or language delay.

The Committee also concluded that additional studies were needed to establish or reject a causal relationship.

Further, the Committee concluded that the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders was biologically plausible – but, *though the hypothesis advanced was that the Thimerosal in vaccines was linked to mercury poisoning*, the Committee incongruously neither addressed this evidence-supported reality nor the implications that Thimerosal-containing vaccines were mercury poisoning the fetus, children and adults.

However, the Committee did think that the effort to remove Thimerosal from vaccines was "a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible."

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[206] Transcript of the closed session of the organizational meeting of the "IMMUNIZATION SAFETY REVIEW COMMITTEE," National Academy of Sciences, Institute of Medicine, held on 12 January 2001 at the National Academies Building, 2101 Constitution Avenue, NW, Washington, DC. The US CDC contracted for, and set the boundary framework and constraints for, this committee.

Furthermore, in this regard, the Committee urged that "full consideration be given to removing Thimerosal from any biological product to which infants, children, and pregnant women are exposed" – the petitioners only wish that the Secretary of HHS, and FDA and CDC officials had followed the IOM Committee's lead and removed Thimerosal from all biological drug products.

10. 2002 – 2007: Recent Activities

In spite of:

- An unrefuted significant birth-defect risk that was strongly linked to Thimerosal in 1977;
- The prohibition of the use of Thimerosal in topical antimicrobial drugs and vaginal contraceptives in 1998 because they had been found to be neither safe nor effective;
- The 1998, 1999 and 2000 meetings about mercury toxicity and Thimerosal in vaccines;
- The 1999 joint government/industry/healthcare provider pledge to "remove mercury from childhood vaccines as soon as possible";
- An on-going failure of the vaccine manufacturers to comply with the legally binding CGMP minimum requirement that, *for all preserved biological drug products, including Thimerosal-preserved vaccines*, the preservative must be proven to be "sufficiently nontoxic ..." in the formulation given to the recipient (see 21 C.F.R. Sec. 610.15(a)) – rendering each batch released for distribution adulterated under 21 U.S.C. 351(a)(2)(B);
- An ongoing failure on the part of the FDA to enforce the applicable drug statutes against adulterated drugs; and
- The failure of the Secretary of HHS and his subordinates to comply with **42 U.S.C. § 300aa-27(a)(2)** mandating all possible actions to reduce the risk of adverse reactions in childhood vaccines,

the DHHS' CDC, without any proof of safety to the fetus from *reproductive toxicity studies*[207] or scientifically sound and appropriate proof of safety to the standard "sufficiently nontoxic ..." for developing children, recommended, *for women pregnant during the "flu season" and children*:

- In 2002, Thimerosal-preserved influenza vaccines be administered to pregnant women in their second and third trimesters (the period from the end of month "3" through delivery), and children 6 months to 23 months of age during the "flu season,"
- In 2004, an extended the age range for children to 35 months of age and broadened the "at risk" groups,
- In 2006, Thimerosal-preserved influenza vaccines be administered to pregnant women throughout their pregnancy, extended the age range for children to 59 months, and further broadened the "at risk" group, and
- In 2007,[208] specifically widened the age range for children with "risk" factors to receive 2 doses of influenza vaccine the first time they are vaccinated to essentially from 6 months up to 9 years of age ("107+ months"), increased the definition of children in a "risk" group to the point that at least half of all children fall in a risk group, and recommended children in a "risk" group essentially be vaccinated every year throughout their childhood and, if in a "risk" group that extends into adulthood, every year thereafter.

In addition, CDC and FDA officials and press releases began making false and/or misleading claims that: **a)** Thimerosal had been removed from the vaccines given to children or **b)** Thimerosal had been removed childhood vaccines except for some influenza vaccines.

Further, officials falsely claimed that all Thimerosal-preserved vaccine doses of the childhood vaccines had expired in 2002 or that, *with the exception of influenza vaccines*, Thimerosal had been

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[207] In general, scientifically sound and appropriate *reproductive toxicity studies* are required for drugs that are approved for universal administration to pregnant women.

[208] http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5606a1.htm

Thimerosal Content in Currently Manufactured U.S. Licensed Vaccines				
Vaccine	**Trade Name**	**Manufacturer**	**Thimerosal Concentration[1]**	**Mercury per dose**
DTaP	Tripedia[2]	Aventis Pasteur, Inc	≤ 0.00012%	**≤ 300 ng/0.5 mL**
DTaP-HepB-IPV	Pediarix	GlaxoSmith-Kline	< 0.000005%	**< 12.5 ng/0.5 mL**
DT	No Trade Name	Aventis Pasteur, Inc	< 0.00012% (single dose)	**< 300 ng/0.5mL**
Td	No Trade Name	Mass Public Health	0.0033%	**8,300 ng/0.5 mL**
	Decavac	Aventis Pasteur Inc	≤ 0.00012%	**≤ 300 ng /0.5 ml**
Hepatitis B	Engerix-B Pediatric/adolescent	GlaxoSmith-Kline	< 0.0002%	**< 500 ng/0.5 mL**
HepA/HepB	Twinrix	GlaxoSmith-Kline	< 0.0002%	**< 1,000 ng/1.0mL**
Meningococcal	Menomune A, C, AC and A/C/Y/W-135	Aventis Pasteur, Inc	0.01% (multidose)	**25,000 ng/0.5 mL**

removed from vaccines when, *to this day*, the multiple-dose Menomune® vaccine, currently being recommended for middle-school and high-school children, is Thimerosal-preserved and some other vaccines approved for routine childhood immunizations contain some Thimerosal:[209]

19. Current Reality Regarding Added Mercury Compounds in Drug Products

a. Serum Products [http://www.fda.gov/cber/blood/mercplasma.htm, last updated "9/9/2004"]

Currently, all the FDA-licensed Rho(D) products distributed in the U.S. (RhoGAM®, Ortho Clinical Diagnostics, Inc.; BayRho®, Bayer Corporation; and WinRho®, Cangene Corporation) are claimed to be free of Thimerosal (of these three, only the WinRho never contained Thimerosal).

In addition, because the manufacturers of immune globulin products have removed mercury, only four other plasma-derived products that may contain Thimerosal or Thimerosal and phenylmercuric acetate remain on the market.

These serum drug products are:

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[209] http://www.fda.gov/cber/vaccine/thimerosal.htm

"Antivenin (Crotalidae) Polyvalent (Equine); Pit viper snake antivenom, Wyeth Pharmaceuticals Inc
Antivenin (Micrurus fulvius); Coral snake antivenom (Equine), Wyeth Pharmaceuticals Inc
Crotalidae Polyvalent Immune Fab (Ovine); Pit viper snake antivenom, Protherics Inc
Antivenin (Lacrodectus mactans); Black Widow spider antivenom Equine), Merck & Co, Inc"

Pit Viper [Antivenin (Crotalidae) Polyvalent, licensed 1954] and Coral Snake [Antivenin (Micrurus fulvius), licensed 1967] antivenoms by Wyeth

These products are equine antisera.
They are in lyophilized form and when reconstituted contain 0.005% thimerosal (50 micrograms per milliliter). The diluent, WFI, contains the preservative phenylmercuric nitrate at 0.001% concentration (10 micrograms per milliliter). A patient bitten by a snake may receive 15 or more vials (doses of 50 vials have been reported) if the envenomization is severe. A 15 vial dose of this antivenom would contain 4.7 milligrams of mercury.

Wyeth plans to discontinue these products; however, the current supply will last several years, until each lot reaches its expiration date.
Rattlesnake bites are dangerous and can cause serious morbidity or mortality. In the interest of the public health these products need to be available until sufficient ethyl mercury-free product can be provided to the public.

Pit Viper antivenom [Crotalidae Polyvalent Immune Fab (Ovine) licensed October 2000, Protherics]

Mercury is not added to the final product in the form of a preservative, but thimerosal is used to assure that the chromatography columns used in the manufacturing of this product do not become bacterially contaminated with repeated use. The product was approved but the ethyl mercury content was limited to not more than 104.5 micrograms ethyl mercury per vial, with a recommended maximum dose of 18 vials. A patient receiving this product would receive about 1.88 milligrams of mercury.

Black Widow Spider antivenom [Antivenin (Lactrodectus mactans), licensed 1936, Merck]

This product is an equine antiserum. The reconstituted product contains 0.1 milligrams of mercury per milliliter, so that the maximum 2-vial dose would contain 0.25 milligrams of mercury. Black Widow Spider bites can be lethal, and the dose is limited to not more than two vials. It has been determined that removal of the product from the market by the FDA would not be in the best interests of public health."

Thus, *in the area of serum products*, by 2004, manufacturers and the FDA have acted to stop using mercury-containing serum and/or serum diluents for all serum products.

Unfortunately, the use of Thimerosal in other types of FDA-approved drug products continues even though the requisite proofs of safety are missing.

b. Vaccine Products

1. Vaccines in General

Though the manufacturers and the DHHS have had eight years to remove Thimerosal from all

vaccine products that may be administered to children (generally, humans under the age of 18) to meet their 1999 pledge and the Secretary of HHS has had almost two decades to meet the statutory requirement to reduce adverse reactions to vaccines covered by the National Vaccine Injury Compensation Program (NVICP),[210] the "remove Thimerosal" goal has not been met.

The table, starting on the next page, lists all U.S. FDA-licensed vaccines except for the anthrax, smallpox and avian influenza vaccines (omitted because they are not *currently* being administered to civilians in the U.S.A.) and the influenza vaccines (omitted because they are less than effective[211,212]).

Since the cited published studies have clearly established that the human influenza vaccines are not effective and a recent publication[213] has established that daily doses of 1,000 to 3,000 IU (25 to 75 micrograms) of vitamin D_3 during the "flu season" are effective in preventing a person from contracting human influenza, the petitioners see no justification for the continued licensing of drug products that, *in use*, are not effective in preventing those inoculated from contracting the influenza virus while, *for the majority of doses*, mercury poisoning, *to varying degrees*, those inoculated.

Therefore, the petitioners are also petitioning the Secretary of HHS to *immediately* revoke the licenses for all human influenza vaccines since they have been demonstrated not to be effective in protecting Americans from getting or spreading human influenza.

Reviewing the preceding table and excluding the human influenza vaccines, the petitioners note that the FDA has continued to license five (5) Thimerosal-preserved vaccines as well as six (6)

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[210] When enacted, the NVICP originally only intended to cover "childhood vaccines. However, when the general-population hepatitis A, hepatitis B, and human influenza vaccines were added to the vaccines covered without restricting that coverage to children, the addition of these vaccines effectively broadened the law to cover all persons for these vaccines.

[211] Jefferson T. Influenza vaccination: Policy versus evidence. ***BMJ*** (***British Medical Journal***) 2006 October 28; **333**: 912-915.

[212] Geier DA, King PG, Geier MR. Influenza Vaccine: Review of effectiveness of the U.S. immunization program, and policy considerations. **JAPS** (***Journal of American Physicians and Surgeons***) 2006 Fall; **11**(3): 69-74.

[213] Cannell JJ, R. Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, Giovannucci E. Epidemic influenza and vitamin D. ***Epidemiol. Infect.*** 2006 Dec; **134**(6): 1129-1140.

"reduced Thimerosal" vaccines, only one (1) of which, GlaxoSmithKline's Pediarix, may contain a

"Effective" U.S.-Licensed Vaccines Currently Given to Civilians (as of 21 March 2007)
(CBER's "Table 3" at http://www.fda.gov/cber/vaccine/thimerosal.htm)

Thimerosal Content in Currently Manufactured U.S. Licensed Vaccines				
Vaccine	**Trade Name**	**Manufacturer**	**Thimerosal Concentration[1]**	**Mercury per dose**
DTaP	Tripedia[2]	Aventis Pasteur, Inc	≤ 0.00012%	**≤ 300 ng/0.5 mL**
	Infanrix	GlaxoSmith-Kline	"0"	"0"
	Daptacel	Aventis Pasteur, Ltd	"0"	"0"
DTaP-HepB-IPV	Pediarix	GlaxoSmith-Kline	< 0.000005%	**< 12.5 ng/0.5 mL**
DT	No Trade Name	Aventis Pasteur, Inc	< 0.00012% (single dose)	**< 300 ng/0.5mL**
		Aventis Pasteur, Ltd[3]	0.01%	**25,000 ng/0.5 mL**
Td	No Trade Name	Mass Public Health	0.0033%	**8,300 ng/0.5 mL**
	Decavac	Aventis Pasteur Inc	≤ 0.00012%	**≤ 300 ng /0.5 ml**
	No Trade Name	Aventis Pasteur, Ltd	"0"	"0"
Tdap	Adacel	Aventis Pasteur, Ltd	"0"	"0"
	Boostrix	GlaxoSmith-Kline	"0"	"0"
TT	No Trade Name	Aventis Pasteur Inc	0.01%	**25,000 ng/0.5 mL**
Hib	ActHIB/OmniHIB[4]	Aventis Pasteur, SA	"0"	"0"
	HibTITER	Wyeth-Lederle	"0"	"0"
	PedvaxHIB liquid	Merck	"0"	"0"
Hib/HepB	COMVAX[5]	Merck	"0"	"0"
Hepatitis B	Engerix-B Pediatric/adolescent Adult	GlaxoSmith-Kline	< 0.0002% < 0.0002%	**< 500 ng/0.5 mL** **<1,000 ng/1.0 mL**
	Recombivax HB Pediatric Adult Dialysis	Merck	"0" "0" "0"	"0" "0" "0"
Hepatitis A	Havrix	GlaxoSmith-Kline	"0"	"0"
	Vaqta	Merck	"0"	"0"

"Effective" U.S.-Licensed Vaccines Currently Given to Civilians (as of 21 March 2007)

[Continued]

Vaccine	Trade Name	Manufacturer	Thimerosal Concentration[1]	Mercury per dose
HepA/HepB	Twinrix	GlaxoSmith-Kline	< 0.0002%	**< 1,000 ng/1.0mL**
HPV	Gardasil	Merck	"0"	"0"
IPV	IPOL	Aventis Pasteur, SA	"0"	"0"
	Poliovax	Aventis Pasteur, Ltd	"0"	"0"
Japanese Encephalitis[6]	JE-VAX	BIKEN	0.007%	**35,000 ng/1.0 mL** **17,500 ng/0.5 mL**
MMR	MMR-II	Merck	"0"	"0"
MMRV	ProQuad	Merck	"0"	"0"
Meningococcal	Menomune A, C, AC and A/C/Y/W-135	Aventis Pasteur, Inc	0.01% (multidose)	**25,000 ng/0.5 mL**
			"0" (single dose)	"0"
	Menactra A, C, Y and W-135	Aventis Pasteur, Inc	"0"	"0"
Pneumococcal	Prevnar (Pneumo Conjugate)	Lederle Laboratories	"0"	"0"
	Pneumovax 23	Merck	"0"	"0"
Rabies	IMOVAX	Aventis Pasteur, SA	"0"	"0"
	Rabavert	Chiron Behring	"0"	"0"
Typhoid Fever	Typhim Vi	Aventis Pasteur, SA	"0"	"0"
	Typhoid Ty21a	Berna Biotech, Ltd	"0"	"0"
Varicella	Varivax	Merck	"0"	"0"
Varicella zoster	Zostavax	Merck	"0"	"0"
Yellow Fever	Y-F-Vax	Aventis Pasteur, Inc	"0"	"0"

Table Footnotes

1. Thimerosal is approximately 50% mercury (Hg) by weight. A 0.01% solution (1 part per 10,000) of thimerosal contains 50,000 ng of Hg per 1 mL dose or 25,000 ng of Hg per 0.5 mL dose.
2. Aventis Pasteur's Tripedia may be used to reconstitute ActHib to form TriHIBit. TriHIBit is indicated for use in children 15 to 18 months of age.
3. This vaccine is not marketed in the US.
4. OmniHIB is manufactured by Aventis Pasteur but distributed by GlaxoSmithKline.
5. COMVAX is not licensed for use under 6 weeks of age because of decreased response to the Hib component.

E-VAX is manufactured by BIKEN and distributed by Aventis Pasteur. Children 1 to 3 years of age receive a half-dose of vaccine, i.e., 0.5 mL (17,500 ng of mercury/dose).

level of Thimerosal (< 25 ng/0.5 mL) that may be below the level of "mercury" that may be toxic for most infants.

Further, neither the DHHS nor the FDA nor any other federal governmental agency has published any scientifically sound and appropriate toxicology studies establishing that any dose of these Thimerosal-containing vaccines is "sufficiently nontoxic ...."

Moreover, as far as the petitioners can ascertain, the FDA has taken no action to:

a. Compel the manufactures of vaccines to conduct and submit those scientifically sound and appropriate toxicity studies required to prove that any Thimerosal-containing vaccine is "sufficiently nontoxic ..." or

b. Revoke the license for any Thimerosal-preserved vaccine and take legal action against their manufacturers for marketing drugs that are obviously adulterated under **21 U.S.C. § 351(a)(2)(B)**, *as the FDA should*, because of the manufacturers' knowing failure to comply with the CGMP regulations set forth in **21 C.F.R. § 610.15(a)**.

2. Influenza Vaccines

The petitioners have segregated the human influenza vaccines from the other vaccines because the recent published studies by Jefferson[214] and by Geier et al.[215] have shown that these vaccines are less than effective despite the efficacy claims: **a)** made by their makers and **b)** approved by the FDA.

Unlike other vaccines recommended for universal vaccination programs in the U.S.A., where the anti-body "efficacy" minimum for the immune-triggering agents in the formulation is greater than 80%,[216] the FDA has allowed a lower "efficacy" level for the influenza vaccines and, because, "strain match" is an issue, the government (CDC) knows that the true effectiveness of a given year's influenza vaccine is less, *and often much less*, than the claimed "efficacy" levels in the licensed vaccines.

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[214] Jefferson T. Influenza vaccination: Policy versus evidence. ***BMJ*** (British ***Medical Journal***) 2006 October 28; **333**: 912-915

[215] Geier DA, King PG, Geier MR. Influenza Vaccine: Review of effectiveness of the U.S. immunization program, and policy considerations. **JAPS** (***Journal of American Physicians and Surgeons***) 2006 Fall; **11**(3): 69-74.

[216] http://medical-dictionary.thefreedictionary.com/efficacy -- efficacy /ef·fi·ca·cy/ (ef'i-kah-se) 1. ... 2. the ability of a drug to produce the desired therapeutic effect. Dorland's Medical Dictionary for Health Consumers. **[Note:** For influenza vaccines, given annually, the approval values are prospective estimates based on antibody titer.**]**

U.S.-Licensed Influenza Vaccines (as of 21 March 2007)

Thimerosal Content in Currently Manufactured U.S. Licensed Vaccines				
Vaccine	**Trade Name**	**Manufacturer**	**Thimerosal Concentration[1]**	**Mercury per dose**
Influenza, Inactivated	Fluzone[2]	Aventis Pasteur, Inc	0.01%	**25,000 ng/0.5 mL**
	Fluvirin	Evans	0.01%	**25,000 ng/0.5 mL**
	Fluzone (no thimerosal)	Aventis Pasteur, Inc	"0"	"0"
	Fluvirin (Preservative Free)	Evans	< 0.0004%	**<1,000 ng/0.5 mL**
	Fluarix (licensed 2005)	GlaxoSmith-Kline	< 0.0004%	**<1,000 ng/0.5 mL**
	FluLaval **(licensed 2006)**	ID Biomedical Corporation of Quebec	0.01%	**25,000 ng/0.5 mL**
Influenza, live virus	FluMist[3]	MedImmune	"0"	"0"

Table Footnotes

1. Thimerosal is approximately 50% mercury (Hg) by weight. A 0.01% solution (1 part per 10,000) of Thimerosal contains 50 nanogram (ng) of Hg per 1 ml dose or 25,000 ng of Hg per 0.5 ml dose.

2. Children under 3 years of age receive a half-dose of vaccine, i.e., 0.25 mL (12,500 ng of Hg/dose.)

3. Requires 21-day post-inoculation quarantine to minimize risk of triggering a secondary outbreak.

Since each year's flu vaccines are "new" vaccines, the preceding "current" list reflects the licensed influenza vaccines for the manufacturers approved to distribute influenza vaccines in the U.S. in 2006.

Given the "sufficiently nontoxic ..." CGMP minimum set forth in **21 C.F.R. § 610.15(a)** for preserved biological drug products has <u>not</u> been met for Thimerosal-preserved vaccines, the Thimerosal-preserved formulations of Fluzone, Fluvirin and FluLaval are adulterated drugs that, by statute, are illegal to distribute.

In addition, the FDA's approval of FluLaval in 2006 is an apparently illegal act since it increases the risk of Thimerosal-related adverse reactions and, *since Congress has added all influenza vaccine doses to the coverage of the National Vaccine Injury Compensation Program in 2005*, the applicable statute implicitly requires the FDA to do all that it can, *including declining to license*, to reduce the risk of adverse reactions to any vaccine covered by the NVICP.

Moreover, *since no toxicological proof has been submitted that lower levels of Thimerosal are "sufficiently nontoxic ...,"* the "no Thimerosal" version of Fluzone appears to be the only formulation of the inactivated influenza vaccines that may be being legally marketed provided it could be proven, *contrary to apparent reality*, said "no Thimerosal" vaccine is truly effective in use.

c. Ophthalmic and Otic Drug Products [66 products listed]

The FDA has allowed and continues to allow formulations of these drug products to be marketed with preservative systems that use Thimerosal as a preservative or include Thimerosal in the preservative mixture without requiring scientifically sound and appropriate toxicity studies to prove that each such formulation is "sufficiently nontoxic."

In 1999, as required by Section 413(a) of FDAMA, the FDA published a list, which was subsequently placed on line and last updated on June 3, 2006, of approved drug products, other than the biologicals (drugs and serums that the petitioners have already listed), which contain mercury.[217]

However, *as the FDA admits*, the Agency does not know which of these products are currently being marketed.

In addition, there may be drug products that have an undeclared low-level mercury content since the current FDA guidance only requires that impurities on drugs that are 0.1% or higher be identified and quantitated.

With these caveats in mind, the FDA's list of ophthalmic and otic products containing added mercury in any form starts on page P-185.

d. Nasal Sprays [40 products listed]

On the next page, the petitioners offer the following list of nasal sprays, most of which are in the FDA list:

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[217] http://www.fda.gov/cder/fdama/mercury300.htm, last visited on 17 June 2007.

Manufacturer [1]	Name of Product	Ingredient [2]	% [3]
Altaire Pharmaceuticals	Nasal Relief 12 Hour Spray	PMA	NS
American Assn. Retired Persons	Oxymetazoline Nasal Spray	PMA	0.002
American Pharmaceutical	12 Hour Nasal Solution	PMA	NS
Appletree Markets	Long Lasting Nasal Spray	PMA	NS
B.F. Ascher and Company	*Ayr™ Saline Nasal Mist*	*TM*	*0.01? 0.001?*
C.O. Truxton Inc.	Decongest Nasal Spray	PMA	NS
CVS	Nasal Spray Pump	PMA	NS
CVS Revco DS Inc.	12 Hour Decongestant Pump Nasal Spray	PMA	NS
Dorex International Corp.	Long Acting Nasal Spray	PMA	0.002
Drug Guild Distributors	Long Acting Nasal Spray Kolex LA	PMA	0.002
Family Independent Pharmacy	12 Hour Nasal Decongestant Spray	PMA	NS
Family Independent Pharmacy	Long Acting Nasal Spray	PMA	NS
Fays Drug Services	12 Hour Nasal Spray Pump	PMA	NS
Federated Foods	Long Acting Nasal Spray	PMA	0.002
Fleming Companies	12 Hour Nasal Spray	PMA	0.002
Foxmeyer Drug Co.	Nasal Spray Pump	PMA	NS
Harris-Teeter	Oxymetazoline Nasal Spray	PMA	0.002
Hi Tech Pharmacal Co.	Long Acting Nasal Spray	PMA	0.002
Hudson Corp.	Nasal Spray Extended Relief	PMA	NS
Kinray	Oxymetazoline Nasal Spray	PMA	0.002
Leader	12 Hour Nasal Spray	PMA	Leader
Leader	Nasal Pump Spray	PMA	NS
Medalist Laboratories	Long Lasting Nasal Spray Pump	PMA	NS
Meyers Supply Inc.	Long Acting Nasal Spray	PMA	0.002
Navresso	Long Acting Nasal Spray	PMA	NS
Parade (Grocer's Supply)	Oxymetazoline Nasal Spray	PMA	0.002
Pay N Save Corp.	Decongestant Nasal Spray	PMA	NS
Prime Natural Health	12 Hour Nasal Spray	PMA	NS
Publix Inc.	Long Acting Nasal Spray	PMA	NS
Publix Supermarkets	Long Acting Decongestant Nasal Spray	PMA	NS
Qualitest Pharmaceuticals	Nasal Spray Solution	PMA	NS
RDS Acquisition Corp.	12 Hour Nasal Spray	PMA	NS
Republic Drug Co.	12 Hour Nasal Spray	PMA	0.002
Super Laboratories	Long Acting Nasal Spray	PMA	NS
Taro Pharmaceuticals *	Taro Nasal Decongestant Spray	PMA	0.002
Thames Pharmacal Co.	12 Hour Nasal Spray	PMA	NS
Thrifty Payless Inc.	Nasal Spray Pump Formula	PMA	NS
Thrifty Payless Inc.	Decongestant Nasal Spray Pump	PMA	NS
Weeks and Leo Co. Inc.	Long Acting Nasal Spray Solution	PMA	0.002
Whitehall-Robins *	Dristan 12-Hour Nasal Spray	TM	0.002

1. The names of products submitted in response to any of the call-for-data notices are followed by an asterisk (*) and the entry in *italics* is one example of a petitioner-purchased product that belongs to a category that the FDA list apparently does not address: preserved saline.
2. The mercury ingredients are abbreviated as TM for thimerosal, PMA for phenylmercuric acetate, PMN for phenylmercuric nitrate, MA for mercuric acetate, MN for mercuric nitrate, MB for merbromin, and MOY for mercuric oxide yellow.
3. NS means "not stated" in the agency's Drug Registration and Listing System.

FDA's 1999 List of Ophthalmic and Otic Drug Products

Manufacturer[1]	Name of Product	Ingredient[2]	%[3]
Akorn Inc.	AK Spore Ophthalmic Solution	TM	.001
Akorn Inc.	AK Spore HC Ophthalmic Combo Drops	TM	NS
Akorn Inc.	Fluoracaine Ophthalmic Solution	TM	NS
Akorn Inc.	AK Spore HC Otic Suspension	TM	NS
Alcon Laboratories *	Profenal 1% Ophthalmic Solution	TM	.005
Alcon Laboratories *	Adsorbonac 2% Ophthalmic Solution	TM	.004
Alcon Laboratories *	Adsorbonac 5% Ophthalmic Solution	TM	.004
Allergan America	Ocufen Ophthalmic Solution	TM	.005
Allergan America	Poly Pred Ophthalmic Suspension	TM	.001
Allergan Inc.	Blephamide SOP Ophthalmic Ointment	PMA	.0008
Allergan Inc.	Bleph-10 Ophthalmic Ointment 10%	PMA	.0008
Bausch & Lomb *	Neomycin & Polymyxin B Sulfates & Gramicidin Ophthalmic Solution	TM	.001
Bausch & Lomb *	Neomycin & Polymyxin B Sulfates & Hydrocortisone Otic Suspension	TM	.01
Bausch & Lomb *	Sulfacetamide Sodium & Prednisolone Sodium Phosphate Ophthalmic Solution 10%/0.23%	TM	.01
Bausch & Lomb *	Neomycin & Polymyxin B Sulfates & Gramicidin Ophthalmic Solution	TM	.001
C.O. Truxton Inc.	Bio-Cot Otic Suspension	TM	.01
Cheshire Pharmaceutical	Otocort Otic Suspension	TM	.01
Cheshire Pharmaceutical	Ocutricin Ophthalmic Solution	TM	.01
Cheshire Pharmaceutical	Sulfapred Ophthalmic Solution	TM	NS
C.O. Truxton Inc.	Bio-Cot Otic Suspension	TM	.01
C.O. Truxton Inc.	Decongest Nasal Spray	PMA	NS
DRX Pharmaceutical	Blephamide Ophthalmic Ointment	PMA	NS
DRX Pharmaceutical	Cortisporin Ophthalmic Suspension	TM	.001
DRX Pharmaceutical	Neomycin Polymyxin B Sulfates Hydrocortisone Ophthalmic Suspension	TM	NS
C.O. Truxton Inc.	Decongest Nasal Spray	PMA	NS
DRX Pharmaceutical	Blephamide Ophthalmic Ointment	PMA	NS
DRX Pharmaceutical	Cortisporin Ophthalmic Suspension	TM	.001
DRX Pharmaceutical	Neomycin Polymyxin B Sulfates Hydrocortisone Ophthalmic Suspension	TM	NS
DRX Pharmaceutical	Neomycin Polymyxin B Hydrocortisone Otic Suspension	TM	.01
DRX Pharmaceutical	Neomycin Polymyxin B Gramicidin Ophthalmic Solution	TM	.01
DRX Pharmaceutical	Vasocidin Ophthalmic Solution	TM	NS
DRX Pharmaceutical	Colymycin S Otic Suspension	TM	.002
DRX Pharmaceutical	Pediotic Otic Suspension	TM	NS
Hurst Pharmaceutical	Duomycin-HC Otic Suspension	TM	.01
King Pharmaceuticals *	Cortisporin Ophthalmic Suspension	TM	.001
King Pharmaceuticals *	Neosporin Ophthalmic Suspension	TM	.001
King Pharmaceuticals *	Viroptic Ophthalmic Solution	TM	.001
King Pharmaceuticals	Neomycin Polymyxin B Sulfates Hydrocortisone Otic Suspension	TM	NS

FDA's 1999 List of Ophthalmic and Otic Drug Products [Continued]

Manufacturer [1]	Name of Product	Ingredient [2]	% [3]
King Pharmaceuticals *	Pediotic Suspension	TM	.001
King Pharmaceuticals *	Cortisporin Otic Suspension	TM	.01
Major Pharmaceuticals	Cortomycin Ophthalmic Suspension	TM	NS
Major Pharmaceuticals	Sulfacetamide Sodium & Prednisolone Sodium Phosphate Ophthalmic Solution	TM	.01
Major Pharmaceuticals	Cortomycin Otic Suspension	TM	.01
Major Pharmaceuticals	Neocidin Ophthalmic Solution	TM	.01
Parkedale Pharmaceuticals*	Coly-Mycin S Otic Suspension	TM	.002
Pharmedix	Bleph 10 Ophthalmic Solution 10%	TM	.005
Pharmedix	Viroptic Ophthalmic Solution 1%	TM	.001
Pharmedix	Blephamide Ophthalmic Ointment	PMA	NS
Pharmedix	Triple Antibiotic Ophthalmic Solution	TM	.01
Pharmedix	Colymycin S Otic Solution	TM	.002
Pharmedix	Neo Poly with HC Otic Suspension	TM	.01
Physicians Total Care Inc.	Neomycin Polymyxin B Sulfates Hydrocortisone Ophthalmic Suspension	TM	NS
Physicians Total Care Inc.	Viroptic Ophthalmic Solution	TM	.001
Physicians Total Care Inc.	Cortisporin Ophthalmic Suspension	TM	.001
Physicians Total Care Inc.	Ocufen Ophthalmic Solution	TM	.0005
Physicians Total Care Inc.	Vasocidin Ophthalmic Solution	TM	NS
Qualitest Pharmaceuticals	Antibiotic HC Otic Suspension	TM	NS
Schering-Plough Animal Health *	Gentocin Durafilm Ophthalmic Solution (for dogs only)	PMN	.002
Sight Pharmaceuticals	Neomycin Polymyxin B Sulfates Hydrocortisone Otic Suspension	TM	NS
Sight Pharmaceuticals	Sulfacetamide Sodium & Prednisolone Sodium Phosphate Ophthalmic Solution	TM	.01
Teral Laboratories	Oticin HC Otic Suspension	TM	.01
United Research Labs	Antibiotic Ear Suspension	TM	.01
United Research Labs	Neomycin Polymyxin B Sulfates Gramicidin Ophthalmic Solution	TM	.01
US Ophthalmics	Fluorescein Sodium Ophthalmic Solution	TM	NS
US Ophthalmics	Sulf-10 Ophthalmic Solution	TM	NS
US Ophthalmics	Vasocidin Ophthalmic Solution	TM	NS
US Ophthalmics	Phenylephrine HC1 Ophthalmic Solution 10%	TM	NS
USCO Logistics	Procofen Ophthalmic Solution	TM	.005
USCO Logistics	Profenal Ophthalmic Solution	TM	.005
VEDCO Inc.	Tribiotic Ophthalmic Solution	TM	NS

1. The names of products submitted in response to the FDA notices are followed by an asterisk (*); "ophthalmic" ➔ "eye" and "otic" ➔ "ear".
2. The mercury ingredients are abbreviated as TM for thimerosal, PMA for phenylmercuric acetate, PMN for phenylmercuric nitrate, MA for mercuric acetate, MN for mercuric nitrate, MB for merbromin, and MOY for mercuric oxide yellow.
3. NS means "not stated" in the agency's Drug Registration and Listing System.

e. Other Products [24 products listed]

The FDA's published list of other products is as follows:

Manufacturer[1]	Name of Product	Ingredient[2]	%[3]
American International Chemical	Thimerosal (bulk chemical)	TM	100
American International Chemical	Thimerosal (bulk chemical)	TM	100
American International Chemical	Thimerosal USP 97% (bulk chemical)	TM	97
Bristol-Myers Squibb *	Fungizone Lotion	TM	.01
Bristol-Myers Squibb *	Fungizone Cream	TM	.01
Dolder Ltd.	Thimerosal (bulk chemical)	TM	100
Dysers Sal	Thimerosal (bulk chemical)	TM	NS
Farm Fresh Inc.	Hemorrhoid Relief Ointment	PMN	.01
Harco Drug #	Mercurochrome Aqueous Solution	MB	2
K and B Distributors #	Mercurochrome Aqueous Solution	MB	2
Laboratori Derivati	Adrenal Cortex Injection	TM	.01
LS Raw Materials Ltd.	Mercurochrome NF 12 100% (bulk chemical)	MB	100
Martin Surgical Supply	Testosterone Injection Suspension 50 mg	TM	.008
Martin Surgical Supply	Testosterone Injection Suspension 100 mg	TM	NS
Mays Drug Stores	Hemorrhoid Relief Ointment	PMN	.01
Omicron Quimica SA	Thimerosal USP 97% (bulk chemical)	TM	97
Ping On Ointment Co. Ltd.	Ping On Topical Ointment	Mercury	NS
Primedics Laboratories	Testosterone Injection Suspension 50 mg	TM	.008
Scrivner, Inc.	Hemorrhoid Relief Ointment	PMN	.01
Spectrum Quality Products	Merbromin (bulk chemical)	MB	100
Spectrum Quality Products	Mercuric Oxide Yellow (bulk chemical)	MOY	100
Spectrum Quality Products	Thimerosal (bulk chemical)	TM	100
Spectrum Quality Products	Thimerosal (bulk chemical)	TM	100
Waldbaum Inc.	Hemorrhoidal Ointment	MN	NS

1. The names of products submitted in response to any of the call-for-data notices are followed by an asterisk (*) and the entries marked with a pound sign (#) seem to be drug products banned in 1998.
2. The mercury ingredients are abbreviated as TM for thimerosal, PMA for phenylmercuric acetate, PMN for phenylmercuric nitrate, MA for mercuric acetate, MN for mercuric nitrate, MB for merbromin, and MOY for mercuric oxide yellow.
3. NS means "not stated" in the agency's Drug Registration and Listing System.

Thus, the FDA-listed drug products range from bulk ingredients to injectable preparations.

In addition to the drugs listed, the petitioners have verbal reports that some monoclonal antibody drugs (e.g., Humira) contain undeclared Thimerosal.

20. U.S. Government's Defenses for Failing to Ban Thimerosal from Medicine

a. Introduction

In response to a previous citizen petition,[218] *submitted on August 4, 2004*, asking the Secretary of HHS and the Commissioner of the FDA to:

- Take action to ban certain mercury-containing drug products, including vaccines;

[218] FDA Public Docket: 2004P-0349/CP1.

- Comply with the statutory mandates set forth in 42 U.S.C. Sec. 300aa-27(a)(2);
- Enforce 21 C.F.R. Sec. 610.15(a);
- Restrict their use of administrative discretion to the clear boundaries set forth by the U.S. Supreme Court in Berkovitz v. U.S.;[219]
- Provide full disclosure of the true risks and their incidence as well as the potential benefits and the cost-effectiveness of each vaccine so that the public can truly give its informed consent for inoculation; and
- Stop the influenza program since it is a clear violation of American's bodily integrity when an ineffective Thimerosal-preserved influenza vaccine is administered because each dose of such vaccines mercury poisons each recipient to some degree causing some immune-system dysfunction but does not effectively protect each such person from contracting influenza,

FDA officials, *after being sued on August 1, 2006*,[220] issued a letter denying said citizen petition.[221]

However, in that letter, date-stamped "SEP 26 2006," the FDA officials failed to address the statutory and the regulatory "safety not proven" issues raised in August 4, 2006 citizen petition.

Instead, the Agency created issues, like "all licensed and approved products containing Thimerosal are unsafe," that that citizen petition, 2004P-0349/CP1, did not raise.

Then, the FDA simply addressed the issues the Agency created without providing, *in most cases*, any citations of published scientifically sound and appropriate toxicological studies or, *for that matter*, scientifically sound epidemiological reports that supported the positions the FDA was espousing to support the Agency's statements.

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[219] Kevan *Berkovitz*, a Minor by his Parents and Natural Guardians Arthur Berkovitz, et ux., et al., Petitioners, *v. UNITED STATES*. Case No. 87-498. 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USL W 4549. (Cite as: **486 U.S. 531, 108 S.Ct. 1954.**)

[220] Paul King et al. v. Michael Leavitt et al, U.S. District Court for the District of Columbia case 1:06CV01357.

[221] FDA Public Docket: 2004P-0349/PDN1

Thus, except for those issues associated with "bodily integrity" and "informed consent," the responses provided by the FDA failed to *directly* address the legal issues (statutory and regulatory) that 2004P-0349/CP1:

- Unmistakably and repeatedly raised, and
- Clearly supported with scientifically sound and appropriate reasoning and references for each legal point raised.

Since petitioners in an FDA citizen petition are required to include "representative data and information known to these petitioners that are unfavorable to the petition," the petitioners have included a transcription of the 2004P-0349/PDN1, the FDA's decision letter.

Following the transcription of 2004P-0349/PDN1, the petitioners have then included an in-depth, evidence-supported review of 2004P-0349/PDN1.

b. Defenses Asserted by the FDA

Thus, the FDA's defenses for the failure of the Secretary of HHS and the responsible Agencies within the Department of Health and Human Services, *including but not limited to the CDC, FDA, and NIH*, to comply with all applicable statutes and laws governing their conduct, and, where appropriate, require drug manufacturers to comply with all the applicable statutes and laws (regulations) governing the manufacturer of drug products lawfully distributed in the United States of America are set forth and embodied in the FDA's "SEP 26 2006" decision letter, 2004P-0349/PDN1.

In addition, said FDA letter claims to address the requests made in 2004P-0349 concerning drug products containing added mercury compounds.

That having been said, the FDA's "SEP 26 2006" decision letter, 2004P-0349/PDN1, with the correction of some spelling and typographical errors, states:

DEPARTMENT OF HEALTH & HUMAN SERVICES Public health Service

Food and Drug Administration
Rockville MD 20857

"SEP 26 2006" [stamped/not typed]

Paul G. King, Ph.D., and Other Representatives for CoMed **[sic; CoMeD]**
Coalition for Mercury-Free Drugs
33A Hoffman Avenue
Lake Hiawatha, NJ 07034-1922

Re: Docket Number CP2004P-0439/CP1

Dear Dr. King and Others:

This letter is in response to your citizen petition dated July 30, 2004, in which you asked the Secretary of Health and Human Services or the Commissioner of the Food and Drug Administration (FDA) to take numerous actions pertaining to vaccines and other FDA-regulated products containing thimerosal or other mercury-based preservatives. We apologize for the delay in responding to the petition. After review and consideration, we deny the petition for the reasons stated below in this response.

We first address the underlying basis for all the actions you request: your contention that all licensed and approved products containing thimerosal are unsafe. The first part of our discussion explains how FDA came to the conclusion that those licensed and approved products are safe. The second part explains why the studies on which you rely do not support your contention.

Following that science-based discussion on safety, we address your legal arguments. We reiterate that for the scientific reasons explained above, none of the legal actions or remedies you seek are **[sic; is]** warranted. We then explain why your claims that the government has violated people's rights lack merit and do not support your petition.

Here is an outline of our response:

I. LICENSED AND APPROVED PRODUCTS ARE SAFE

A. Exposure to Mercury through Vaccines is Minimal

1. *Thimerosal in routinely recommended pediatric vaccines has been removed or reduced.*

2. *Adult exposure to thimerosal through vaccines has been reduced.*

B. Exposure to Mercury through other Biologics and Drugs is Minimal

1. *Most plasma derivative products are thimerosal-free; the few snake and spider antivenoms that contain thimerosal create minimal exposure.*

2. *Exposure to mercury through phenylmercuric acetate and thimerosal in nasal and ophthalmic drug products is minimal.*

C. The Few Products that Still Contain Thimerosal are Safe

1. *To be safe means that the benefits outweigh the risks.*
2. *For the vaccines that still contain thimerosal, the evidence favors rejecting your allegations about risks, and the benefits are lifesaving and well established.*
3. *For the drug products that still contain phenylmercuric acetate or thimerosal, the amounts of mercury are at levels well below what any evidence suggests could pose significant risks to human health.*

II. THE STUDIES CITED AND RELATED ARGUMENTS DO NOT SUPPORT PETITIONERS' CONTENTIONS

A. The Cell Culture Studies Cited do not Demonstrate Harm in the Human Body

B. The Argument that Thimerosal-Containing Products Harm a "Susceptible Population" of Humans is not Supported by the Evidence

1. *The susceptible population annual studies cited do not prove, or even conclude themselves, that a significant risk exists for susceptible populations among humans.*

2. *The references cited that report an increase in the autism rate do not link any increase to vaccines, nor support petitioners' argument.*

3. *The mercury excretion studies in humans do not support petitioners' argument that thimerosal in vaccines causes autism.*

C. Arguments that Thimerosal in the Current Amounts is Insufficient to Quality as a Preservative or an Adjuvant are Flawed; Thimerosal does Meet the United States Pharmacopeia Standard for a Preservative where it is being used as One, and Thimerosal is not being used as an Adjuvant

D. The Cited Animal and Human Studies on Thimerosal's Longevity in the Body do not Study the Consequences of that Exposure.

E. The Studies Cited that Recommend Eliminating all Thimerosal from all Products do not Support those Recommendations with Valid Science.

F. The Methyl Mercury Studies Cited are Inconclusive and Inapplicable to Human Vaccines

G. The Ashwood, et al, Mcginnis, and Megson Studies Cited, which Hypothesize that Thimerosal Causes Gastrointestinal Illness, Vitamin A Depletion, and other Problems, Lack Evidence to Support their Theories

III. PETITIONERS' LEGAL ARGUMENTS LACK MERIT

A. The Actions and Legal Remedies Requested are Unwarranted on Scientific Grounds

B. The Constitutional and Civil Rights Claims do not Articulate any Grounds upon which FDA Should or Could Grant the Petition

IV. AGENCY CONCLUSIONS

DISCUSSION

I. LICENSED AND APPROVED PRODUCTS ARE SAFE

A. Exposure to Mercury through Vaccines is Minimal

The FDA recognizes and supports the goal of reducing exposure to mercury from all sources. Consistent with this goal, FDA has been working with manufacturers for several years to facilitate the development of new vaccines without thimerosal as a preservative and to remove or reduce the thimerosal content of existing, licensed vaccines).[Let-1]

Under the FDA Modernization Act (FDA MA) of 1997, FDA conducted a comprehensive review of the use of thimerosal in childhood vaccines. Conducted in 1999, this review found no evidence of harm from the use of thimerosal as a vaccine preservative, other than local hypersensitivity reactions. However, as a precautionary measure, and because the elimination or reduction of mercury in vaccines was a feasible means of reducing an infant's total exposure to mercury in a world where other environmental sources are challenging to eliminate, the Public Health Service (including FDA, the National Institutes of Health, the Centers for Disease Control and Prevention (CDC), and the Health Resources and Services Administration) established the goal of removing thimerosal as soon as possible as a preservative from vaccines routinely administered to infants.

[Let-1] Statement of Karen Midthun, M.D., Director, Office of Vaccine Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, U.S. Department of Health and Human Services, before the Committee on Government Reform, United States House of Representatives, December 10, 2002

1. *Thimerosal in routinely recommended pediatric vaccines has been removed or reduced.*

The FDA's efforts have been successful. Since 2001, all vaccines routinely recommended for children 6 years of age and under (Diphtheria and Tetanus Toxoids and acellular Pertussis Vaccine (DTaP), hepatitis B, Haemophilus b conjugate (Hib), pneumococcal conjugate, Inactivated Polio Virus Vaccine (IPV), Measles. Mumps and Rubella Vaccine (AMR), rotavirus, and varicella) manufactured for the U.S. market have contained no thimerosal or only trace amounts, with the exception of the inactivated influenza vaccine. In 2004, the Advisory Committee on Immunization Practices first recommended the inactivated influenza vaccine for routine use in children 6 to 23 months of age and has since updated the recommendation to children 6 to 59 months of age.

As to those influenza vaccines, FDA has approved preservative-free formulations (which contain either no, or only trace amounts of, thimerosal) for two licensed inactivated influenza vaccines that are indicated for children. These influenza vaccines continue to be marketed in both the preservative-free and thimerosal-preservative-containing formulations. Sanofi Pasteur's Fluzone is approved for use in children down to 6 months of age. However, during the last influenza season (2005-2006), Sanofi Pasteur had a capacity to manufacture only approximately 7 million doses of thimerosal-preservative free influenza vaccine. For the 2006-2007 influenza season, Sanofi Pasteur has stated that it will produce approximately 11 million doses of thimerosal-preservative-free influenza vaccine. Novartis' Fluvirin is approved for individuals 4 years of age and older. For the 2006-2007 influenza season, Novartis has stated that it will produce approximately 3 million doses of thimerosal-preservative-free influenza vaccine for the U.S. market. In addition, GlaxoSmithKline's (GSK) Fluarix contains less than 1.25μg/mercury/dose and is approved for individuals I8 years of age and older. Last season GSK produced approximately 8 million doses of Fluarix. The live attenuated influenza vaccine (FluMist, manufactured by MedImmune) contains no thimerosal, and is approved for individuals 5 to 49 years of age. MedImmune estimates that it will distribute approximately 3 million doses of FluMist in the 2006-2007 season. Clinical studies to evaluate the safety and efficacy of FluMist in children less than 5 years of age have recently been completed and are under FDA review.

Based on an estimated annual birth cohort in the United States of 4 million, there would be approximately 20 million infants and children between the ages of 6 to 59 months, most of whom would need two doses each. The amount of thimerosal-preservative-free vaccine available is well below the amount needed for this age group alone, let alone for the approximately 180 million Americans for whom the vaccine is recommended. FDA is in discussions with manufacturers of influenza vaccine regarding their capacity to increase the supply of thimerosal-preservative-free vaccine.

Prior to the initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury via routine childhood vaccinations during the first 6 months of life was 187.5 micrograms. With the introduction of thimerosal-

preservative-free formulations of DTaP, hepatitis B, and Hib, the maximum cumulative exposure from the routinely recommended childhood vaccines decreased to less than three micrograms of mercury in the first 6 months of life. With the addition in 2004 of influenza vaccine to the recommended vaccines, an infant could receive a thimerosal-containing influenza vaccine at 6 and 7 months of age. This would result in a maximum exposure of 28 micrograms during the first 7 months of life via routine childhood vaccinations. This level is significantly below the Environmental Protection Agency (EPA) calculated exposure guideline for methyl mercury of 65 micrograms during the first 6 months of life for a child in the fifth percentile body weight. (See the enclosure for the table listing the thimerosal content of vaccines routinely recommended for children 6 years of age and younger.)

2. *Adult exposure to thimerosal through vaccines has been reduced.*

Concern about thimerosal in vaccines has focused on infants and children because of the number of vaccines they receive, the size of their bodies, and their developmental status. Your petition, however, extends to vaccines indicated for all ages, not just those used in infants and children. Standard recommendations for adults lead to far fewer vaccinations, and correspondingly lower mercury exposure from vaccines.

Nevertheless, FDA supports the development of adult vaccines in thimerosal-free formulations and has encouraged the reduction or removal of thimerosal from all existing vaccines. As with pediatric vaccines, these efforts have succeeded in reducing mercury exposure from thimerosal in vaccines for adults, For example, all hepatitis B vaccines for adolescents and adults are available only in formulations that are free of thimerosal or contain only trace amounts. Tetanus and Diphtheria toxoids (Td) vaccine, which is indicated for children 7 years of age or older and adults, is now also available in thimerosal-free formulations. These changes have been accomplished by reformulating products in single dose vials that do not contain a preservative. In addition, the agency has recently licensed two combination vaccines, composed of tetanus, diphtheria, and pertussis antigens (Tdap), a meningococcal conjugate vaccine, a zoster vaccine, and a human papillomavirus vaccine, none of which contains thimerosal. The thimerosal content of U.S. licensed vaccines, including those indicated for adults, is posted at http://www.fda.gov/cber/vaccine/thimerosal.html.

The goal of reducing mercury exposure from vaccines must be balanced against the goal of having enough vaccine available. If FDA now revoked the licenses for all thimerosal-containing vaccines, many people would be in serious danger from the diseases that those vaccines prevent. That is true even where a thimerosal-free formulation of the vaccine exists because at this time manufacturers simply cannot produce enough of either formulation for all those who should be immunized. As discussed below in sections I.C and II, neither the evidence you submitted with your petition nor the extensive evidence on the safely of thimerosal-containing vaccines that FDA has reviewed over the years supports your contention that those vaccines are unsafe.

B. Exposure to Mercury through other Biologics and Drugs is Minimal

1. *Most plasma derivative products are thimerosal-free; the few snake and spider antivenoms that contain thimerosal create minimal exposure.*

Regarding plasma derivative products, multi-dose presentations containing thimerosal preservative have been discontinued for all licensed plasma derivative products. All immune globulin preparations including hepatitis B immune globulin and Rho(D) immune globulin preparations are manufactured without thimerosal. In addition, there is no longer any U.S.-distributed Rho(D) immune globulin that contains thimerosal that is still in-date.

Four other plasma-derived products remain on the market that contain ethyl mercury preservatives. They are pit viper (2), coral snake (1) and black widow spider (1) antivenoms. Although FDA encourages current manufacturers of licensed products to decrease the amount of thimerosal in those products, and to develop manufacturing methods that do not use thimerosal, snake and black widow spider bites are dangerous and can cause serious morbidity and mortality. Removal of the product from the market by the FDA would not be in the best interest of the public health when no substitute products are available, and such an action would be likely to result in severe illnesses and deaths. In fact, Wyeth Pharmaceuticals, Inc. has stopped manufacturing its pit viper and coral snake antivenoms, but the in-date product must remain available on the market because Wyeth's is the only licensed coral snake antivenom, and supplies of the other licensed pit viper antivenom are not sufficient at this time.

A list of mercury free and mercury-containing plasma-derived products is posted on the Internet at www.fda.gov/cber/blood/mercplasma.htm.

2. *Exposure to mercury through phenylmercuric acetate and thimerosal in nasal and ophthalmic drug products is minimal.*

Mercury, in the form of phenylmercuric acetate (PMA) and thimerosal, is found in certain types of drug products. PMA is not contained in any prescription nasal solutions or sprays, but it is thought to he used in approximately 40 over-the-counter (OTC) nasal solutions and sprays, and 5 ophthalmic ointment products. A 15-milliliter (ml) bottle (0.02 mg/ml) of nasal solutions and sprays contains approximately 0.3 mg of PMA. PMA is used in ophthalmic ointments at concentrations of 0.0008%. For the reasons set forth in section 1.C.3 below, FDA believes that the mercury exposure from such products is minimal, and the products are safe.

C. The Few Products that Still Contain Thimerosal are Safe

1. *To be safe metals that the benefits outweigh the risks.*

Safety is relative, rather than absolute. FDA regulations define safety as "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation

to the condition of the recipient at the time" (21 CFR § 600.3(p)). If the benefit of the vaccine or other pharmaceutical product outweighs the risk of the side effects, then FDA finds the product safe. Applying that relative standard for safety is critical to the public health because virtually every vaccine — and every drug, for that matter — carries the risk of some side effects. In applying the regulatory standards, FDA must weigh the risk of a vaccine — indeed, the risk of any drug — against its benefits when determining whether the product is safe.

2. *For the vaccines that still contain thimerosal, the evidence favors rejecting your allegations about risks, and the benefits are lifesaving and well-established.*

Thimerosal has a long record of safe and effective use in preventing bacterial and fungal contamination of vaccines, with no ill effects established other than hypersensitivity and minor local reactions at the site of injection. Nevertheless, some people have raised concerns about the use of thimerosal in vaccines, and in particular about potential adverse effects of the cumulative amount of mercury that might be administered to a child as a result of routine childhood immunization. These concerns were based on increased awareness of a potential for neurotoxicity of mercury, and on the increased number of thimerosal-containing vaccines that were added to the infant immunization schedule in the 1990's.[Let-2]

In 2001, the Institute of Medicine's Immunization Safety Review Committee issued a report, based on a review of available data, concluding that the evidence was inadequate to either accept or reject a causal relationship between thimerosal exposure from childhood vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder, and speech or language delay. The Committee stated that the effort to remove thimerosal front vaccines was "a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible."[Let-3] The IOM issued a follow-up report on May 17, 2004, based on the IOM's extensive review of the epidemiological studies performed after it issued the 2001 report, some of which you also cited in your petition (in endnotes 38.1, 38.2, 38.3, 34, 40.1, 40.2, 40.3 and 40.4).[Let-4] The IOM explained its conclusions as follows:

> Epidemiological studies examining thimerosal-containing vaccines and autism, including three controlled observational studies (Hviid. et al., 2003; Verstraeten et al., 2003; Miller, 2004) and two uncontrolled observational studies (Madsen et al., 2003; Stehr-Green et al., 2003), **consistently provided evidence of no association between thimerosal-containing vaccines and autism,** despite the fact that these studies utilized different

[Let-2] Thimerosal in Vaccines. Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, http://www.fda.gov/cber/vaccine/thimerosal.htm.

[Let-3] IOM (Institute of Medicine). Thimerosal-containing vaccines and neurodevelopmental disorders. Washington, DC: National Academy Press, 2001.

[Let-4] IOM (Institute of Medicine). Immunization Safety Review: Vaccines and Autism. Washington, D.C.: National Academy Press: 2004 (Executive Summary, at 4) (emphasis added)

> methods and examined different populations (in Sweden, Denmark, the United States, and the United Kingdom). Other studies reported findings of an association, These include two ecological studies (Geier and Geier, 2003a; 2004), three studies using passive reporting data (Geier and Geier, 2003a,**b,** d), an unpublished study using Vaccine Safety Datalink (VSD) data (Geier and Geier, 2004b,c), and one unpublished uncontrolled study (Blaxill, 2001). However, the studies by Geier and Geier cited above have serious methodological flaws and their analytic methods are nontransparent making their results uninterpretable, and therefore non-contributory with respect to causality .... The study by Blaxill is uninformative with respect to causality because of its methodological limitations.

FDA concludes that the evidence reviewed by the IOM does not support an association between thimerosal-containing vaccines and autism. In particular, the data from Denmark and Sweden, where exposure to thimerosal in vaccines was eliminated in 1992 and where autism rates continued to increase, underscore this finding (Stehr-Green. et al., 2003). Furthermore, recent data from a study conducted in Quebec, Canada, also found that there is no relationship between the level of exposure to thimerosal in vaccines and autism (Fombonne, et at.. 2006). This conclusion is further supported by an analysis by Parker, et al., 2004 (Ped. 114: p. 793), who conducted a systematic review of published articles that report original data pertinent to the potential association between thimerosal-containing vaccines and attention deficit disorders/neurodevelopmental disorders. The authors concluded that available data did not demonstrate a link between thimerosal-containing vaccines and autism spectrum disorders.

On the other hand, it is well established that vaccines have widespread, life-saving benefits. As discussed above, FDA must weigh theoretical risks against the known benefits of vaccines that would be greatly reduced if FDA were to revoke the licenses for all thimerosal-containing vaccines. As to the influenza vaccine, for example, recent analyses estimate an average of 36,000 annual deaths from influenza during the 1990s and an average number of hospitalizations between 114,000 and 200,000, with rates highest among those under 23 months of age and those over 65 years of age.[Let-5] During the 2003-2004 influenza season, several states had reported by December 2003 severe complications and deaths related to influenza in children (MMWR 12/19/03, 52(49)1197-1202), Since some of these deaths were in children under 23 months of age, it is clear that there is an actual risk of preventable disease causing death as compared to the theoretical risk of vaccine causing autism.

[Let-5] Plotkin, Stanley A. et al., Vaccines, 4th Edition, Chapter 17 (2004)

3. *For the drug products that still contain phenylmercuric acetate or thimerosal, the amounts of mercury are at levels well below what any evidence suggests could pose significant risks to human health.*

   a. PMA in nasal and ophthalmic drug products

PMA is an organic (aryl) form of mercury that is rapidly metabolized to an inorganic form of mercury. PMA is used in nasal sprays and ophthalmic drug products. It has the chemical structure, $C_6H_5HgOOCCH_3$ (Sax 1984). The rapid conversion of PMA from the organic form to the inorganic form is an important factor in PMA's toxicity profile. Although organic methyl mercury is detectable in experimental animals for weeks after a single injection, phenylmercuric salts are completely converted to the inorganic form within days of dosing (Clarkson 1972). The relatively rapid clearance of inorganic mercury compared to organic methyl mercury helps to render the inorganic forms generally less toxic. Thus, the toxicity caused by PMA is similar to inorganic mercury, with the kidney as the target organ.

In a review of the scientific literature, we found two chronic toxicity studies of PMA in rats. The EPA used the most conservative study to establish acceptable daily exposure limits. This study was conducted for two years in rats (0.1 to 160 parts per million (ppm) of PMA in the diet), and toxicity consisting of kidney damage was detectable at 0.5 ppm (Fitzhugh, et al., 1950). EPA determined that the No Observable Effect Level (NOEL) from this study was 0.1 ppm PMA (equivalent to 5 micrograms per kilogram per day (μg/kg/day) mercury, assuming rats consumed 5% of their body weight/day) with a final NOEL calculation of 8.4 μg/kg/day PMA (id.). We used this value below to estimate the risk of PMA in nasal solutions and sprays and in ophthalmic ointment.

A second chronic rat study with PMA exposures via oral dosing of two years duration also demonstrated renal toxicity (Hayes 1982). However, the NOEL was much higher than in the previous study, at 2 milligrams per kilogram per day (mg/kg/day) or 40 ppm. This study confirmed the target organ for PMA as the kidney, but this study was not used for risk estimation because the study by Fitzhugh and colleagues (1950) yielded a more conservative value.

No prescription nasal solutions or sprays contain PMA; however, PMA is thought to be used in approximately 40 OTC nasal solutions and sprays and five ophthalmic ointment products. As an exposure estimate for nasal solutions and sprays, a 15-milliliter (ml) bottle (0.02 mg/ml) contains 0.3 mg PMA. The recommended usage for these products is 2 to 3 sprays in each nostril not more than every 10 to 12 hours. These products are not generally intended for chronic treatment of rhinitis. However, even people who do not use such sprays chronically may experience rebound nasal mucosal vasodilation and congestion called "rhinitis medicamentosa", which may result in further increased use. A reasonable maximal exposure estimate in humans would be 3 sprays per nostril every 4 hours for a total of 36 actuations per day, 0.07 ml/actuation, resulting in a total daily PMA exposure of 0.05 mg. Because mercury accounts for 86% of PMA by molecular

weight, the daily exposure to mercury from this product approximates 43.34 µg/day or 0.87 µg/kg/day, assuming a 50-kg individual. Thus, the NOEL dose from the two-year study in rats provides a 9.7-fold safety factor compared to the maximum human exposure if the maximum recommended dosage as labeled was used chronically, assuming that intranasal exposure in humans is comparable to dietary exposure in rats. There are currently no pharmacokinetic data available to support this assumption; however, accumulation of mercury following chronic use is not expected due to the relatively quick clearance of inorganic mercury. In addition, these products are labeled for adults and children ages 6 years and older. For children under 6, the labeling states to "consult a doctor." Therefore, children under 6 are less likely to have any exposure to these products at all, or at least to be exposed with medical supervision to help ensure that the exposure is not excessive.

PMA is used in five prescription ophthalmic ointments. Based on the three ophthalmic ointments for which PMA concentration appears on drug product listing forms, the concentration is 0.0008% in these products. Because mercury is present in PMA at a level of 86%, based on molecular weight, the maximum mercury concentration in PMA-containing ophthalmic products is approximately 0.00069%. The recommended usage for these products is 1 cm ribbon in each eye four times a day, At a volume of 500 µl per application, the total daily exposure to mercury would be 27.5 µg/day or 0.55 µg/kg/day in a 50-kg person. Thus, the NOEL dose from the two-year study in rats provides a 15-fold safety factor compared to the maximum human exposure. Therefore, we believe that the use of PMA in ophthalmic products does not pose a threat to human health.

b. Thimerosal in ophthalmic, nasal, and otic drug products

Thimerosal has been used in pharmaceutical products since the 1930s and is used in ophthalmic and nasal products (Golightly, et al., 1998). It is also found in a few otic products.

In a review of thimerosal reactions, Golightly and colleagues (1988) reported that a T-lymphocyte-mediated hypersensitivity response had been observed in patients with ocular discomfort and conjunctivitis and in intradermal and dermal patch tests with thimerosal solutions or ointments. Signs of ocular and dermal sensitivity resolve spontaneously after cessation of the use of thimerosal and do not, themselves, indicate toxicity. There was no mention in the report of any target organ or reproductive toxicity, and the hypersensitivity response is not directly related to specific mercury toxicity. Therefore, the data are insufficient for exposure comparisons to set limits based on toxicity.

In a study submitted to an approved new drug application (NDA), chronic toxicity data on 0,001% thimerosal was provided. In that study, rabbits were dosed in the right eye with 2 drops of 0.001% thimerosal 3 times per day for one year and then subjected to full histopathologic evaluation of organs and tissues, including an ophthalmic evaluation that utilized scanning electron microscopy of the corneas. There were no signs of ophthalmic